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ENCYCLOPEDIA OF ENDOCRINOLOGY

by

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CANCELLED

SECTION IV

OVARY

VOLUME VII

OVARIAN TUMORS

Published by
RICHARDSON, BOND AND WRIGHT,
MONTREAL, CANADA.

X. B. 13. a

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to

MY WIFE,

THE MOTION PICTURE INDUSTRY

and

THE NEW YORKER MAGAZINE

Without whose refreshing influence the boredom of this venture could not have been endured.

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FOREWORD

The main purpose of this Encyclopedia is to demonstrate—using endocrinology as an example—the essential feasibility of a rational classification and evaluation of all publications pertinent to a large field of medicine. It is perhaps not inappropriate, therefore, to briefly discuss the rôle played, in contemporary medical literature, by the classification of scientific data.

It is my impression that we are now in the process of entering a new era, not only in medicine, but in all fields of research. In our century, much more than ever before, investigations are subsidized by governments, research foundations, industry and private individuals. This has helped to increase the quantity, but could undoubtedly do much more than it has to raise the quality of investigative work. Too often those whose duty it is to assess the value of an investigator, are largely unfamiliar with his special field. Hence, in decisions concerning his promotion in academic life, or the placement of additional facilities at his disposal, too great emphasis is placed on quantitative rather than qualitative criteria. As a result of all these factors, an enormous mass of factual evidence—some important, some less so—is continuously brought to light and published in the scientific journals of all countries. It is quite obvious to anyone who has followed this increase in scientific production, that if it continues to proceed at the present rate, many of the published results will soon be lost merely because no one will be able to keep track of them. Unless we can cope with this problem, science will actually suffer from its own disproportionate growth and chaos must inevitably ensue when investigators are no longer able to keep themselves informed of current advances in their own fields.

I believe that mass production is the most characteristic feature of the present era in research, and hence calls for the development of special methods which can deal with it efficiently. Only if this is achieved will investigators have the leisure to evaluate published data to full advantage. In this connection it may be permissible to say a few words about the place of evaluation in the medical sciences.

During and before the Middle Ages disputation and argument went to such extremes that any attempt to find the truth by mere dialectics gradually became thoroughly discredited. In those days so few scientific facts were available that little could be gained by their collection, classification and critical evaluation. The only outlet for the curious intellect was to speculate about the few available scientific data and there appeared to be no possibility of making much progress until adequate technics for accurate investigation were developed to unearth more facts.

It is regrettable, however, that as a reaction to this sterile, theoretic approach, mistrust of its loopholes has brought it into such disrepute that reviewing is not only considered to be distinct from research but humiliatingly unoriginal. It has now become fashionable to avoid theoretic considerations as mere hocum and with an air of self-righteousness, to limit scientific papers to the mere tabulation of facts. This reaction is just as damaging to the progress of science as the excesses of speculation which provoked it. Many of us tend to forget that, scientific facts are of value, not in themselves, but only if they permit some degree of generalization. Experiments are but models in which we observe the behaviour of nature under certain conditions, in order to supply material for inductive reasoning, applicable to other similar conditions. The same is true of "interesting" clinical case reports. Publication of information, gathered in diagnosing or treating the disease of a certain patient, is of no value to readers in connection with that same patient, whom they will never see. Such information is instructive only if we have reason to believe that the lessons derived from it will be applicable to other cognate conditions. The correlation and fruitful evaluation of data is our highest objective, yet the reviewer in science is regarded as somewhat comparable to the non-combatant soldier in the army. This is so entirely unjustified that it is difficult to understand how such a point of view can be so tenaciously held. Is the power of observation a higher intellectual accomplishment than the power of correlation and evaluation? Does the former require greater innate gifts or more extensive training? Does it do more for the promotion of knowledge? As one who has, on a modest scale, participated both in original investigations and in critical reviewing, to an approximately equal extent, I certainly do not believe this to be so. To begin with, the reviewer must have a good deal of research experience in order to give a balanced evaluation of the literature, he must be well acquainted not only with the main subject which he discusses and with many allied fields, but also with the languages in which the various publications are written; and finally, unlike the original investigator's success, that of the reviewer is less favored by mere chance. Only profound knowledge of his field and a deep understanding of the underlying problems can make his efforts fruitful.

Although all these facts are self-evident, they do not register sufficiently in the minds of many contemporary investigators. Too many workers perform experiments merely because "this has never been done" or publish clinical observations because they have "hitherto not been described", irrespective of what can be learned from them. These are inadequate reasons for increasing our already unwieldy scientific literature.

In order to plan work rationally it is essential to acquire a thorough knowledge of the pertinent litera-

ture. This is impossible with the antiquated registration systems now in use. The importance of all research technics (histological, surgical, chemical, physical, etc.) is universally recognized, but scientists are not yet clearly aware of the fact that in most fields of research special technics of learning are necessary in order to sort out the relevant literature, so often buried in the irrelevant. The scientific indexes represent a valiant effort in this direction. Although abstracts of publications usually are made by competent scientists, unfortunately those entrusted with the indexing of papers are rarely trained to cope with the entire field for which they are responsible. As a result, the available indexes are constructed mainly on the basis of certain "key words" contained in the title. Thus it is largely a matter of chance whether a certain publication appears under one or another of several possible headings, and the collection of all relevant publications pertaining to a certain fact is impossible.

These considerations convinced me some seventeen years ago that it would be of the greatest importance to show the feasibility of efficient registration of scientific data in any one field of investigation. Since I was particularly interested in endocrinology I decided to use this science as an example. From then on I concentrated all my efforts on obtaining enough personal research experience in various fields of experimental and practical medicine as well as and a fair knowledge of the leading modern languages to enable me to survey the endocrine literature from various points of view. These loose-leaf volumes represent a first tentative effort to make the entire endocrine literature easily accessible to research workers and clinicians. The methods of classification which I adopted will be described in detail in the first volume of each section of this Encyclopedia. Suffice it here to state that my aim has been to report the pertinent literature as completely as possible and to develop a system of rules which would enable us to discuss a certain discovery under one heading only, so that the reader who does not find it in the expected place need search no further (for technical details consult "Introduction").

The literature concerning hormones is growing at a particularly rapid rate so that most investigators find it increasingly difficult to keep themselves fully informed; yet because of the manifold correlations through which the endocrine glands influence each other, and indeed most organs in the body, it is especially important to refrain from overspecialization in this science. Unlike many other disciplines, there is no contemporary handbook from which the investigator can obtain a critical and up to date evaluation of any data pertaining to endocrine literature. The subject is so vast and touches on so many fields of physiology, medicine, morphology and chemistry, that the task of preparing a handbook of this type requires the major part of a lifetime. Furthermore, the expense connected with such a venture is very great, since it is technically impossible to review the immense literature on endocrines, without accumulating the relevant publications in one library. Fortunately, towards the end of the last century, when endocrinology began to take shape as a separate science, Professor Stricker of Vienna established a nucleus for such a library in a small reprint collection, which was carefully kept up to date by my late teacher, Professor Arthur Biedl, of Prague, (the author of the first reference book on hormones) and after his death, by myself. Perusal of all relevant sections in the "Quarterly Cumulative Index Medicus", the "Index Catalogue of the library of the Surgeon-General's Office, U.S. Army", as well as the many reprints, doctor's thesis and monographs kindly contributed by my colleagues from every part of the globe, has helped to cover the world literature on endocrinology more completely than has been possible in the past. My library now contains approximately 250,000 entries (reprints, abstracts or microfilms). During the last twelve years, a detailed subject index has been prepared which places the data of the library in a readily available form. As such, the collection has provided our group as well as occasional visitors from other universities, with a reasonably complete set of references on any subject pertaining to the glands of internal secretion.

It has been suggested repeatedly that the library should be made more generally available, in the shape of an Encyclopedia of Endocrinology. The "Classified Index of the Steroid Hormones and Related Compounds", published in 1943, represented the first effort in this direction. To my great satisfaction, I learned from my colleagues, interested in the steroid field, that the "Index" was of use to them inasmuch as it made the literature concerning the chemistry, pharmacology and metabolism of the steroids readily available. Encouraged by these comments, I decided to proceed with the publication of the remaining sections of the Encyclopedia and the present volume on Ovarian Tumors represents one part of Section IV, which will be devoted to the Ovary. It is hoped that, if these volumes succeed in convincing the medical public of the great advantages inherent in such systematic reviewing, similar efforts will be made by others in different fields, not only in medicine, but in other sciences as well. If this modest experiment, undertaken by a single author, should prove successful, then perhaps the ministries of education, the national research councils and the scientific foundations of various nations can be induced to organize similar efforts on a larger scale, proportionate to their much greater resources. It is tempting to conclude this discussion with the thought of what could be done along similar lines for research by an international organization subsidizing the work of scientists especially trained in the technic of reviewing and working with a polyglot staff of trained librarians and secretaries in a complete, international library.

INTRODUCTION

SCOPE OF THE VOLUME ON OVARIAN TUMORS

It has been emphasized frequently that no organ of the human body forms such a variety of neoplasms as the ovary. Only the female gonad is the source of the gigantic neoplasms, whose weight may exceed, by far, that of the host's entire body; only the ovary forms the manifold cystic blastomas; only ovarian tumors are subject to the great variety of complications (torsion, rupture, migration), which lead to important diagnostic problems. The tumors of no other organ have stimulated so much discussion concerning the fundamental pathogenic problems of neoplastic growths in general. It is not surprising, therefore, that the literature dealing with the tumors of the ovary is more voluminous than that concerning the neoplasms of other organs.

These facts—as well as the enormous progress made during the past few decades in the domain of the sex hormones, with the ensuing great advances in the diagnosis, therapy and interpretation of ovarian disease—created a pressing need for an encyclopedic treatise of this field. A systematic classification and critical evaluation of the pertinent publications could be of invaluable aid not only to the gynecologist and endocrinologist, but also to the pathologist and oncologist who is interested in neoplastic growths in general. If this immense and confusing part of medical literature could be successfully surveyed, this would prove the essential feasibility of writing a *complete* review on an extensive field, an enterprise which has hitherto not been attempted in any domain of medicine.

It was obviously impossible to read in their entirety all publications quoted in this volume. In some instances only brief abstracts were available, while in others the description given was so lengthy and confusing that a complete scrutiny of the text did not appear instructive or even feasible. Such publications are listed according to the "*principle of progressive specification*". This principle postulates that the evidence given in any publication be listed under the most specific caption of which the reviewer can be certain. To take a case in point the specificity of the information, contained in publications concerning an ovarian tumor, may increase in the following order:

Tumor
Tumor, cystic.
Tumor, cystic, large.
Tumor, cystic, large, multilocular.
Tumor, cystic, large, multilocular, serous.

If a neoplasm is merely described as an ovarian tumor, without giving any of its structural characteristics, it will be listed among the case reports, in the chapter on Ovarian Tumors in General. As such, this information will be of little value except perhaps in connection with the clinical manifestations of the growth; generally these are described in the original article and may help the statistical evaluation of the manifestations of ovarian neoplasms in general. Any information concerning such a case becomes increasingly more valuable in proportion to the available specific data regarding its structure.

It is of interest to note that the historic development of our knowledge, in almost any field of science, progresses according to this same principle. For instance, if we take the ovarian tumors as an example, we see that our knowledge progressed from noting first the basic fact that growths may develop in the gonads, through a number of increasingly more specific stages of knowledge in which first the macroscopic, then the microscopic features were gradually observed until eventually complete characterization of the neoplasm became possible. Thus a review, constructed in accordance with the principle of progressive specification, follows the natural course of the development of scientific progress.

CLASSIFICATION

The entire Encyclopedia of Endocrinology will consist of ten sections:

I Classified Index of the steroid Hormones and Related Compounds. (Published in 1943).
II Adrenal.
III Hypophysis.
IV Ovary (of which the present volume represents one part).
V Pancreas.
VI Parathyroid.
VII Pineal.
VIII Testis.
IX Thymus.
X Thyroid.

The material concerning the Diseases of the Ovary (Section IV, Vol. VI "Ovarian diseases other than Tumors" and Vol. VII "Ovarian Tumors") has been prepared for immediate publication. For technical reasons, however, the sections and volumes are not numbered in the chronological order of their publication but in the manner indicated above.

The material concerning the ovaries (Section IV) has been subdivided as follows:

I *MORPHOLOGY* (Anatomy, histology, comparative anatomy, embryology).

II *CHEMISTRY AND PHARMACOLOGY* (Chemical composition of the ovary, chemistry and pharmacology of the ovarian hormones).

III *EXPERIMENTAL PHYSIOLOGY* (Changes produced by ovariectomy or by treatment with ovarian hormones).

IV *EXPERIMENTAL PATHOLOGY OF THE OVARY* (Experimentally induced ovarian changes).

V *METABOLISM OF OVARIAN HORMONES* (Ovarian hormone content of various body fluids and tissues, under normal and abnormal conditions).

VI *OVARIAN DISEASES OTHER THAN TUMORS.*

VII *OVARIAN TUMORS.*

The data concerning ovarian tumors (Section IV, Vol. VII) have been subdivided further into chapters, the first of which contains the facts pertinent to ovarian tumors in general and comparative considerations regarding the various specific tumor types (e.g. differential diagnosis, relative incidence, etc.). Each of the subsequent chapters deals with a separate tumor entity.

In the chapter on Tumors in General, and in those dealing with special tumor types, the material is classified under the following headings:

Synonyms
Reviews
Definition
History
Classification
Pathologic Anatomy
Chemical Composition
Incidence
Pathogenesis
Clinical Course
Complications
Diagnosis
Prognosis
Therapy
Tumors in Para-ovarian Region
Tumors in Animals

In order to facilitate consultation of cross-references, the various subdivisions of the text are designated by consistent terms. A "*section*" means all volumes dealing with any one of the endocrine glands; the four volumes of the "Index of Steroid Hormones" are also regarded as a separate section. By "*volume*" we mean any individual loose-leaf book within a section. The volume in turn is subdivided into "*chapters*". In the case of the present volume these deal with any one of the specific tumor types and are further subdivided into "*parts*" as indicated by the headings listed in the preceding paragraph. Thus, for example, reference to the size of ovarian fibromas may be made as follows:

Section IV:	Ovary.
Volume VII:	Ovarian Tumors.
Chapter:	Fibromas.
Part:	Pathologic Anatomy.
Paragraph:	Size.

In this manner, precise cross-references can be made even to subjects which are to appear in future sections of the Encyclopedia, that is to text which has no page number as yet.

TECHNIC OF PRESENTATION

In all the Sections of the Encyclopedia the loose-leaf system is used, since it is obviously of the utmost importance to keep these volumes up to date and the expense of publishing frequent new editions would be prohibitive. The loose-leaf folders permit the insertion of additional pages and the substitution of new sections for those which have become antiquated; hence, they lend themselves well to this type of publication. It was felt, furthermore, that it would be especially desirable to present this Encyclopedia in a form which would enable every investigator, teacher and clinician to adapt it to his particular requirements. The choice of a standard type of binder—for which additional sheets are readily obtainable—appears to solve this problem, since readers who wish to add personal notes to chapters which are of particular interest to them, may readily do so, using the printed pages and tabs as a basis for the classification of their own data. In this manner, the book may be moulded into a rather personal tool of investigation.

In connection with these volumes the provision is contemplated of an abstract service by the issue of supplementary pages, which will take the place of the old ones, whenever important additions are to be made. Thus it will be possible to keep these volumes up to date, at a comparatively low cost, by printing additional loose-leaf sheets corresponding to an entire new chapter, should a new tumor entity be discovered in the future; similarly when important progress is made in the understanding of one of the already known tumor types, the pages which now describe it will be discarded, and the corresponding chapter will be completely re-written in loose-leaf form. New pages, substituting for old ones, will be issued under the same page numbers. Thus, if an antiquated chapter can be brought up to date by re-writing it in the same number of pages, no renumeration will be necessary. If, on the other hand, additional sheets are required, they will be given the number of the page after which they are to be inserted, followed by a decimal point and a numeral indicating the position they will take after the original page. The system is illustrated by the following example; a new page to be added after page 37 will be marked 37.1, the next inserted page,

37.2 etc. It is evident that such a system of numbering is readily expandable to any number of subsequent supplemental issues; e.g. if, in the above example, a page should have to be inserted at a still later date, between 37.1 and 37.2, it would bear the number 37.1.1.

The accession numbers of each publication are used for the sake of uniformity, since many publications will be quoted in different sections of the Encyclopedia. At the end of each section, the references are enumerated (in the case of large sections, in a separate volume) in the order of their accession numbers, which means that only a small portion of the existing numbers (namely, 1-100,000 and A1-A100,000 and B1-B50,000) will be used in any one section. When reading the text, it is convenient to note—without having to consult a separate list of quotations—the names of the authors and the dates of the publications to which reference is made. In view of the extensive literature, which has to be quoted in this Encyclopedia, it would be difficult to enumerate names, accession numbers and publication dates in the text, without interfering with its legibility. For this reason a special system has been introduced, in which exponential, small numerals are used in the text; these refer the reader to the foot of the same page, where all relevant publications are indicated by the name of the author, the accession number and (after a stroke) the last digits of the year in which the publication appeared. Thus, even without consulting the reference volume, it is evident that the quotation, "Meyer A76843/12", for instance, refers to a paper published by Meyer in 1912 and bears the accession number A76843. Those who wish to have the complete reference will find it in the reference volume, (Volume IV Ref.) where the authors are listed in alphabetic order. The references are in a separate volume, since this makes it possible to keep the text volume open at the page containing the required information and, simultaneously, to consult the references in the second volume. The reference volume is not printed in loose-leaf form, since insertions in the alphabetic list of authors would not be possible in any case. References for future additional sheets will be issued on loose-leaf pages, to be attached to the text volume.

In order to increase the international value of the Encyclopedia, special care was taken to list foreign review articles concerning each subject. These will enable workers, who are not very familiar with the English language, to prepare themselves for the study of the present volume by reading a review in their native tongue. Data concerning the geographic distribution or the influence of regional conditions upon the disease, can be obtained readily also by comparing reviews written by authors of different countries.

Since the primary object of these volumes is to serve as a guide to, and critical summary of, the relevant literature, great care has been taken to check all data for correctness and completeness; still, considering the vastness of the field, many errors and omissions have probably escaped attention. *I shall be very grateful if the readers will bring any such shortcomings to my attention, so that they may gradually be corrected when antiquated pages are replaced by new ones.*

ACKNOWLEDGMENTS

The compilation of this work was possible only owing to the generous help received from many co-workers and colleagues. It was, indeed, a source of deep satisfaction and constant encouragement to note that even in our uprooted era of international conflict and competitive struggle, the desire to help the progress of knowledge for its own sake, is still strong enough to move so many persons, in such different walks of life, to contribute to the success of this venture.

The author's gratitude is due, firstly, to the two great Universities, on whose staffs he served while writing this volume. The extraordinarily co-operative attitude of the McGill Medical Library staff was indispensable in the compilation of the extensive literature cited, while the appreciative understanding received from the Authorities of the University of Montreal, helped greatly in solving the many problems of organization which arose in connection with the editorial and secretarial work.

Special gratitude is also due to the Surgeon General's Library for donating the numerous microfilms of papers not otherwise available to the author.

We are also indebted to Professors W. U. Gardner, E. C. Hamblen, H. T. Karsner, J. V. Meigs, E. Novak, Drs. E. C. Hay, H. E. MacDermot, F. L. Selye, Donald C. Wilson, Mrs. C. Friedman and Mrs. M. McCairns for reading part or all of the manuscript and proofs as well as for their useful suggestions concerning the presentation of the material.

Our gratitude goes furthermore to Professors L. Berger, H. T. Karsner, P. Masson, E. Novak, L. C. Simard, T. R. Waugh as well as the Department of Radiology of the Royal Victoria Hospital, of Montreal, for contributing illustrative material.

Thanks are due, also to Messrs J. M. Christie and R. S. Donald, of Richardson, Bond and Wright, Publishers, for doing their utmost to present this book as well as possible, at a time when almost all the necessary materials were unusually expensive and difficult to obtain.

The author is especially indebted to Mr. Kai Nielsen, Superintendent of the Institute of Experimental Medicine and Surgery, of the University of Montreal, who prepared all the photographs, which appear in this book, except those specifically acknowledged to outside sources.

Last, not least, I wish to take this opportunity to express my deep gratitude to my secretaries. The conscientious and devoted attention which they gave to the preparation of this manuscript was far greater than their normal duties demanded and I am well aware of the fact that it was their desire to do their share in the creation of this reference work, that induced them to accept the strain and monotony of such tasks as the compilation and verification of references, many of which appeared in foreign languages. Space does not permit complete enumeration of all those from whom I received secretarial help but this book would not be complete without mentioning Mrs. McCairns and Misses M. Alius, B. Burton, A. Fischer, J. Gougeon, P. Hart, B. Plante, H. Stone and L. Théberge.

The International Cancer Research Foundation, helped the research work of this Institute on problems concerned with tumor formation and thereby increased my appreciation of this subject.

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OVARIAN TUMORS IN GENERAL

REVIEWS

DANISH: *Müller* A74637/04.

DUTCH: *ten Berge* A96669/40.

ENGLISH: *Johnstone* A70759/, A70758/29-30, *Kilgour* A88230/843, *Tilt* A88250/850, A88251/851, *Gaston* A88225/854, *Tweed* A86107/857, *Adams* A81078/859, *Hamilton* A81134/862-5, *Wells* A88252/867-8, A74792/868-81, A40558/882, A74795/882, *Guernsey* A74709/877-8, *Atthill* A29362/880, *Carmichael* A40465/884-5, *Young* A42110/886, *Lee* A42111/886, *Howell* A74826/888, *Darling* A42195/888, *Sutton* A43490/890, A74815/894-5, *Kelly* A46445/893, *Gage* A47072/894, *Burford* A48965/897, *Davison* A50994/899, *Alexander* A50984/899, *McMurtry* A50978/899, *Maxwell* B13333/06-7, *Spilsbury* A68525/10-1, *Goodall* A64762/12, A64763/20, A74124/35, *Giles* A68470/12-3, *Geist* A64759/22, *Clark* A68507/23, *Waring* A68484/23, *Bishop* A68461/24, *Gardner and Traut* A70720/28, *Lanman* A68183/29, *Taylor* B5989/29, *Weber* A68053/29, A68129/29, *Bride* A65602/29-30, *Turlington* A65574/30, *Curtis* A63170/30-42, *Lochrane and Keating* A64232/31, *Meyer* A62941/31, *Green-Armytage* A65155/31, A64221/31, *Stevens* A64846/31, *Guggisberg* A64766/31, *Dudgeon* A62294/32, *Shaw* A61896/32, *Bell and Datnow* A66142/32, *McNamara et al.* A51751/34, *Meigs* A64792/34, A98168/43, *Novak* A53103/34, A38097/42, *84959*/44, B109/44, *Ewing* A64873/28-42, *Novak and Gray* A61851/36, *Bernstein* 81758/36, *Schiller A64891/36*, *Fenton* A96023/37, *Cooke* A94777/37, *Nielsen* A95081/37, *Bang* A94664/38, *MacCallum* A94851/38, *Chaney and Greenblatt* A95386/38, *Mathews and Winder* A96515/38, *Schattenberg* A97183/38, *Bernstein and Bernstein* B5328/38, *Smith* A97315/38, *Bergstrand* A97255/39, *Karsner* A32285/40, *Danforth* 82843/40, *Counseller* A34421/40, *Dockerty and Counseller* A34416/40, *MacCarty* A35987/41, *Dockerty* A36015/41, *Block* A96671/41, *Lipscomb* A97491/41, *Taylor* A97529/41, *Dockerty and Masson* A38032/41, *Geist B6672*/42, *Schulze* A37817/42, *Scheffey* A97824/42, *Goldsmith and Joseph* A57683/43, *Geist and Spielman* A58179/43, *Gallagher* A71298/43, *Barzilai* A71883/43, *Khanolkar* B10138/43, *Reimann and Keller* A98224/43, *Long and Biskind* A98163/43, *Menon and Veliath* B10139/43, *Way* B10829/44.

FINNISH: *Limnell* A74817/898, A74811/03.

FRENCH: *Malassez* A88236/874, *Nicaise* A40319/881, *Wells* A41283/883, *Auché* A41731/886-7, *Lambilliotte* A47066/894, *Picqué* A48317/896, *Le Dentu and Bonnet* A74703/01, *Mériel* A68476/10, B11254/10, *Vanverts* A68481/10, *Bonamy and Péraire* A68462/11, *Schickele* A68480/22, *Masson A64989/22*, A94889/22, A64790/23, *Keller* A68472/22, *Guillaume-Louis* A68471/25, *Peyron and Montpellier* A64821/32, *Adrian* A64722/35, *Papin* A61854/35.

GERMAN: *Hennig* A88228/875, *Klebs* 39061/876, *Marchand* A70821/879, A70819/880, *Aschenbonn* A29426/880, *Küstner* A29740/880, *Boettger* A40271/882, *Breisky* A40561/882, *Olshausen* A82260/884, *Kovacs* A41315/884, *Fränkel* A41774/887, *Brandt* A74789/893, *Heine* A77546/894, *Köring* A47065/894, *Orthmann* A64820/899, *Martin* A96900/899, A96823/899, *Kippenberg and Martin* A96838/899, *Seydel* A83111/01, A83112/04, *Ehrlich* A68468/08, *Pfannenstiel* A64886/08, *Meyer* A74962/13, A64796/18, *Lehmann* A68473/17, *Sternberg* A64845/26, *Neumann* B8051/26, 42639/27, *Mayer* A99597/26, *Fischer-Wasels* B6758/27, *Kermauner* A64880/32, *Hannes* A61928/33, *Miller A18279*/37, *Novak* A96636/41.

HUNGARIAN: *Kovacs* A88231/884, A64430/30.

ITALIAN: *Spantigati* A88246/875, *Wells* A40782/884, *Mo* A43401/889, *Clementi* A44077/891, *D'Urso* A48434b/896, *Puccioni* A65627/29, *Fornero* B10306/36, *Zagni* A95459/39, *Gaifami* A97370/39.

JAPANESE: *Higasiwara* A46470/893, *Takeda* A74816/899.

LATIN: *Strauss* A88210/859, *Levedag* A88203/860, *Bamberg* A88198/864.

NORWEGIAN: *Harbitz* B6786/31.

POLISH: *Rosner* A44835/894.

PORTUGUESE: *Wolff Netto* A97326/38, *Rodrigues* A96938/41.

RUMANIAN: *Stoia and Stancuilescu* A28179/34.

RUSSIAN: *Ostrogradski* A43284/889.

SPANISH: *Villa* B16021/24, *Vanrell* A62955/32, *Diaz Colodrero* A97267/38, *Echeverri Marulanda* A97421/40, *Collillas and Diaz Colodrero* A96676/40, *Brea* A98145/42.

DEFINITION

In a voluminous reference work, whose primary function is to supply the reader with a complete survey of the relevant literature, it becomes necessary to provide space for generalizations and for the correlation of the specific data. Thus, in this volume devoted to the ovarian tumors, the present chapter is primarily reserved for a general survey of the diverse ovarian tumors which will be discussed individually in the specific chapters devoted to them. Here, we shall attempt to classify and correlate the various tumors, to analyze statistical data pertaining to their relative incidence, to compare their morphologic and clinical characteristics, to consider data which will help in the differential diagnosis of the various types of ovarian tumors, etc.

We wish to emphasize, however, that this general chapter also has a secondary, somewhat less obvious function. It is to act as a framework for a discussion of incompletely identified ovarian tumors. In some instances the original case reports themselves contain insufficient data, in others the original papers were not available, so that we had to quote them from incomplete abstracts.

The problems presented by the ovarian tumors are discussed in this chapter under the same subheadings (Definition, History, Pathologic Anatomy etc.) which will be used in connection with the special problems of each tumor type in the chapters devoted to them.

In agreement with this plan, the first task of this part of the present chapter would be to specify what is meant by an ovarian tumor. It must be admitted at the outset, however, that the concept of a true tumor or neoplasm cannot be clearly defined. It has been stated that "a tumor is an autonomous new growth of tissue";[1] or that "a tumor proper is a mass of cells, tissues, or organs resembling those normally present, but arranged atypically. It grows at the expense of the organism, without, at the same time subserving any useful function";[2] or that it is "a

[1] *Ewing* A64873/42.

[2] *Adami* B10856/11-4.

circumscribed growth, not inflammatory in character, arising from pre-existing tissue, but independent of the normal rate or laws of growth of such tissue, and subserving no physiological function".[1] None of these—and none of the numerous other definitions given in the literature—are very satisfactory and we have no better substitute to offer. It is hardly surprising that we cannot clearly define a type of pathologic growth about whose etiology and inherent characteristics we know so little. In the present state of our profound ignorance, the concept of tumorous growth—as that of any other great mystery of life and even the concept of life itself—is embraced by experience and not by rational delimitation. It is for these reasons, that it was not deemed advisable to devote any space in this section to a dialectic approach towards the particular problems presented by the ovarian tumors.

We shall discuss certain ovarian growths which are definitely not considered to be true neoplasms (e. g. follicle retention cysts, corpus luteum cysts, etc.) merely because their clinical behaviour and their ability to produce hormones makes it expedient to review them in conjunction with corresponding true neoplasms of the ovary (e.g. folliculomas, corpus luteum tumors). Endometriosis is also included in the present volume, partly because in its morphology and clinical course it resembles the more orthodox ovarian growths and partly because we are not convinced of its non-neoplastic nature. Up to now, on the basis of the now rather generally-accepted transplantation theory of endometriosis, it has rather illogically, but uniformly, been listed among the non-neoplastic diseases. It will be noted that autonomously-growing transplants, which in their new location no longer perform any useful function, fit any of the popular definitions of a tumor, and this is certainly true of the spontaneously-occurring endometriosis. Yet the disease is included in this volume, not because of any desire to decide in favor of its neoplastic nature, but merely because it is felt that at least ovarian endometriosis can most profitably be discussed in connection with the ovarian neoplasms. The extra-ovarian form is reviewed conjointly with the ovarian only in order to avoid a redundant duplication of data concerning the pathogenesis, diagnosis, therapy, etc., which would in general apply to both types.

HISTORY

Tumors of the ovary have interested physicians, biologists and even laymen since time immemorial. This is hardly surprising in view of the enormous size they may attain and the great morphologic and functional diversity of these growths. Although many of the early descriptions are too vague to permit exact idenification of the growth, numerous interesting descriptions of ovarian tumors will be found in the early literature.[2] For historically interesting descriptions of individual types of ovarian tumors, the reader is referred to the sections specifically devoted to cysts, dermoids, carcinomas, endocrine tumors etc.

CLASSIFICATION

Ewing[3] states in his book on neoplastic diseases that "ovarian tumors present a wider scope of structure, greater individual variation and a more complex embryologic and histogenetic basis than those of any other organ, and for these reasons they have escaped satisfactory classification." He adds, furthermore, that "in a substantial proportion of ovarian tumors as they actually occur, the diagnosis is largely a matter of arbitrary decision on the part of the observer. The recent contributions are chiefly important in facilitating the recognition of certain typical tumors, the exact position of which has heretofore been uncertain." These facts render a logical systematic classification of the ovarian tumors extremely difficult and most if not all systems proposed up to the present time are rather artificial.

The prevalent criteria upon which classifications have been based are morphologic, (e.g. separation of cystic from solid, epithelial from mesenchymal tumors), embryologic or histogenetic (e.g. separation of growth originating from the follicles, interstitial cells, ectopic tissue inclusion) and clinical (e.g. separation of benign from malignant or of hormone-producing from endocrinologically "silent" growths). The greatest difficulty is that no matter how we formulate our subdivisions, whether we use morphologic or functional criteria as the basis of our classification, there are always so many intermediate groups and so many overlappings between different groups, that in most instances a tumor appears to fit into several groups with almost equal justification. A purely "phenotypical", morphologic subdivision is impossible because of the many transitional, mixed types of tumors and our knowledge concerning the embryologic origin of these blastomas is too uncertain to serve as a basis for classification. A purely clinical system of classification is manifestly impossible, because a large number of non-hormone-producing growths with vast morphologic differences present themselves under the same clinical picture. Furthermore, as we shall see in subsequent chapters, morphologically similar growths may produce entirely different clinical manifestations. Thus folliculomas,

[1] *Garber in Stedman's Practical Medical Dictionary* B10855/42.

[2] *Monro* A74813/747, *Faleti* A88223/789, *Michener* A88238/818, *Cocchi* A88218/824, *Brunn* A88200/831, *Bright* A74800/838, *Bird* A88215/847, A88216/852, *Coleman* A88219/848-9, *Kuchenmeister* A88233/849, *Ulich* A88211/852, *Weinreich* A88212/854.

[3] A64873/42.

Brenner tumors, and even dermoids have been known to cause virilization, although the cells of these growths are certainly not of the type usually associated with testoid hormone production.

The following are a few examples of systems of classification devised by various investigators who made especially detailed studies of ovarian oncology. They are listed here to familiarize the reader with the various points of view emphasized by different authors:

The classification of ovarian tumors according to *Goodall*[1] rests on an embryologic basis:

Origin	*Clinical Pathology*			
Graafian follicles	1. Small cystic ovary, hydrops folliculi			
	2. Corpus luteum cysts			
	3. Granulosa tumors	Benign.		
		Malignant		
Ova	1. Dermoids.			
	2. Teratomas.			
Embryonic rests—adenomas	1. Cystic	1. Serous	1. Benign	1. Simple
				2. Multiple
				3. Papilliferous.
			2. Malignant	1. Papilliferous.
				2. Carcinomatous.
		2. Pseudomucinous.	1. Benign	1. Simple
				2. Multiple
				3. Papilliferous.
			2. Malignant	1. Papilliferous.
				2. Carcinomatous.
	2. Solid	1. Benign.		
		2. Malignant, carcinomatous		
	3. Special	1. Tubulare testiculare.		
		2. Arrhenoblastoma, andreioblastoma.		
		3. Seminoma.		
Interstitial cells	1. Endotheliomas.			
	2. Peritheliomas.			
Connective tissue cells	1. Fibroids.			
	2. Myomas.			
	3. Sarcomas.			
Special tissues	1. Neuromas.			
	2. Antiomas.			
Ectopic inclusion tumors	1. Hypernephromas.			
	2. Endometriomas.			
	3. Ectopic gestation.			
Metastatic	1. Krukenberg's tumors (gastric).			
	2. Mucous carcinomas (intestinal).			
	3. General metastatic.			

[1]A74124/35.

The classification of ovarian tumors proposed by *Conill*[1] is strictly morphologic:

Cystische Tumoren:	Adenocystom—serös, pseudomuzinös Dermoidcystom (in solider Form: Teratom) Paraovarialcystom Endometriom
Vegetierende Tumoren:	Papilome Fibrome
Solide Tumoren:	Sarkome Carcinome {Primäre (auch cystische Form) / metastasierende} Disgerminome (Rob. Meyer)—(Seminome)
Hormonale Tumoren:	Arrhenoblastome Hypernephrom Granulosazelltumore

The following predominantly morphologic classification of ovarian tumors is favoured by *Barzilai*.[2] It gives very secondary importance to the benign or malignant character of the blastoma and recognizes the endosalpingioma as a separate entity:

1. Tumors in which cells and structures may be traced back to developmental and cyclic phases of the Graafian follicle:

   Granulosa cell tumor

   Theca cell tumor

2. Tumors in which cells and structures may be traced back to different stages of development of the male gonad:

   Arrhenoblastoma

   Virilizing lipoid cell tumor (?).

3. A tumor in which cells and structures may be traced back to the cell type seen in the early mesenchymal core of the ovary:

   Disgerminoma

4. Tumors composed of tissues belonging to almost any part of the somatic body that may be traced to a totipotent or nearly totipotent cell, such as a somatic blastomere or the early mesenchyme:

   Adult teratoma

   Embryonal teratoma

5. Tumors in which cells and structures may be traced back to tissues normally found in the extrafollicular portion of the ovary, and which may possibly represent a one-sided developed teratoma:

   Fibroma

   Sarcoma

6. Tumors that cytologically and histologically may be traced back to structures belonging to organs that in adult stages are adjacent to the ovary, and in embryonal stages are closely entwined with the ovarian anlage (Müllerian, Wolffian and enteric tissue), and which may also represent a one-sided developed teratoma:

   Brenner tumor

   Endosalpingioma

   Seroanaplastic carcinoma

   Pseudomucinous adenoma

   Pseudomyxoma ovarii et peritonei

   Pseudomucinous adenocarcinoma

   Mesonephroma

7. Secondary ovarian tumors showing (a) anaplastic and regressive changes leading to a pattern that does not recall the primary growth, and (b) leading to a pattern that clearly points to the structure of the primary tumor:

   Krukenberg tumors

   Other secondary tumors

[1] A61843/36.

[2] A33688/36-7, A71883/43, B10814/44.

Schiller[1] in his classification of the ovarian tumors disregards the question of malignancy as far as the system of subdivision is concerned:

Cysts

a. Follicular

b. Corpus luteum

c. Corpus atreticum, luteinized—lutein cysts

True Tumors

A. Ovariogenic—derived from ovarian tissue

a. Granulosa cell tumor

I. Homogeneous

II. Trabeculated

III. Follicular

b. Fibroma

I. Simple

II. Luteinized — xanthofibroma thecacellulare

c. Myoma, angioma, luteinoma

B. Heterotopic—derived from tissue not normally present in ovary.

a. By pathological differentation

I. From surface epithelium—prosoplasia in direction of Müllerian duct.

1. Serous cystoma—tube

2. Endometrioma—endometrium

3. Pseudomucinous cystoma—cervix

II. From mesenchymal core by error in sex chromosomes

1. Arrhenoblastoma—male

2. Dysgerminoma—neutral

b. From displaced tissue

I. In fetal life

1. Early—teratoma

Mature—dermoid

Immature—embryoma

2. Late—tissue from vicinity

Ganglioneuroma

Hypernephroma

Mesonephroma

Brenner's tumor—urogenital epithelium

II. In adult life

1. By implantation—endometrioma

2. By metastases of malignant tumors—e.g. Krukenberg carcinoma.

The cystomas of B, a, I, 1-3 are to be characterized as unilocular or multilocular and as simple or papillomatous.

The surface papilloma may be classified under B, a, I, 1, papillomatous, the folliculoma lipidique Lecène tentatively under A, a, the myxoma under B, b, I, 1.

The arrhenoblastoma of B, a, II, 1, may be characterized as homogeneous, trabeculated or adenomatous-testicular.

[1]A33388/40.

Novak[1] uses the benign or malignant nature of Ovarian tumors as the most important criterion for his classification:

Benign Tumors

1. Cystic
   - a. Non-neoplastic
     - Follicle cysts
     - Lutein cysts
       - Corpus luteum cysts (including corpus albicans cysts)
       - Theca lutein cysts
     - Germinal inclusion cysts
     - Endometrial cysts
   - b. Neoplastic
     - (1) Cystadenoma
       - pseudo-mucinous
         - simple
         - papillary
       - serous
         - simple
         - papillary
     - (2) Dermoid
2. Solid
   - a. Papilloma, fibro-adenoma, fibroma, fibromyoma, angioma lymphangioma, chondroma, osteoma
   - b. Brenner tumors
   - c. Adrenal tumors (masculinovoblastoma)

Malignant Tumors

1. Carcinoma
   - a. Primary solid carcinoma
     - Adenocarcinoma
       - nonpapillary
       - papillary
     - Medullary carcinoma
     - Carcinoma simplex
     - Scirrhous carcinoma
     - Alveolar carcinoma
     - Plexiform carcinoma
     - Mesonephroma (not clearly established as yet)
     - Embryonic or dysontogenetic
       - Granulosa-cell carcinoma (often cystic)
       - Arrheno-blastoma
       - Dysgermin-oma (seminoma)
     - Chorionepithelioma
   - b. Cystic carcinoma
     - Pseudomucinous cystadenocarcinoma
     - Serous papillary cystadenocarcinoma
     - Epidermoidcarcinoma arising in dermoid cyst
2. Secondary or metastatic carcinoma
   - a. Adenocarcinoma, simple
   - b. Krukenberg tumor
   - c. Epidermoid carcinoma
   - d. Chorionepithelioma
   - e. Hypernephroma
3. Teratoma (including struma ovarii)
4. Sarcoma (round-cell, spindle-cell, mixed-cell)
5. Melanoma

[1]A94367/44.

The classification of ovarian tumors given in the text book by *Ten Teachers*[1] is also based on the benign or malignant nature of the growth:

Innocent Tumours

1. Distension cysts.
   (a) Atretic follicles.
   (b) Hydrops follicularis.
   (c) Theca-lutein cyst; compound theca-lutein cyst.
   (d) Blood cyst.
2. Tumours of epithelial origin: cystic growths of new formation.
   (a) Cystadenoma.
      (α) Pseudo-mucinous. Multilocular.
      (β) Granulosa-celled cyst.
   (b) Papilliferous cyst.
3. Arrhenoblastoma.
4. Cystic teratoma (commonly called dermoids)
5. Tumours of connective-tissue origin.
   Fibroma, Fibromyoma, fibrous papilloma (warty ovary).
6. Broad ligament cyst.
   (a) Fimbrial cyst.
   (b) Parovarian cyst.
   (c) Hydrosalpinx of an accessory tubal ostium, cyst of the hydatid of Morgagni.
7. Tubo-ovarian cyst.

Malignant Tumours

1. Carcinoma: tumours of epithelial origin.
   (a) Primary.
      (α) Solid carcinoma, adeno-carcinoma malignant granulosa-celled tumour.
      (β) Cystic carcinoma.
   (b) Secondary.
2. Sarcoma: tumours of connective-tissue origin.
      (α) Primary.
      (β) Secondary.
3. Melanoma, endothelioma, and perithelioma.
4. Malignant teratoma.

[1]B6383/38.

Miller[1] classifies the ovarian cysts and tumors as follows:

I. *DIE EINFACHAN ZYSTEN DES EIERSTOCKES*

1. Zysten ohne offene Verbindung mit dem Eileiter

I. Zysten der Eierstocksrinde

A. Aus Follikeln entstandene Zysten

1. a) Follikelzysten

b) Luteinzysten
Mehrfache Luteinzysten

2. a) Zystische Corpora lutea

b) Zystische Corpora albicantia

B. Aus dem Oberflächenepithel entstandene Zysten

3. Endometrioide Zysten

1. Die makroskopische Anatomie der endometrioiden Zysten

2. Die mikroskopische Anatomie der endometrioiden Zysten

3. Die Häufigkeit der endometrioiden Zysten

4. Das Alter der Frauen mit endometrioiden Zysten

5. Die Entstehung der endometrioiden Zysten

6. Das Verhalten des Eierstocksrestes

7. Begleit- und Folgezustände

8. Das Verhalten der Nachbarorgane

4. Perioophoritische Rindenzysten

5. Durch Spaltenverklebung gebildete Zysten

II. Zysten des Eierstocksmarks und -hilus

C. Markstrangzysten

D. Retezysten

2. Zysten in offener Verbindung mit dem Eileiter

a) Echte Tuboovarialzysten

1. Die makroskopische Anatomie der Tuboovarialzysten

2. Die mikroskopische Anatomie der Tuboovarialzysten

3. Die Entstehung der Tuboovarialzysten

4. Das Verhalten des Eierstocksrestes

5. Begleit- und Folgezustände

6. Das Verhalten der Nachbarorgane

b) Pseudo-Tuboovarialzysten

II. *DIE HOMOLOGEN GEWÄCHSE DES EIERSTOCKES*

I. Die Stützgewebsgewächse des Eierstockes

a) Die Fibrome und Myofibrome des Eierstockes

Die lipoidspeichernden Fibrome des Eierstockes

b) Die Myome und Fibromyome des Eierstockes

c) Die sog. Myxome des Eierstockes

d) Die Lipome des Eierstockes

e) Die Angiome des Eierstockes

f) Die sog. Chondrome des Eierstockes

II. Die epithelialen Gewächse des Eierstockes

a) Die (serösen) Oberflächen-oder Flimmerepithelgewächse des Eierstockes

α) Die (massiven) Adenofibrome und die Fibroadenome des Eierstockes.

Die Kystome des Eierstockes

Die serösen Kystome des Eierstockes

β) Die glattwandigen Kystome des Eierstockes

Die traubigen Kystome des Eierstockes

γ) Die papillären Flimmerepithelkystome des Eierstockes

b) Die Brennerschen Tumoren (Oophorome) des Eierstockes

c) Die tubulären Adenome des Eierstockes

III. Die Teratoiden Neubildungen des Eierstockes

Die Entstehung der teratoiden Neubildungen

a) Die Dermoidzysten des Eierstockes

1. Die makroskopische Anatomie der Dermoidzysten

αα) Typische Dermoidzysten

ββ) Atypische Dermoidzysten

2. Die mikroskopische Anatomie der Dermoidzysten

[1]A18279/37,

aa) Typische Dermoidzysten

bb) Atypische Dermoidzysten

3. Die Häufigkeit der Dermoidzysten des Eierstockes

4. Das Alter der Trägerinnen von Dermoidzysten

5. Das Verhalten des Eierstocksrestes

6. Der Stiel der Dermoidzysten

7. Begleit- und Folgezustände

8. Sekundäre Veränderungen der Dermoidzysten

9. Das Verhalten der Nachbarorgane

b) Die Schleimepithelgewächse (Pseudomuzingeschwülste) des Eierstockes

1. Die ganz oder teilweise massiven, fälschlich als solide bezeichneten Adenome des Eierstockes

2. Die glattwandigen Pseudomuzinkystome des Eierstockes

Die traubigen pseudomuzinösen Kystome des Eierstockes

3. Die papillären Pseudomuzinkystome des Eierstockes.

III. *DIE HETEROLOGEN GEWÄCHSE DES EIERSTOCKES*

I. Die Stützgewebsgewächse des Eierstockes

a) Die Eierstockssarkome

aa) Die primären Sarkome des Eierstockes

Die Melanosarkome des Eierstockes

bb) Die sekundären Eierstockssarkome

cc) Die metastatischen Eierstockssarkome

dd) Die fortgeleiteten Eierstockssarkome

Die Tochtergewächse der Eierstockssarkome

b) Die Rhabdomyome des Eierstockes

c) Die metastatischen Gliome und Neuroblastome des Eierstockes

II. Die epithelialen Gewächse des Eierstockes

a) Die Eierstockskrebse

aa) Die primären, massiven ("soliden") Eierstockskrebse

Sonderformen des primären Eierstockskrebses

A. Die Basalzellgewächse (Granulosazellgeschwülste) des Eierstockes

B. Die Seminome des Eierstockes

bb) Die aus einem homologen Tumor entstandenen Eierstockskrebse

α) Die verkrebsten serösen Blastome des Eierstockes

αα) Die verkrebsten ganz oder teilweise massiven Fibroadenome des Eierstockes

ββ) Die verkrebsten glattwandigen Kystome des Eierstockes

γγ) Die verkrebsten papillenführenden Kystome des Eierstockes

α) Die verkrebsten Schleimepithelgewächse des Eierstockes

β) Die verkrebsten Dermoidzysten des Eierstockes

γ) Die — angeblich — verkrebsten endometrioiden Zysten

cc) Die metastatischen Eierstockskrebse

dd) Die fortgeleiteten Eierstockskrebse

Die Tochtergewächse der Eierstockskrebse

α) Der Sitz der Tochtergewächse

β) Die Ausbreitungswege der Eierstockskrebse

b) Die Hypernephrome des Eierstockes

aa) Die primären und fortgeleiteten Hypernephrome des Eierstockes

bb) Die metastatischen Hypernephrome des Eierstockes

Die Metastasen der Eierstockshypernephrome

c) Die Chorionepitheliome des Eierstockes

aa) Die primären Chorionepitheliome des Eierstockes

bb) Die metastatischen Chorionepitheliome des Eierstockes

cc) Die fortgeleiteten Chorionepitheliome des Eierstockes

Die metastasen der Chorionepitheliome des Eierstockes

d) Die zur Vermännlichung führenden Eierstocksgewächse

III. Die teratoiden Neubildungen

a) Die Teratome des Eierstockes

Die Metastasen der Eierstocksteratome

b) Übergangsformen zwischen Dermoidzysten und Teratomen.

Geist[1] suggested the following classification:

NEOPLASTIC

Surface Origin
Primary
Benign

- Serous cystadenoma
  - Unilocular
    - Simple
    - Papilliferous
    - Glandular
  - Multilocular
    - Simple
    - Papilliferous
    - Glandular
- Pseudomucinous cystadenoma
  - Unilocular
    - Simple
    - Papilliferous
    - Glandular
  - Multilocular
    - Simple
    - Papilliferous
    - Glandular

Surface Origin
Primary
Malignant

Serous cystadenocarcinoma
Pseudomucinous cystadenocarcinoma
Carcinoma—solid or simple
Adenocarcinoma

Subsurface (Parenchymal) Origin
Primary
Benign

Granulosa cell tumor—luteinized or not
Theca interna cell tumor—luteinized or not
Rete cell tumor (arrhenoblastoma)
Indifferent cell tumor (dysgerminoma) (?)
Brenner tumor

Subsurface (Parenchymal) Origin
Primary
Malignant

Granulosa cell tumor—nonluteinized
Theca interna cell tumor—nonluteinized
Rete cell tumor (arrhenoblastoma)
Indifferent cell tumor (dysgerminoma)

Secondary Epithelial
Malignant

Cystocarcinoma
Chorionepithelioma
Melanocarcinoma

Metastatic Epithelial
Malignant

Hypernephroma
Chorionepithelioma
Melanocarcinoma
Krukenberg carcinoma
General carcinomatosis

Inclusion Epithelial
Malignant

Hypernephroma

Ovular Origin
Benign

Dermoid cyst (cystic teratoma)

Ovular Origin
Malignant

Solid teratoma (teratoblastoma)
Chorioblastoma

Stromatogenous
Primary
Benign

Fibroma
Fibromyoma
Myoma
Angioma
Neuroma
Perithelioma (?)
Endothelioma (?)

Stromatogenous
Primary
Malignant

Spindle cell sarcoma
Polymorphous cell sarcoma
Giant cell sarcoma
Round cell sarcoma

Stromatogenous
Secondary
Malignant

Sarcoma in fibroma or cyst

Stromatogenous
Secondary
Metastatic

From general sarcoma

NON-NEOPLASTIC

Follicular cyst
Corpus luteum cyst
Regression cysts
Rete and medullary cord cysts

[1]B6672/42.

The classification of ovarian tumors according to *Taylor*[1] is partly morphologic and partly clinical:

I. Dysfunctional cysts of the follicle and corpus luteum.

II. Endometrial cysts and endometriosis.

III. Primary neoplasms of the ovary.

A. Epithelial tumors.

1. Serous cystadenoma and cystadenocarcinoma.

   Special type: Adenoid cystic fibroma (Frankl).

2. Pseudomucinous cystadenoma and cystadenocarcinoma.

   Special type: Mucous fibroepithelioma (Brenner).

B. Connective tissue tumors.

1. Fibroma and fibrosarcoma.
2. Rare connective tissue tumors (Myoma, lymphangioma etc.).

C. Teratomas.

1. Dermoid (cystic teratoma).
2. Complex (solid) teratoma.

   Special type: struma ovarii.

D. Tumors arising from the specific cells of the gonad.

1. Granulosa cell tumor.

   Special types: a. Folliculome lipidique (Lecène).

   b. Theca cell tumor.

2. Arrhenoblastoma.

   Special type: Testicular adenoma (Pick)

3. Dysgerminoma.

E. Doubtful tumors.

1. Endothelioma.
2. Hypernephroma.
3. Mesonephroma (Schiller).

IV. Metastatic tumors of the ovary.

[1]A35246/40.

TABLE ILLUSTRATING CLASSIFICATION OF OVARIAN TUMORS USED IN THIS ENCYCLOPEDIA.

BENIGN	MALIGNANT
POTENTIALLY ENDOCRINE NEOPLASMS	*POTENTIALLY ENDOCRINE NEOPLASMS*
Follicle cysts (persistent follicles) *Small cystic degeneration* *Folliculomas* *Lipid cell tumors* Corpus luteum cysts, corpus luteum adenomas, Leydig cell adenomas Adrenal rest adenomas Testoid hyperthecosis *Tubular adenomas* (arrhenoblastomas) *Thyroid tumors* (struma ovarii)	——— ——— *Malignant folliculomas* (granulosa cell carcinoma) *Malignant lipid cell tumors* Corpus luteum carcinomas (and sarcomas?) Leydig cell carcinomas Malignant hypernephromas ——— *Seminomas* (dysgerminomas) ——— *Chorionepitheliomas*
NON-ENDOCRINE TUMORS PREPONDERANTLY EPITHELIAL NEOPLASMS	*NON-ENDOCRINE TUMORS* PREPONDERANTLY EPITHELIAL NEOPLASMS
Common Cysts *Serous*: Macrocystic, Microcystic, Tubular adenomas, Papillomas, Racemose cystomas, Peritoneal papillomatosis (Mesonephromas) *Pseudomucinous*: Macrocystic, Microcystic, Tubular adenomas, Papillomas, Racemose cystomas, Pseudomyxoma peritonei (Brenner tumors) ——— *Endometriosis* *Dermoids and embryomas* *Benign nerve tissue tumors*	*Common Carcinomas* *Serous*: Primary solid carcinomas, Carcinomatous serous cystomas, Metastatic serous carcinomas (Malignant mesonephromas) *Pseudomucinous*: Carcinomatous pseudomucinous cystomas, Metastatic pseudomucinous carcinomas (including Krukenberg tumors) ——— *Malignant endometriosis* *Solid teratomas* (carcinomatous or sarcomatous dermoids) *Malignant nerve tissue tumors*
NON-EPITHELIAL NEOPLASMS	NON-EPITHELIAL NEOPLASMS
Fibromas *Myxomas* ——— ——— ——— *Lipomas* *Chondromas* *Osteomas* *Leiomyomas* *Rhabdomyomas* *Hemangiomas* *Lymphangiomas* ——— ———	*Common sarcomas* (spindle and round cell) *Myxosarcomas* *Melanosarcomas* *Lymphosarcomas* *Myelomas and chloromas* *Lipsarcomas* *Chondrosarcomas* *Osteosarcomas* *Leiomyosarcomas* *Rhabdomyosarcomas* *Hemangiosarcomas* *Lymphangiosarcomas* *(Endotheliomas)* *(Peritheliomas)*

Many other systems of classification have been devised[1] but it would hardly be profitable to list more of them in detail here.

We shall classify the ovarian growths in this Encyclopedia according to a system which is partly based on their morphologic structure, but mainly on their hormone-producing ability. This appears advisable for the purpose of an encyclopedia of endocrinology, but it is admitted that our classification is not entirely natural and that those interested in the ovarian tumors merely from the pathologist's, embryologist's, or surgeon's point of view may find other systems more satisfactory. Although simple cysts are not generally included among the ovarian tumors, they will be listed with the latter here since in many cases the transition between simple cysts and blastomas is morphologically ill-defined, and since endocrinologically certain tumors are so closely related to cysts (e.g. folliculomas and follicle cysts) that their conjoint discussion offers definite didactic advantages.

PATHOLOGIC ANATOMY

The morphologic features of ovarian tumors are extremely diverse since a variety of fundamentally different neoplasms may develop in the female gonad. Their *size* varies from minute growths detectable only under the microscope to the largest tumors ever seen in the human being. Tumors weighing about 30 lbs. or more are comparatively common both among the solid and cystic varieties,[2] but the largest so-called "mammoth tumors" are all cystic and have therefore been discussed in the chapter on Common Cystomas. Suffice it to mention here that in a good many cases the dissected ovarian cyst weighed considerably more than the patient herself after ablation of the neoplasm. Quite a few of these mammoth tumors weighed more than 200 lbs. and three of the largest on record weighed 225[3] and 245[4] and 328 lbs.[5] respectively. Such enormous tumors not only immobilize the patient, in the sense of preventing her from walking, but make it impossible even to turn around in bed without assistance. These tumors hang down below the knees and deform the thorax as well as the pelvic bones by the pressure of their tremendous weight. Another common consequence of their increase in size is the production of vascular disturbances with "caput medusae", varicose veins, edema of the thighs, legs and the abdominal wall, gangrene of the skin, prolapse of the uterus and vagina, development of herniae, compression of the lungs with subsequent dyspnea etc. In modern days ovarian neoplasms are generally removed before they reach such an enormous size, but at a time when any type of abdominal surgery was still fraught with considerable danger, these cases were by no means rare. The chronic and intense suffering to which women with large ovarian tumors were exposed left their characteristic mark on their faces so that the ancient physicians frequently spoke of the typical "facies ovariana".[6]

The *shape, consistency* and *color* of ovarian neoplasms is obviously variable and dependent upon the type of tumor under consideration. In these respects no generalizations can be made other than to point out that extensive adhesions are most common among the malignant neoplasms and that reddish or brown patches are characteristic of hemorrhages into the tumor tissue, while black or bluish-black coloration is typical of the rare melanomas (for further details see the special chapters dealing with the various types of ovarian tumors).

The *position* of ovarian tumors is determined by the direction in which they grow. Usually they extend craniad into the abdominal cavity, but not uncommonly they tend to develop into the mesovarium and broad ligament.[7]

Unless extensive adhesions form, most ovarian tumors are attached by means of a stalk or *pedicle* either to the ovarian surface or to the ligaments.[8] If this stalk is short and thick it rarely causes any important complications, but ovarian tumors attached by thin long pedicles are highly subject to torsion (see chapter on Torsion in Sect. IV, Vol. VI). Within the pedicle course the frequently very large blood vessels. In the stalk of large ovarian tumors the arteries may have the caliber of the radial or brachial artery and the ovarian veins may develop important varicosities.[6] The lymph vessels of the stalk may also become unusually prominent and dilated.[9] The consistency of the pedicle is of practical importance for the surgeon, since ligatures placed upon soft brittle stalks may cut through the tissues and cause hemorrhages during the intervention.

In the course of their development ovarian tumors tend to *migrate* from their original position in the pelvis towards Douglas' space where they may become impacted, or towards the abdominal cavity where there is more space for their expansion. In the course of this migration the neoplasms may com-

[1] *Clivio* A68466/07. *Graves* B11668/22, *Neumann* A68478/25, *Sternberg* A64845/26, *Mayer* A99597/26, *Curtis* A63170/30-42, *di Paola* A98170/42, *Zuckermann* B11752/43.
[2] *Wythes* A87243/860, *Smith* B13148/06, *Gloeckner* B13377/07, *Favell* B11323/10, *Garner* B11269/10, *MacMullan* B11272/10, *Franz* B9510/17-8, *de Rouville et al.* B8052/25-6, B7096/26, *Mozumdar* B7245/27, *Corlette* B15470/27, *Boerma* B15458/27, *Jeanneney* A62305/32, *Arenas et al.* B10129/42.
[3] *Binkley* A48369b/897.
[4] *Bullitt* A83452/899, A83453/00.
[5] *Spohn* A91842/05-6.
[6] *Miller* A18279/37.
[7] *Noeggerath* A86244/879, A86576/879, *Miller* A18279/37.
[8] *Martin* A96822/899.
[9] *Ando and Narimatsu* A66137/31, *Miller* A18279/37.

press or stretch the urinary bladder, oviduct and uterus frequently causing complications due to interference with these organs. This normal ascension of the tumors, which occurs when they become too large to fit easily into the pelvis, may be prevented by immobilizing adhesions, intraligamentous development, a second abdominal tumor, pregnancy or abnormal tension or adiposity of the abdominal wall. A survey of 3629 ovarian tumors collected at random from the literature showed that *intraligamentous development* occurred in 440 cases, that is, 12.1% of the patients observed.[1]

Contrary to the view frequently expressed in the old literature, there is no great preponderance of left-sided ovarian tumors and our own survey of 2250 ovarian neoplasms gathered at random from the literature revealed 990 *left-sided,* 952 *right-sided* and 308 *bilateral* tumors. In evaluating the results of seven large series of diverse ovarian tumors observed by different investigators (as quoted by Miller)[2] we find that, if all cases are taken into account, among a total of 1464 ovarian tumors 17.5% were bilateral; 1173 of these growths were benign, and 291 malignant. In the benign group the incidence of bilateral ovarian involvement was 12.5%, while in the malignant group both ovaries were affected in 35.6% of the cases. Additional data concerning bilateral ovarian tumors will be found in the case reports which describe such neoplasms.[3]

Several *statistical* surveys deal with the characteristics of ovarian tumors in general[4] and additional pertinent data will be found in the many relevant *case reports.*[5]

SECONDARY CHANGES IN THE TUMOR AND IN THE REMAINING OVARIAN TISSUE: Adhesions may connect ovarian tumors with the Fallopian tube, uterus, oviduct, various parts of the gastrointestinal system, urinary bladder, ureter, gallbladder, spleen, or liver; in brief, with practically any peritoneal organ.[6] A review of 647 cases, selected at random from the literature, indicates that among the 525 benign neoplasms of this series, 137 (38%) and among the 122 malignant blastomas 54 (64%) formed adhesions.[1] The relevant reports of individual investigators are rather variable since it is difficult to arrive at uniform standards by which borderline cases, with only a few unimportant adhesions, can be classified. It is obvious, however, that the malignant growths are more prone to become adherent than the benign neoplasms.

Malignant transformation of originally benign neoplasms can often not be distinguished from primarily malignant growths. The incidence of malignancy among all ovarian neoplasms has, however, often been subjected to statistical analyses and a survey of 16025 ovarian tumors selected at random from the literature showed that among these 2281 or 14.23% were malignant. This includes metastatic ovarian carcinomas and sarcomas.[1] Among 1101 ovarian tumors observed at the Mount Sinaï Hospital in New York 17% were malignant; in the premenopausal age group (963 cases) 11.5% and in the postmenopausal (138 cases) 58%.[7]

The incidence of the various types among malignant neoplasms in a series of 36 of these tumors was as follows: 5 sarcomas, 1 myxoma, 2 sarcomatous cysts, 14 carcinomas, 5 carcinomatous cysts, 4 carcinomatous papillomas and 5 carcinomatous papillary cystomas.[8] In another series, which comprised 120 solid malignant tumors of the ovary, the distribution was the following: 60 sarcomas, 6 "endotheliomas", 47 carcinomas and 7 carcinomatous papillomas.[9]

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[1]*Miller* A18279/37.

[2]A18279/37.

[3]*Reber* A40025/881, *Bixby* A40528/882, *Metzler* A74812/889, *Harrison* A43536/890, *Fleischmann* A48344/896, *Abadie* A75306/01, *Bauby* A75309/04, *Desurmont* A68504/11, *Paucot and Houcke* A28168/35, *Anagnostidis* A59871/36.

[4]*Nyhoff* B11257/10, *Miller* A18279/37, *Kristensen* A95446/39, *Lacroix* B15912/40, *Tanaka* A97718/40.

[5]*Barker* A74796/792-829, *Schmitt* A88243/825, *Schoenfeld* A88244/838-9, *Williams* A88254/847, A88253/879, *Mayne* A75325/852-8, A69751/857, *Lesouëf* A69749/859, *Channing* A69745/859-60, *Merrill* A86572/863, *Harrinson* A69747/870, *Taylor* A69759/877-8, *Weber* A69760/878, *Erdman* A34828/878, *Thomas* A86103/878, *Goodell* A29541/879, A41244/883, *Kidd* A29395/880, *Ogata* A29335/880, *Robbins* A29599/880, *Scott* A29701/880-1, *Roberts* A29789/881, A75330/899, *Oettinger and Tissier* A40227/881, A40550/882, *Bang* A29895/881, *Kellar* A29942/881, *Westbrook* A40453/882, *Thornton* A40555/882-3, *Meyer* A40899/884, *Drysdale* A40707/885, *Chaleix* A74701/885, *Apolant* A40848/885, *Branfoot* A75311/887, A74799/887, *Gardner* A69590/888, *Dalal* A42437/888, *Chrobak* A42369/888, *Doleris and Petit* A74704/888, *Doran* A42341/888, *Emery* A69586/888-9, *Freund* A45247/889, A43503/890, *Thiriar* A45131/889, *Long* A43281/889, *Brichetti* A42674/889, *Holt* A42604/889, *Holmes* A69670/889-90, *Mohr* A74790/890, *Hardon* A75321/890, *Pawlik* A45858/891, *Mendes de Leon* A45841/891, *Cabrera* A44166/892, *Renton and Bryce* A47366/893-5, A44670/894, *Warren* A46315/893, *Skene* A44792/894, *Bidone* A74798/895, *Sato* A75332/896, A75331/896, *Crofford* A48300/896, *Smith* A47367/896, A48453/896, *Picqué* A48317/896, *Bishop* A47399/896, *Audebert* A49079/897, *Witherow* A48402b/897, *Dale* A49021/897, *Jouin* A75305/898, *Jessett* A50935/898, *Murray* A75326/899, *Dantzler* A74613/899, *Malcolm* A74636/899, *Castaing* A75313/00, *Wood* A74635/00, *Beatson* A74797/00, *Phocas* A75327/01, *Earnest* A75316/01, *Collins* A75314/02, *Miyata* A74629/02, *Battle* A69542/02, *Dobratvorsky* A75304/03, *Martinotti* A75324/03, *Blau* A74627/03, *Jaboulay* A69609/03, *Vignard* A75335/04, A75336/06, *Anonymous* B12840/04, *Le Fort* B9103/04, *Reid* A83107/05, *Pollosson* A75329/05, *Godlewski* A74707/05, *Hamilton* A74825/05, *Amann* A74819/05-6, *Burlew* B13173/06, *Gabbett* A74706/06, *Gargano* A75318/06, *Porterfield* B13270/06-7, *Anderson* B13202/07, *Lucio* B9416/07, *Debeyre* B13320/07, *Meyer* B11326/10, *Proust and Maurer* B11291/10, *Althabe* B16222/15, *Pemberton* B21315/17, *Darnall* B8557/22, *Iversen* B13537/22, *Colaneri* A62873/32, A62872/32, *Rodriguez* A97433/39, *Konuralp* A97386/39, *Kobayashi* A97557/41, *Basu* A98141/42.

[6]*Thornton* A82555/878, *Miller* A18279/37.

[7]*Bernstein* 81758/36.

[8]*Fontane* A83126/895.

[9]*Dreyfus* A78223/07.

Among the secondary changes which may occur in ovarian tumors *liquefaction necrosis, calcification, ossification, edema, mucoid degeneration, fatty degeneration and hemorrhage* should also be mentioned, but no reliable statistical data are available to show their incidence in the various tumor groups (see also Sect. IV, Vol. VI).

OVARIAN TUMORS IN COMBINATION WITH EXTRAOVARIAN TUMORS: As indicated in the chapters dealing with the various specific tumor types, ovarian tumors are frequently accompanied by simultaneously-developing extraovarian neoplasms. In such instances either of the two tumors may be a *metastasis* of the other. The metastases of malignant primary ovarian tumors may spread through lymph or blood vessel channels and it is generally agreed that usually the carcinomas tend to metastasize through the former, the sarcomas through the latter pathway, although both routes of spread are possible in the case of either tumor type.[1] The formation of secondary nodules through direct peritoneal transplantation of malignant cells into adjacent organs is likewise very frequent and particularly common in carcinomatous papillomas.

The possibility must also be kept in mind, however, that the hormones produced by certain ovarian growths may be oncogenic and thus induce primary tumor formation in another organ. This is particularly true of the neoplasms which secrete an excess of folliculoid compounds (e.g. folliculomas, follicle cysts) since experimental work proved the possibility of producing neoplasms by continued treatment with such hormones.

The development of *ovarian and para-ovarian tumors* due to simultaneous neoplastic changes in the ovary and the rudimentary embryonic vestiges of the broad ligament is likewise noteworthy[2] and will be discussed in more detail in the chapters dealing with specific tumor types.

CHEMICAL COMPOSITION

The chemical composition of ovarian tumors has not been the subject of adequate, systematic investigation. It is of interest, for instance, that in one of the leading treatises on the biochemistry of tumors[3] the subject index does not even contain a reference to the chemical composition of ovarian tumors. However, some work has been done on the chemical composition of certain ovarian tumors, such as the folliculomas, teratoids, etc., and for such specific information the reader is referred to the corresponding chapters.

INCIDENCE

The *general incidence* of ovarian tumors is usually expressed as a percentage of the total number of admissions in a gynecologic clinic. In this sense the incidence of women with any type of ovarian tumor is estimated to represent the following proportions of the gynecologic patients in various hospitals: 1.4%,[4] 1.44%,[5] 1.83%,[6] 2.87%,[7] 3.3%,[8] 4.8%,[9] 5.3%,[10] 5.39%,[11] 6.74%,[12] 6.8%,[13] 7.7%,[14] 9.9%.[15] The average of all the percentages given above is 5.5%, a figure which is much too high as judged by our own calculations. We find that usually authors who report on small series of cases record a higher percentage of ovarian tumors than those who publish on a large statistical scale. This may be due to the different standards according to which patients are admitted in the various clinics. Obviously the percentual incidence of ovarian tumors will be comparatively low in those hospitals in which women are admitted for minor ailments requiring no operative intervention.

A personal statistical analysis of the 160,324 gynecologic patients—which includes all cases recorded in the above-mentioned smaller series—indicates that 4503, or 2.8% of them suffered from ovarian tumors. This figure, being based upon a very large number of cases observed by many investigators of different countries, is probably the closest approximation to a true incidence of ovarian tumors expressed as a percentage of the total number of admissions in the average gynecologic clinic.

Statistical data concerning the relative incidence of the various tumor types will be found in the chapters specifically devoted to each neoplastic entity. For comparative purposes, it may be useful to cite the percentual incidence of various tumors in one series of 1101 patients[16] which was as follows:

Follicle cysts	36%
Dermoid cysts	16%
Serous papillary cystadenocarcinomas	14%
Corpus luteum cysts	11%
Pseudomucinous papillary cystadenomas	6%
Endometriosis of the ovary	4%
Serous papillary cystadenomas	3%

[1] *Kanomori* A74616/899, *Garner* B11306/11, *Miller* A18279/37, *Novak* A63534/41.
[2] *Roberts* A47085/894-5.
[3] *Stern and Willheim* B7056/43.
[4] *Martin* A83032/895.
[5] *Schmidlechner* A82394/08.
[6] *Lippert* A64789/05.
[7] *Pflaum* A70215/10.
[8] *Stübler and Brandess* A76588/24.
[9] *v. Winckel* A70449/886-90.
[10] *v. Scanzoni* A70261/867.
[11] *Drexler quoted by Miller* A18279/37.
[12] *Lippert* A64789/05.
[13] *v. Varo* A80120/27.
[14] *Norris and Vogt* A78764/25.
[15] *v. Velits* A73010/06.
[16] *Bernstein* 81758/36.

"Tubo-ovarian cysts"	2.6%
Fibromas	2%
Pseudomucinous papillary cystadenocarcinomas	1%
Solid, medullary and undetermined carcinomas	1%
Sarcomas	0.8%
Malignant teratomas	0.7%
Krukenberg tumors	0.5%
Squamous carcinomas in dermoid cysts	0.2%
Seminomas	0.2%
Carcino-Sarcomas	0.1%

The *age incidence* of ovarian tumors differs greatly depending upon the type of tumor considered (see chapters dealing specifically with the various types of ovarian tumors). In general, it may be said however, that ovarian neoplasms are most commonly observed in women 30-40 years of age.[1] This was confirmed on a series of 1101 ovarian tumors studied at the Mount Sinai Hospital in New York. In this group the percentual incidence during the various decades was as follows:[2]

Years	%
10-19	12.4
20-29	27.0
30-39	31.0
40-49	19.0
50-59	8.3
60-70	2.3

Our own analysis of 2943 ovarian tumors published by different investigators[3] indicates the following age distribution:

Years	%
1-19	4
20-29	24
30-39	27
40-49	23
50 & over	21

These statistics clearly show that the incidence is highest during the child-bearing period; it must be kept in mind, however, that numerous cases have also been reported in children[4] as well as in women aged 80 years or more.[5]

Data concerning the *pregnancy incidence* of ovarian tumors are variable. Among 32,148 deliveries of the Charité hospital in Berlin only 8 were complicated by an ovarian tumor.[6] In other series the tumor incidence among pregnant women was given as 3.45%,[7] 1.3%,[6] 0.13%[8] and 0.09%[9] respectively. The pregnancy incidence among women with various types of ovarian tumors is higher, and is variously estimated as 3.4%[9] and 4.3%.[8]

More specific data concerning the occurrence during gestation of the various tumor types are given in the chapters dealing with the individual groups of ovarian neoplasms. It is obvious, however, that in many instances pregnancy does occur in tumor-bearing women, indeed, fertility is not necessarily decreased even by bilateral ovarian growths. The percentual incidence of infertility among tumor-bearing patients is variously estimated as 12.7%,[10] 14.7%,[9] 16%,[11] 26.4%[7] or even 52.6%.[12] Intraligamentous development is particularly likely to interfere with conception.[13] It is not definitely established whether pregnancy stimulates the development of ovarian tumors by virtue of the pelvic hyperemia, the high level of folliculoid hormone production, metabolic changes or other accompaniments of the gestation period. It may be said, however, that many investigators believe that pregnancy predisposes to ovarian tumor formation and this view appears to receive, at least partial, support from the numerous cases of ovarian tumors which have been

[1] *v. Scanzoni* A70261/867, *Martin* A83032/895, *Limnell* A83637/05, *Nyström* A76231/11.
[2] *Bernstein* 81758/36.
[3] *Olshausen* A41468/877-86, *Pean* A77265/880, *Blau* A73309/02, *Grillmeier quoted by Miller* A18279/37.
[4] *Campbell* A69770/851, *Corse* A69772/863, *Garrod* A69776/865, *Alcock* A74871/871, *Dickinson* A69774/873-4, *McGraw* A74878/877, *Neville* A74880/879-80, *Evers* A69775/884, *Wagner* A74883/884, *Cameron* A42551/889, *Hamaker* A42683/889, *Forbes* A44841/894, *Herzog* A73778/897, *Maisch* A49105/897, *Bonnar* A75827/01, *Gibb* B8948/03, *Schwarz* B12843/04, *Finaly and Winternitz* A75829/05, *Winternitz and Finaly* B9121/05, *Donhauser* A75828/06, *Gaudier and Debeyre* B13353/07, *Casabona* A82403/13, *Fischer* A82401/17, *Froelich and Mathieu* A82404/20, *Mayo* A62940/32, A96516/38, *Delascio and Dellivenneri* A97579/39.
[5] *Olshausen* A41468/877-86, *Baer* A41646/886, *Homans* A42348/888, A42349/888, *Owens* A42150/888-9, A93368/894, A47504/895, *Edis* A93338/892, *Smith* A44790/894, *Bush* A93328/894, *Remfry* A48318/896, *Cartledge* A49138/897-8, A93331/898, A50498/898, *Krusen* A93356/01, A93357/01, *Shands* A91836/04, *Wiel* A79203/05, *Butler* A77415/07, *Spencer* A70963/23, *Heekes* A63517/29.
[6] *Martin* A83032/895.
[7] *Lippert* A64789/05.
[8] *v. Varo* A80120/27.
[9] *Stübler and Brandess* A76588/24.
[10] *Olshausen* A41468/877-86.
[11] *Nyström* A76231/11.
[12] *v. Scanzoni* A70261/867.
[13] *Miller* A18279/37.

noted in pregnant women.[1] This high pregnancy incidence is particularly noteworthy since ovarian tumors undoubtedly must decrease fertility to some extent, at least in the cases in which they destroy a considerable part of the gonadal tissue. Conversely, it will be kept in mind that during gestation and delivery an otherwise latent ovarian neoplasm is particularly prone to elicit complications and thus comes to the attention of the gynecologist. Hence, in spite of much discussion concerning this subject, the question whether pregnancy accelerates the growth of ovarian tumors is still unsolved.

The *puerperal incidence* of ovarian neoplasms is comparatively low, since in most women who have ovarian tumors the growth would more probably be detected during the preceding gestation and delivery period. A few cases have, however, been observed soon after childbirth.[2]

The *racial incidence* of ovarian tumors has been discussed at some length in the chapters devoted to the specific tumor types. Thus, data concerning the purportedly enormous incidence of dermoids among Negroes and Japanese will be found in the chapter on teratoid tumors. Little is known, however, concerning the importance of racial factors for susceptibility to ovarian tumor formation in general.

The observation of an incompletely identified ovarian tumor in a *mulatto* woman[3] is mentioned here—for want of a better place to list it.

[1] *Williams* A69896/843-4, A29754/880, *Bradford* A69811/870, *Wernich* A69895/872-3, *Brons* A69798/873, *Hillas* A87059/875, *Crawford* A29587/880, *Sells* A86278/883, *Elsasser* A41037/885, *Montgomery* A41892/886-7, *Harvey* A41943/887-8, *Hicks* A42556/889, *Runge* A44041/891-2, *Feilchenfeld* A46588/893, *Lawrence* A91680/893, A91679/893, *Ross* A91739/893, *Rosen* A48236/895, *Löhlein* A91686/895, *Duncan* A75835/896, *Openshaw* A91707/896-7, *Löongvist* A49182/897, *Riddell* A91737/897, *White* A91765/897, *Martin* A96826/899, *Fehling* A75836/00, *Flaischlen* A91639/02, *Rausch* B8978/03, *Guicciardi* A91652/04, *Lea* A75838/04, *Heuck* A75837/04, *Coudert* A75834/04, A75315/04, *Maclean* B9114/05, *Lindquist* B9115/05, *Kynoch* A91677/06, *Büttner* A75833/06, *Marshall* B11321/10, *Brauns* B11314/11, *Keyes* A82373/11, *Wiesinger* A82431/12, *Muret* A82421/13, *Massart* A82420/20, *de Fourmestraux* A82415/21, *Björkenheim* B11736/21, *Souba* B11770/22, *Kogan* A82418/24, *Ingraham* A82417/25, *Stübler* B7252/27, *Urievsky* A96746/28, *Saitz* A28173/35, *Wilson* A95125/37, *Turtola* A97320/38, A97319/39, *Traut and Kuder* A97720/40, *Seibels* A96639/41, *Martini* A98167/42, *MacKenzie* A97809/42, *Ravagnan* A97823/42.

[2] *Limont* A69624/886-7, *Saitz* A28173/35.

[3] *Stone* B11868/18.

TABLE ILLUSTRATING PROBABLE DEVELOPMENT OF GONADAL STRUCTURES AND TUMORS WHICH MAY ARISE FROM THEM IN THE FEMALE.

Embryonic Structure	Mature Structure		Tumor to which it may give rise in the Female
	In Male	In Female	
Germinal epithelium	Seminiferous tubules	Ova and follicles	All types of *serous cysts, papillomas* and *carcinomas?*
Primary germinal cords	Seminiferous tubules	Medullary cords	*Arrhenoblastomas, seminomas, mixed teratoids* (by parthenogenesis)?
		Rete of ovary	*Rete adenomas, rete cysts. Brenner tumors?*
	Leydig cells	Leydig cells	*Leydig* (or hilus) *cell tumors*
Secondary germinal cords	Seminiferous tubules	Ova and follicles	*Folliculomas, corpus luteum tumors.* *Mixed teratoids* (by parthenogenesis)? All types of *pseudomucinous cysts* and *carcinomas* (by parthenogenesis as "pure enteroid teratoids")? *Brenner tumors* (from Walthard's rests or parthenogenetically as abnormal "enteroid" teratoids)? *Struma ovarii, rhabdomyomas, chorionepitheliomas,* etc., (by parthenogenesis as pure one-sidedly-developed teratoids)
	Testis stroma	Ovarian stroma	*Fibromas, sarcomas*
Pronephros?	Appendix of epididymis	Hydatid of Morgagni and Kobelt's tubules	*Cysts of infundibulum tubae* *Cysts of Kobelt's tubules?*
Urogenital junction tubules	Connection between rete and epididymis	Absent	*Junctional cysts*
Wolffian body (cranical part)	Ductuli efferentes of epididymis	Epoophoron (Epi-oöphoron, par-ovarium organ of Rosenmüller)	*Cysts, adenomas* and *carcinomas* of *epoöphoron-Mesonephromas?* "Epithelioma Wolffien"?
Wolffian body (caudal part)	Paradidymis	Paroöphoron (Parepoöphoron)	*Cysts, adenomas* and *carcinomas* of *paroöphoron*
Wolffian duct (cranial part)	Duct of epididymis	Duct of epoöphoron	*Cyst of Kobelt's tubules?*
Wolffian duct (caudal part) = Gartner's duct	Duct of epididymis	Gartner's duct remnants	*Gartner's duct adenomas*
Müllerian duct (cranial part)	Appendix testis	Oviduct with infundibulum (accessory tubal ostium, tubal diverticulum)	All types of *serous cyst papillomas* and *carcinomas,* ("salpingiomas") Ca of Fallopian tube, *para-ovarian cysts* due to hydrosalpinx of accessory tubal ostium or diverticulum
Müllerian duct (caudal part)	Utriculus prostaticus	Uterus and vagina	*Endometriosis,* (tumors of uterus and vagina not to be discussed here)
Adreno-cortical primordium	Accessory adrenal cortex in region of testis	Accessory adrenal cortex in region of ovary	*Hypernephroma ovarii*

PATHOGENESIS

The *histogenesis* of the ovarian tumors has been discussed separately in the individual chapters devoted to each specific tumor type since the various tumors appear to arise from different primordia. In this chapter in which we deal with ovarian tumors in general, it is appropriate, however, to survey the most convincing relevant data conjointly. At the same time we may refresh our memory concerning the embryologic development of the female sex organs, the knowledge of which is indispensable for the understanding of ovarian oncology. In order to facilitate this survey the adjacent schematic drawing and table have been constructed. The reader is also referred to several reviews dealing with the histogenesis of ovarian tumors.[1]

Little is known about the *functional pathogenesis* of the ovarian tumors, that is to say, the physiologic factors likely to promote tumor formation in the female gonad. Innumerable theories have been put forward, for over a hundred years, concerning the role of pelvic inflammation, trauma, a common cold during the menstrual period, complications of child birth, unsatisfied sexual desire, unnatural sexual intercourse, pressure by stiff girdles, etc.[2] In fact, one may say that there are few circumstances in the physical or social life of woman which, at one time or another, have not been held responsible for ovarian tumor formation.

Among the possible etiologic factors most worthy of attention are the sexual life and pregnancy. As early as the middle of the nineteenth century it was noted[3] that married women suffer from ovarian tumors much more frequently than spinsters. This view received confirmation by numerous subsequent investigators. Thus in a series of Finnish women aged 20-45 years and suffering from diverse ovarian tumors it was found that 28.4% were unmarried and 71.6% were married. Widows were eliminated from this series. It is true that among the general population of Finland, married women are also more numerous than spinsters, but further calculation showed that the percentage of married women was 43.24 among the tumor bearers and 22.36 among the general population. From this it was concluded that "the danger of developing an ovarian tumor is considerably greater for the married than for the unmarried women".[4] It will be noted that all these data apply to women aged 20-45 years.

A series of 3888 women with ovarian tumors whose case histories were taken from 11 independent statistical surveys, showed that 22% occurred among unmarried and 78% among married women. The deplorable possibility that an unmarried woman may differ from a married woman only in her legal and not in her biologic status does not appear to have occurred to many of these reviewers. It is, therefore, of special interest that data gathered from 13 separate statistical series and comprising 3847 tumor-bearing women showed that 34.5% were childless, while 65.5% had given birth to children. This series, in which the marital status was disregarded, confirms that pregnancies increase the likelihood of developing an ovarian tumor.[5]

The importance of *hereditary factors* has frequently been emphasized on the basis of simultaneous tumor development in several members of the same family. Many such cases are listed in the chapters dealing with specific tumor types, but it may be mentioned here that definite proof of a hereditary predisposition has not been furnished as yet.[5] In our opinion this is due to the difficulty of proving the point in a statistically significant manner on human material. It must be kept in mind, however, that in animals the great importance of hereditary influence upon tumor formation has definitely been demonstrated and it is hardly probable that the human being would essentially differ from other mammals in this respect (see also parts on Racial Incidence in this, as well as in other chapters of the present volume).

Whether *X-ray treatment* may be the cause of ovarian tumor formation is debatable, but the possibility has been considered in the part on Therapy (see passage on X-ray therapy below).

CLINICAL COURSE

Ascites may develop with practically any type of ovarian tumor. With regard to physical and chemical characteristics, the peritoneal fluid accumulation is essentially the same as that seen in other pathologic conditions conducive to the formation of such transudates. It is usually water clear, slightly yellowish, brownish or greenish, sometimes with a pink tinge. Only in the case of hemorrhagic ascites is the fluid frankly red or (in chronic cases) brown. The amount of ascites is variable. In some cases it may be so great that continuous tappings are necessary in order to relieve intra-abdominal pressure if the growth cannot be surgically removed.[6]

The incidence of ascites among ovarian tumors in general is variously given as 6-35%[5] and this great variability is probably due to the fact that certain tumor types—especially the malignant neoplasms,

[1]*Stratz* A46458/893, *Weith* A74818/896, *Wendeler* A96821/899, *Miller* A18279/37, *Zagni* A95459/39, *Novak* A63534/41.
[2]*Tahère* A87498/839, *v. Roehr* A81059/842, *Laskowski* A82578/867.
[3]*Lee* A70107/848.
[4]*Nyström* A76231/11.
[5]*Miller* A18279/37.
[6]*Budin* A69743/875, *Reber* A40294/883, *Quenu* A41968/887, *Gundelach* A41832/887, *Mackenzie* A45840/891, *Wood* A50654/898, *Pollosson and Murard* A68547/12, *Levin* A68542/15-6, *Miller* A18279/37.

the papillomas and the fibromas—are much more likely to produce ascites than other forms. The frequency of ascites in any one series of observations will naturally be influenced, therefore, by the incidence of these specifically ascites-producing neoplasms.

Pleural fluid accumulations are less commonly seen in patients suffering from ovarian tumors[1] and, if present, they usually occur in conjunction with ascites. It is considered most probable that in these instances the fluid enters through lymphatic channels from the peritoneum into the pleural cavity. The association of ovarian fibromas with peritoneal and pleural fluid accumulations, known as "Meigs' syndrome", is discussed in greater detail in the chapter on Ovarian Fibromas.

Histologic changes in the *uterus* are inconstant in patients with ovarian tumors, but they sometimes cause irregularities in the menstrual cycle[2] and metrorrhagias.[3] Uterine bleeding can even be caused by such growth after the menopause or following a transitory period of amenorrhea before the climacteric age.[4] Proliferation of the endometrium,[5] sometimes conducive to the formation of endometrial polyps,[6] may also occur in the bearers of ovarian tumors and the comparatively frequent co-existence of uterine fibroids and ovarian neoplasms has repeatedly been noted.[7] It appears rather probable that only those tumors of the ovary which produce sex hormones, especially folliculoids, stimulate the growth of uterine structures. A detailed discussion of this problem will be found in the chapters on Follicular Cysts, Small Cystic Degeneration of the Ovaries and Folliculomas. The development of ovarian tumors in patients with uterine malformations[8] may probably be ascribed to a predisposition of the ovary for tumor formation in congenitally stigmatized women.

Changes in the *oviduct* are usually secondary to adhesions produced by the ovarian tumor or to invasion by malignant cells. Most commonly, these changes consist in the formation of a hydrosalpinx or hematosalpinx[9] but sometimes the oviduct is merely displaced or elongated[10] by the adjacent ovarian growth.

The occasional occurrence of *mammary gland* engorgement, tenderness or lactation, in bearers of ovarian tumors,[11] is difficult to explain; it is probable that such changes only occur if the tumor produces sex hormones capable of stimulating the mammary glands. Mammary growth and milk secretion are comparatively common with follicle cysts, folliculomas and chorionepitheliomas of the ovary, that is, tumors known to produce sex hormones (see chapters specifically devoted to the above tumor types).

Fertility is not necessarily influenced even by bilateral ovarian tumors so long as an adequate amount of normal gonadal tissue remains. The percentage of sterile women among patients suffering from diverse types of ovarian neoplasms is variously given as between 12 and 53%[12] (see also part on the Pregnancy Incidence of the various tumor types).

Ectopic, especially tubal pregnancies, are comparatively common in women with ovarian tumors, perhaps owing to the interference by such neoplasms with the passage of ova through the oviduct. However, a review of this problem led Miller[13] to conclude that the incidence of ectopic pregnancies is not greater among bearers of ovarian tumors than among normal women.

The most constant and important clinical manifestations of ovarian tumors are *changes due to the physical presence of the growth* itself. Since these are of special diagnostic significance they will be discussed in the part on Diagnosis. It may be mentioned here, however, that large ovarian tumors may cause disturbances owing to vertical *displacement of the heart*[14] or *pressure upon the stomach*,[15] while *compression of the urinary bladder* may lead to cystitis, pericystitis and incontinence.[16]

Among the least constant manifestations of ovarian tumors the occasional occurrence of *leucocytosis*,[17] *paraplegia*,[18] *scleroderma*,[19] *pigmentation of the skin*,[20] and *glycosuria*[21] are mentioned only for the sake of completeness, since their causal connection with the ovarian tumor is not definitely ascertained. It will likewise suffice merely to remind the reader of the numerous symptoms and signs which may be elicited by the metastases of malignant ovarian tumors; they will be discussed with the individual specific tumor types.

COMPLICATIONS

The usual clinical course of ovarian tumors is frequently altered by a variety of complications.

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[1] *Resinelli* A74621/00, A74622/00, *Leo* B7066/26.
[2] *Piyadé* A68528/, *Füth* A68538/08, *Wieber* A68531/10, *Lepper et al.* A96507/38.
[3] *Lewers* A74618/06.
[4] *Jalland* A50540/898.
[5] *Kreyberg* A95271/37.
[6] *Thornton* A82554/878.
[7] *Grenser* A88227/875, *Ferrant* A88224/877, *Terrier* A41220/883.
[8] *Bracklow* A49078/897, *Küstner* B11750/22.
[9] *Playfair* A41865/887.
[10] *Lepmann* A81152/01.
[11] *Miller* A18279/37, *Lepper et al.* A96507/38, *Ten Teachers* B6383/38.
[12] *Miller* A18279/37.
[13] A18279/37.
[14] *Glasgow* A83118/892.
[15] *Rövekamp* B5982/29.
[16] *Mézan* A96716/28.
[17] *Kopp* A74628/894.
[18] *Emery* A47304/895.
[19] *Steven* A50908/898.
[20] *Sorrentino* A96551/38.
[21] *Croom* A47299/895, A47301/895.

REVIEWS: Dudley and Coe A40589/882, *Ten Teachers* B6383/38, *Novak* A63534/41, B109/44, *Geist* B6672/42.

Among these torsion of the pedicle rupture of cysts, hemorrhage and secondary infections, and incarceration of the growths are most common. All these are discussed at some length in the chapters specifically devoted to these changes (see Sect. IV, Vol. VI) where they are treated in conjunction with similar lesions in non-tumor bearing ovaries. Suffice it therefore to give a very brief outline of these conditions here, to render the present volume fairly self-contained without too much duplication.

Torsion occurs most frequently if the ovarian tumor possesses a long and comparatively thin pedicle. It may be chronic or acute. In the case of chronic torsion the symptoms are usually not very dramatic and generally due to the development of inflammatory changes and adhesions between the tumor and the neighboring organs. Conversely, sudden torsion usually produces very sudden and alarming symptoms due to the fact that rapid occlusion of the blood vessels within the pedicle causes severe circulatory disturbances, sometimes accompanied by massive hemorrhage into the tumor or the peritoneal cavity. Even complete necrosis of the tumor may ensue, with secondary infection and the symptomatology of an acute peritonitis. In some instances even self-amputation may occur (see chapter on Self-Amputation in Sect. IV, Vol. VI) with absorption of the tumor mass or its transplantation into an adjacent organ.

Torsion can be elicited by physical exercise, change in the position of the tumor occasioned by pregnancy, labor or childbirth, peristaltic movements of the intestines or uneven growth of the neoplasm itself.

The symptoms of acute torsion are extremely dramatic. They resemble those of a perforated gastric ulcer, ileus, renal or biliary colic, ruptured ectopic gestation or acute appendicitis. There may be constipation or diarrhea and vomiting; the temperature tends to be subnormal and the pulse is often feeble. Fainting spells, and, in later stages, signs of peritonitis with fever and tachycardia may develop while the outlines of the cyst become indistinct due to abdominal distention. This often renders the diagnosis difficult. In the more chronic form repeated but generally milder attacks of abdominal pain are seen sometimes in conjunction with a rise in temperature and pulse rate.

Rupture and hemorrhage are most common in cystic tumors. These complications result from degenerative changes which weaken the tumor walls, or from some mechanical trauma, for instance, that incident to bimanual palpation, the pressure of a pregnant uterus, or torsion of the pedicle. Following rupture the cyst contents are discharged into the peritoneal cavity and lead to the sudden development of ascites or, if the cyst contents are infected, to peritonitis. Hemorrhage is a frequent accompaniment of rupture and may be very severe even if only a normal ovarian follicle or a corpus luteum bursts.

Infection of ovarian tumors is also most frequent in the cystic variety, especially in dermoids. It may occur due to migration of micro-organisms through adhesions from the intestinal tract into the tumor, or it may be secondary to pelvic peritonitis, salpingitis or septicemia. The causative agents are usually streptococcus pyogenes, pneumococcus, B. coli, tubercle or typhoid bacilli.

Infection of the tumor tends to cause tenderness, pain and fixation of the growth, with irregular fever and other signs due to the absorption of toxic products.

Incarceration of ovarian tumors within the pelvis is usually due to its immobilization by intraligamentous growth, adhesions, a pregnant or a fibromatous uterus. It often manifests itself by signs of pressure upon blood vessels or the genital and other pelvic organs. Perhaps the most important results of incarceration are those due to pressure upon the bladder[1] or the ureters with consequent hydronephrosis or even uremia.[2]

Among other events which may complicate the clinical course of ovarian tumors, we may mention the simultaneous development of a *hernia* due to increased intra-abdominal pressure,[3] a *tubal pregnancy,*[4] *pyosalpinx,*[5] *intestinal obstruction,*[6] *appendicitis,*[7] *peritonitis,*[8] *circulatory disturbances in the lower extremities,* sometimes conducive to gangrene[9] and in rare instances *miliary tuberculosis.*[10] For more detailed data, especially those concerning the rare complications of ovarian tumors, the reader is again referred to the individual chapters dealing with specific tumor types.

DIAGNOSIS

The diagnosis of ovarian tumors is an important and often difficult problem which has been discussed in many *reviews* from the middle of the 19th century

[1]*Bloch* A49137/897.
[2]*Part* A88359/853-4, *Pitts* B8881/03, *Nassauer* B12870/05, *Raux* A68529/11, *Pallasse and Colas* A28126/35, *Morris and Juracsek* A95299/37.
[3]*Yamayaki* B13341/07.
[4]*Voelcker* A96747/28, *Müller* A96718/28.
[5]*Wagner* B8977/03.
[6]*Ridout* A74632/00-1, *Yamada* A95458/38.
[7]*Stone* A74625/05-6.
[8]*Begouin and Bardon* A68532/20.
[9]*de Closmadeuc* A87101/867, *Fitzgibbon* A74614/875-7.
[10]*Fitzgibbon* A74614/875-7, *Dudley* A41306/884.

up to the present time.[1]

The *past history* and *general clinical symptomatology* of the patient frequently furnish important data. Usually ovarian tumors remain asymptomatic during the initial stages of their development and, except in the hormone-producing tumors, the most frequently presented complaint is a painless enlargement of the abdomen which frequently raises the suspicion of pregnancy. Occasionally pressure by the growing tumor elicits symptoms due to interference with other abdominal organs and severe complications may arise as a result of torsion, secondary infection or rupture of cystic tumors (see part on Complications).

Although usually there are no menstrual disturbances, menorrhagia or metrorrhagia may occur, the latter especially with malignant tumors. Amenorrhea and dysmenorrhea may also be seen but they are rare. After the menopause, on the other hand, ovarian tumors frequently cause slight uterine hemorrhages which must carefully be distinguished from those due to uterine cancer. Except in the case of hormone-producing tumors, fertility is rarely impaired unless the tumor causes pronounced cachexia or is bilateral and destroys all, or most, of the ovarian tissue (see also part on Pregnancy Incidence).

If the tumor is incarcerated in the pelvis, and thus prevented from ascending into the abdominal cavity, it may cause pressure symptoms after reaching a certain size. There may be edema of the legs (unilateral edema is suggestive of malignant tumors), hemorrhoids, pain in the sacral region and the legs (usually due to pressure upon the sacral plexus and also most common with malignant tumors), painful defecation and difficulty or frequency of micturition.

If the tumor ascends into the abdomen, as it normally does, it may cause cardiovascular and respiratory disturbances due to pressure upon the diaphragm. Pain is frequently elicited by a sudden increase in the size of the tumor, torsion, rupture or inflammation within the growth. The occurrence of pain a few days before menstruation is not uncommon and may be due to an increased blood supply to the ovaries at that time. Considerable amounts of ascites are rarely seen except with fibromas, papillomas and malignant tumors. If the ureters are occluded by pressure, hydronephrosis and even uremia may ensue. Sometimes there is frequency of micturition. After some time the patient may become extremely emaciated.[2]

With regard to the *methods of investigation* upon which the diagnosis is to be based, *palpation* always was—and still is—the most important. Whenever possible it should be performed bimanually after evacuation of the bladder and rectum, the patient being placed in a position suitable for palpation of the particular region in which the tumor is felt. Sometimes palpation may have to be performed under light anesthesia and in the event of considerable ascites, after evacuation of the free peritoneal fluid by tapping.[3] The introduction of a kolpeurynter into the rectum[4] recommended around the turn of the century for the palpation of the ovarian region, has not fulfilled the hopes originally attached to it. It is not within the scope of this Encyclopedia to discuss the standard technics of bimanual palpation, but the reader interested in the palpatory findings characteristic of the various specific tumor types is referred to the corresponding chapters of this volume.

X-ray studies are useful[5] especially in the case of calcified tumors[6] (see chapters on Calcification and Ossification in Sect. IV, Vol. VI) and dermoids (see chapter on Dermoids) in which the concretions, teeth and bones are often clearly visible. The establishment of a pneumoperitoneum has been found useful, even in the diagnosis of non-calcified ovarian neoplasms[7] and important information may sometimes also be gained by salpinography.[8]

Bioassays and chemical analyses of blood and urine for the presence of *hormones* are useful in connection with the detection of neoplasms producing excessive amounts of folliculoids (follicle cysts, folliculomas), luteoids (corpus luteum cysts, luteomas) or hypophysoid gonadotropic hormones (teratomas, chorionepitheliomas). Ovarian tumors capable of producing large quantities of gonadotropic hormones are exceedingly rare, hence the presence of such substances in excessive amounts in the urine may help the differentiation of ovarian neoplasms from normal or ectopic pregnancies, which frequently cause differential diagnostic difficulties.[9] For a detailed discussion of the hormone-metabolism disturbances in women with ovarian tumors, see the chapters dealing with the individual hormone-producing neo-

[1] *Tilt* A82277/852, *Jacob* A82125/856, *Atlee* A82131/860-1, *Dammann* A82122/862, *Hulke* A82241/863-4, *Otto* A82261/866, *Jacobsthal* A82126/872, *Drysdale* A82148/873, *Svensson* A82275/875-6, *Thornton* A88249/876, *Dillon* A82147/877, *Stahl* A88247/877, A82274/879, *Wells* A82283/878, *Hovious* A82240/879, *Jastrebow* A40051/881, *Lusk* A40261/883, *Borck* A41578/883, A40623/883, *Hamilton* A41333/883-4, *Goodell* A82230/884, *Griffith* A82231/884, *v. Ramdohr* A42004/885-6, *Baldy* A83612/888, *Jacobi* A42506/888, *Harvey* A42422/888, *Richelot* A83621/891, *Robson* A44039/891-2, *Russell* A44217/892, *Goggans* A44612/893-4, *Murray* A49243/896, *Davenport* A48435/896, *Sharp* A49110/897, *Gruzdeff* A83119/898, *Martin* A96835/899, *Doran* A83116/04, *Franqué* B13208/06, *Vignard* A82375/10, *Haymann* B11215/10, *Hauptmann* A53165/33, *Chimenti* A95243/37, *Pruis* A97305/38, *Sardi and Arrighi* A97524/41.

[2] *Ten Teachers* B6383/38.

[3] *Martin* A96835/899, *Novak* A63534/41.

[4] *Jacobs* A82244/888, A82245/888.

[5] *Ducuing et al.* B20711/26.

[6] *Stevenson* A97716/40.

[7] *Chueco* A82372/22, *Heuser* B7484/24.

[8] *Mandler* B5935/29.

[9] *Machado Espinosa* A95285/37.

plasms of the ovary (this volume) and chapters on the hormone content of blood and urine in the sections on the Hypophysis, Ovary and Testes.

The final and definite diagnosis is, however, usually only possible after morphologic examination of the tumor tissue itself. In order to obtain specimens for this purpose, various technics of *exploratory colpotomy* and *laparotomy* have been devised.[1] Since the best therapy of most ovarian tumors is their surgical removal, it is advisable to make such exploratory interventions part of the operation required for the ablation of the tumor. Some tumors will readily be recognized by naked eye inspection of their tissue and the contents of the cystic cavities which they contain. Usually, however, it is best to prepare frozen sections of the tumor tissue and examine them during the operation. This procedure will help to determine the extent of the necessary intervention. The importance of such exploratory biopsies is emphasized since the choice between conservative and radical interventions should be based, not upon the preferences of the operator derived from his personal previous experience, but upon carefully analysed statistical data regarding the incidence of recurrence of similar tumors described in the literature. The danger of producing metastases by biopsy procedures though real, has perhaps been over-emphasized as judged by animal experiments. Thus in the case of rat carcinomas and mouse sarcomas, even excessive aspiration biopsy procedures did not result in implantation along the needle tract or any other evidence of increased spread.[2]

In connection with the morphologic diagnosis of Ovarian tumors, we wish to draw special attention to The American Registry of Ovarian Tumors, sponsored by The American Gynecological Society. To quote from its announcement, "The registry is to be looked upon as a co-operative project among the gynecologists and pathologists of the country, and it is earnestly hoped that all will develop the routine of sending material from all interesting ovarian tumors, with adequate clinical data, to the Committee for study and registry".[3] We feel that this Committee can do much to promote our knowledge of ovarian tumors and strongly urge that material be mailed to Dr. Emil Novak, Laboratory of Gynecologic Pathology, Johns Hopkins Hospital, Baltimore.

From the point of view of *differential diagnosis,* the most common sources of error are the *inflammatory processes* in the ovarian and para-ovarian region, namely inflammatory tubo-ovarian cysts, salpingitis, perimetritis, pelvic abscesses etc.[4] The diagnosis of the latter conditions will rarely cause serious difficulties, however, if the past history and the signs and symptoms typical of ovarian and periovarian inflammations (see Sect. IV, Vol. VI) are taken into account.

In the event of a *hydrosalpinx* the past history of the patient usually reveals a preceding pelvic inflammation and, in most cases, bimanual palpation shows the tumor to be bilateral and tender. Its walls are thin to the touch and the uterine end of the distended tube may be palpable. Furthermore, a hydrosalpinx cannot be as clearly separated from the uterus as an ovarian tumor and is frequently fixed by adhesions.[5] Differentiation from other *para-ovarian* tumors[6] is usually more difficult.

Ectopic pregnancies frequently led to errors in diagnosis especially at the time when no conclusive pregnancy tests were available.[7] Now the demonstration of excessive gonadotropic hormone elimination through the urine (Aschheim-Zondek test, Friedman test or similar bioassays) greatly facilitates the correct diagnosis in such cases. Furthermore, a history of pelvic inflammation followed by a period of sterility, or a missed menstrual period with morning sickness usually gives cause to suspect that the patient is pregnant. The uterus is somewhat bulky and in most cases the tumor lies to one side of it and not behind it (as do most ovarian tumors) unless there is a hematocele. Unlike ovarian tumors, the mass can frequently not be clearly separated from the uterus. A history of an attack of abdominal pain accompanied by metrorrhagia, and sometimes the passage of a decidual cast, are noted if the ovum has died.[5]

Normal pregnancy is less likely to be confused with ovarian tumors, although sometimes this error can occur[8] especially if the uterus is retroflexed or if Hegar's sign is marked. In the former case, the uterus cannot be felt in its usual position and the cervix is pushed forwards and upwards so that palpation may be difficult. There often is frequency of micturition or retention of urine. Sometimes the mass can be pushed out of the pelvis and this helps to identify the body of the uterus. Furthermore, upon handling, the retroverted or retroflexed uterine muscle tends to change in consistency due to contraction. During the first ten weeks of pregnancy an error in diagnosis can also occur due to the fact that the gestation sac occupies the upper part of the uterus, while the lower portion of the organ is empty and soft, the cervix itself remaining fairly rigid. In

[1] *Neale* A83618/868, *Wood* A83591/876, *Perkins* A86578/887-8, *Tzonciu* A42544/888, *Terrillon* A45157/889, *Törngren* A45824/891, *Hirons* A83616/891.
[2] *McLean and Sugiura* B21544/37.
[3] *Novak et al.* B7054/44, *Novak* B7053/44.
[4] *Doran* A83114/888-9, A83115/890-1, *Martin* A96835/899, *Novak* A63534/41.
[5] *Ten Teachers* B6383/38.
[6] *Martin* A96835/899.
[7] *Tait* A86288/875, *Stern* A46379/893, *Morrison* A44723/894.
[8] *Reimann* A40552/882, *Davis* A83113/889-91, *Champneys* A48428b/896-7, *Neel* A74630/03-4.

such cases, the firm cervix may be mistaken for the uterus, and the upper part of the womb—which contains the ovum and is also firm—appears to be a separate mass, readily mistaken for a pelvic tumor. As in ectopic gestation, the increased gonadotropic content of the urine is the most reliable indication of an existing pregnancy and will almost invariably prevent such errors.

Uterine fibroids are sometimes almost indistinguishable from ovarian tumors[1] especially if they are connected with the uterus only by a long and narrow pedicle. Frequently these are additional fibroids in the submucosa or the body of the uterus; however, these cause a generalized enlargement of the organ and tend to produce menorrhagias which help to identify the true nature of the growth. It should also be remembered that ascites is more common with ovarian tumors, and menorrhagia with uterine fibroids.

Tumors of the intestinal tract, especially carcinomas of the cecum or sigmoid, are sometimes mistaken for ovarian neoplasms.[2] A past history of bloody or mucous discharge from the rectum and diarrhea alternating with constipation are characteristic of intestinal growths. Although it is, of course, possible for a primary cancer of the intestine to invade the ovaries, the latter are usually not affected and may be palpable in their normal position separately from the tumor. Sigmoidoscopy may be helpful in confirming the diagnosis in such cases.[3] *"Fecal tumors",*[4] *neoplasms of the omentum,*[5] *mesentery*[6] or *anterior abdominal wall*[7] should also be mentioned as potential sources of diagnostic errors, although they are less commonly mistaken for ovarian neoplasms.

Generalized obesity may be difficult to differentiate from an ovarian tumor although the latter usually causes a swelling limited to the abdomen, while the former affects the entire body and produces folds of fat which can be felt between the skin and the abdominal muscles. In many instances, however, ovarian tumors develop in obese women, a circumstance which further complicates the diagnosis. It will be remembered that the contours of ovarian tumors are usually distinct, yet in the case of thin-walled, soft ovarian cysts, the outlines may not be distinguishable, so that obesity is simulated. Upon deep percussion ovarian tumors are dull, while the abdomen of obese women is resonant. A useful aid in palpation is to place one hand on each side of the abdomen and try to make them meet. This will not be possible if a tumor is present. In some cases palpation under an anesthetic will be necessary.[3]

A *distended bladder* may form an elastic mass at the brim of the pelvis—sometimes extending to the level of the umbilicus—and elicit a "false incontinence of urine" which imitates an ovarian cyst. Therefore, in all cases of pelvic tumors, especially those complicated by urinary symptoms, it is best to pass a catheter before examination.[3]

One of the most important differential diagnostic problems is the distinction of ovarian tumors from *ascites.* On inspection, with the patient lying on her back, with ovarian cysts the abdomen is prominent especially in the mid-line, while the flanks are but slightly expanded. Ascites, on the other hand, flattens the center of the abdomen and causes the flanks to extend sideways. The umbilicus may project in both cases. Upon palpation ovarian tumors, unlike ascites, prove to have distinct outlines. With ascites a thrill can be obtained over the entire abdomen provided that there is enough fluid free in the peritoneal cavity; ovarian cysts reveal a thrill only if their cavities are very large and even then the thrill is noted only over the tumor area. Upon bimanual palpation the uterus proves to be more mobile in the case of ascites, than with large ovarian cysts. Percussion reveals a dull sound over the tumor region, that is, usually in the center of the abdomen, while the resonant intestines are mostly in the flanks. Conversely, in ascites the central region is resonant, since it contains the intestines which tend to float on the fluid; the latter occupies the flank region giving it a dull percussion note. The well-known sign of a "shifting dullness"—which always occupies the lower part of the abdomen no matter what position the patient takes—is also characteristic of ascites. The greatest girth is measured below the level of the umbilicus in ovarian cysts, and at the level of the umbilicus in ascites. In some patients, however, all these signs do not permit a definite differential diagnosis: then it becomes necessary to consider such factors as renal, cardiac, or pulmonary disease which are likely to produce ascites and hence make its presence probable.[3]

Among other conditions which sometimes may cause differential diagnostic difficulties, we may also mention *encysted pelvic collections of fluid,*[3] *accidental pelvic hemorrhage,*[8] *distended bowels,*[3] *intra-abdominal hernia,*[9] *tuberculous peritonitis,*[10] *tumors of the liver,*[11] *splenomegaly,*[12] a *rotated*[13] or *wander-*

[1]*Lowder* A29841/880, *Dambrin et al.* B8024/26.
[2]*Roux de Brignoles and Aubert* A82374/23, *Ohligmacher* A97300/39.
[3]*Ten Teachers* B6383/38.
[4]*Hunter* A82242/881.
[5]*Reiss* A82129/886, *Hellier* A83120/04,
[6]*Cappellani* A96769/28,
[7]*Weinlechner* A40252/883.
[8]*Roberts* A96727/38.
[9]*Hennig* B20716/26.
[10]*Novak* A63534/41.
[11]*Duffey* A83117/877-80, *Weishaupt* B11312/10, *Stevens* B20823/25.
[12]*Costa* A97174/38,
[13]*Croly* A47377/896.

ing spleen,[1] and a *neoplastic*[2] or *ectopic kidney.*[3] The term "*false renal colic*" was coined[4] to designate cases in which ovarian neoplasms produced clinical manifestations similar to those characteristic of true renal colics. If all these sources of error are kept in mind, the differentiation of these conditions from true ovarian neoplasms is usually possible on the basis of their characteristic symptomatology. (For additional data concerning differential diagnosis see chapters dealing with the specific tumor types).

The *differentiation of benign from malignant ovarian tumors* is often extremely difficult not only on the basis of clinical findings alone, but even after direct inspection at operation. This is especially true of borderline cases in which an originally benign tumor is in the process of malignant transformation. Malignancy may be suspected on clinical grounds, however, if there is rapid loss of weight with a small ovarian tumor. Benign cysts may be associated with cachexia, but this is rare unless they are very large. A considerable amount of ascites, unilateral edema of the vulva or legs, demonstrable malignant foci elsewhere in the body, the presence of irregular nodules on the surface of the neoplasm, extensive adhesions and bilateral development of the tumor are all rather characteristic of malignancy,[5] yet none of these signs is pathognomonic.

PROGNOSIS

It is difficult to discuss the prognosis of the various ovarian tumors conjointly. The clinical course of these blastomas—whether they remain untreated or whether ovariectomy or other therapeutic measures are applied—always depend upon their inherent growth tendency. For relevant data the reader is therefore referred to pertinent reviews[6] as well as to other chapters of this volume in which the individual tumor types are discussed.

Suffice it to say here that, if no treatment is applied, the course of true ovarian neoplasms is progressive. The tumor may grow slowly or rapidly, but spontaneous recovery is extremely rare.[7] The few instances of apparently spontaneous regression are due to the rupture of cysts with subsequent absorption of their contents. In such cases the recovery is rarely permanent, however, since usually after some time new loculi are formed from microscopic alveoli in the wall of the ruptured cyst and fluid accumulation in them restores the tumor. Perhaps recurrences can also occur owing to obliteration of the rupture point following scar formation. In the case of ovarian tumors with comparatively thin and long pedicles torsion may lead to the amputation of the stalk with consequent absorption of the entire tumor mass. This process will not effect a cure, however, unless the growth tendencies of the tumor are comparatively weak. If actively growing tumors undergo self-amputation, they often transplant themselves to some other part of the peritoneum and continue to grow there.

As stated in the part on Therapy, among all the curative procedures, radical surgical removal of the growth assures the best prognosis. The post-operative course of the various ovarian tumors has been discussed in the chapters devoted to each of them. Suffice it here to quote the results of one statistical survey in which the fate of a number of ovarian tumors has been followed comparatively over a period of several years following ovariectomy.[8]

Tumor type	No. of Cases	No. Free of Recurrences
Fibromas	9	8
Sarcomas	15	6
Endotheliomas	1	0
Simple serous Cystomas	29	28
Cystadenomas	285	269
Cystic Papillomas	19	17
Primary Carcinomas	36	13
Secondary Carcinomas	11	1
Dermoid Cysts	48	46
Struma ovarii	1	1
Para-ovarian Cysts	39	38

This brief table clearly shows that with the exception of malignant tumors, the post-operative prognosis of ovarian neoplasms is very good. Of course, the technic of the operator also plays an important role in determining the prognosis and in general the more radical the intervention, the better the chances of the patient. Naturally, this advantage must be balanced against the obvious disadvantages of mutilating surgical interventions.

[1] *Sen* B20820/25.
[2] *Altounyan* A82370/24, *Ruzicska* A52302b/34.
[3] *Rubin* A97588/39.
[4] *Pinheiro* A96620/41.
[5] *Ten Teachers* B6383/38.
[6] *Martin* A96837/899, *Miller* A18279/37, *Karsner* A32285/40, *Geist* B6672/42.
[7] *Peebles* A88242/851.
[8] *Glockner* A70015/06.

The prognosis of radium or X-ray treatment is generally not nearly as good as that of surgical intervention and therefore such therapeutic procedures should be used only in inoperable cases or post-operatively as a prophylactic measure in malignant tumors where the danger of recurrences is otherwise great (see part on Therapy).

THERAPY

The therapy of ovarian tumors has been the subject of many *reviews*.[1]

In spite of many enthusiastic statements to the contrary, it is our opinion that, whenever technically feasible, the best therapy for any type of ovarian tumor is its complete surgical removal. The operation should be performed as soon as possible, since it is almost never certain that the growth is not malignant or at least in the process of malignant transformation. It should also be remembered that by postponing these operations the likelihood of complications caused by adhesions to adjacent organs, hemorrhage, torsion, etc. is only increased.

There are certain conditions, however, which represent exceptions to the general rule that ovarian tumors should be removed as soon as they are recognized. If a woman is in labor when the ovarian tumor is diagnosed, its removal may be postponed if it does not mechanically interfere with delivery. During the first three months of gestation ovariectomy entails the danger of abortion and if the tumor is not malignant and no immediate danger of a complication exists it may be advisable to postpone intervention until later in such cases. No ovariectomy is necessary, furthermore, in women with corpus luteum cysts, which generally accompany hydatidiform moles of the uterus. Here the uterine growth must be removed but the ovarian cysts retrogress spontaneously as soon as the source of the gonadotropic hormones (namely the uterine blastoma) is no longer present. Theoretically the same argument would apply to corpus luteum cysts caused by uterine chorionepitheliomas; however, since these highly malignant neoplasms must usually be treated by radical interventions which include ovariectomy it is of no importance that the cysts would regress after ablation of the chorionepithelioma tissue.

The technical details of ovariectomy will be discussed in another volume of this Encyclopedia. Suffice it to say here that generally speaking ovarian tumors should be removed by the abdominal and not by the vaginal route. Through a comparatively large suprapubic incision the operator gains a good view of the neoplasm and will be able to remove it without having to tap cysts (a procedure which often leads to transplantation of tumor cells and consequently to recurrences); there will be comparatively little danger of scattering micro-organisms from infected cysts or of spreading malignant cells, especially from the papilliferous type of ovarian carcinoma.

Should the radical removal of a malignant tumor become technically impossible, owing to metastases or its size and adhesions to other organs, conservative measures may be adopted. These consist in the repeated withdrawal of ascitic fluid to relieve intra-abdominal tension, or in the partial removal of the neoplasm followed perhaps by X-ray or radium therapy in order to postpone the fatal outcome.

Many additional data concerning ovariectomy are discussed in the chapters specifically dealing with the individual types of tumors and in the *case reports* of ovariectomies performed for incompletely identified tumors.[2]

[1] *Mayer* A99597/26, *Curtis* A63170/30-42, *Geist* B6672/42, *Novak* B109/44.

[2] *Chéveau* A86892/843-4, *Phillips* A86963/844, *Buckner* A87096/850, *Myrtle* A87143/851, *Sloan* A87158/852, *Erichsen* A83288/853, *Smith* A86282/855, *Litzenburg* A87134/856, *Edwards* A87110/856-7, *Peaslee* A87149/857, A88206/872, *Warren* A87175/859, *Cooper* A87102/861, *Wells* A87177/861-2, A86407/864, *Beatty* A74820/862-5, A74972/863, *Packard* A87147/862-74, A87146/871, *Macilwain* A83135/863, *Carr* A87097/864-5, *Smyly* A75719/866, *Maslovski* A86862/866, *Nicolaysen* A74904/867, *Potter* A87231/867-8, *Lilly* A87132/869, *Stokes* A87162/870, *McReddie* A86235/870, *Emiliani* A87112/870, *Chase* A87099/870, *Mack* A87223/871, *Thorburn* A86989/871, *D'Hanens* A83280/871, *Woodward* A87181/872, *Beebe* A86876/872, *Thompson* A87166/873, *Mason* A87139/874, *Kidd* A74898/874, *Hoegh* A86350/874, *Gleaves and Jordan* A86561/876, *Lueck* A87135/876, *Thomas* A83508/876, A86397/879, *Derville* A87107/876, *Holmes* A87124/876, *Burgess* A87193/876-7, *Mossop* A86238/876-7, *Chesney* A87100/877, *Stilling* A87161/877, *Carreras* A87098/878, *Morales y Arjona* A87142/878, *Hegar* A87123/878, *Carrow* A86890/878, *Creus* A87105/878, A87104/878, *Horr* A87125/878, *Péan* A87148/878, A41294/883, *Southam* A87160/878, *Wheeler* A87179/878, *Lipscomb* A87133/879, *McGuire* A86364/879, *Neville* A74880/879-80, *Borck* A29405/879-80, A29449/880, *Bryant* A29431/880, *Boeckel* A29476/880, *Chenoweth* A29539/880, A40586/882, *Cattani* A83183/880, *Wireback* A29390/880, *Goodell* A29589/880-1, A75819/888, *Drysdale* A40013/881, *Negri* A40457/882, A40254/882, A40781/884, *Thornton* A41299/882-3, *Williams* A41227/883, *Sacré* A41598/883, *Gallard* A41241/883, *Cole* A41527/883, *Irish* A41313/884, *Taylor* A40807/884-5, A53108/34, *Helmuth* A40714/884-5, *Tait* A88248/884-5, *Reinlein* A88207/885, *Maynard* A41054/885, *Lediard* A41485/885, *v. Dittel* A42020/885, *Word* A40846/885-6, *Wilkinson* A41701/886, *Postemski* A42275/886-7, *Küstner* A41746/887, *Koehler* A41963/887, *Barton* A42291/887-8, A42335/888, *Jacoby* A45133/888, *Brown* A42295/888, *Montgomery* A45099/888-9, A48447/897, A50646/898, *Picqué* A45255/889, *Serrano* A42657/889, *Holland* A45178/889, *Hall* A43634/890, A44228/892, A88040/03, *Palmer* A43478/890, *Sandberg* A75821/890, *Vawdrey* A43562/890, *Nancrede* A43313/890, *Altabas* A88874/890, *Hamilton* A45756/891, *Carpentier* A45686/891, *Gaston* A45754/891, *Fink* A45866/891, *Blanks* A45829/891, *Fulton* A44026/892, *Martin* A46497/892-3, *De Renzi* A46525/893, *White* A46553/893, *Jacobs* A93078/894, *Falckner* A47127/894, *Carstens* A44799/894, *Rogée* A47322/895, *Vanderveer* A47478/895, *Fullerton* A47452/895, *Westerfield*

Footnote cont'd.

The ablation of very *large* ovarian tumors may be technically difficult; it sometimes results in severe circulatory disturbances owing to the removal of a great tissue mass which is usually very well supplied with blood vessels. Even huge tumors can be removed in a single session, however, as shown by the many case reports describing ovariectomies for gonadal neoplasms weighing 20-30 lbs.,[1] 30-40 lbs.,[2] 40-50 lbs.,[3] 50-60 lbs.[4] and even 60 lbs. or more.[5]

In some cases ovarian tumors, most frequently cysts, have to be removed during *pregnancy,* since they may mechanically interfere with the growth of the uterus and with parturition.[6] It should be kept in mind that special technical precautions must be observed if this surgical procedure is to be performed during gestation and that in early pregnancy treatment with luteoid hormones must be instituted to compensate for the loss of the corpus luteum of gestation (see also part on Therapy in chapter on Common Ovarian Cysts).

In some instances, if the tumor is small, encapsulated and obviously benign, it is advisable to remove benign ovarian tumors by *conservative interventions* such as partial resection of the ovary, wedge excisions,[7] or even mere enucleation.[8]

As stated above, *X-ray therapy* is indicated chiefly as a palliative measure in the case of inoperable tumors and as a prophylactic step to decrease the likelihood of recurrences.[9] Occasionally, however, the growth rate of an ovarian tumor is perhaps actually accelerated following X-ray therapy.[10] For this reason and because it rarely effects a permanent cure radiation therapy—including treatment with radium and other radio-active elements[11]—is not recommended for the treatment of any type of ovarian neoplasm which can be surgically removed.

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[2]cont'd A47480/895-6, *Werder* A50667/896, A50686/898-9, *Gow* A49120/897, *Coen* A49167/897, *Campbell* A50631/898, *Bouilly* A74830/899, *Yoshida* A75825/899, *Martin* A96839/899, *Chapman* A69562/02, *Ikeda* A93076/02, *Delfosse and Bennet-Laborderie* A93031/02, *Heillier and Smith* A93072/02, *Hashimoto* A75820/02, *Briggs* A88899/02, *Kaan* A83653/04, *Gowans* A82383/04, *Polano* A83654/05, *Sarwey* A75822/06, *Polano* B13258/06, *Ogata* B13299/07, *Gayet and Alamartine* A82382/09, *Proust and Maurer* A94163/10, *Rawls* A82392/10, *Bock* A82376/15, *Bryson and Montgomery* A82379/16, *Gupta* B21263/20, *Ziemer* A82378/20, *La Roque* B21053/23, *Ingraham* B20798/26, *Leo* A94159/27, *Miller* A64439/30, *v. Fekete* A62066/36.

[1]*Bird* A87188/844, *Dickin* A87199/845, *Gay* A87207/857, *Simonton* A87235/859-60, *Lyon* A87222/863-4, *De Renzy* A87198/871, *Laub* A87221/871, *Bixby* A87189/872, *Buckham* A87192/875-6, *Gorell* A87210/876, *Greene* A87212/876, *Erdman* A87205/877.

[2]*Bird* A87187/844, *Meeker* A87224/848-9, *Nunneley* A87227/864, *Wells* A87241/864-5, *Morgan* A87226/865, *Dawson* A87197/867, *Buchanan* A87191/867-8, *Howard* A87217/869-70, *Edwards* A87203/869-70, *Tate* A87237/870, *Hinsey* A87216/876, *Wall* A87238/878-9, *Harvey* A87215/879.

[3]*Dunlap* A87201/854, *Peaslee* A87230/856, *Kimball* A87218/864.

[4]*Clay* A87195/844-5, *Dolson* A87200/871-2, *Hamilton* A87214/876-7.

[5]*Dunlap* A87202/864, *Ormes* A87228/873, *Wall* A87239/878-9.

[6]*v. Varo* B7358/26.

[7]*Siauve* A82396/14.

[8]*Hughes* A41612/883-4, *Lapeyre* B8789/03.

[9]*Eymer* A82381/12, *Kroemer* A82386/12, *Kukulka* A82377/12, *Brocq* B15462/27, B15463/27, *Werner* B7118/27, *Holzknecht* B15665/27, *Weisswange* A98091/41, *Schmitz* A94430/44.

[10]*Lavenant* A82388/23, *Vogt* B7111/26, B7112/26, B7113/26.

[11]*Schmitz* A94430/44.

PARA-OVARIAN TUMORS IN GENERAL

SYNONYMS: Broad ligament tumors. The terms "parovarian tumors" or "tumors of the Wolffian body" etc. are often used as synonyms for para-ovarian cysts, but this is inadmissible for reasons given below in the part on Definition.

REVIEWS

ENGLISH: Barnard A91281/01-2, *Doran* A91305/03-4, *Geist* B6672/42, *Novak* B109/44.

FRENCH: Savariaud A91355/06, *Deniker* A91273/10, *Bégouin and Papin* A91544/21, *Forgue and Crousse A91554/25, A91555/25,* A91556/27, *Bégouin et al.* A91542/25, *Dambrin and Dambrin* A91548/34.

GERMAN: Schmidt A88208/879, *Strangmeier* A88209/884, *Kossmann 966841/899, Schow* A91277/899, *Ekler* A77178/13, *Mayer* A99597/26.

ITALIAN: Miani A91565/23, *Roffo* A91570/29.

SPANISH: Serfaty A91359/18.

DEFINITION

In this Encyclopedia we shall discuss under the designation "para-ovarian tumors", all neoplasms situated in the immediate vicinity of the ovary within its ligaments.

Many of these growths are described in the literature under such terms as tumors of the broad ligament, Wolffian body, parovarium (epoöphoron), paroöphoron, rete ovarii, pronephric remnants, Müllerian or Wolffian duct remnants, Gartner's duct remnants etc. The most common designations are "parovarian tumors" and "broad ligament tumors". While many, if not all, the embryologic vestiges mentioned above may be the site of tumor formation, it appears extremely questionable to us whether in the majority of the tumors described in the literature, the exact derivation from any one of these cell types could be proven with certainty. In the parts on the pathogenesis of the parovarian tumors in general and on parovarian common cysts, the evidence in favor of the derivation of certain neoplasms from one or the other embryologic vestige will be carefully surveyed. In the majority of the published cases, however, no definite statements can be made concerning the histogenesis of these growths; hence, they could not be discussed under any heading if a general section on para-ovarian tumors were not created. We feel, therefore, that the non-committal, rather all inclusive terms of para-ovarian tumors—which only implies that the neoplasm or cyst is in the immediate vicinity of the ovary—is to be recommended for all those relevant blastomas in which the histogenetic mechanism is in doubt. It is particularly objectionable to use the term "parovarian tumor" as synonymous with para-ovarian neoplasms since the parovarium is a well defined morphologic structure derived from the Wolffian body and no neoplasm should be described as parovarian unless it demonstrably originates in this organ.

CLASSIFICATION

Forgue and Crousse[1] proposed the following classification for the para-ovarian tumors:

A. Neoplasms primarily developing between the laminae of the broad ligament.

1. Mesodermal tumors
   - a. Fibromas
   - b. Sarcomas
   - c. Lipomas
2. Dermoid cysts
3. Structures originating from embryonic inclusions in the connective tissue of the pelvic organs, especially the broad ligament (parovarian cysts, solid or cystic tumors of Gartner's duct, adenomyomas, hypernephromas etc.)
4. Parasitic tumors (echinococcus)

B. Neoplasms originating in adjacent organs and secondarily included in the broad ligaments.

- a. Uterine tumors with intraligamentous development
- b. Ovarian tumors with intraligamentous development
- c. Tumors of the round ligaments, the ligamentum ovarii and infundibulo-ovarian tumors
- d. Fallopian tube tumors

C. 1. Ectopic pregnancies with intraligamentous development

2. Chorionepitheliomas with intraligamentous development

This classification of the intraligamentous growths includes many tumor types which we do not consider under the heading of para-ovarian neoplasms. Thus, for instance, primary tumors of the oviducts, ectopic pregnancies or ectopic chorionepitheliomas not even secondarily involving the ovaries are not discussed in this Volume. It will also be kept in mind that well characterized ovarian neoplasms (e.g. lipomas, dermoids, sarcomas, fibromas) are discussed in special chapters irrespective of whether they do or do not exhibit intraligamentous development, while similar

[1]A91555/25.

tumors which originate in the para-ovarian region are treated in special chapters immediately following those devoted to the corresponding ovarian growth (e. g. para-ovarian fibromas follow the ovarian fibromas).

In this Encyclopedia the following system will be used as a basis for the presentation of the literature concerned with para-ovarian neoplasms in the sense of our definition:

A. PARA-OVARIAN TUMORS IN GENERAL.

Under this heading, (that is in the present chapter), we shall discuss only those data which are of importance for the para-ovarian neoplasms irrespective of their origin or histologic structure.

The evidence in favor of the derivation of certain para-ovarian cystomas, cystadenomas or adenomas from specific embryologic remnants (e. g. paroöphoron, Gartner's duct etc.) will be discussed in the part on Pathogenesis within this chapter.

B. COMMON PARA-OVARIAN CYSTOMAS.

In this section we shall discuss all those para-ovarian neoplasms which have been identified as cystic growths and are lined by a serous or pseudomucinous epithelium. Occasionally portions of the tumor or the entire growth are macroscopically solid and microscopically of the microcystic, adenomatous variety (cystadenomas, adenomas, adenofibromas).

C. NEOPLASMS WHOSE HISTOLOGIC STRUCTURE IS WELL-DEFINED (e. g. lipomas, dermoids, sarcomas, fibromas), will be treated in the corresponding chapters on ovarian tumors with a similar histologic structure.

Of course, the above is not offered as a true system of classification, but merely as a guide to the procedure used for the registration of data concerning para-ovarian neoplasms. In our opinion a special system of classification for the para-ovarian tumors is not necessary since most of them are structurally similar to ovarian growths, and hence the system of classification which we proposed for the latter is also applicable to the former (see chapter on Ovarian Tumors in General, part on Classification). The reader is also referred to the part on Pathogenesis in this chapter, where the para-ovarian tumors are classified according to their histogenesis.

PATHOLOGIC ANATOMY AND INCIDENCE

Since the great majority of all para-ovarian tumors are cystic, their pathologic anatomy and incidence will be discussed in the chapter on "Para-Ovarian Common Cystomas". Relevant data concerning histologically well-defined solid para-ovarian tumors will be found following each of the chapters specifically devoted to the corresponding ovarian neoplasms (e.g. fibromas, lipomas, myomas).

PATHOGENESIS

Histogenesis. The histogenesis of the para-ovarian tumors has been the subject of many *review* articles[1] and yet this problem is still in a state of confusion. In reviewing the field it must be admitted that the following derivations of para-ovarian tumors are at least theoretically possible:

A. PRIMARY PARA-OVARIAN TUMORS.

1) Hydatid of Morgagni (pronephric?)
2) Kobelt's tubules (pronephric?)
3) The Wolffian body, also known as parovarium, epoöphoron or organ of Rosenmüller (mesonephric).
4) The Wolffian duct (cranial part of mesonephric duct).
5) Gartner's duct (caudal, usually obliterated, part of mesonephric duct).
6) The junctional or rete tubules (usually obliterated connecting tubules between ovary and parovarium).
7) The paroöphoron (mesonephric).
8) Accessory Fallopian tubes (Müllerian).
9) Diverticula of the Fallopian tubes (Müllerian).
10) Independent tumors of the connective tissue elements in the broad ligaments (e.g. fibromas, lipomas, sarcomas, lymphangiomas).

B. SECONDARY PARA-OVARIAN TUMORS.

1) Metastases from distant malignant neoplasms.
2) Transplants of self-amputated benign neoplasms (usually of ovarian origin).
3) Endometriosis (uterine mucosa transplants).
4) Endosalpingiosis (tubal mucosa transplants).

It is possible that every one of the above listed possible derivations may give rise to para-ovarian tumors. Hence, this enumeration may also be used as a system for their classification on a histogenetic basis.

Now let us consider the above mentioned histogenetic possibilities individually in the light of available evidence.

[1] *Kossmann* A96841/899, *Robinson* A88725/03, *Santi* A91431/05, *Schickele* A81109/06, *Forgue and Crousse* A91555/25, *Gilbert and Sheorey* 82747/41.

Hydatid of Morgagni and Kobelt's Tubules. Within the group of primary para-ovarian tumors the first two, developments from the hydatid of Morgagni and Kobelt's tubules, may be considered conjointly since both of these are—at least probably—of pronephric origin and hence closely related to each other. In the immediate vicinity of the hydatid of Morgagni (a cystically transformed fimbria of the tubal ostium) there is often a second small pedunculated cyst which represents the dilated end of the Wolffian duct. In its vicinity several additional small cysts of a similar type may develop from the cranial (lateral) diverticula of the Wolffian duct, the so-called Kobelt's tubules. These are referred to as Kobelt's cysts. In some cases there may be a connective tissue connection between the distal end of the Wolffian duct and the end of the Fallopian tube. A small cyst which occasionally occurs in this connection is also presumed to be of pronephric origin. The cysts derived from these pronephric structures are always small and lined by a flat epithelium.[1] Their identification may be difficult, but if they are small and there is a definitely demonstrable direct connection between them and an ovarian fimbria (hydatid of Morgagni) or the distal end of the Wolffian duct (Kobelt's cysts) then their nature may be regarded as established.

Wolffian Body. The Wolffian body (parovarium, epoöphoron, organ of Rosenmüller) is one of the most common sources of para-ovarian neoplasms, especially cysts. It must be kept in mind, however, that many para-ovarian cysts are incorrectly designated as "parovarian" merely because they are in the immediate vicinity of the ovary. Further confusion is created by the fact that certain investigators[2] purposely designate all tumors derived from the Wolffian body, its duct (including Gartner's duct) or the paroöphoron as "parovarian" neoplasms. In order to clarify this point, let us reiterate that the distal portion of the Wolffian duct, which descends along the uterus and vagina in certain mammals and the human fetus, is usually obliterated and disappears completely in the adult human being. The term "Gartner's duct" (not Gärtner's as so many authors call it) is limited to the caudal part of the Wolffian duct if and when it persists. The true parovarian cysts are derived from the genital tubules of the parovarium which branch off the main duct. In most instances they are small and lined by a simple columnar epithelium which is usually—but not always—devoid of cilia. The lining is surrounded by a coat of smooth muscle fibers.[3]

It is of *historic* interest that cystic dilation of parovarian tubules was noted as early as 1848 by Meckel[4] and that numerous subsequent early investigators reported similar cases.[5]

All these authors agree that the *size* of true parovarian cysts is variable but usually small. This may perhaps be explained, at least partly, by the circumstance that very large parovarian tumors could hardly be recognized with certainty as such. While the cyst is small, its connection with the parovarium may be directly demonstrated by dissection, thus showing an anatomic continuity with the parovarium; in the case of voluminous cysts this is rarely possible. *Multilocular* parovarian cystomas are certainly rare although they occur occasionally.[6]

The *position* of parovarian cysts is usually in the close vicinity of the normal parovarium; quite frequently a connection with the latter, or a patent communication with persistent remnants of the Wolffian duct, are anatomically demonstrable.[7] It is of interest that occasionally these cysts have been claimed to occur in the connective tissue just underneath the peritoneal covering of the oviduct[8] and because of this unusual location their parovarian nature has been doubted. It is not impossible that some of these structures are derivatives of accessory Fallopian tubes or tubal diverticula.[9] Presumed parovarian cysts have also frequently been reported in other unusual positions, for instance, in the retroperitoneal space,[10] the vicinity of the suprarenal gland,[11] the pancreas,[12] or the kidney.[13]

Some investigators[14] claim to have seen *bilateral* parovarian cystomas.

It has been stated that cystic dilation of parovarian tubules is impossible because they do not possess any secretory *epithelium.* If its lining could secrete, it has been contended, the parovarium would always be cystically dilated.[9] This argument is not valid. If it were accepted we would also have to conclude that the lining cells of the peritoneum, the pleural cavity, the hydatid of Morgagni etc., are non-secreting, as these organs are usually not filled with large amounts of fluid. In all these cavities—as probably also in the tubules of the parovarium—there is usually a balance between secretion and re-

[1] *Tocheport* A48256/896, *Kossmann* A96841/899, *Podgoretski* A90251/04, *Waters* B9465/19.
[2] *Ten Teachers* B6383/38.
[3] *Gilbert and Sheorey* 82747/41.
[4] B6391/848.
[5] *Follin* A87814/850, *Broca* B6392/851, *Barth* A78022/851, *Verneuil* A87840/857, *Rokitansky* A70247/861, *Förster* A76963/863, *Waldeyer* A73013/870, A11808/870, A63430/871, *Gusserow* B6393/876, *Kossmann* A96841/899.
[6] *Krönig* A90246/01, *Lance and Theuveny* B6446/02, *Bouvier* A88801/02, *Chevrier* A88697/02, *Berkley* B6447/05, *Tagliavacche and Pastorini* B11340/29-30.
[7] *Souligoux* A91979/894, *Girard* B6445/894.
[8] *Doran* A40937/882-3, B6394/886.
[9] *Kossmann* A96841/899.
[10] *Pozzi* A70225/897, *Vanverts* A66932/11, *Ashhurst and McGuire* B11329/20, *Lapointe* B11334/22.
[11] *Mauclaire* A90247/12.
[12] *Monprofit* A90248/04, *Donoghue* A90240/06.
[13] *Aguirre and Oliver* A90272/04.
[14] *Chevrier* A88697/02, *Dauber* A90274/05.

absorption, so that fluid accumulation never becomes considerable. Under pathologic conditions, however, this is not necessarily so, and a decrease in absorption or an increase in secretion may lead to accumulation of fluid in these hollow organs. There is, furthermore, a great difference between mere fluid accumulation and actual neoplastic proliferation. Even if we assumed that cystic dilatation of parovarian tubules is not possible—an entirely unfounded assumption—this would not exclude the possibility that the organ may be the site of true cystic, adenomatous neoplastic growth.

On the inner surface of presumably parovarian cysts, *papillary proliferations* and sometimes even true papillomas have repeatedly been seen.[1] The occurrence of many smooth muscle fibers in the walls of such cysts and the presence of papillomatous proliferations on their inner surface led to the view[2] that most, if not all of these tumors, are derived from the oviducts and represent cystic accessory Fallopian tubes or tubal diverticula. While this may be true of some cysts described as "parovarian" it hardly applies to all of them. That the presence of smooth muscle cells does not necessarily exclude parovarian origin is explained below. With regard to the papillomatous proliferations, it must be kept in mind that according to the endosalpingiosis theory of similar ovarian tumors, such proliferations could be due to cyst formation in ectopic oviduct-mucosa islets. This problem will be discussed in more detail below, in the paragraph dealing with endosalpingiosis as a cause of parovarian tumorigenesis. Suffice it to say here, that we have no definite evidence that papillomatous proliferation of the epithelium cannot occur in parovarian neoplasms.

The fact that the walls of parovarian cysts usually contain *smooth muscle fibers* has led to many polemical discussions. Some investigators stated that the normal parovarian tubules are surrounded by connective tissue only, without any muscle coat,[3] but this has been contradicted by others.[4] It is very probable that the failure of early investigators to demonstrate smooth muscle in the walls of parovarian tubules was due to faulty histologic technic and that such muscle fibers do occur in the parovarium under normal conditions. Hence the argument that cysts whose walls contain smooth muscle fibers cannot be derived from the parovarium[2] is not tenable.

Some observers mentioned the structural resemblance of certain parovarian tumors with hypernephromas,[5] or adenomas.[6]

Many additional data concerning supposedly parovarian or "Wolffian" cysts will be found in the numerous relevant *case reports*.[7]

Wolffian Duct. Cysts of the horizontal, cranial part of the Wolffian duct are very rare.[8] The literature contains a number of supposedly relevant case reports,[9] but it is somewhat doubtful whether all these cysts were really derived from the Wolffian duct.

A number of early investigators expressed the opinion that the so-called *cystic fibroids* of the uterus are also derived from the Wolffian duct, occasionally perhaps from its distal (Gartner's duct) segment,[10] but others[11] considered them as Müllerian derivatives. It is highly probable that at least the majority, if not all, these cystic myomas are the result of endometriosis within fibroids.

Gartner's Duct. Gartner's duct is not infrequently the site of neoplastic growth. The Danish anatomist Gartner[12] and after him several other investigators[13] showed that in various mammals the remnants of the Wolffian duct are demonstrable all the way down to the vagina and the orifice of the urethra. This could be demonstrated both by injection of fluid into the Wolffian duct and by serial sections throughout its entire length.

It was later demonstrated that in the human fetus the lower part of the Wolffian duct, namely

[1] *Fischel* A70687/880, *Coblenz* A40334/881, *Doran* A70475/884, *Hume* A88736/884-5, *Killian* A90174/885, *Arima* A88834/899, *Pfannenstiel and Krömer* A64886/08, *Frankl* B9508/18, *Forgue and Crousse* A91555/25.

[2] *Kossmann* A96841/899.

[3] *Farre* B6396/, *Virchow* A77123/848, *Kölliker* A61174/867, *Waldeyer* A63430/871, *Popoff* B6397/893.

[4] *Gebhard* A88830/894, *Kossmann* A88832/894, B6432/894, *Ampt* B6395/895, *Pick* A88838/899, *Brunet* A88835/04.

[5] *Pettis* A90250/13.

[6] *Aschoff* A90238/899.

[7] *Lucas-Championnière* B6455/, *Labadie et al.* B6464/, *Verneuil* A87840/857, *Tait* B6461/883, *Moseley* A45100/888-9, *Villeneuve* A46606/892, *Souligoux* A91979/894, *Girard* B6445/894, *Mounet* B6462/895, *Johansen* A88673/895, *Laroche* A91370/896, *Park* A90249/896, *Legueu* A91406/896, A48312/896, *Peters* A90225/897, *Raimondi* A91372/897, *Castadena* B6444/897, *Coquelet* B6465/897, *Bouilly* A50918/898, *Baron* A50957/898, *Hartz* A90242/899, A90243/01, *Jeanbrau and Moitessier* A88713/00, *Mauclaire* A88466/01, *Lerivrain* A91371/03, *Sorel* A91435/03, *Sikora* B6456/03, *Cann* B6460/04, *Vanverts* A88825/05, *Rioms* B6457/06, *Lance* B6466/07, *Pfannenstiel and Krömer* A64886/08, *Cole* B6389/10, *Chamazon* B6463/10, *Luker* A93688/12, *Warthin* B11341/17, *Agostini* B6458/19, *Sappey and Tzélépoglou* A81800/19-20, *Gayet and Gauthier* B11331/22, *Binet and Fourche* A91505/23, *Loubat* B6454/23, *Madier and Nathan* B11335/24, *Sihol and Bourde* B11339/24, *Hinman et al.* B11333/24, *Giannelli* B11332/25, *Harris* A94671/26, *Stacy et al.* B7353/26.

[8] *Gilbert and Sheorey* 82747/41.

[9] *Löwenthal* A87815/890, *Klein* A87827/890, *Muscatello* A87832/892, *Amann* A90273/897, *Meusel* A50487/898, *Lewers* A91408/09-10, *Gudim-Levkovich* A90275/14, *Piette* B11338/23-5, *Schmid* A92780/32.

[10] *Breus* B6407/894, *Gottschalk* B6409/894, *v. Recklinghausen* B6405/895.

[11] *Schröder* B6413/, *Diesterweg* B6433/882, B6418/882, *Babes* B6417/883, *Ruge* B6414/889, B6415/889, *Kossmann* A96841/899.

[12] B6401/824.

[13] *Kobelt* B6402/847, *Follin* A87814/850, *Bullinger* A97853/897.

Gartner's duct, is also patent,[1] although subsequently this lower segment tends to become obliterated and more or less completely absorbed. In certain instances, however, remnants of Gartner's duct are detectable in the normal adult woman, and hence it is not surprising that the lining epithelium of the vestiges may be the site of neoplastic transformation. Since in the human fetus Gartner's duct is still clearly demonstrable, all the way down the mesometrial attachment of the uterus and vagina to the hymen, it is understandable, furthermore, that neoplasms of the duct may occur along this entire line. Many of the vaginal cysts, especially those found at the height of the cervix, are possibly of Gartnerian origin. The neoplasms of Gartner's duct may be benign small cysts (sometimes multiple cysts along the entire length of the mesometrial uterine attachment), adenomas, cystadenomas and indeed occasionally even malignant tumors of the carcinomatous type.[2]

In two interesting cases[3] Gartner's duct did not form a tumor, although it persisted in a patent condition during adult life. In one of these cases the duct could be penetrated by a probe and was patent all the way up to the kidney region. It produced about two ounces of fluid daily and in order to cure this condition an anastomosis had to be performed between the duct and the bladder.

Junctional or Rete Tubules. The junctional or rete tubules may be the site of para-ovarian cyst formation although more frequently they give rise to neoplasms which form a single anatomic unit with the ovary (e.g. rete adenomas and rete cysts of the ovary). Junctional cysts are usually lined by a simple, squamous epithelium and their walls consist of connective tissue only; smooth muscle fibers are absent.[4]

Paroöphoron. Cysts of the paroöphoron (parepoöphoron) are usually found near the uterus in that part of the broad ligament in which the normal paroöphoron is detectable. In most cases such cysts are lined by a columnar or cuboidal epithelium.[5]

The possibility that the paroöphoron may also be the source of cyst formation was probably first envisaged by Waldeyer.[6] Orth[7] made the surprising statement that "all the cysts of the broad ligament which resemble parovarian cysts, on whose wall however, the parovarian itself is still detectable" are of paroöphoric origin. Apparently he felt that if the normal parovarium is still present it could not have given rise to cyst formation, an assumption which is obviously not justified since it is quite conceivable that a cyst may form from part of this organ without destroying it entirely. The lack of characteristic histologic criteria makes it rather difficult to diagnose a cyst as being of paroöphoric origin and indeed some investigators doubt the possibility of cyst formation from this embryonic vestige.[8]

Accessory Fallopian Tubes and Diverticula of Fallopian Tubes. One of the most discussed histogenetic derivations of para-ovarian cysts is their development from Müllerian remnants, mainly accessory Fallopian tubes and diverticula of the Fallopian tubes. These two pathogenic possibilities are best considered conjointly, since in the case of such vestigial, incompletely developed structures it is impossible sometimes to differentiate between cysts arising from malformed accessory tubes or diverticula of otherwise normal tubes. It has often been claimed that the presence of tubal fimbria around a cyst necessarily proves its Müllerian origin, but this argument is hardly valid since para-ovarian cysts may grow into the vicinity of the tubal ostium and hence secondarily surround themselves with tubal fimbria.[9] The following are the main arguments in favor of the Müllerian origin of certain para-ovarian cysts:

1) duplications of the oviduct are commonly found in the embryo;

2) accessory tubal ostia are not infrequent;

3) blind tubal diverticula are often observed.[10]

These considerations—as well as the previously mentioned fact that many para-ovarian cysts contain a rather muscular wall and a lining with papillomatous excrescences, reminiscent of the Fallopian tubes—led to the belief that duplications and malformations of the Müllerian ducts frequently give rise to para-ovarian cyst formation.[11]

In some cases, derivation from accessory Fallopian tubes was quite clearly demonstrated.[12] Other investigators speak of *tubo-para-ovarian cysts,* that is cystic formations in the para-ovarian region which communicate with the lumen of the tube. It is not impossible that in these cases we are dealing with

[1]*Meyer* B6410/897, *Klein* A90264/897.
[2]*Freund* B6419/, *Veit* B6424/867, *Winckel* B6429/871, *v. Preuschen* B6425/877, *Gräfe* B6420/882, *Rieder* A90104/884, *Johnston* B6421/887, *Kümmel* B6422/888, *Poupinel* B6403/889, *Chalot* B6423/892, *Girerd* A88683/894, *Routh* A44730/894, A47433/895, *Zweigbaum* B6427/896, *Meyer* B6410/897, A90102/00, A90268/03, A90355/03, A90358/07, *Weber* B6428/898, *Klein* A90100/898, *Thumin* A90107/00, *Fredet* A90262/04, *Lewers* A91408/09-10, *Moukayé* B6411/22, *Tédenat* B6412/25. *Petridis* A92782/26, *Douay and Soimaru* B6400/26. *de Rouville* B6399/28, *Wagner* B6416/29, *Schmid* A92780/32, *Dvorzak* B6404/34, *Froboese* B6408/34, *Laffont et al.* B6406/35, *Danneel* B6398/35, *Rust* A92786/36, *Rockstroh* A92785/36, *Reeb* A92783/37, A92784/37, B21548/37.
[3]*Milton* A90103/893.
[4]*Muller* A52170/34, *Gilbert and Sheorey* 82747/41.
[5]*Gilbert and Sheorev* 82747/41.
[6]A63430/871, A11808/870, A73013/870.
[7]A10561/893.
[8]*Kossmann* A96841/899.
[9]*Roth* B6430/882, *Rossa* A91206/899.
[10]*Kossmann* B6431/, A96841/899, A70779/895, *Cole* A91376/12.
[11]*Handley* B13002/04, *Bell* B12974/04.
[12]*Handley* A91396/03, A91397/05.

cystically dilated tubal diverticula which communicate with the oviduct.[1]

In connection with para-ovarian cysts of Müllerian origin the reader is also referred to the discussion on *endometriosis* and *endosalpingiosis* as a pathogenic factor capable of para-ovarian cyst formation (see below). The so-called Wolffian duct neoplasms (usually cysts within uterine fibroids) have been discussed above, and it was stated there that most of them are probably due to endometrosis within uterine fibroids. It is well to remember in this connection, however, that in the older literature such instances have frequently been regarded as due to abnormal development of accessory Müllerian vestiges.[2]

Connective Tissue of Broad Ligament. The connective tissue elements in the broad ligament may give rise to independent para-ovarian tumors. Thus fibromas, lipomas, sarcomas, lymphangiomas, chondromas, myomas, etc. may occur in the para-ovarian region. These develop from pre-existing mesenchymal elements in the pelvic ligaments and their pathogenesis hardly requires a detailed discussion. For relevant data the reader is referred to the specific chapters dealing with each of these tumor types, which will be found immediately following those concerned with the corresponding ovarian tumors.

Secondary Para-Ovarian Tumors. Secondary para-ovarian tumors are by no means uncommon. They may be due to deposition in the para-metria of *metastatic foci* from primary neoplasms of the ovary or some other more distant organ.

Self-amputation of benign or malignant primary ovarian neoplasms often follows extensive torsion of their pedicle. Such free tumors may re-implant themselves at some distance from their original site and, not uncommonly, they are found in the parametria. Among other varieties *dermoid cysts,* which are very subject to torsion and self-amputation, are often found in the parametrium due to re-implantation (see chapter on Para-Ovarian Teratoids). Of course this does not mean that dermoid, or other teratoid tumors, could not be formed primarily from embryonic vestiges in the para-ovarian region.

In connection with the para-ovarian *adenofibromas*[3] and *adenomyomas*[4] of the literature, their possible interpretation as due to pelvic endometriosis should be considered.

Endometriosis and *endosalpingiosis* undoubtedly may lead to the formation of secondary para-ovarian tumors. According to the most generally accepted theory, endometrosis of the pelvic organs occurs as a result of regurgitation of endometrial cell groups through the oviducts and their re-implantation in the pelvic peritoneum. Endosalpingiosis could arise through a similar mechanism from regurgitated oviduct mucosa cells. It is readily understandable, therefore, that implantation of endometrial or endosalpingial cell groups in the para-ovarian region may lead to "neoplasms" which could be regarded as para-ovarian growths. Since endometriosis and endosalpingiosis are discussed in other chapters of this book, we need not consider them in great detail here. Suffice it to point out that unmistakable *endometriosis of the broad ligaments*[5] and *round ligaments*[6] have frequently been described, the latter sometimes as "*adenomyomas of the round ligaments*"[7] or "*adenofibromas of the round ligament*".[8] These lesions are often associated with generalized pelvic endometriosis and manifestly represent the same type of lesion.

On the other hand, there is no reason to doubt the possibility that some of these foci could originate from para-ovarian embryonic vestiges.

In one case an "adenomyoma" of the ovary itself was considered to be of parovarian origin.[9]

In an "*adenomylipoma of the oviduct*"[10] there was a direct transition between salpingiomatous and lipomatous tissue.

The possibility of *pseudomucinous* cyst formation within the para-ovarian embryonic vestiges has often been considered, because pseudomucinous cysts are occasionally—though not very commonly—found in this region.[11] It is probable, however, that these cysts are secondary tumors originating in the ovary, or perhaps in the alimentary tract, where primary pseudomucinous cysts are common.

The same pathogenic interpretation probably also holds in the case of a *serous racemose cystoma* which was described as "parovarian"[12] merely because the ovaries were intact and not connected with it. It is not impossible that such tumors could arise in the ovaries, forming pedunculated surface cysts which could become completely separated from the gonad, leaving the latter intact, and re-implant themselves

[1] *v. Ott* A46344/892. A44235/892.
[2] *Kossmann* A96841/899.
[3] *Cleveland* A88836/892, *Meyer* A83479/02-3, *Grigsby* A91557/24.
[4] *Pick* A88838/899, *Brunet* A88835/04, *Avoni* A91541/12, *Schwarz* A91357/20.
[5] *Dawson* B5693/31, *Stabile* B10368/37.
[6] *Hickel* B6810/23. *Michon and Compte* B10659/28, *Crousse and Anciaux* B5720/30, *Palazzo and Sammartino* B5682/30, *Marcus* B5743/31, *Haselhorst* B20273/32, *Ringsted* B6900/32, *Brodsky* B5774/33, *Kaulich and Gömöri* B20306/33, B5827/34, *Beck* B20332/36, *Fleming* A33597/39, *Dickinson* A33601/39, *Dannreuther* A36032/41, *Baraldi* B10876/42.
[7] *Cullen* A48386/896, A48333/896, A50528/898. *Blumer* A49163/898, *Sitzenfrey* A68449/10, *Frankl* A68489/11, *Hines* B16195/16, *Schwarz* B13406/17, *Broun* B9461/19, *Shaw* B7513/25.
[8] *Szili* B8879/02, *Slesareff* B12208/30.
[9] *Katzenstein* A62093/36.
[10] *Shaw* B8244/28.
[11] *Gillette* A76973/877, *Kossmann* A96841/899, *Mauclaire* A81117/04, *Forgue and Crousse* A91555/25.
[12] *Werth* A73082/895.

in the para-ovarian region. For these reasons para-ovarian growths, which imitate the structure of common ovarian tumors—especially those which are subject to self-amputation—should always be viewed with a critical eye, keeping in mind the possibility of re-implantation. (For a detailed discussion of the Para-ovarian common cystomas see chapter specifically devoted to them, following the chapter concerned with the corresponding ovarian cystomas).

Functional Pathogenesis. The functional pathogenesis of para-ovarian cysts is governed by factors about which no definite information is as yet available. The unusual post-natal persistence of embryonic vestiges in the para-ovarian region is probably of importance. It is not known, however, what factors are responsible for the neoplastic proliferation of these vestiges, which occur in some women but not in others. It has been considered that perhaps pelvic trauma—incidental to surgical intervention—or ovarian deficiency, may, occasionally, play a certain role, since several cases have been seen in women subsequent to ovariectomy.[1]

[1]*Chalier* A94016/25, *Vautrin* A94031/27, *Hamant and Cornil* A94023/27.

OVARIAN TUMORS IN GENERAL IN ANIMALS

Although spontaneous ovarian tumors are quite common among animals, comparatively little is known about them; in the great majority of the cases they have received little attention. Thus there are no monographs devoted specifically to the ovarian neoplasms of animals although a few such growths are mentioned in the reviews dealing with the spontaneous tumors of animals in general.[1] In most instances, relevant tumors are merely identified as "growths of the ovary"; even in the cases in which the histologic structure is briefly discussed, it is usually difficult to classify these tumors on the basis of the published data. Those ovarian neoplasms which definitely resemble specific blastomas of women, are discussed in conjunction with the latter in separate chapters which follow immediately upon those devoted to the corresponding tumors of human pathology. In the present chapter we shall limit ourselves to a general consideration of those ovarian tumors of animals, which are but incompletely identified.

In *fish* ovarian neoplasms, sometimes accompanied by ascites, have been noted in Cyprinus auratus[2] as well as in other types.[3]

In a *frog* an incompletely identified ovarian tumor has also been described.[3]

In *birds* ovarian tumors are comparatively common. They have been seen, for example, in the fowl[4] and the pheasant.[5] It will be recalled in this connection that in most birds, including the fowl, the right ovary is normally vestigial and may give rise to testis-like structures. This occurs with particular frequency in birds in which the fully developed left gonad is destroyed by disease or trauma. Under such conditions, a growth is found in the region of the right gonad which bears a striking resemblance to incompletely developed, or immature, testis tissue and may hence be difficult to distinguish from arrhenoblastoma- or seminoma-like growths. Such transformation in the gonads is often accompanied by (though not necessarily the cause of) external manifestations of "defeminization" and "masculinization". This subject has been discussed in great detail in connection with the effect of ovariectomy on the accessory sex organs and plumage, in the passages dealing with ovarian changes subsequent to partial ovariectomy (Sect. IV, Vol. IV), and in the chapters on Arrhenoblastoma and Seminoma (present volume). Suffice it to say that several instances of histologically incompletely identified ovarian tumors in fowl have also been noted to occur in conjunction with pseudohermaphroditic traits[6] (see also chapter on Ambisexuality in Sect. IV, Vol. VI).

In *cattle* an incompletely identified pedunculated ovarian neoplasm has been described in one instance[7] and a report has been published on the neoplasms encountered in federally-inspected establishment in Denver, Colorado.[8]

A peculiar ovarian blastoma in a *dog*[9] as well as a masculinizing tumor (perhaps an arrhenoblastoma) in a *horse*[10] have also been reported.

[1]*Schlegel* B16196/16, *Feldman* B11531/32, *Courteau* B127/35.
[2]*Davaine* A87516/866.
[3]*Plehn* B20949/24.
[4]*Engelmann* A29835/881, *May* B13231/06, *Eber and Kriegbaum* B5903/16, *McGowan* A67342/30.
[5]*Slater* A69758/878-9.
[6]*Berner* 6314/26, *Krediet* A31306/38.
[7]*Koller* A96785/28.
[8]*Davis Leeper and Shelton* B6578/33.
[9]*Pesce* B6612/05.
[10]*Krediet* A64230/31.

PLATE I

SCHEMATIC DRAWING ILLUSTRATING THE DEVELOPMENT OF THE OVARY AND PARA-OVARIAN STRUCTURES

(Modified after Keith and Doran B6387/10, Keith B6386/23, Ten Teachers B6383/38, Gilbert and Sheory 82747/41, Novak A59426/43).

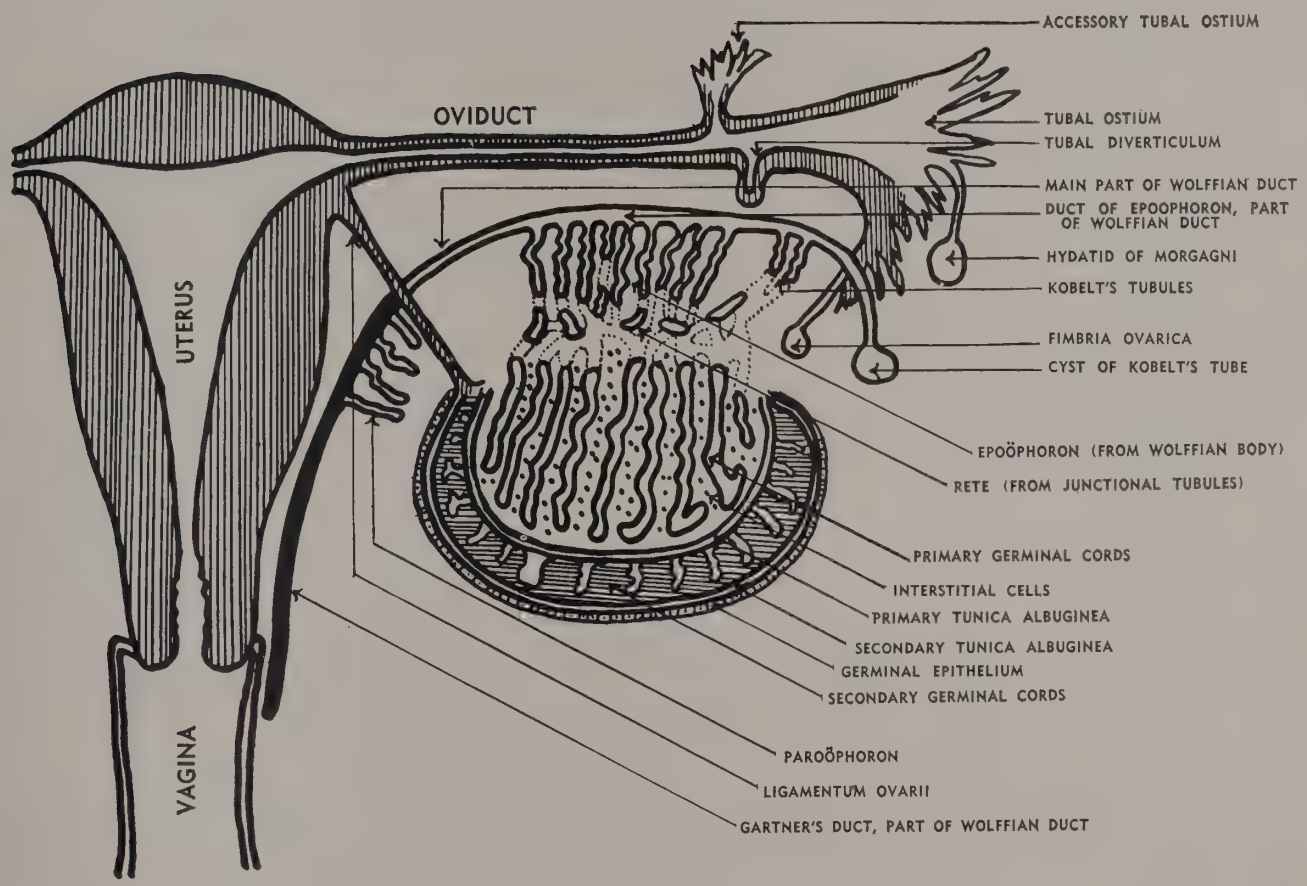

PLATE II

SCHEMATIC DRAWINGS ILLUSTRATING POSITION OF TRUE AND FALSE PARA-OVARIAN TUMORS

(Slightly modified after Forgue and Crousse A91555/25, Miller A18279/37).

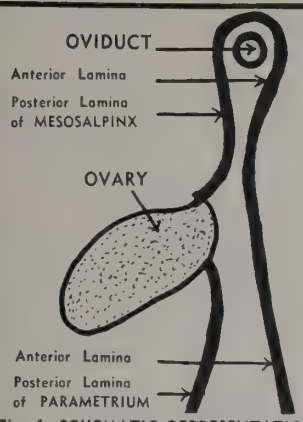

Fig. 1. SCHEMATIC REPRESENTATION OF THE NORMAL RELATIONS BETWEEN OVIDUCT, MESOSALPINX, OVARY AND PARAMETRIUM. (In all drawings of this table the heavy, solid line represents the peritoneal lining; the tumor area is indicated by shading and adhesions by interrupted shading).

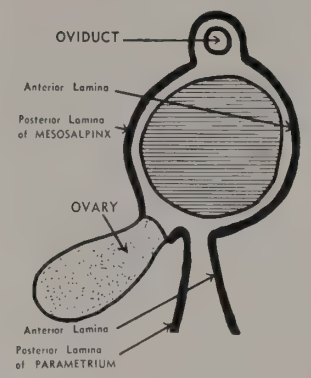

Fig. 2. PARA-OVARIAN INTRALIGAMENTOUS TUMOR IN MESOSALPINX.

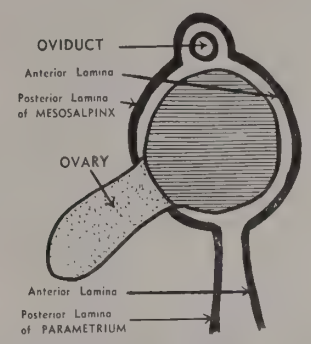

Fig. 3. OVARIAN TUMOR WITH INTRALIGAMENTOUS SPREAD INTO MESOSALPINX.

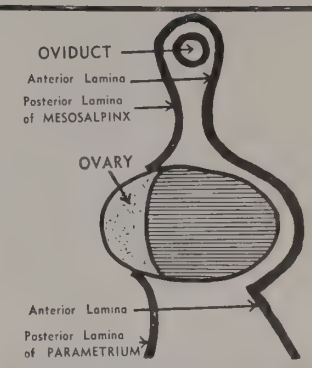

Fig. 4. OVARIAN TUMOR SPREADING INTO LOWER PART OF BROAD LIGAMENT; MESOSALPINX INTACT.

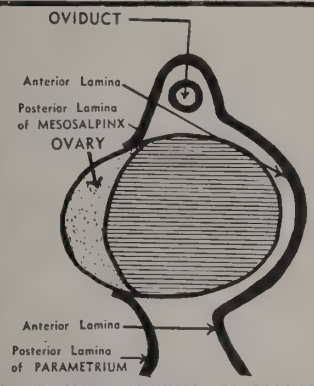

Fig. 5. OVARIAN TUMOR SPREADING INTO BOTH PARTS OF BROAD LIGAMENT.

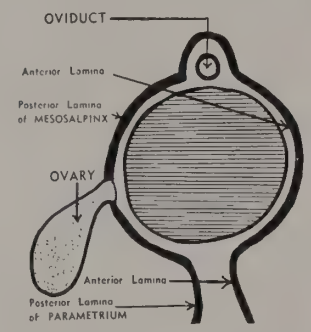

Fig. 6. PARA-OVARIAN TUMOR SPREADING INTO BOTH PARTS OF BROAD LIGAMENT.

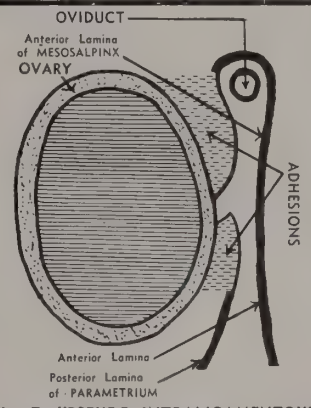

Fig. 7. "PSEUDO INTRALIGAMENTOUS" OVARIAN TUMOR ENCLOSED WITHIN A CAPSULE OF OVARIAN TISSUE. Adhesion between tumor-containing ovary and posterior lamina of mesosalpinx simulates conditions shown in Fig. 3; adhesion between ovary and posterior lamina of broad ligament simulates condition illustrated in Fig. 4, while adhesion to both these ligaments simulates condition indicated in Fig. 5.

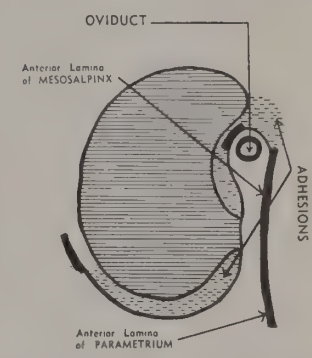

Fig. 8. "PSEUDO INTRALIGAMENTOUS" OVARIAN TUMOR (SO-CALLED "PAWLIK TUMOR"). Tumor (usually a cyst) adherent to mesosalpinx, parametrium and Douglas' space.

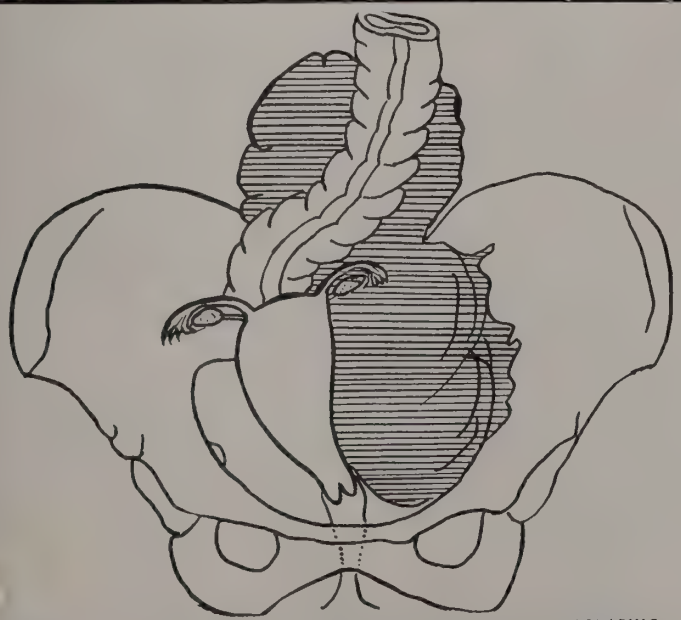

Fig. 9. ANTERIOR ASPECT OF PELVIS ILLUSTRATING TOPOGRAPHIC RELATIONS OF LEFT PARA-OVARIAN TUMOR, WITH INTRALIGAMENTOUS DEVELOPMENT, SPREADING INTO THE RECTO-SIGMOID MESENTERY. Note that the tumor lifts the uterus out of the pelvis and displaces it slightly to the right. Such tumors are likely to press upon the iliac vessels, ureter, and sigmoid colon.

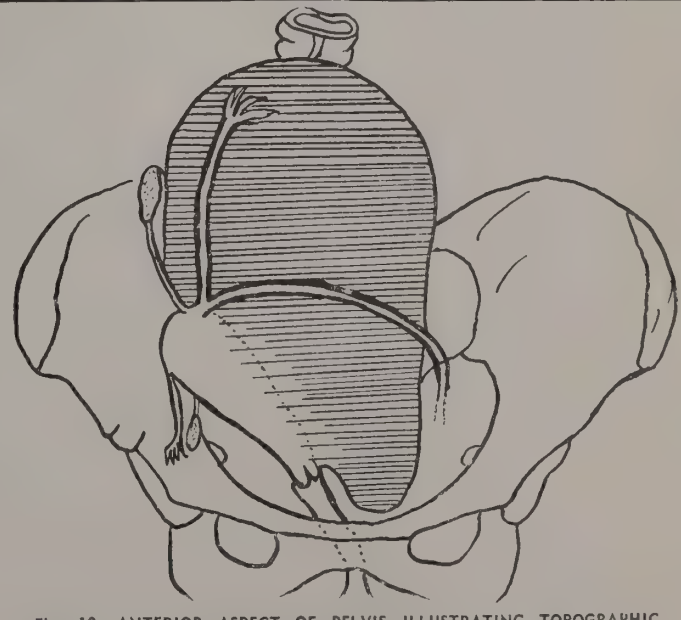

Fig. 10. ANTERIOR ASPECT OF PELVIS ILLUSTRATING TOPOGRAPHIC RELATIONS OF LARGE, INTRALIGAMENTOUS PARA-OVARIAN TUMOR DEVELOPING WITHIN THE BROAD LIGAMENT. Note elevation, dextroversion and elongation of uterus, with displacement of Fallopian tube and ovary; the tumor is situated just behind the round ligament and presses the rectum and sigmoid backwards against the bony pelvis.

PLATE III

PARA-OVARIAN TUMORS

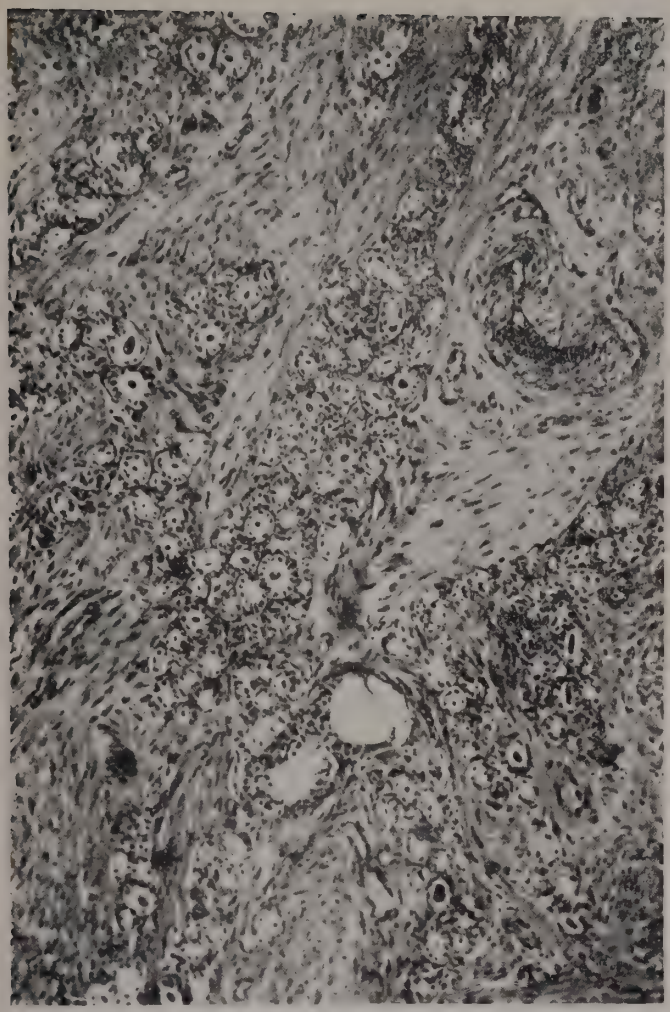

Fig. 1. ADENOMA OF GARTNER'S DUCT (after Reeb A92784/37). 37-year-old patient with slight bleeding from what appeared to be an erosion on anterior lip of cervix. Biopsy identified the tumor and was followed by complete hysterectomy. Operation revealed that tumor arose from upper lateral aspect of cervix and converged towards the mid-line, reaching its maximum development in the cervical stroma. Histologically, it consisted of small tubules lined by cuboidal cells which did not stain with muci-carmine: nuclei very rich in chromatin. This structure is quite characteristic of Gartner's Duct adenomas in general.

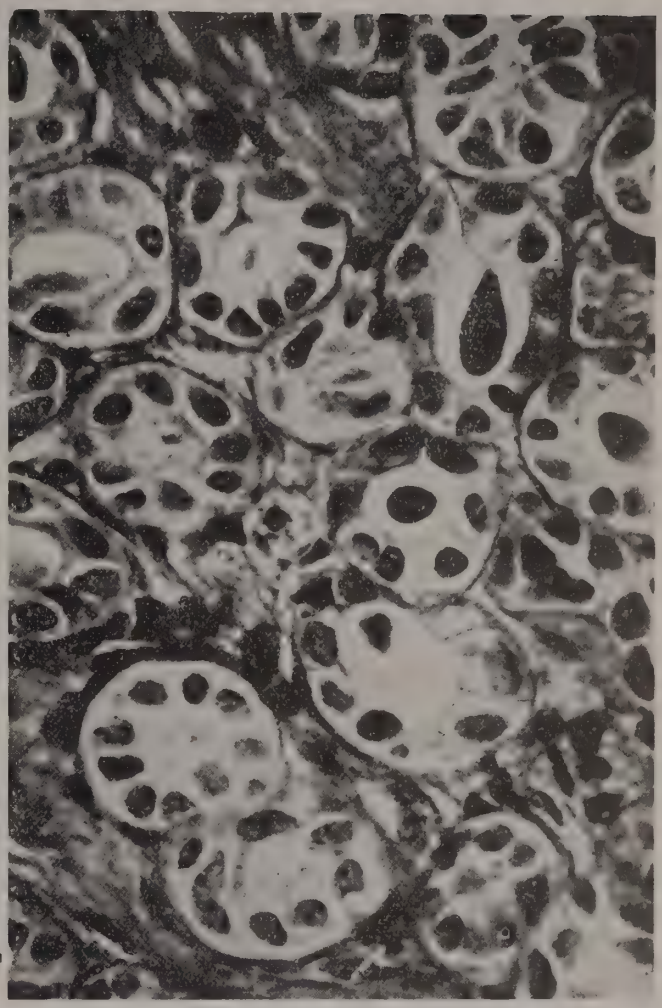

Fig. 2. ADENOMA OF GARTNER'S DUCT. Tumor shown in Fig. 1, under higher magnification. Note cuboidal cells with dark nuclei.

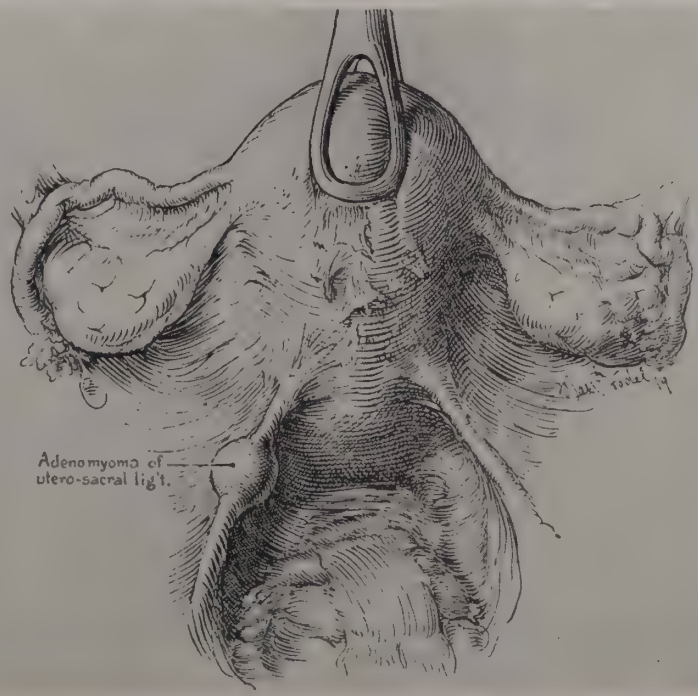

Fig. 3. ADENOMYOMA OF UTERO-SACRAL LIGAMENT (after Novak B109/44).

OVARIAN FOLLICLE CYSTS

(Note that, because of the great practical importance of metropathia hemorrhagica, the entire next chapter is devoted to it although in most cases this endometrial lesion is merely a consequence of persistent follicle cysts.)

SYNONYMS: Simple cyst of the follicle, persistent follicle, hydrops of the follicle.

REVIEWS

ENGLISH: Taylor A59480/36, Geist B6672/42.

FRENCH: Portes A95313/36, *Varangot* A96081/38, *Ferrier and Carbonnier* A96071/39, *Gennes* A96075/39, *Seguy* A98422/41.

GERMAN: v. Kahlden A81139/00, *Iseki* A92417/24, *Tietze* A64855/34, *Miller A18279/37, Schröder* B5046/39.

ITALIAN: Motta A59471/36.

DEFINITION

Follicle cysts are enlarged and usually abnormally persistent Graafian follicles. It is important to realize, however, that in many cases the lining cells of such cysts are not sufficiently characteristic to permit certain identification of granulosa elements; hence, confusion with other unilocular ovarian cysts may readily occur. It is not uncommon, furthermore, to find two or more follicle cysts in the same ovary. Thus, transitional types between multiple follicle cysts and so-called "small cystic degeneration of the ovaries" are formed and these may give rise to difficulties of classification. The fact that both follicle cysts and small cystic ovaries may elicit clinical manifestations of hyperfolliculoidism adds to the difficulty of clearly differentiating between these conditions. In this chapter we shall limit our discussion to those cases in which only one or a few follicles reach unusual proportions.

HISTORY

The simple follicle cyst has been known to pathologists and clinicians ever since 1848 when Virchow[1] attempted to differentiate it from other ovarian cysts. Most cases described in the old literature are not pictured in sufficient detail, however, to permit differentiation from unilocular serous cysts. Galabin[2] studied the "Limpid cystoma from Graafian Follicles." Under the heading of "simple cysts" Olshausen[3] describes as "Hydrops folliculorum Grafii" or "Hydrops ovarii' a condition which may be regarded as belonging to this category, although some of his cases were probably what we now describe as small cystic ovaries. Similar formations were reported by several other early investigators.[4] It was not until comparatively recently, however, that the follicle cyst could be delimited from other ovarian cystomas on a functional basis. This became possible because the follicle cyst exhibits a great tendency to produce excessive amounts of folliculoid hormones and through these, metropathia hemorrhagica as well as other signs of hyperfolliculoidism.[5]

PATHOLOGIC ANATOMY

The enormous clinical literature on metropathia hemorrhagica is in sharp contrast to the comparatively meager data concerning the morphologic structure of follicle cysts, although these are by far the most common cause of the above clinical syndrome. This is due mainly to the fact that surgical interventions are rarely indicated in pure forms of this disease and hence the pathologist can obtain but little material for the study of this ovarian lesion. Thus, among 466 cases of metropathia hemorrhagica studied by one author,[6] only 20 were available for systematic microscopic examination of both ovaries.

Macroscopically, these cysts were described as between "walnut" and "apple size". Miller[7] believes that their maximum diameter is about 5 cm. It is reasonable to assume that follicle cysts rarely become very large and even if they did, it would be difficult to diagnose them correctly due to pressure changes in their greatly distended walls.

Histologically, the granulosa is readily recognizable. It consists of several layers surrounded by a fine basement membrane, which in turn is enveloped by the theca interna. Occasionally, however, there are atrophic areas in the cyst wall which are lined by a flat epithelium but may be completely denuded of lining cells. Only rarely is there any widespread atresia of the granulosa.[8]

Among the 20 cases of metropathia hemorrhagica in one series,[6] 18 proved to have follicle cysts lined by a typical granulosa; one had a very recent corpus luteum cyst (rupture may have occurred before the uterus had time to manifest a progestational change), and only one case showed no evidence of a follicle cyst or recent corpus luteum formation. Further data

[1]A77123/848.
[2]A29245/879.
[3]A41468/886.
[4]*Birch-Hirschfeld* A17086/882-96, *Ziegler* A69397/884-02, *Neumann* A76203/886, *Nagel* A63609/888, *Winkel* A69392/890, *Steffeck* A43591/890, *Fehling* A69393/893, *Orth* A10561/893, *Fritsch* A69394/894, *Hofmeier* A69395/898, *Pfannenstiel* A7554/898, *Gebhard* A73657/899, *Martin* A78665/899, *v. Kahlden* A81140/00, A81141/00, A81139/00, *Vanwart* A81245/07.
[5]*Meyer* 49962/09, *Schröder* A7569/15.
[6]*Tietze* A64855/34.
[7]A18279/37.
[8]*Kermauner* A73104/32, *Tietze* A64855/34, *Miller* A18279/37.

concerning the morphology of follicle cysts will be found in the numerous published *case reports* although many of them represent merely macroscopic or superficial histologic studies.[1] One worker[2] estimated that there are one or two large follicle cysts in at least 60% of the metropathia hemorrhagica cases, while another author[3] regarded them as almost constant.

FOLLICLE CYSTS IN COMBINATION WITH OTHER OVARIAN TUMORS: Simultaneously with simple follicle cysts there may be found a *dermoid* cyst in the same ovary,[4] or *common serous cysts and papillomas* in the contralateral gonad.[5] Usually, however, simple follicle cysts receive so little attention if they occur in patients with other ovarian neoplasms, that they are not even recorded in the case reports.

INCIDENCE

Because of the inherent difficulties of a certain anatomic diagnosis, there are no adequate statistical data concerning the general incidence of this disease. We have every reason to believe, however, that metropathia hemorrhagica is usually caused by follicle cysts, and this endometrial disease is certainly very common. One investigator[6] claims that among 100 pairs of ovaries, obtained at random from routine autopsies, 77% had ovarian cysts, and that among these, 55% were simple follicle cysts. It is almost certain, however, that this astonishingly high percentage results from the inclusion of normal large follicles.

The same diagnostic difficulties prevent any large scale statistical analysis of the *age* incidence of follicle cysts. Metropathia hemorrhagica has a double peaked age incidence curve, with a first small maximum at or immediately after puberty, followed by a minimum between 31-35 years and a second very high maximum at or after the menopause, between 45 and 65 years.[7] It is very probable that disturbances in the hormonal interrelations between the pituitary and the ovaries are responsible for the high incidence of follicle cysts (the most probable cause of the metropathia) at the onset and termination of normal menstrual periods.

Several instances of follicle cysts have been described in newborn babies[8] in whom they are probably caused by "synkainogenesis", the transition of maternal (in this case gonadotropic) hormones from mother to embryo. In older children follicle cysts may produce the symptomatology of precocious pseudopuberty[9].

The development of follicle cysts during *pregnancy*, and under the influence of chorionepitheliomas and hydatidiform moles, will be discussed in the chapters devoted to the effect of these conditions on the ovary (see Sect. IV, Vol. IV and VI). It is probable that here again a disturbance of gonadotropic hormone production is responsible for the development of the cysts. (See also passage on pregnancy incidence in chapter on Metropathia Hemorrhagica).

It is not uncommon to observe the development of follicle cysts immediately following pregnancy during the *puerperium*,[10] a phenomenon reminiscent of the "post-partum estrus" of lower mammals.

PATHOGENESIS

v. Kahlden[11] claimed that the follicle cysts should be regarded as true adenomas formed from proliferations of the germinal epithelium. This concept is not acceptable[12] and has now been generally abandoned. According to the currently prevailing view, these cysts develop from fully-formed follicles and give rise to functional disturbances either because the follicle persists for an unusually long period[13] or because there is a continuous process of repeated follicle formation without luteinization.[14] Probably both these processes are of etiologic significance and, in any case, both would result in the syndrome of hyperfolliculoidism.

While the development of the cysts from follicles is well established, the functional mechanism which elicits them is still not fully understood. It is generally assumed that they are caused by a hormonal dysfunction; more specifically by a derangement of the normal sequence in the elaboration of follicle-stimulating and luteinizing gonadotropic hormones. This view is supported by the fact that metropathia hemorrhagica occurs most frequently at the beginning and at the end of normal menstrual life, and that women who have gone through a large number of pregnancies are especially predisposed.[7]

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[1]*Waldeyer* A73013/870, *Malassez and de Sinety* A29383/881, *Nagel* A7548/887, *Pozzi* A43584/890, *Pfannenstiel* A76283/890, *Schultz* A81291/01, *Delle Chiaie* A68648/03, *Meurer* A64991/05, *Disse* A92812/06, *Vanwart* A81245/07, *Pfannenstiel and Krömer* A64886/08, *Mulon* A93572/09-10, *Gaifami* A81657/13, *Saxon* A81108/14, *Goodall* A73686/19-20, A64763/20, *Colberg* A81651/23, *Fekete* A79279/27, *King* A62244/32, *Mengert* A31404/39.
[2]*Babes* A79243/24.
[3]*Shaw* A64838/29.
[4]*Treub* A70422/899.
[5]*Lippert* A64789/05, A76008/05, *Stübler and Brandess* A76588/24, A70975/25, *Flemming* A64219/31, *Kermauner* A64880/32.
[6]*Bufe* A96007/37.
[7]*Tietze* A64855/34.
[8]*Gerlach* A97063/38.
[9]*Meurer* A64991/05, *Coldberg* A81651/23, *Mengert* A31404/39.
[10]*Köver* A77009/04, *Miller* A18279/37.
[11]A81142/02.
[12]*Miller* A18279/37.
[13]*Schröder* A7569/15.
[14]*Meyer* 49962/09.

At one time it had been thought that follicle cysts are due to inflammatory lesions, especially to perioöphoritis, with excessive development of the connective tissue capsule around the ovary and consequent mechanical interference with follicle rupture. This view has now been generally abandoned, although it is not improbable that this mechanism is operative in the pathogenesis of small cystic degeneration of the ovaries. One author[1] reported a series of 167 cases of appendicitis among which 23 were accompanied by right-sided, and only 4 by left-sided retention cysts. He expressed the opinion that the "chronic oöphoritis resulting from the appendicial infection causes a sclerosing of the tunica albuginea, failure of the follicles to rupture when mature, hypersecretion of the follicular membrane and the resultant retention cysts". It is very probable from his description that, at least in some cases, he dealt with small cystic ovarian degeneration. His data give further support to the concept that close correlations exist between this latter condition and the simple follicle cysts.

It has been claimed[2] that hysterectomy, salpingectomy and unilateral ovariectomy predispose to follicle cyst formation. The effect of these interventions on the ovary in man and in experimental animals is discussed at some length in the corresponding parts of Sect. IV, Vol. IV. It is highly probable that all these interventions act on the gonad through the intermediary of a disturbance in gonadotropic hormone formation.

The possible role of a *hereditary* predisposition should also be kept in mind[3] although it has not been definitely established as yet.

CLINICAL COURSE

The repeated formation, or unusual persistence of follicles which fail to luteinize, causes symptoms of hyperfolliculoidism similar to those elicited by folliculomas. Depending upon the age of onset, follicle cysts may lead to precocious pseudopuberty or to the adult type of hyperfolliculoidism in which the leading symptom is metropathia hemorrhagica.

In children, follicle cysts cause *precocious pseudopuberty* with development of the mammary glands, growth of axillary and pubic hair, enlargement of the labia and precocious uterine bleeding.[4] Perusal of the purportedly relevant case reports indicates, however, that, at least in some cases, confusion with small cystic degeneration may have occurred. The psyche may remain infantile.[5]

In adult women the most prominent sign is *metropathia hemorrhagica*[6] often accompanied by the formation of *uterine fibroids*[7] or *endometriosis*.[8] In one series of 203 patients with internal endometriosis, follicle cysts were found in 22% of the cases.[9]

Although usually the resulting persistent follicular phase endometrium causes *metrorrhagias*,[10] sometimes it may lead to *amenorrhea*.[11] It must be kept in mind, however, that many other ovarian lesions can have the same effect. This is particularly true of the various types of folliculomas and of some cases of small cystic degeneration. But even certain ovarian tumors which have hitherto not been regarded as hormonally active (serous papillary carcinomas, Brenner tumors etc.) may, occasionally, elicit similar endometrial changes. (For a detailed description of metropathia hemorrhagica see next chapter).

Enlargement and tenderness of the *mammary glands*, sometimes accompanied by lactation, is common not only in children, but also in adult patients with follicle cysts and disappears after ablation of the latter.[12]

Whether *asthmatic spells* could occasionally be elicited by persistent follicles[13] is rather doubtful. It has also been claimed that hyperfolliculoidism may play a role in the pathogenesis of certain *psychoses*.[14]

COMPLICATIONS

As in the case of other ovarian cysts, those of the follicles may become complicated by *hemorrhage, abscess formation* and *torsion*. Such complications are discussed in the chapters specifically devoted to these changes (see Sect. IV, Vol. VI).

The comparatively frequent complication with *appendicitis*[1] has already been discussed in the part on pathogenesis.

DIAGNOSIS

The diagnosis of follicle cysts is usually made—at least presumptively—on the basis of clinical symptoms suggesting hyperfolliculoidism (e.g. precocious puberty, metropathia hemorrhagica). Yet certain differentiation from hormonally similar tumors (e.g. folliculomas) is impossible without biopsy.

Rupture of a persistent Graafian follicle may simulate *appendicitis*[15] and in rare instances a follicle cyst may give rise to confusion with normal *pregnancy*,[16] but this is unusual.

[1] *Weinstein* A64027/31.
[2] *Taylor* A59480/36.
[3] *Løvset* A96699/40, A99187/40.
[4] *Meurer* A64991/05, *Colberg* A81651/23, *Mengert* A31404/39.
[5] *Meurer* A64991/05.
[6] *Vanwart* A81245/07, *Meyer* 49962/09, *Schröder* A7569/15.
[7] *Whitherspoon* A29216/35, *Lepper et al.* A96507/38.
[8] *Whitherspoon* A29216/35, *Fallas and Rosenblum* A33798/40.
[9] *Frank and Geist* A56288/42.
[10] *Charbonnel and Ringebach* A97048/38, *Macau* A99602/40.
[11] *Bickers* 85346/44.
[12] *Lepper et al.* A96507/38.
[13] *Wagner* B5047/39.
[14] *Baruk et al.* A96068/39.
[15] *Ravdin* B7669/23.
[16] *Voigt* A52192/34.

PROGNOSIS

From the point of view of prognosis, a sharp distinction must be made between the neoplastic follicle cysts and the ordinary persistent follicles, which fail to luteinize, but rarely reach a considerable size and are disturbing mainly because of their uterine sequelae.

As stated above, in children follicle cysts elicit precocious pseudopuberty and if untreated they tend to persist and grow at an early age but, as we shall see in the part on Therapy, complete cure may be effected by their surgical removal.[1]

In typical cases of metropathia hemorrhagica *in pubertal or adult females* the prognosis is favorable, although in a few cases the intractable bleeding may result in fatal anemia unless suitable therapy is instituted. On the other hand, spontaneous recovery occurs not infrequently for reasons which are not as yet understood.[2] In two patients normal pregnancies ensued following mere therapeutic curettage.[3] Spontaneous cures are especially frequent in the pubertal and early post-pubertal cases.

An important consideration in connection with the prognosis is the possible development of *cancer* as a final outcome of prolonged endometrial hyperplasia. Most gynecologists are agreed that contrary to theoretical expectations, uterine carcinoma rarely develops in patients suffering from metropathia hemorrhagica; yet this possibility must be kept in mind (see Morphologic Characterization in chapter on Metropathia Hemorrhagica).

THERAPY

(See also Therapy of Metropathia Hemorrhagica). In cases with large cystic follicles, especially if these develop in children and cause precocious pseudopuberty, the best treatment is the surgical *removal* of the cyst which is usually followed by a return of the accessory sex organs to the infantile condition.[4] Small cystic follicles, on the other hand, should not be removed. *Puncturing of follicles* and *partial ovariectomy* have occasionally been reported to bring at least temporary relief,[5] but it must be borne in mind that partial ovariectomy is in itself conducive to cystic degeneration of the ovarian remnant and hence such interventions should be avoided whenever possible. *Complete ovariectomy* is unjustified except in postmenopausal cases.

In many instances *X-ray treatment of the ovaries* proved to exert a beneficial effect and this is especially indicated in postmenopausal cases. In young women, the danger of subsequent sterility is a contraindication of this treatment.[6]

The most popular treatment—especially in the case of comparatively small persistent follicles—is the consecutive administration of *folliculoid* and *luteoid hormones* to imitate a normal cycle.[7]

It has been claimed that certain follicular cysts are beneficially influenced by mecholyl (*choline* derivative) iontophoresis,[8] but further work along this line will be necessary before reaching a definite conclusion.

[1] *Mengert* A31404/39.
[2] *Tietze* A64855/34.
[3] *Fluhman* A63533/39-40.
[4] *Meurer* A64991/05, *Mengert* A31404/39.
[5] *Novak* A63534/41.
[6] *Kurzrok* A32392/37.
[7] *Kaufmann and Giesen* A97554/41, *Bickers* 85346/44.
[8] *Jacoby and Der Brucke* A97805/42.

METROPATHIA HEMORRHAGICA

Since the most important clinical manifestation of cystic and persistent follicles is metropathia hemorrhagica, this latter condition will be discussed in some detail in this chapter. It must be kept in mind, however, that in many of the clinical cases reported, the anatomic condition of the ovaries was not ascertained, and other ovarian diseases, which cause hyperfolliculoidism (e.g. folliculomas, small cystic degeneration), may induce similar endometrial changes.

SYNONYMS: Endometritis fungosa, chronic hyperplastic endometritis, endometritis cavernosa, endometritis ovarialis, hyperplasia endometrii ovarialis, hyperplasia endometrii pituitaria, endometritis glandularis, glandular hyperplasia of the endometrium, "Swiss cheese" endometrium, endometrial hyperplasia, endometropathia ovarigena, polypoid hyperplasia.

The designation "*anovulatory bleeding*" is not strictly synonymous as it is applied to various types of hemorrhage which are unaccompanied by ovulation whether a corpus luteum (atreticum) is formed or not The terms puberty, maturity and menopausal bleeding are often used to designate metropathia hemorrhagica if it develops during these periods of life.

The expression "*functional uterine bleeding*" is sometimes used as a synonym, although it may apply to a variety of other conditions as well. The designation "*adenomiosi uterina interna emorragica*" favoured by Italian workers, should only be applied if internal endometriosis (adenomyosis) and metropathia hemorrhagica develop simultaneously. "*Oestriosis*" has been used as a generic term which includes all manifestations of hyperfolliculoidism (Whitehouse A59075/43).

REVIEWS

ENGLISH: Cooke B5755/32, *Novak and Yui* A64817/36, *Winder* B20350/36, *Jeffcoate* A69531/37, *Kurzrok* A32392/37, *Newell* B10339/37, *Payne* A69532/37, *Hamblen* A99981/39, *Novak* A63534/41, B109/44, *Cullen* A98375/42, *Simms* A98549/42, *Millen and Shepard* A98384/43, *Hartman* B10838/44.

FRENCH: Seguy A62613/32, *Lobel* A96066/36, *Layani* B199/36, *Béclère* A95348/38, *Varangot* A97024/38.

GERMAN: Schickele and Keller 50329/12, *Schröder* A7569/15, A69533/19, *Meyer* 10521/20, *Adler* A69527/28, *Beckman* A69529/29, *Hofbauer* 6264/30, *Kleine* A99119/42.

HUNGARIAN: Kup A95371/38.

ITALIAN: Bertone A60034/36.

PORTUGUESE: Medina A51996/33, *Wolff* A53019/34.

SPANISH: Prestini A67256/30, *Garcia Amo* A96072/34.

DEFINITION

Metropathia hemorrhagica is a condition of the endometrium in which the changes, characteristic of the follicular phase of the cycle, are exaggeratedly developed. Usually the total height of the endometrium is far above normal, many of the glands are cystically dilated ("Swiss cheese" appearance), mitotic figures in the epithelial cells are plentiful and there is a great tendency to irregular, and more or less continuous bleeding. Not infrequently the uterus also shows other signs of hyperfolliculoidism such as endometrial polyps, epithelial metaplasia, fibroids or endometriosis.

HISTORY

It is of historic interest that metropathia hemorrhagica was known to pathologists for a very long time without being clearly differentiated from other types of irregular bleeding, because neither the histologic basis of the endometrial change nor its ovarian origin were understood. The earliest systematic report which I was able to find is that of Olshausen.[1] In 1875 this author gave a detailed description of the condition under the name of "endometritis fungosa" or "chronic hyperplastic endometritis". He also reviewed the still more ancient literature on the subject[2] but data published before his paper are too vague to be of real value. It is noteworthy, however, that in 1853 Nélaton[3] was the first to advise the use of the curette—which Récamier[4] had described a few years earlier—for the treatment of "fongosités utérines". However, this "brutal and dangerous" treatment was rather uniformly rejected by the medical authorities of that time.[5] Subsequently metropathia hemorrhagica attracted the interest of many pathologists, and a considerable literature, mainly descriptive, accumulated in which the age incidence, the type of uterine bleeding and the endometrial histology occupied a prominent position.[6]

It is of special interest that long before the normal correlations between the uterine and ovarian cycle were understood, clinicians suspected the ovarian origin of metropathia hemorrhagica.[7] As early as 1877 Kisch[8] stated that "in the climacteric the greatly thickened albuginea is a very tangible impediment to the growth and eventual rupture of the follicle" and he concludes "it appears that the thickening of the albuginea which prevents follicle rupture is the cause of the menstrual disturbances which occur at this age". In 1882 Brennecke[9] stated: "It may be assumed that from a follicle whose growth is thus inhibited there arise stimuli, long before eventual rupture occurs, which elicit a continuous reflex

[1] A64494/875.
[2] *Robert* A69523/846, *Nélaton* A69522/853, *Becquerel* A69521/860.
[3] A69522/853.
[4] A69518/850.
[5] *Aran* A69519/856, A69516/858, *Becquerel* A69517/859, A69520/859.
[6] *Bischoff* A69513/878, *Ruge* A69514/880, *Möricke* A69515/882, *Brennecke* A69499/885, *Franz* A3208/898, *Cullen* A69528/00.
[7] *Klebs* A71439/868-80.
[8] A69511/877.
[9] A3192/882.

hyperemia of the endometrium". Such insight into the utero-ovarian correlations is truly surprising if we remember that these statements were made long before anything was known about the existence of ovarian hormones.

It is undoubtedly the great merit of Schröder,[1] however, to have clarified the pathogenesis of the disease, showing that follicle persistence and lack of corpus luteum formation are responsible for the endometrical changes to which he gave the now almost generally accepted name "metropathia hemorrhagica".

PATHOLOGIC ANATOMY

Since in most cases of metropathia hemorrhagica the ovaries have not been examined histologically, a considerable part of the relevant material cannot be classified on an etiologic basis. There is good evidence, however, that the majority of patients suffering from metropathia hemorrhagica develop this condition because of persistent follicle cysts and defective corpus luteum formation. Hence, in this section we shall discuss the literature concerning metropathia, including data derived from patients in whom the ovaries were not directly observed.

MACROSCOPIC CHARACTERISTICS: In advanced cases, the endometrium is thickened with many polypoid excrescences. It is this appearance which suggested the term "endometritis fungosa" or "polypoid hyperplasia". Less frequently, the thickness of the endometrium may be normal, or even below normal, although it exhibits the characteristic histologic structure. The polypoid excrescences suggest a direct transition to true endometrial polyps which probably can also develop under the influence of hyperfolliculoidism.

For statistical data the reader is referred to the numerous published *case reports* dealing with metropathia hemorrhagica.[2]

MICROSCOPIC CHARACTERISTICS: The histologic appearance of the endometrium is so characteristic that it usually makes diagnosis comparatively simple. The endometrial glands are of uneven diameter, some being cystically dilated, while others retain their normal caliber. The *epithelium* is cuboidal or cylindric with hyperchromatic nuclei. It shows stratification only in the small glands where it is not subject to any considerable distention. Mitoses are numerous in the epithelium and may occasionally be found even in the usually abundant and dense stroma. All these phenomena are characteristic of hyperfolliculoidism in the absence of progesterone. Necroses in the endometrial lining are not infrequent, but their part in the causation of metrorrhagias is a matter of dispute; they are often associated with thromboses of the mucosa vessels. Many excellent descriptions deal with these histologic changes.[3]

Glycogen is usually absent.[4]

In a high percentage of the cases there is *endometrial edema*[5] not unlike that characteristic of the "endometrial moles" experimentally produced by the combined action of folliculoid hormone overdosage and uterine trauma in animals.

It has been stated that the *lymphatic accumulations,* which are normally prominent in the endometrium of the follicular phase, are especially well developed in women with metropathia hemorrhagica.[6]

Even the *cervical mucosa* participates to some extent in the proliferative changes characteristic of metropathia hemorrhagica.[7]

The occasional appearance of *secretory changes* in the epithelium[8] and *decidual transformation of the stroma* in patients suffering from what otherwise appears to be metropathia hemorrhagica has led to some confusion (see also chapter on Corpus Luteum Cysts and Tumors) Burch et al.[9] clearly state that "if these progestational changes are present one is not dealing with endometrial hyperplasia."

In the great majority of cases, the appearance of the endometrium is evidently benign, but sometimes there is such marked glandular proliferation that *adenoma-like structures* result; these may be mistaken for cancer. The frequent association of metropathia hemorrhagica with *endometriosis* interna and *fibroids of the uterus* has also been noted in women with follicle cysts.[10] Among 260 cases of internal or external endometriosis of one series, 14.2% were associated with follicle cysts, 10.7% with "endometrial hyperplasia" and 8.0% with endometrial

[1] A7569/15.

[2] *Ferguson* A95005/24, *Babes* A93987/26, *Marino* A95026/26, *Criscitielle* A93998/28, *Hintze* A95013/29, *Morilla Una* A95028/30, *Tietze* A95041/30, *Fluhmann* A95006/31, *Franck* A95007/31, *Hofbauer* A95016/31, *Adler* A93986/32, *Massazza* B20281/32, *Cornil and Mosinger* A93997/33, *Holliday* A95017/33, *Moulonguet and Gasne* A95029/34, *Farthing* A95003/34, *Ingleby* A95019/34, *Goecke* A95008/35, *Pazourek* A95035/35, *Breipohl* A93990/36, *Blair* A93989/36, *Hamblen and Thomas* A95010/36, *Henrichsen* B10319/37, *Payne* A95033/38, *McNamara* A95025/38, *Osathanondh* A95031/38, *Rocmans* A95038/38, *Shields* A95040/38, *Fels* A95004/39.

[3] *Schröder* A7569/15, 41431/24, *Seitz* A89644/22, *Westphal* B6991/23, *Novak and Martzloff* B20618/24, *Shaw* A64838/29, *Fluhmann* A94363/29, B5648/29, 58684/31, *Novak* A74155/33, *Cornil and Mosinger* B20296/33, *Burch and Burch* A64739/33, *Burch et al.* 54581/34 *Ingleby* B5825/34, *Lepper et al.* A96507/38, *Kotz and Parker* 76825/38, *Cooray* B5072/40, *Masshoff* A99681/41.

[4] *O'Leary* 28797/29.

[5] *Derichsweiler* B5814/34.

[6] *Mönch* B20617/18.

[7] *Sjövall* A97314/38.

[8] *Gruner* A99113/42.

[9] 54581/34.

[10] *Massazza* B20281/32, *Derichsweiler* B5814/34, *Lepper et al.* A96507/38, *Henderson* A37331/41.

polyps.[1]

Especially on the exposed surface part of the polypoid growth, squamous *metaplasia* of the epithelium is not infrequent, a fact which adds to the difficulty of distinguishing some of these lesions from endometrial carcinomas.[2]

Transition of metropathia hemorrhagica to true uterine *cancer* may also occur,[3] but it is rare except in post-menopausal cases.[4] In one[5] series, the incidence of superimposed carcinoma was only 2.4%. The possibility of such malignant transformation must be considered when deciding about the therapeutic procedure to be employed.[6] That this danger really exists in hyperfolliculoidism, is best shown by the numerous instances of uterine cancer following prolonged metropathia hemorrhagica in patients with folliculomas, (see chapter on Folliculomas). It should also be kept in mind that there is considerable experimental evidence indicating the possibility of producing malignant tumors through prolonged treatment with folliculoid hormones.

INCIDENCE

Metropathia hemorrhagica is one of the most common complaints in a gynecologic practice. It may occur at any *age* (e.g. as a result of folliculoma development) but the common type which is caused by persistent follicles tends to occur at puberty in the form of the so-called "puberty or juvenile metrorrhagias"[7] and at, or soon after, the menopause as "climacteric or senile metrorrhagias.[8] In a series of 114 postmenopausal women who suffered from anomalous bleeding, the incidence of metropathia hemorrhagica was 7.0%.[9] Both these conditions will be discussed in detail in Sect. IV, Vol. VI, dealing with Ovarian Diseases other than Tumors. Suffice it to say here, that at the beginning and at the end of the normal child-bearing period of life the correlation between pituitary and ovarian secretion is often disturbed so that follicles tend to persist and corpora lutea fail to form. As a result of this the endometrium is long exposed to the unopposed effect of folliculoid hormones and metropathia hemorrhagica is the result.

The *pregnancy* incidence of metropathia hemorrhagica is naturally very low because both the ovarian (lack of ovulation) and the uterine (lack of progestational proliferation) changes characteristic of this condition are unfavorable for the fertilization and nidation of an ovum. It is possible, however, that a woman who chronically suffers from metropathia hemorrhagica and persistent follicles could sporadically ovulate and subsequently form a sufficient amount of luteoid hormone to permit nidation. This is the only explanation we can offer for the occasional occurrence of pregnancy in these women.

It is noteworthy that in a series of 18 women who suffered from metropathia hemorrhagica, subsequently 8 became pregnant—some of them repeatedly—and one had a tubal gestation.[10] Of course, once pregnancy is established the endometrium changes its follicular phase character and becomes progestational.

In a few instances metropathia hemorrhagica has also been observed during the *puerperium* following a normal gestation.[11]

PATHOGENESIS

It would not be pertinent to give a detailed account of the pathogenesis of all types of metropathia hemorrhagica in this section. Yet to complete the picture it may be mentioned that *corpora lutea have only rarely been found* in women suffering from this disease[12] and it is reasonable to assume that even in some of these cases the corpora lutea were either too recent or too old to be functionally important. It has also been claimed, in an effort to explain such cases, that chronic follicular hormone stimulation renders the endometrium insensitive to the corpus luteum hormone.[13]

Shaw[14] held the view that "the polypoidal endometrium reacts upon the ovaries to produce an inhibition of follicle ripening or of ovulation or of full formation of the corpus luteum". This theory has had to be abandoned, however, since several experimentors[15] *produced typical "Swiss cheese" endometrium in animals overdosed with folliculoid hormones* and Kaufmann[16] reproduced it in castrate women by treatment with folliculoids.

There is a high incidence of metropathia hemorrhagica in women who had formerly undergone unilateral ovariectomy.[17] This is of interest in connection with the observation that *partial ovariectomy*

[1] *Fallas and Rosenblum* A33798/40.
[2] *Umeda* A95045/25, *Momigliano* A93983/28, *Engelhard* A93981/35, A93980/35, *Aschheim* A93979/38.
[3] *Fluhmann and Stephenson* B6103/29, *Novak and Yui* A64817/36, A95030/37, *Mazzola* A95027/38, *Kotz and Parker* 76825/38, *Salerno and Marelli* A95039/39, *Rodrigues* B10041/39, *Fernandes* A98381/42.
[4] *Schröder* A7569/15, *Cullen* A94364/28, *Hintze* A95013/29, *Mack* A68101/29, *Novak* A74155/33, *Tietze* A64855/34.
[5] *Payne* A69532/37.
[6] *Taylor* A64851/32.
[7] *Neumann* B15313/37, *Ten Teachers* B6383/38.
[8] *Treite and Pallos* A96646/40, *Rochat* B10142/43.
[9] *Schwartz* A98385/43.
[10] *Büttner* A63897/42.
[11] *Tietze* A64855/34.
[12] *Meyer* B8488/20, *Novak and Martzloff* A64818/24, *Babes* A79243/24, *Shaw* A64838/29.
[13] *Meyer* B8488/20.
[14] A64838/29.
[15] *Burch. et al.* 44156/31, B5754/31, *Wolfe et al.* 3716/32, *Burch and Burch* B20311/33, *Zuckerman and Morse* 54682/35, *Lipschütz* B15607/36.
[16] 4533/33.
[17] *Graves* A94365/30.

causes the formation of persistent cystic follicles in the remaining ovarian tissue (see Sect. IV, Vol. IV).

While there is still a good deal of controversy concerning the pathogenesis of this condition, most investigators agree that *metropathia hemorrhagica is an endocrine disease* conditioned by abnormalities in the elaboration of gonadotropic hypophysoid hormones, which in turn cause excessive production of folliculoid hormones by the ovary; this is usually associated with follicle persistence.[1]

It has been claimed that *syphilis,*[2] *abortions and pregnancies,*[3] *heredity,*[4] *ascorbic acid deficiency*[5] and *seasonal influences*[6] play important roles in the pathogenesis of metropathia, but this is still subject to confirmation.

CLINICAL COURSE

The clinical symptomatology of metropathia hemorrhagica is usually dominated by the irregular and often persistent *uterine bleeding.* The loss of blood may take the form of a continuous bloody-mucoid discharge with occasional exacerbations which imitate an irregular menstrual rhythm. In other cases, the bleeding is definitely periodic, lasting two or more weeks at a time and being followed by one or more weeks of amenorrhea. Occasionally there may be persistent, severe bleeding with the formation of clots and in some instances the loss of blood eventually leads to fatal anemia. It is especially noteworthy that these menstrual disturbances are *rarely accompanied by dysmenorrhea.* The abnormal bleeding may start with the first menstrual period at puberty, but usually the full development of the condition is preceded by a series of irregular periods. The menopausal type may begin immediately after the termination of normal menstrual periods or following an interval of amenorrhea. The transitory conditions of "puberty metrorrhagias" and "menopausal metrorrhagias" are probably due to temporary predominance of follicle formation with a resultant transient type of metropathia hemorrhagica. According to one investigator[7] about 15% of the metropathia patients suffer from *oligo- or amenorrhea.* It appears that the so-called "Swiss cheese" type of endometrium is not in itself responsible for the hemorrhages and it is probable that accompanying vascular changes are the actual cause of the blood loss.[8]

The ovum is not discharged from the follicle cysts and the endometrium is not suitable for the implantation of ova which may have come from still normal follicles. Hence this condition is almost invariably accompanied by *sterility*[9] (see, however, passage on pregnancy incidence above).

The *vaginal smears* of women with metropathia hemorrhagica are characterized by a large number of small nucleated cells and large flat cornified elements with pyknotic nuclei, characteristic of a high folliculoid hormone level.[10]

DIAGNOSIS

Several *reviews*[11] deal specifically with the diagnosis of metropathia hemorrhagica.

Upon *physical examination,* the uterus is usually enlarged and hard, but if bleeding has persisted for a long time it may become "flabby". It is mobile and in a position of anteversion and anteflexion. The parametria are free, but the ovaries are frequently enlarged, even though the individual cysts are rarely large enough to be palpable.[12]

For the diagnosis of metropathia hemorrhagica, endometrial *biopsy*—preferably taken with one of the specially designed suction curettes—[13] plays the most important role. The histologic criteria of the endometrial lesion have been discussed in the part on Pathologic Anatomy. In very young girls, in whom there is no gross pelvic change and biopsy is inadvisable, diagnosis may be aided by a past history of irregular periods at, or immediately after, puberty. The uterus is usually enlarged but only during the active bleeding period and it regresses to approximately normal size in the amenorrheic intervals.

Hormonal studies reveal that the presence of folliculoids and F.S.H. in the blood and urine are extremely variable in patients suffering from metropathia hemorrhagica. Hence they are of little diagnostic value[14] except in the case of large, tumor-like, follicle cysts which lead to excessive urinary folliculoid elimination.[15] Those interested in this subject will find additional relevant data in the section on the hormone content of blood and urine (Sect. IV, Vol. V).

From the *differential diagnostic* point of view it is important to remember that *carcinoma of the*

[1] *Ramirez* A64718/29, *Szarka* A61736/33, *King* A95021/33, *Tietze* A95044/34, *Neumann* B15313/37, *Limburg* A95023/38, *Honermeier* A95018/38, *Sage* B20243/38, *Tscherne* A99239/40.
[2] *Kreis and Rigaut* B5676/30.
[3] *Heitagress* A95011/38.
[4] *Mazza and Emanuel* B15304/36.
[5] *Bonilla* A98379/42.
[6] *Schmitz and Cliever* A99586/42.
[7] *Payne* A69532/37.
[8] *Burch et al.* 54581/34, *Kurzrok* A32392/37, *Novak* A63534/41, *Bickers* 85346/44.
[9] *Lane-Roberts et al.* A63535/39.
[10] *Traut and Papanicolaou* 82645/42.
[11] *Burch* B20351/36, *Ten Teachers* B61383/38.
[12] *Tietze* A64855/34, *Kurzrok* A32392/37.
[13] *Klingler and Burch* B20279/32, *Burch et al.* 54581/34.
[14] *Burch et al.* 54581/34, *Kurzrok* A32392/37.
[15] *Mengert* A31404/39.

fundus is often difficult to distinguish from metropathia hemorrhagica because the persistent irregular bleeding is characteristic of both conditions. Furthermore, both these lesions tend to develop at or immediately after the menopause. Recurrence of comparatively normal cycles separated by periods of irregular bleeding is more characteristic of metropathia, but only biopsy specimens can allow definite differentiation. Even the histologic structure of the endometrium may leave some doubt and in the case of uncertainty, especially in menopausal women, it is advisable to be cautious and to recommend complete hysterectomy.[1]

Cervical carcinomas are palpable and visible at an early stage of their development and cause completely irregular bleeding from the onset. Hence these are not likely to be confused with metropathia hemorrhagica.

Polyps, if situated within the cervix, are often visible at an early stage and tend to cause bleeding immediately after sexual intercourse or physical strain. Intra-uterine polyps are difficult to distinguish from metropathia without biopsy and even histologically there is sometimes little difference between the polypoid type of metropathia and large individual endometrial polyps.[2] Probably there is no essential difference between these two disease entities and it is rather likely that large polyps develop from a folliculoid-sensitized endometrium under the influence of local stimuli just as placentomas develop from a progesterone-sensitized uterine mucosa.

In the case of *incomplete abortion* the uterus is soft and large and the past history suggests a previous pregnancy. A high gonadotropic hormone (L.H.) content in the urine, if demonstrable, is almost certain evidence of placental remnants, although occasionally the F.S.H. titer of the urine may be high in metropathia, and in many bioassay technics L.H. is not readily distinguishable from F.S.H. In postabortal endometritis, the blood loss is usually associated with the normal periods and often there is fever.

Submucous myomas initially cause prolonged and excessive bleeding; after a certain time this is followed by some blood loss soon after the normal menstruation and later more or less irregular intervals between the periods. Only after a considerable period of growth do such myomas induce continuous persistent bleeding. It must be kept in mind, however, that fibroids and metropathia hemorrhagica often co-exist.[3] According to one worker,[4] fibroids are found in 35% of all metropathia cases and metropathia is detectable in 17% of all women suffering from uterine fibroids. Others[5] expressed the opinion that the frequent association between metropathia hemorrhagica and uterine fibroids could be due to a common pathogenic mechanism inasmuch as both conditions may result from hyperfolliculoidism. This view appears to receive further support from experimental work indicating that fibroid-like uterine growths can be produced in laboratory animals by continued folliculoid hormone overdosage (see chapter on the effect of folliculoids on the uterus in Sect. IV, Vol. III).

From the preceding discussion it is evident that endometrial polyps and fibroids may also be manifestations of an excessive endogenous folliculoid production, but the evidence now available is not sufficiently conclusive as yet to regard them as definitely endocrine diseases. Hence, it does not appear justified at this time to discuss the entire relevant literature in this Encyclopedia.

PROGNOSIS

Spontaneous cures and recurrences are not infrequent. In other cases, the more or less continuous bleeding is followed by periods of complete amenorrhea lasting several months or even years. It should be kept in mind that even during these prolonged amenorrheic periods the endometrium retains its typical cystic glandular character.[6]

THERAPY

The therapy of metropathia hemorrhagica has been the subject of many *reviews.*[7] In the average case, and especially in preclimacteric women, the endometrium should first be removed by *curettage.* Usually this in itself brings only temporary relief, but it is necessary for diagnostic purposes and it increases the efficacy of subsequent endocrine therapy as it eliminates the pathologic tissue. Quite frequently, however, even mere curettage effects a permanent cure.[8] In one series of observations[9] following simple curettage, recurrences were seen in 67.2% of the women under 35 years and in 36.3% of the older patients; but such statistics are difficult to evaluate. Their results depend largely upon the criteria used by the different surgeons to select cases suitable for this type of therapy. Except in intractable postmenopausal hemorrhages and in those in which the possibility of cancer is difficult to eliminate, *hysterectomy* or "*defundation of the uterus*" should not be performed to check metropathia hemorrhagica although these methods had their proponents.[10]

[1] *Novak* A63534/41.
[2] *Berezin* B10622/36.
[3] *King* A60661/33.
[4] *Payne* A69532/37.
[5] *Witherspoon* A61740/33, *Witherspoon and Butler* A53018/34.
[6] *Novak* B109/44.
[7] *Hamblen* A36671/39, B125/45, *Machado* A97403/40, *Novak* A63534/41, B109/44, *Hoffmann* B6643/44.
[8] *Koster* A95022/37, *Fluhmann* A63533/39-40.
[9] *Tietze* A64855/34.
[10] *Hertzler* B10638/28.

Partial resection of the ovary[1] has been practiced in order to remove the source of excess folliculoids. In the light of contemporary knowledge this intervention is not recommendable, since we know that the ovarian remnant tends to become cystic after partial ovariectomy even in normal individuals (see part on Pathogenesis).

X-ray treatment of the pituitary has been suggested as a means of inhibiting its hormone production and consequently its effect on the ovary.[2] Since the dosage is difficult to determine, this therapy is fraught with the danger of eliciting permanent damage.[3] *X-ray castration,* on the other hand, is not dangerous and yields almost 100% cures; hence, this technic is highly advisable if the patient is past the menopause or not desirous to have children.[4]

The *radium* treatment of metropathia hemorrhagica is usually likewise inadvisable,[5] although it is claimed that in intra-uterine application of 200-400 mg. hours, 80% of the adult patients secure satisfactory reduction of flowing without experiencing premature menopause.[6]

The method of choice is *endocrine therapy.*[7] In young girls this should be administered without preliminary curettage, whenever possible, since the latter often causes severe mental upset at this age. In adult women, on the other hand, it is well to remove the pathologic endometrium before the administration of hormone therapy. This precaution is particularly indicated whenever polypoid excrescences assume large dimensions. If curettage is to be avoided it may be well to give *testoid compounds* for a short period with the view of obtaining involution of the endometrium instead of its mechanical removal. Such therapy must be limited to the minimum absolutely necessary, in order to avoid virilization. It should be kept in mind, however, that some prominent gynecologists are strongly opposed to the use of testoid compounds in females regardless of what may be its supposed indication.[8]

The most recommendable treatment is to administer *progesterone* in adequate doses (up to 20 Rb. U/day) for two weeks at a time in order to substitute for the lack of endogenous corpus luteum hormone production.[9] These progesterone treatment periods must be separated by two weeks of rest, during which the endogenous folliculoids have time to develop a proliferative endometrium. It is true that even this therapy is merely symptomatic since it deals only with the result of the ovarian change and does not prevent follicle persistence. It may be stated, however, that for reasons which are not as yet quite clear, in many instances intermittent progesterone therapy re-establishes the normal interrelations between the ovary and pituitary and thus results in a more or less permanent cure. In the comparatively rare cases of metropathia with amenorrhea, alternate folliculoid and luteoid treatment has been recommended. Thus 5.0 mg. of stilbestrol daily for 10 days supplemented with 5.0 mg. of progesterone during the last 5 days was followed by uterine bleeding within 3-4 days after discontinuation of treatment. This procedure may be repeated once monthly to imitate a cycle, but often spontaneous menses are re-established at least for some time.[10]

Short treatment with very high doses of *folliculoids* —the so-called "folliculin shock treatment"—has also been attempted[11] but does not enjoy great popularity.

A more rational therapy will only be possible when the various *gonadotropic hormones* become available in a pure form. In the past these have not given very encouraging results.[12] More recently it has been claimed that *prolactin* is beneficial in "functional bleeding,[13] but it is not known how many of the women so treated actually suffered from metropathia hemorrhagica.

Among other therapeutic measures occasionally attempted, we may mention *diathermy,*[14] *placental blood transfusion*[15] and *ascorbic acid* administration.[16]

For detailed data concerning the action of various hormones on metropathia hemorrhagica, consult volume on Ovarian Diseases other than Tumors where this problem is discussed in conjunction with the endocrine therapy of other menstrual anomalies.

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[1]*Engl* B7471/25, *Henkel* A97769/28, *Cuizza* B5956/29.
[2]*Spack* B10481/37.
[3]*Kurzrok* A32392/37.
[4]*Novak* B109/44.
[5]*Reynolds* B10362/37, *Pastorini and Irigoyen* A98008/43.
[6]*Keene and Payne* B14523/33, B14524/37, *Hamblen* B125/45.
[7]*Gram* B20714/26, *Kraul* B5488/38, *Giudici* A98944/39, *Vöge* A99768/41.
[8]*Hamblen* B125/45.
[9]*Clauberg* A96319/36, *Allen and Heckel* A98134/43.
[10]*Bickers* 85346/44.
[11]*Uceida Losada* A98386/42.
[12]*Damm* A95001/35, *Jürgens* B15297/36, *Jeffcoate* A69531/37, *Dahl-Iversen and Jorgensen* A93999/37, B20186/37, *Moricard and Palmer* B20142/38, *Rydberg* B20242/38, *Vöge* A99768/41, *Hamblen* B125/45.
[13]*Goldzieher* B9422/45.
[14]*ten Berge* B5773/32.
[15]*Pastorini et al.* A98012/43.
[16]*Giuffrida* A97221/39.

OVARIAN FOLLICLE CYSTS AND METROPATHIA HEMORRHAGICA IN ANIMALS

Persistent follicle cysts are quite commonly found in the ovaries of animals. They may lead to endometrial hyperplasia, similar to the metropathia hemorrhagica of women.[1] It will be recalled that chronic treatment with various natural and artificial folliculoids has been shown to elicit similar uterine changes in various types of laboratory animals (see Sect. IV, Vol. III); hence, it is proven that the endometrium of species which do not menstruate, is also subject to this change. It will also be kept in mind that many of the cystic formations found in the ovaries of animals (see chapter Common Cysts in Animals) may have been follicular retention cysts. This appears probable especially in view of the fact that in so many instances these ovarian cysts produced nymphomania or other signs of hyperfolliculoidism.

A *cat* with prolonged estrus, which lasted for 6 weeks, was shown at autopsy to possess several large cystic follicles in the ovaries.[2] In another similar instance, follicle retention cysts led to the formation of a "Swiss cheese" endometrium.[3]

In *cattle* persistent follicle cysts are the most common cause of sterility.[4] They are usually associated with nymphomania, cystic transformation of the endometrium and continuous estrus probably due to excess folliculoid hormone production.[5] In the case of anaphrodysia, these same authors observed atrophy or cystic degeneration of the cow ovary. The cystic follicle in the ovary of a nymphomaniac cow can often be palpated and artifically ruptured through the vagina; this intervention tends to restore normal cycles.[6] The study of this condition among veterinarians appears to have progressed without any effort to connect their observations with those of gynecologists. One guileless student of nymphomaniac cows goes so far as to state " . . . It does not seem that there is any human parallel to these symptoms, but it has to be remembered that no such parallel has been sought for, and that for social reasons any such symptoms would be kept in the background. The cow does not undergo the years of training which prompt women to suppress manifestations of sexual desire. The result is frank and obvious nymphomania . . . ".[6] It is a shame that books like mine are likely to disillusion these last surviving champions of Victorian propriety!

Treatment with crude anterior pituitary extract is sometimes successful in nymphomaniac cows.[7]

In the *guinea pig*, nymphomania[8] or at least continuous estrus[2] may result from cystic persistent ovarian follicles.

It is perhaps also pertinent to mention that in one colony of 500 female *rabbits* there were 95 instances of spontaneous hyperfolliculoidism with the development of transplantable endometrial cancers and typical manifestations of folliculoid hormone overdosage in the adrenals, hypophysis, mammary glands etc.[9] It is difficult to identify persistent follicles in the rabbit since in this species the follicles and the condition of estrus are normally of long and rather irregular duration, yet in the above instances there appears to be little doubt concerning the existence of a true state of pathologic hyperfolliculoidism.

[1]*Botteri* B6589/24, *Hetzel* A95012/35.
[2]*Tietze* A17018/38.
[3]*Guttmacher* B6617/24.
[4]*Hammond* 5000/27.
[5]*Frei and Lutz* 28735/29, *Lutz* A94989/29, *Casida et al.* B226/44, *Hartman* B13063/45.
[6]*Pugh* B21067/23.
[7]*Casida et al.* B226/44.
[8]*Courrier* 19452/28, 24723/25.
[9]*Greene and Saxton* B10975/38, B10976/38.

OVARIAN SMALL-CYSTIC DEGENERATION

(See also passage on Ovarian changes in women suffering from uterine fibroids in Sect. IV, Vol. IV).

SYNONYMS: Sclerocystic ovaries, polycystic ovaries, fibrocystic ovaries, ovaritis sclerocystica, oophoritis follicularis, follicular hypertrophy of Ziegler, "ovaire à petits kystes de Trélat".

REVIEWS

ENGLISH: Jones A80949/03-4, *Schwarz* A80606/20, *Spivack* A53010/34, *Stein and Cohen* A33592/39.

FRENCH: Potherat A81287/890, *Conzette* A43445/890, *Fraikin* A68585/899, *Bouilly* A68588/0, *Pichevin* A69199/06, *Forgue and Massabuau* A81366/10, *Guinier* A80581/22, *Demarez and Bédrine* A27903/35.

GERMAN: Bulius A43454/889, A43363/889, *Petitpierre* A45194/889, *v. Babo* A80952/00, *Miller* A18279/37.

ITALIAN: Formiggini A80596/07, *Vitanza* A80609/21, *Catalano* A81166/22, *Manzi* A68105/28, *Feraco* A66117/32, *Lorenzetti* A61284/35.

PORTUGUESE: Sabino Coelho A68599/04, *Bento de Lemos* A80583/24.

SPANISH: de Silva Pereira A97712/40.

DEFINITION

Small cystic degeneration of the ovaries is a condition interpreted differently by various investigators. This is due to the inherent difficulty of clearly delimiting this from other conditions leading to cyst formation and especially from multiple simple follicle cysts. It is considered best to reserve the term small cystic degeneration for cases where there is an increase in the connective tissue stroma with thickening of the ovarian capsule accompanied by the diffuse formation of small follicle cysts throughout the glandular parenchyme. Multiple simple follicle cysts or "retention cysts" are certainly closely related to this condition, but they tend to develop in the ovarian cortex and are usually unaccompanied by any marked degree of fibrosis. It will be noted that corpus luteum formation is deficient in both these conditions and that from a functional point of view, small cystic follicles may lead to the same type of hyperfolliculoidism with which we have become acquainted in the section on simple follicle cysts.

HISTORY

In view of the comparatively vague morphologic descriptions offered by early investigators, it is somewhat difficult to outline the early history of this disease. Boullard[1] reported small-cystic ovaries in a newborn infant but Rokitansky[2] is usually credited with having described the first typical case in an adult woman. Perusal of his publication indicates, however, that his patient suffered from a hydatidform mole. Since in this disease follicle cysts often develop as a result of stimulation by the excessive amounts of gonadotropic hormones produced by the tumor, it is impossible to regard this case as a typical example of small cystic degeneration. More characteristic instances of the small cystic ovary are described by subsequent early workers who also emphasized its frequent association with menstrual disturbances.[3]

PATHOLOGIC ANATOMY

Macroscopically the most striking change in this disease is an increase in the size of the ovary due to an augmentation of all its dimensions. The albuginea is almost invariably greatly thickened and scar-like. The surface is consequently whitish-grey and of a fascia-like appearance. Since the cysts are distributed throughout the parenchyme and do not tend to protrude through the connective tissue capsule, the surface is comparatively smooth in most cases. The even distribution of the small cysts throughout the parenchyme and their tendency to be so closely packed that their walls invaginate into each other is inconstant but, if present, perhaps of diagnostic significance.[4]

Microscopically small hemorrhages, distention of the lymphatic vessels and other *circulatory disturbances* are usually prominent and most investigators mention the scarcity of primordial follicles.[5] Contrary to the statement made by Bulius[6] there is generally very little evidence of *small cell infiltration* or any other change which could be interpreted as inflammatory.[7]

Humiston[8] insisted on distinguishing between "sclero-cystic" and "cirrhotic degeneration" of the ovaries. Some workers claimed[9] that in many of the cystic *follicles* ovum-like formations remain detectable.

In unusual cases of small cystic degeneration there is amenorrhea instead of the usual excessive

[1]A69767/854.
[2]A82042/855.
[3]*Bulius* A43454/880, *Hegar and Kaltenbach* A69689/886, *Petit* A42461/888, *Conzette* A43445/890, *Pilliet* A45603/890, A44598/893, *Bishop and Fothergill* A50959/899, *v. Kahlden* A81139/00, A81142/02.
[4]*Bilius* A43363/889, A69687/891, *de Bustamante* A83338/897, *Martin* A78665/899, *Forgue and Massabuau* A69658/10, *Miller* A18279/37, *Kraus* 4116/33.
[5]*Stratz* A44105/892, *Nagel* A4934/896, *Martin* A78665/899, *Bollenhagen* A69667/00, *v. Babo* A80952/00, *v. Kahlden* A81142/02, *Herrmann* A13017/09, *Forgue and Massabuau* A69658/10.
[6]A43363/889, A69687/891.
[7]*Schultz* A81291/01, *Miller* A18279/37.
[8]A50934/899.
[9]*Nagel* A4934/896, *Bittler* A80930/04.

bleeding. In such cases only a few follicles could be found in which the granulosa is clearly distinguishable, while most cysts were lined by theca cells. As in the ordinary small cystic ovary, the albuginea was thickened and the stroma vessels tortuous and usually distended. In this uncommon type of cystic ovary with amenorrhea *corpora lutea* are frequently present[1] while in the common type, which is associated with metrorrhagias, corpora lutea are absent.[2]

Specific degenerative changes have also been claimed to occur in the *reticular fibers*[3] and *nerves*[4] of the small cystic ovary. Occasionally "sympathetic neuromas" were seen in the ovarian nerves,[5] but further research will be necessary to ascertain the specificity of these lesions.

Additional data will be found in the supposedly relevant *case reports*.[6]

SMALL-CYSTIC DEGENERATION IN COMBINATION WITH OVARIAN TUMORS: Small cystic degeneration of one ovary occurs in combination with *pseudomucinous cysts*,[7] *serous papillomas*[8] or a *fibroma*[9] in the contralateral gonad.

In one instance several minute "fibromas" were found within the ovarian cysts in a case of small cystic degeneration accompanied by obvious signs of hyperfolliculoidism (metropathia hemorrhagica, endometrial polyps, squamous metaplasia and "malignant adenoma of endometrium".[10] Such cases raise the suspicion that close relations may exist between fibromas and thecomas of the ovary. A *sarcoma*,[11] or a *dermoid cyst*[12] may also co-exist with small cystic degeneration.

INCIDENCE

Since only a comparatively small number of the small-cystic ovaries is subjected to adequate morphologic study, the condition is often not recognized as such and hence its frequency is difficult to estimate; yet it is certainly true that the small-cystic ovary is among the more common diseases of the female sex organs. One investigator estimates that 22% of all cystic ovaries belong to this type.[13]

It appears that small-cystic degeneration of the ovaries is not even limited to adult women since supposedly relevant cases have been observed in prepubertal *children*[14] and even in *embryos and newborn infants*.[15] In some of these latter cases, however, differentiation from ordinary follicle cysts is based on insufficient evidence and it will be recalled that in the embryo and the newborn, maternal gonadotropins may cause follicle maturation. Even metropathia hemorrhagica may occur in the newborn, but there does not appear to be any correlation between this change and the occurrence of small cystic ovaries at birth.[16] Probably the uterine change is dependent upon stimulation by maternal hormones, not upon those coming from the infant's own cystic ovaries (see also passage on age incidence of common cysts).

In an exceptional case[17] small-cystic degeneration in the ovaries was claimed to have occurred during *pregnancy*.

PATHOGENESIS

The etiology of small-cystic ovarian degeneration has been the subject of many careful studies[18] but is still not clearly understood. As stated above some investigators believed they saw mild inflammatory lesions within the ovarian stroma and this led to the assumption that the disease is a *specific inflammation*.[19] Several early investigators believed it to be of *syphilitic*,[20] *gonorrheal*,[21] or *tubercular*[22] origin, while others pointed out the frequency of small cystic degeneration in connection with various types of *nonspecific pelvic inflammatory lesions* and implied that the cavities are retention cysts whose rupture was

[1] *Stein and Leventhal* 78805/35, *Stein and Cohen* A33592/39.
[2] *Matsuno* A92443/23.
[3] *Manelli* A81085/21.
[4] *Lhermitte and Dupont* A80600/25, B7332/26, *Bozzi Corso* A66280/29, *Goecke* A17421/38, *Browne* A33397/39.
[5] *Roux* B7992/26.
[6] *Matsuno* A92443/23, *Moulonguet* A96703/28, *Tietze* A95119/37.
[7] *Meerdevoort* A70898/05, *Rouville et al.* A81107/23-4, A77081/24, *Bruns* A658558/24.
[8] *Stübler and Brandess* A76588/24, *McCarthy* A64392/32.
[9] *Abadie* A65782/899.
[10] *Siegert* A94957/37-8.
[11] *Eckhardt* A77464/895, *Massazza* A77673/24.
[12] *Malherbe* A76057/892, *Jessett* A83362/03.
[13] *Bufe* A96007/37.
[14] *Schultz* A81291/01.
[15] *Boullard* A69767/854, *v. Rokitansky* A70247/861, *Grohe* A63572/863, *Runge* A7562/868, *Klebs* A71439/868-80, *Slavjanski* A7571/870, A83026/874, *de Sinéty* A8899/875, *Ruge* A69710/877, A69709/888, *Orth* A83022/878, A10561/893, *deSinéty and Malassez* A82057/878, *Nagel* A63609/888 *Pfannenstiel* A7554/898, *v. Franqué* A50571/898, A88587/898, *Bayer* A10673/02, *Benthin* A3186/10, *Delestre* A20442/11, *Gaifami* A81657/13, *Neumann* A83024/26, A83025/31, *Hartmann* A17592/26. *Harris* A59673/30, *Neumann and Péter* 3347/32, *Spivack* A53010/34.
[16] *Spivack* A53010/34.
[17] *Bossy* A93514/06.
[18] *Pichevin* A68595/03, A69198/06, A68597/06, A68596/06, *Gharzarossian* A68586/03, *Smead* A69683/12, *Forgue and Massabuau* A69658/10, *Castano* A66108/32, *Cotte and Pallot* A53087/34, *Motta* A59470/36, *Diaca* A97051/38, *Pereira* B11447/42.
[19] *Pfannenstiel* A7554/898, *Wolff* A81302/01, *Theilhaber and Meier* A80816/06, *Manzi* A96713/28, *Rowley* A98178/43.
[20] *Ozenne* A80822/03, A69194/03, A80823/03, A80825/04, A80824/04.
[21] *Rosendo Amor* A80604/19-20.
[22] *Erny* B9352/19, *Mallet-Guy* A80601/22.

prevented by perioöphoritis with capsular fibrosis.[1]

It has been especially emphasized that in women suffering from chronic *appendicitis,* small-cystic degeneration of the right ovary in particular, is quite common and this led to the belief that a chronic oöphoritis resulting from the appendical infection may cause such sclerosis of the albuginea that the follicles fail to rupture when they become mature.[2]

The frequent association of small-cystic degeneration of the ovaries with uterine *fibroids* has been the subject of much comment. The relevant literature is discussed in the passage on ovarian changes in women suffering from uterine fibroids (see Sect. IV, Vol. VI). At the present time it is still doubtful whether the uterine or the ovarian change is primary in women simultaneously suffering from uterine fibroids and small-cystic ovaries. It is conceivable that due to nervous stimuli emerging from the fibromatous uterus or as a result of pelvic hyperemia caused by the fibroids; the ovary may become secondarily involved. Conversely it is also possible that increased folliculoid hormone production and lack of progesterone secretion by the small-cystic ovaries, can result in the formation of fibroids. It will be recalled in this connection that prolonged folliculoid hormone treatment causes uterine fibromatosis in the guinea pig (see passage on the effect of folliculoids on the uterus in Sect. IV, Vol. III).

It has been stated that small-cystic degeneration of the ovaries is unusually common among women with *malformations or aplasia of the Müllerian derivatives* (especially the uterus and vagina).[3] This association with such comparatively rare anomalies does not shed any light, however, upon the pathogenesis of the usual cases which are not accompanied by malformations of the internal genitalia.

Perhaps one of the most popular theories is that which ascribes the cystic degeneration to abnormal *nervous stimuli.*[4] It has been claimed[5] that reflex irritation from primary lesions in the sex organs may give rise to cystic degeneration of the ovaries. Thus in a four-year-old girl an erosion of the cervix was believed to have been the cause of the cystic ovarian change. In other cases sexual excesses were assumed to be of etiologic importance. In a large series of cases various intra-cranial processes exerting an increased pressure upon the brain were accompanied by small-cystic degeneration of the ovaries. Since, at the same time, there was proliferation of the basophils in the anterior hypophysis, it was assumed that brain pressure may so influence the pituitary that through its gonadotropic hormone it causes polycystic ovaries.[6]

There are other factors which may be of pathogenic significance; several authors[7] cite cases of small-cystic degeneration in *prolapsed* ovaries and the question arises whether in these, mechanical factors may have acted directly upon the gland causing hyperemia, nervous stimulation or sclerosis of the albuginea.

Some believe[8] that *sedentary life* acts as a predisposing factor; others[9] claimed to have seen this condition with comparative frequency in patients suffering from "status thymico-lymphaticus" and believed *constitutional factors* to play an important part in the pathogenesis of the small-cystic ovary.

From what has been stated above it is evident that the pathogenesis of this disease is still far from understood. Correlation of the clinical literature with what is now known about the endocrine factors influencing ovarian structure indicates, however, that both hormonal and local factors might be of etiologic significance. The fact that pituitary gonadotropins can elicit maturation of an excessive number of Graafian follicles is adequately ascertained by animal experimentation. With the hypophysoid gonadotropic preparations now available, this is as yet difficult to duplicate in the human female, but it is reasonable to assume that the hormonal regulation of follicle maturation in women is essentially similar. The common occurrence of many large cystic follicles in the ovaries of women suffering from chorion-epithelioma or hydatidiform mole (both tumors known to produce an excess of hypophysoid gonadotropins) gives added support to this view. On the other hand, the frequent association of small-cystic ovaries with conditions capable of producing direct ovarian damage (pelvic inflammatory lesions, appendicitis, prolapse of the ovaries) strongly indicates that local stimuli are also of importance. I would therefore like to suggest as a working hypothesis that small-cystic degeneration of the ovaries occurs under the influence of the one-sided stimulation of the gonad by F.S.H., especially when normal follicular development and ovulation are impeded by local stimuli which cause capsular sclerosis. It is conceivable that such mechanical interference with ovulation would so disturb the hormonal relations between the pituitary and the ovaries that, in the absence of follicle rupture, subsequent luteinization would fail to occur. The role of the fibroids—frequently found in the

[1]*Fritsch* A69394/, *Klob* A70086/864, *Virchow* A77876/864-5, *Förster* A76963/865, *Birch-Hirschfeld* A17086/882-96, *Zeigler* A69397/884-02, *v. Winckel* A70449/890, *Orth* A10561/893, *Hofmeier* A69395/898, *Gebhard* A73657/899, *Martin* A78665/899, *Kelly* A83038/899-00, *Hektoen and Riesman* A83037/01, *Vautrin* B13104/06, *Condamin* A65461/29.
[2]*Courtin* A68591/04, *Ortiz-Cano* A68594/05, *Gomez* A80597/17-8, *Hale* A71398/28, *Weinstein* A64027/31.
[3]*Kreis* B10765/28.
[4]*Castano and Introzzi* A65059/30.
[5]*Schultz* A18291/01.
[6]*Kraus* 4116/33.
[7]*Goldspohn* A68657/02, *McGlinn* A82389/16.
[8]*Kraul* A61489/36.
[9]*Bartel* 38177/08, *Herrmann* A13017/09, *Bartel and Herrmann* 48492/11.

uterus of patients suffering from small-cystic degeneration of the ovaries—is still problematic. There is some evidence indicating that primary uterine lesions may secondarily influence the ovaries (e.g. ovarian changes in women whose uterus has been removed or is damaged by some primary uterine disease; corpus luteum persistence in the hysterectomized guinea pig). As we have stated above, it is more probable, however, that in the cases under discussion the fibroids are secondary to the uninterrupted exposure of the organism to folliculoid hormones produced by the cystic ovaries.

CLINICAL COURSE

There is little uniformity of opinion concerning the clinical syndrome associated with small-cystic degeneration of the ovaries. This is probably due to the fact that the very concept of this disease, as well as its anatomic criteria, are variously defined by different investigators and that comparatively few relevant cases have been thoroughly studied by both clinician and pathologist. This lack of systematic investigation is probably also responsible for the comparatively meager attention accorded to this disease, which is not even mentioned in most of the outstanding English gynecologic texts; judged by the French and German literature, small-cystic degeneration of the ovaries is by no means a rare condition.

In the majority of cases the leading symptom is excessive uterine bleeding, which usually takes the form of more or less irregular *metrorrhagias*.[1] In some of these cases the bleeding endometrium reveals the morphologic characteristics of *metropathia hemorrhagica* not infrequently accompanied by endometrial *polyps*, uniform enlargement of the uterus as a whole, or uterine *fibroids*.[2] Some authors[3] doubted that small-cystic degeneration of the ovaries causes irregular uterine bleeding because histologic examination of the ovaries in many of their patients suffering from metrorrhagias revealed no small-cystic degeneration. This argument is hardly relevant, however, since it has not been suggested that all cases of metropathia are due to this ovarian lesion. It was estimated[4] that small-cystic degeneration of the ovaries accounts for 57.1% of the menstrual disturbances in a series of 109 patients in whom disorders of menstruation were accompanied by a detectable ovarian lesion. This estimate may be too high, but the data now available strongly suggests that small-cystic ovaries account for a significant number of metrorrhagias. One author[5] estimates that in 46% of his patients suffering from small-cystic degeneration of the ovaries, there was polymenorrhea, while 48% actually suffered from *oligomenorrhea*. In another series[6] some patients had normal, some irregular and some deficient uterine bleeding. Similar ovarian lesions have even been noted in *amenorrheic*[7] and in frankly *eunuchoid* women.[8] It is quite possible that depending upon the course of the disease the same lesion may lead to either an increase or a decrease in the folliculoid hormone production of the gonads. This is not surprising if we consider that prolonged and abnormal gonadotropic hormone action may result in an exhaustion of the receptor cells or in anti-hormone formation and that the local stimuli, such as inflammatory lesions, may eventually destroy much of the ovarian parenchyme.

It is well to remember in connection with the uterine manifestations of the small-cystic ovary, that the accompanying interference with ovulation and luteinization results in *sterility*.[5] In some patients the condition may be accompanied by persistent *ovaralgia*,[9] *dysmenorrhea*[10] or "*vicarious menstruation*" in the form of epistaxis.[11]

One 15-year-old girl died from a fatal uterine hemorrhage in conjunction with small follicular cysts and absence of corpus luteum formation in the ovaries. In this case the bleeding was ascribed to a lack of uterine tonicity caused by folliculoid hormone deficiency.[12] It is rather doubtful, however, whether this was actually a case of true small-cystic degeneration.

A series of rather unusual small-cystic ovaries appears to have contained some true and some thecal corpora lutea.[13] All these patients suffered from amenorrhea and sterility. Additional cases of a somewhat similar nature are discussed in the chapter on Corpus Luteum Cysts. It must be emphasized, however, that in the typical small-cystic ovary corpus luteum formation is entirely absent.

Nervous manifestations have repeatedly been observed in patients suffering from small-cystic degeneration of the ovaries. It has been claimed that

[1] *Tait* A40668/883, *Hawkins-Ambler* A44254/892, *Bond* A44692/894, *Pozzi* A70225/897, *Gross* A68593/899-00, A68592/00, *Ricci* A68598/02, *Barraud* A68584/03, A68587/03, *Kaji* A22055/10, *Forgues and Massabuau* A69658/10, *Geist* B8529/22, *Matsuno* A92443/23, *Picard and Olry* A61645/33.

[2] *Chénieux* A45876/891, *Bond* A44692/894, *Tingley* A47510/895, *Bollenhagen* A69667/00, *Muller* A61424/32, *Votta* A95436/37, *Siegert* A94957/37-8, *Reycraft* A95420/38, *Fernandes and Lapa* A97476/41.

[3] *Pankow* A23708/11, *Schickele and Keller* 50328/12.

[4] *v. Fekete* A79279/27.

[5] *Kraul* A61489/36.

[6] *Kraus* 4116/33.

[7] *Serdjukoff* B12137/23.

[8] *Bartel* 38177/08, *Herrmann* A13017/09.

[9] *Fenwick* A69588/03.

[10] *Charrier* A44227/892, *Bollenhagen* A69667/00, *Pichevin* A85586/02.

[11] *Ruggi* A50478/898.

[12] *Hamblen and Sprunt* A71237/37.

[13] *Stein and Loventhal* 78805/35, *Stein and Cohen* A33592/39.

hysteria,[1] gastro-intestinal spasms[2] and what the French investigators designate as "uterine cough" (toux uterine)[3] may be caused by this ovarian disease, but the causal connection of these manifestations with the ovarian condition is questionable. Ovaralgia which is often seen in this disease, could, on the other hand, well be due to changes which frequently occur in the nerves of small-cystic ovaries[4] (see above).

Pigmentation of the *skin* ("chloasma uterinum") is exceptional in patients with small-cystic ovaries.[5]

DIAGNOSIS

The clinical diagnosis of the small-cystic ovary is rather difficult since the condition does not tend to manifest itself by specific signs and symptoms.

Upon *bimanual* or *rectal examination* a typical enlarged, hard and somewhat painful ovary cannot always be identified in these cases. This is only to be expected in view of the great morphologic variability of the underlying change.[6] Manual compression of the small-cystic ovary aggravates the pain and tends to cause nausea.[7]

According to Stein and Leventhal,[8] and Stein and Cohen[9] *pneumoroentgenography* helps to demonstrate the usually bilateral ovarian enlargement when palpatory findings are doubtful. Yet in many cases the condition cannot be recognized until ovarian tissue becomes available for histologic study.

It is especially difficult to differentiate it from various types of *chronic oöphoritis* and *simple follicle cysts* since the latter conditions likewise tend to give rise to a painful ovarian enlargement accompanied by menstrual irregularities.[7]

THERAPY

In most cases of small-cystic degeneration of the ovaries, the condition is resistant to all efforts of internal therapy; hence a number of *surgical interventions* have been devised in an effort to improve the condition of patients suffering from this disease.[10]

Complete *bilateral ovariectomy* was the treatment of choice towards the end of the last century,[11] but except in post-menopausal women such a radical intervention is hardly advisable.

Ignipuncture of the follicles[12] or *ligature of the ovarian artery*[13] may give at least temporary relief in some cases, but the method of choice is *partial resection* or *decortication* of the ovary. For this a variety of technics have been devised, among which bilateral wedge excision, with subsequent union of the ovarian wound by suture, is generally considered to be most advantageous.[14] Another modification of this procedure consists in turning the ovary inside out, after the wedge excision, and stabilizing it in this position so as to bury the sclerotic serosal surface and expose the supposedly normal follicles of the medulla.[15] In view of the fact that in experimental animals partial ovariectomy actually stimulates the formation of persistent follicle cysts, the rationale of all wedge excision procedures is somewhat dubious. However, practical experience appears to substantiate the efficacy of these technics and it is conceivable that removal of the fibrous capsule may facilitate subsequent follicle rupture and luteinization.

It has been stated that the ovaralgia which frequently occurs with small-cystic degeneration can be completely cured by bilateral *denervation of the ovaries*[16] and this intervention may perhaps have a beneficial effect on the ovarian lesion itself as well.[17]

Among other therapeutic methods *X-ray*[18] or *radium*[3] irradiation of the ovaries have been claimed to be effective, but in view of the danger of destroying too much ovarian tissue it appears inadvisable to resort to such drastic means as a routine procedure. Considering our deep ignorance of the underlying endocrine disturbance, it is not surprising that *hormonal therapy* has so far proved rather ineffective.[19]

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[1] *Ruggi* A50478/898, *Ricci* A68598/02.
[2] *La Gravinese* A67337/30.
[3] *Bernard* A63808/43.
[4] *Fenwick* B12985/03-4, *Reycraft* A95420/38, *Browne* A33397/39.
[5] *Serdjukoff* B12137/23.
[6] *van Emden* A80594/12.
[7] *Goldspohn* A68657/02.
[8] 78505/35.
[9] A33592/39.
[10] *Neumann* A50615/898, *van Emden* A80594/12, *de Lemos* A80599/23, *Vazquez Amenabar* B21081/23, *Cotte* A80592/25, *Castano* A65456/29, *Smith* A27845/35, *Gonzales Hurtado* A96655/40, *Peralta Ramos* A98086/41.
[11] *Villeneuve* A45650/890, A45743/891, *Carrier* A44227/892, *Bond* A44692/894, *Hogner* A44860/894, *Eastman* A69585/899.
[12] *Coelho* A44817/894.
[13] *Casteno and Introzzi* A65059/30.
[14] *Waldo* A47514/895, *Guillois* A49212/898, *Goldspohn* A68657/02, *Boursier* A68589/03, *Cornil* A68590/04, *Poggi de Figueiredo* A81097/15, *McGlinn* A82389/16, *Le Cacheux* A80582/27, *Castano and Introzzi* A65457/29, *Introzzi* 65071/30, *Stein and Leventhal* 78805/35, *Robinson* B114/35, *Bailey* A95231/37, *Decoulx and Patoir* A96013/37, *Reycraft* A95420/38, *Stein and Cohen* A33592/39.
[15] *Bailey* A95231/37.
[16] *Hamant* B8018/26, *Browne* A33397/39, *Weinstein* 85315/43.
[17] *Imparato* A96759/28, *Grouzelle* A97764/28.
[18] *Potter* A65105/31.
[19] *Stein and Leventhal* 78805/35, *Jeffcoate* A69531/37, *Stein and Cohen* A33592/39, *Papillon* A97630/39.

PLATE IV

SMALL CYSTIC DEGENERATION OF THE OVARIES AND HYPERFOLLICULOIDISM

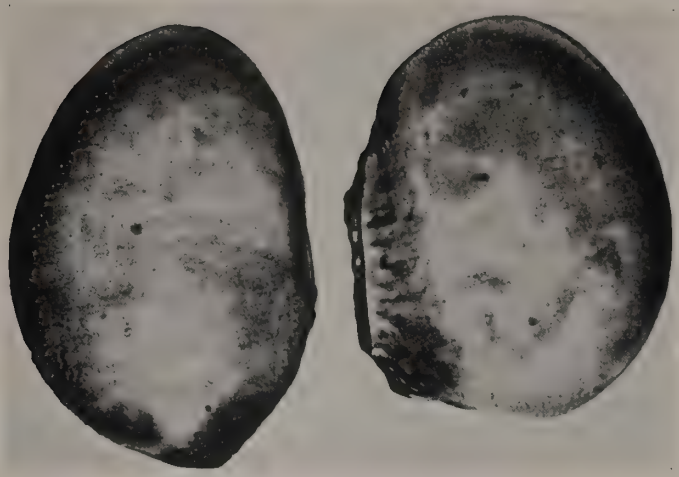

Fig. 1. SMALL CYSTIC DEGENERATION OF THE OVARIES (after E. J. Kraus 4116/33). Naked eye appearance of ovarian surface in a case of pronounced small cystic degeneration. Note the smooth surface devoid of protruding cysts. The patient was 16 years old and suffered from a hydrocephalus internus due to a glioma.

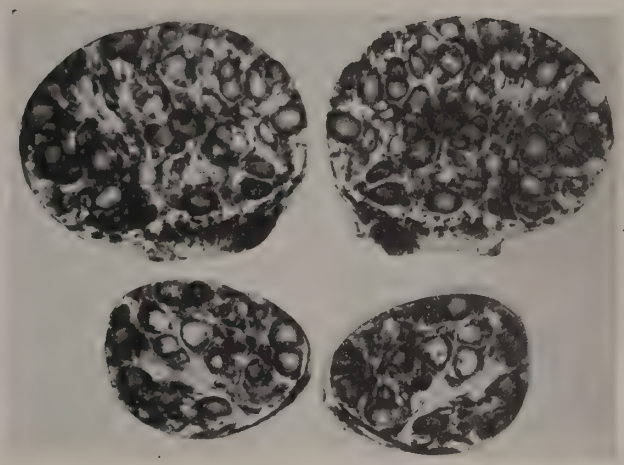

Fig. 2. SMALL CYSTIC DEGENERATION OF THE OVARIES. Cross-section through the ovaries represented in Fig. 1. Note the numerous small cystic cavities, the dense connective tissue stroma and the thickened capsule.

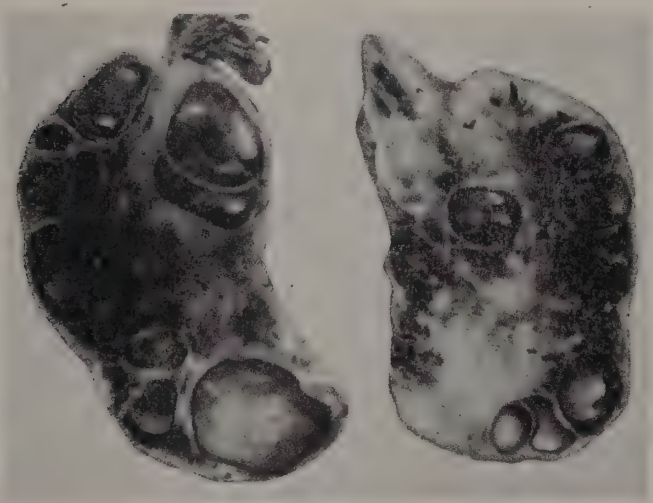

Fig. 3. SMALL CYSTIC DEGENERATION OF THE OVARIES (after E. J. Kraus 4116/33). Naked eye view of a cross-section through the ovary, showing small cystic degeneration. As in the previous illustrations, dense stroma, thick capsule and many irregular, small cystic cavities are evident. The patient was 30 years old and suffered from a glioma of the cerebellum which caused marked intracranial pressure.

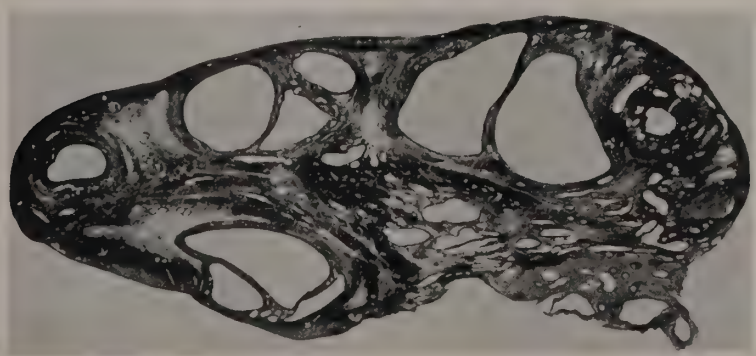

Fig. 4. SMALL CYSTIC DEGENERATION OF THE OVARIES (after E. J. Kraus 4116/33). Very low magnification of a histologic section through the ovary, showing cystic cavities of varying size, dense connective tissue stroma and thick capsule. The patient was 20 years old and suffered from a glioma of the brain.

Fig. 5. GROSS APPEARANCE OF BENIGN POLYPOID HYPERPLASIA OF ENDOMETRIUM (after Novak B109/44). Note physiologic line of demarkation at the internal os. The area in the square is shown under higher magnification in lower right corner.

OVARIAN FOLLICULOMAS

SYNONYMS: The terms *granulosa cell tumor, basal cell tumor of the ovary, Kahlden's tumor* and *folliculoma of the ovary* have been used by previous investigators as synonyms designating those tumors which resemble the granulosa of the follicle. The malignant types of this series were consequently termed *malignant folliculomas, granulosa cell carcinomas* or *folliculoid carcinomas of the ovary.* Burrows[1] proposed to use the term "theloma" to denote all folliculoid hormone-producing tumors irrespective of structure. To avoid confusion it is emphasized here that in the present discussion, the term folliculoma is used as a group designation for all tumors exhibiting the characteristics of the ovarian follicle (see Definition, below).

The term *fibroma thecocellulare xanthomatodes ovarii, Löffler-Priesel tumor, theca cell tumor* or merely *thecoma* has been used to refer specifically to the theca cell-type of the folliculoma. In case of malignancy in the old literature many of these tumors have merely been listed as ovarian sarcomas.

REVIEWS

ENGLISH: Novak and Brawner A52173/34, A64816/34, *Geist* A79284/35, A28064/35, B6672/42, *Schiller* A64891/36, *Sjövall* A64840/36, *Robertson* A97586/39, *Schulze* A93754/39, *Henderson* A36837/41, *Dockerty* A96679/41, *Novak* B109/44.

FRENCH: Varangot 68667/37, A96559/38, A97188/38, *Moulonguet and Varangot* A31323/39, *Gerundo* A97373/40.

GERMAN: Sternberg A64845/26, *Meyer* A65042/30, *v. Szathmary* A79399/32, *Schiller* A64834/34, *Lambertz* A93727/36, *Straube* A93729/36, *Parschau* A93728/36, *Schütterle* A93772/37, *Miller* A18279/37, *Jockusch* A93770/39.

ITALIAN: Dellepiane A97142/38.

PORTUGUESE: Delascio A93768/38.

SPANISH: Wood and Guzman A99030/42.

DEFINITION

The folliculoma is a tumor of the ovarian follicle which may produce an excessive amount of folliculoid hormone. It has been customary, in the past, to distinguish sharply between granulosa and theca cell tumors on the basis of purely morphologic characteristics. It is true that some folliculomas resemble the granulosa, while others approximate the structure of the theca. In the vast majority of the cases which we obtained for study, however, both granulosa and theca elements, as well as transition forms between these, were present in different regions of the same growths. As we shall see from the passage dealing with the etiology of folliculomas, it is probable that the tumors arise from undifferentiated cells having potentialities for the formation of either granulosa or theca cells. Therefore we consider the prevalence of theca or granulosa-like elements in a tumor of no more fundamental significance than the predominance of follicles, tubules, trabeculae etc. within the "granulosa cell tumor" group. On the other hand, all morphologic types of the folliculoma group are, at least potentially, capable of producing the clinical manifestations of folliculoid hormone overdosage; hence the tumors of the follicle form a rather well defined endocrinologic entity and will be discussed collectively under the name of folliculoma. Tumors characterized by the prevalence of one or the other histologic element will be regarded as different manifestations or types within this group.

Since cases of morphologically typical folliculomas have been known to result in no excess formation of folliculoids, it would appear unjustified to limit this term—as Varangot[2] did—solely to the cases with detectable overdosage symptoms.

HISTORY

It was apparently v. Rokitansky[3] who first described a tumor, which he did not specifically name, but which—according to most investigators—appears to have been a typical folliculoma. Acconci[4] is often quoted as having described another early case. Perusal of his publication shows that he dealt with a bilateral papilliferous cystoma of the ovary within which he saw "neoplastic egg formations". While this interpretation of his observation is rather dubious, it appears probable that his case belongs to the papilliferous type of folliculoma, a type which received little attention until quite recently. Under the title of "Ueber maligne Ovarialtumoren mit Bildung von Primordialeiern" Emanuel[5] described a tumor in which he detected "blastomatous ovogenesis". Varangot[2] believes that this case was merely an example of a common ovarian carcinoma with folliculoid rosettes. In view of more recent investigations (to be discussed later in this chapter), it appears probable that much confusion occurred in the early literature because of the unduly sharp distinction made between folliculomas of the carcinomatous type and the so-called serous papillary carcinomas of the ovary.

It was undoubtedly the merit of v. Kahlden[6] to distinguish as a separate entity under the heading of "adenoma of the Graafian follicle" a relevant neoplasm containing some folliculoid and some cylindromatous areas. Granulosa cell carcinomas were studied by several early investigators.[7] Some

[1]A71758/43.
[2]68667/37.
[3]A66870/859, A80030/859.
[4]11476/890.
[5]A11546/893.
[6]A47460/895.
[7]*v. Mengershausen* A64793/895, *Pozzi and Beaussenat* A49007/897, *Gottschalk* A64878/899, A64879/02, *Voigt* A82889/01, A64860/03.

of these tumors were probably papillary granulosa cell carcinomas. Schroeder[1] was the first to use the name folliculoma for a granulosa cell-imitating tumor with folliculoid rosettes. He also emphasized the presence of endometrial hyperplasia in his patient, although he failed to see any relationship between the ovarian tumor and the uterine condition. Subsequently v. Werdt[2] reported six cases under the name of granulosa cell tumor.

In the meantime, the discovery of the theca cell-type of folliculoma appears to have proceeded along entirely independent lines. v. Rokitansky[3] in his early publication on malformations of the corpus luteum, described a growth under the name of "corpus luteum fibroma" and similar instances were later reported by Böshagen[4] as "Corpus fibrosum hypertrophicans". These, as well as several other investigators,[5] regarded the lesions as abnormalities in the involution of corpora lutea rather than as true blastomas. A similar case was subsequently described by Twaites-Lastra and Colilias[6] but it was not until Löffler and Priesel[7] reported one under the name of "fibroma thecocellulare xanthomatodes ovarii" that the theca cell-type of folliculoma was recognized as a distinct entity. The tumor described by Masson[8] under the name of "Pflügeroma" was probably not a distinct type of growth, but (according to a personal communication from Professor Masson) probably a common, granulosa cell-type of folliculoma with large cells superficially resembling ovogonia.

PATHOLOGIC ANATOMY

MACROSCOPIC CHARACTERISTICS: The macroscopic appearance of the folliculomas is extremely variable, a fact which is hardly surprising in view of their great histologic polymorphism. Their *shape* may merely imitate that of a large ovary, but it may be a smooth or nodular tumor, with or without a pedicle.[9]

The *size* is equally variable, some tumors having a diameter of a few millimeters,[10] while others are described as being "the size of a man's head" or even larger.[11] Occasionally they were claimed to fill the entire abdominal cavity[12] but such large folliculomas are certainly very rare. In one series[13] the largest tumor measured 18 x 20 x 22 cm., while others[14] described a folliculoma weighing 34 lbs. (15.5 kg.). One large folliculoma weighed 20¼ lbs. and had a diameter of 30 cm.[15]

The *position* of folliculomas is also subject to great variation. The small tumors usually remain in the region of the ovary, while the larger ones tend to sink into the pelvic cavity, to protrude towards the posterior wall of the vagina, and to exert pressure on neighboring organs. They may develop retroperitoneally[16] or within the broad ligament.[17] Folliculomas which are apparently entirely extraovarian, have been discussed in the chapters dealing with tumor formation in accessory ovaries.

The *color* of folliculomas depends largely on their fat and blood content. The fatty tumors tend to have a yellowish color, while marked vascularity and hemorrhages produce a dark red or bluish tinge. The majority of folliculomas are soft, sometimes actually of a mushy *consistency* with occasional *cystic* cavities, although if they contain much fibrous tissue, they may be quite hard or elastic.[18] A few are definitely *cystic* or polycystic. In one case 30 pints of fluid were removed from a cyst whose wall consisted of granulosa cells.[19]

Occasionally pedunculated folliculomas undergo *torsion* (see chapter on Torsion in Sect. IV, Vol. VI), while in others massive *hemorrhage* from such tumors led to serious bleeding into the peritoneum (see chapter on Hemorrhage in Sect. IV, Vol. VI). In accordance with the classification used in this Encyclopedia these complications are not to be considered here. Folliculomas usually develop in one ovary only, but some have been found to be *bilateral*.[20] Statistical studies show that about 6.2%[21] to 7.0%[22] of all folliculomas are bilateral. This is approximately in agreement with our own calculations, and it is difficult to explain why in one particular series[23] 15 of 50 cases happened to be bilateral, unless the authors interpretation of the granulosa cell tumor concept is perhaps broader than that of other investigators. In commenting upon these statistics, Miller[24] expressed similar doubts.

[1] A64835/01.
[2] A79417/14, A64866/14.
[3] A66870/859.
[4] A3191/04.
[5] *Klob* A66703/866, A66704/866, *Patenko* A70202/880, A70203/881, *Kusuda* A82387/25.
[6] A69400/26.
[7] A62937/32.
[8] A79329/12.
[9] *Miller* A18279/37.
[10] *TeLinde* A64448/30, *Kermauner* A73104/32, *Schiller* A64834/34, *Traut and Marchetti* A33420/40.
[11] *Habbe* A65156/31, *Kermauner* A73104/32, *Klaften* A62933/32.
[12] *Fauvet* A61750/32, *Klaften* A79305/33, *Kleine* A79312/35, *Schiller* A64891/36.
[13] *Traut and Marchetti* A33420/40.
[14] *Dockerty and MacCarty* A31395/39, *Dockerty* A31809/39.
[15] *TeLinde* A64448/30.
[16] *Dworzak and Podleschka* 44647/33.
[17] *Fauvet* A61750/32, *Novak* A51974/34.
[18] *Dockerty and MacCarty* A31395/39.
[19] *McIlroy* A34556/39.
[20] *Polano* A64823/04, *Schmelz* A79385/27, *Rummeld* A65175/31, *Soltmann* 5537/32, *Placeo* A79366/32, *Holmer* A61408/33, *Neumann* A61477/33, *v. Szathmary* A61900/33, *Schiller* A64834/34, *Arenas* A94793/37, *Treston and Malone* A93766/38, *Weed* A36891/41, *Froldi* A98116/41, *Molina* B10140/43.
[21] *Klaften* A62933/32.
[22] *Kahr* A95265/37.
[23] *Kermauner* A73104/32.
[24] A18279/37.

The so-called "papillary granulosa carcinomas" are quite frequently bilateral.[1]

MICROSCOPIC CHARACTERISTICS: The histologic structure of folliculomas is extremely variable. Various authors pointed out that these tumors may appear in different forms and it is quite usual to distinguish the folliculoid, tubular and theca cell types. A detailed analysis of the literature, however, leads us to distinguish a number of additional forms which may be accepted as different manifestations of the folliculoma. These are the following:

1) Folliculoid (a) microcystic, (b) macrocystic.
2) Diffuse.
3) Tubular.
4) Trabecular (often "gyriform").
5) Papillomatous.
6) Carcinomatous.
7) Theca cell-type.
8) Sarcomatoid type.
9) Mixed folliculomas.
10) Various types of folliculomas combined with other ovarian tumors.

In the vast majority of cases the tumor is of a mixed type with one element prevailing and pure representatives of the first 8 types are rather exceptional. Thus, in the vicinity of folliculoid or diffuse granulosa cell proliferations, the connective tissue tends to assume the general characteristics of theca elements. Furthermore, the stroma of tubular tumors is not uncommonly of the sarcomatoid type. It will be noted, however, that the mixed tumors mentioned as type 10 represent a different category altogether, as these are folliculomas developing simultaneously with other tumors such as teratomas, common cystadenomas, etc., that is to say, growths which do not belong to the folliculoma group.

The Folliculoid Type. This, in its *microcystic* or *microfollicular* form, is by far the most common pure type of the folliculoma. It usually consists of small polyhedral cells which bear a striking resemblance to those of the normal granulosa. These epithelial elements constitute the parenchyme of the tumor and are subdivided by usually dense bands of connective tissue stroma. Within the parenchyme small cysts are formed apparently through the same mechanism which is responsible for the development of a normal antrum folliculi. The occasional cell degenerates and forms a vacuole within the parenchyme. This vacuole, with its contained cell debris, corresponds to the so-called "Call-Exner bodies" of the normal granulosa. Subsequent gradual increase in the fluid content of the vacuole renders it similar to a follicular cavity. True ovocytes are never found in these tumors, although occasionally the swollen degenerating granulosa cells, which are frequently present have been confused with ova or their precursors.

The stroma in the vicinity of the granulosa cells tends to undergo thecal transformation[2] and in some regions it may become difficult to distinguish between the granulosa and the theca cell type because of gradual transitions between the two. Many of the folliculomas described in the literature are comparatively pure examples of this microfollicular type.[3]

In view of the frequent intermingling of theca and granulosa cells, it has been attempted to differentiate between the two by reticular stains, such as the silver impregnation method of Foot and Foot.[4] Some authors[5] state that a silver-stainable reticulum surrounds the theca but not the granulosa cells of folliculomas; in this they resemble the corresponding cells of the normal follicle. These authors claim to be able to distinguish between granulosa and theca-type tumors with the help of this technic. Subsequent investigations[6] largely confirmed these findings, although they left some doubt about the diagnostic value of this differential stain.

The *macrocystic* or *macrofollicular type* does not differ essentially from microfollicular variety and many transitions between the two may occur within the same tumor.[7] Special mention is made of this type only because it gave rise to confusion with the well-known thyroid tumors of the ovary, which will be discussed in a later chapter. A relevant case was published[8] as a "folliculoma a struttura pseudostrumosa", and several other instances have been seen.[9]

The term "*folliculome lipidique of Lecène*" has been employed to describe granulosa cell-type folliculomas in which the epithelial cells contain many lipid granules. They somewhat resemble luteomas although the cells are usually not as large as corpus luteum cells and their arrangement may be tubular or trabecular.[10] Functionally they belong to the folliculomas since they produce cystic-glandular endometrial changes. It is possible, however, that the luteinization process may proceed so far that the tumor appears to be a transition form between a folliculoma and a luteoma.[11]

[1] *Seegar and Jones* A32004/39.
[2] *Varangot* A93832/38.
[3] *Schröder* A64835/01, *Aschner* A79241/20, *Lagarde* A79316/22, *Abrahamer* A66136/32, *Meigs* 33256/35, *Schattenberg and Harris* A32319/39, *Lull* A36030/41.
[4] B224/32.
[5] *Traut et al.* A93790/40, *Traut and Marchetti* A33420/40.
[6] *Henderson* 83191/41.
[7] *Hacks* A93804/37.
[8] *Accardo* A27986/35.
[9] *Varangot* 68667/37.
[10] *Plate* A61969/33, A93826/33, A61970/33, A53105/33, *Vayssière et al.* A64859/36, *Varangot* A68667/37, *Miller* A18279/37, *Thomson and Stabler* A93789/38, *Seegar and Jones* A32004/39.
[11] *Benda and Kraus* A52254/34.

The Diffuse Type. In its pure form this is a comparatively rare variety of the granulosa cell type. As the name implies it is characterized by the more or less diffuse growth of granulosa-like cells which appear to exhibit no tendency to form rosettes, tubules or any other definite type of structural differentiation.[1] If they form epithelial nodules within a dense connective tissue stroma, these tumors may resemble the so-called Brenner tumors, although their cells are generally denser and more basophilic.

The Tubular Type. The formation of tubules or epithelial cylinders is not a rare occurrence in folliculomas. These tubular tumors resemble the fetal seminiferous tubules of the arrhenoblastoma more than the granulosa, yet they appear to produce folliculoid hormones, as judged by their clinical manifestations. Many instances of this type have been described.[2]

It should be specially emphasized that the terms "cylindromatous" or "cylindroid" are generally reserved by the pathologist for epithelial tumors whose stroma is undergoing mucoid or hyaline degeneration. Ewing[3] defines a cylindroma as "a tumor structure in which the stroma appears in the form of elongated, twisted, thickened cords of hyaline material". In this sense, the adjective cylindroid refers to the shape of the connective tissue bands and not of the epithelial tubules. Many authors fail to realize this and rather confusingly speak of cylindroid folliculomas or "cylindromas"[4] when describing tumors possessing epithelial tubules. Among the folliculomas true stroma cylindroids likewise are common, especially within the trabecular group although they may also occur in the tubular variety.

Since in most folliculomas the lumina of the "tubules" are inconspicuous, the distinction between the tubular and trabecular variety is often a matter of sujective interpretation.

The Trabecular Type. Tumors of this variety are characterized by the presence of massive epithelial bands usually only a few cell layers thick. In some instances, these trabeculae tend to run parallel and are comparatively regular, while in other instances they irregularly intermingle with each other and the resulting pattern is often described in the literature as "plexiform", "moiré silk-like" or "gyriform".[5]

The Papillomatous Type. It has been found that uterine bleeding is unusually common (45%) in cases of ovarian tumors hitherto described as papillary serous cystadenocarcinomas. It is possible, however, that many—if not all—of these growths are actually papillary granulosa cell carcinomas since their histologic structure reveals striking similarities to granulosa cell blastomas.[6] Should this interpretation prove correct, a very significant number of common ovarian carcinomas will be added to the folliculoma group. We have also seen several serous cystadenocarcinomas which resembled malignant folliculomas and are tempted to subscribe to the above interpretation. The so-called benign papillomatous folliculomas, which have been submitted to us for study, proved to be pseudopapillomas in which the "arborizations" arose owing to irregular confluence of cystic spaces.

The Carcinomatous Type. Although all published cases of malignant papillomatous folliculomas are papillary carcinomas, we discussed them above in a separate group because their rather distinctive appearance and frequency endows them with special importance. It is noteworthy, however, that solid granulosa cell tumors can also become malignant and assume the characteristics of what was previously the only accepted type of a granulosa cell carcinoma.[7] It is of diagnostic value to remember that the size of the nucleolus, in proportion to that of the nucleus, usually rises parallel with the degree of malignancy in granulosa cell carcinomas,[8] as it does in many other types of neoplasms.

Perusal of the relevant literature gives us the impression that many of the so-called common primary solid or microcystic ovarian cancers belong to this group. Should this interpretation be correct, a large number of the macroscopically solid ovarian carcinomas would have to be regarded as potentially capable of folliculoid hormone production. This may explain the frequent occurrence of uterine hypertrophy and bleeding in the bearers of such neoplasms.

[1] *Dockerty* A31809/39, *Palmer* A31407/39.

[2] *Neumann* 42642/27, *Traut and Butterworth* 78785/37, *Varangot* 68667/37, *Miller* A18279/37, *Barnes and Barnes* A34219/40, *Zemke et al.* A37341/41.

[3] A64873/28-42.

[4] *Sternberg* A64845/26.

[5] *Miller* A18279/37, *Varangot* 68667/37, *Stabler and Thomson* A33350/40, *Bach and Montgomery* A36705/41, *Stohr* A55557/42.

[6] *Seegar and Jones* A32004/39.

[7] *Lönnberg* A64883/01, *Donald and Fothergill* A79268/02, *Delepine and Augier* A79265/03, *Gottschalk* A74666/03, *Liepmann* A64788/04, *Peritz* A91987/06, *Schmincke* A79387/07, *Meyer* A64794/15, *Neumann* A79348/23, A79349/23, A64814/25, A79350/25, A79352/32, *Robinson* A64827/23, *Ulesko-Stroganova* A64858/23, *Goldberger* A75845/24, *Schiffmann* A64831/26, *Schmelz* A79385/27, *v. Fekete* A79279/27, *Scheyer* A64829/27, *Garfinkiel* A79283/29, *Wallart* A64862/29, *Wijsenbeek* A68061/29, A79421/29, *Brakemann* A79258/29, *Arnold and Mathias* A43354/30, *Habbe* A65156/31, *Blau* A61365/32, *Frank* 58775/32, *Klaften* A62933/32, *Soltmann* 5537/32, *Eiss* A61406/33, *Holmer* A61408/33, *Dworzak and Podleschka* 44647/33, *Kleine* A61566/33, *Merhaut* A51966/33, A79331/33, *Novak and Long* A61572/33, A51974/34, *Lyday* A52122/34, *Cabot* A64740/35, *Dreyfus* A59684/36, *Kelley and Gnassi* A59693/36, *Novak and Gray* A61851/36, *Compton* A93797/37, *Verebely* A9218/37, *Arenas* A94793/37, *Wood et al.* A95128/37, *Hückel* A93799/37, *Norris* A93802/38, *Daniel and Babes* A97358/39, *Gross* A97376/40, *McCartney* A32575/40, *Froldi* A98116/41, *Gnassi et al.* A38325/42, *Harris* A62912/42, *Henderson* A37766/42, *Banks* B11405/44.

[8] *Page and MacCarthy* A95087/37.

The Theca Cell Type. The so-called thecomas are made up of spindle-shaped, lipid-containing cells which resemble those of the normal follicular theca. Special stains help to distinguish them from myomas (which do not stain with connective tissue stains), fibromas (which are poor in fat granules) and atypical granulosa cell tumors (which possess no argyrophil reticulum). It is rather characteristic of these tumors that large areas in them tend to become transformed into hyaline plaques. Because of their comparatively high fat content, the theca cell tumors have a yellow color upon naked eye inspection; cystic cavities due to liquefaction necrosis are not uncommon in them.

Thecomatous stroma changes are often also found in association with the granulosa cell type of blastoma, but many *case reports* describe growths consisting exclusively, or almost exclusively, of theca-like cells.[1]

The diffuse hyperplasias of theca cells[2] and *hilus cells*,[3] both of which can be conducive to virilism, are endocrinologically separate entities. They are mentioned here merely because of their morphologic relationship to the thecomas.

The Sarcomatoid Type. It is not uncommon to find sarcomatoid areas within folliculomas of various types, but growths in which the sarcomatoid tissue is the only—or at least the predominant—blastomatous constituent, are comparatively rare.[4] It is quite probable that many of the so-called ovarian sarcomas, which led to precocious puberty or feminization,[5] were actually sarcomatoid folliculomas. This may perhaps also be true of an "ovarian sarcoma developing from the theca externa".[6] Certain ovarian "carcinosarcomas"[7] probably also belong to this group.

The Mixed Folliculomas. As previously stated, all the above mentioned types are infrequently found in a pure form. The various modifications of granulosa cell tumors tend to occur in conjunction, and these in turn are frequently combined with "thecalization" of the stroma or frank thecoma formation. Because of the frequency of these mixed folliculomas, and because of the many combinations which can occur, it does not appear profitable to classify the cases according to the tissue elements detectable within the same tumor. It is worth mentioning, however, that combinations of folliculoid and tubular forms,[8] and especially tubular forms with a sarcomatoid stroma,[9] are particularly common.

In addition to the cases specifically mentioned above under the various subheadings, a large number of folliculomas have been described and the relevant *case reports* may be consulted to good advantage by those who desire to collect statistical data.[10]

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[1]*Altschuler* A75839/17, *Kusuda* A82387/25, *Soltmann* A93758/31, *Schulze* A93753/31-9, *Fernando* A92248/32, *Melnick* A93844/33, A70165/33, *Masciottra and Sertinez de Hoz* A93744/34, *Löffler and Priesel* A53179/34, *Melnick and Kanter* A53100/34, *Campana* A93773/35, *Gala and Skorpil* A28063/35, *Conill* A93735/35, *Thornton* A27716/35, *Brosig* A59923/36, *Solomons* A93763/36, *Schmidt* A93757/36, *Ratto et al.* A91990/36, *Meigs and Parsone* A91982/36, A91983/37, *Patterson and McCullagh* A70204/36, *Ruzicska* A93752/37, *Daniel and Babes* A93736/37, *Verebely* A9218/37, *Mocquet et al.* A96519/37, *Macafee* A92250/37, *Prestini and Arau* A93750/37, *Meeker and Localio* A91981/37, •A93745/38, *Iwanow* A95263/37, *Pratt* A93749/37, *Pallos* A93777/37, *Hammar* A93841/37, *Varangot* 71521/37, *Traut and Butterworth* 78785/37, *Neely* A95077/37, *Schockaert and Brenez* A93762/37-8, *Geist* A93838/37-8, *Greenhill and Greenblatt* A93840/38, *Geist and Gaines* A93839/38, *Fischer* A93836/38, *Dellepiane* A93737/38, *Delarue and Isidor* A92245/38, *Jeanneney and Rousseau* A93741/38, A92249/39, *Burke* A93733/38, *Pavlova* A93746/38, *Cadiz and Saavedra* A93760/38-40, A92242/39, *Sant'Anna* A93849/39, *Plate* A93847/39, *Collins et al.* A30943/39, *Moulonguet and Varangot* A31323/39, *Putzu Doneddu* A93827/39, *Salgado* A93761/39, *Penna de Azevedo* A93747/39, *Migliavacca* A93776/39, *Penick* A91986/39, *Harvey and Dawson* A93815/39, *Claës von Numers* A93734/39, *Dockerty* A32558/40, *Dionisi* A97359/40, *v. Pallos* A96569/40, *Voight* A93850/40, *Traut and Marchetti* A33420/40, *Barnes and Barnes* A93759/40, *Spitz* A93755/40, *Traut* A93829/40, *Curtis* A38063/41, *Henderson* 83191/41, A37766/42, *Porter and Bramhall* A37837/41, *Batizfalvy and Dubrauszky* A98099/41, *Fränkel* A69401/41, *Dubreuil* A38140/41, *Wolfe and Neigus* A36880/41, *Danforth* A37764/42, *Dowling* A98108/42, *Arenas et al.* B10130/42, A96907/42, A98138/43, • *Fallas* A56094/42, *Held* B10133/43, *Molina* B10140/43, *Turner* A61334/43, *Kirshbaum* A63370/43, *Rubin et al.* B6263/44, *Perlmutter* A71795/44, *McGoldrick and Lapp* B6256/44.

[2]*Fraenkel* A69401/41, A63355/43, *Turner* A61334/43.

[3]*Lewin* 26049/26, *Berger* A55382/42, *Simard* A55385/42.

[4]*Mollof* A66942/24, *Eerland* A61747/32, *Varangot* 68667/37, *Vogt* A34640/40, *Fuller* A37138/41.

[5]*Eastlake* A64218/31.

[6]*Russel and Schenck* A69438/02.

[7]*Akimoto* A64724/25, *Brakemann* A79258/29.

[8]*Dockerty and MacCarty* 77978/39.

[9]*Varangot* 68667/37, *Dockerty and MacCarty* 77976/40.

[10]*Voigt* A64860/03, *Ingier* A79295/07, *v. Werdt* A64866/14, *Aschner* A64727/22, *Schröder* A64836/22, *Walthard and Werdt* A79415/22, *Konschegg* A79313/23, *Babes* A79243/24, A79244/27, A64729/28, *Krompecher* A64781/25, *Ujma* A64857/25, *Isbruch* A64772/26, *Manheims* A79327/26, *Schiffmann* A64831/26, *Tietze* A79409/27, *Hörrmann* A79293/28, *Picard* A64822/28, *Pytel and Corjajeva* A79374/28 *Tesauro* A64852/28, *Hamant et al.* A65610/29, *Hamant and Mosinger* A79290/29, *Tietze* A79410/29, *Davanzo* A64420/30, *Klaften* A65164/30, A62933/32, A79305/33, A28157/35, *Lissowetsky* A79322/30, A79323/33, *Schuschania* 2647/30, *Vollmar* A79414/30, *TeLinde* A64448/30, A65187/30, *Habbe* A65156/31, *Massazza* A79328/31, *Lastra et al.* A64785/31, *Rummeld* A65175/31, *Lepper et al.* A62935/32, *Brewer and Jones* A79259/32, A61456/33, *Nathan* A61623/32, *Dworzak* A66155/32, *Fauvet* A61750/32, *Plate* A61890/32, *Stefancsik* A79396/32, A79397/32, *v. Szathmary* A66215/32, A61900/33, A79402/36, *Daily* A61922/33, *Dougal* A79269/33, A79270/36, *Deutsch* A79267/33, *Kleine* A53171/33, A79312/35, *Lebowich* A79318/33, *Lellbach* A61760/33, *Schulze* A79390/33, *Wolfe and Kaminester* A62129/33, A62330/36, *Barzillai* A64730/34, *Cannon* A52089/34, *Muller* A52286/34, *Seelaus* A79392/34, *Bland and Goldstein* A52086/34, A27987/35, *Opitz* A28066/35, *Thornton* A27716/35, *Bailey* A79247/36, *Gospe* A59928/36, *Grevle* A59929/36, *Rockstroh* A62171/36, *Zikmund* 36746/36, *Solomons*

Footnote cont'd.

SECONDARY CHANGES IN FOLLICULOMAS AND IN THE REMAINING OVARIAN TISSUE: In the case of this very multiform neoplasm most of the secondary degenerative changes, which tend to occur in the tumor tissue itself, have been discussed separately with each histologic type (see above) for the sake of clarity. Suffice it to mention here that malignant folliculomas may damage the substance of the ovary and the neighboring organs by direct *invasion.* One enormous folliculoma of the granulosa cell-type appears to have originated in the retroperitoneal tissue and *spread* into the mesosigmoid.[1] It must be remembered, however, that the majority of these growths are benign. A folliculoma may also affect structures in its vicinity by *adhesion,* or *torsion* occasionally involving the Fallopian tube. Sometimes it compresses other pelvic organs and if it reaches a certain size it may completely fill out the pelvic cavity and become impacted in it. Folliculomas have also been known to cause prolapse of the vagina.[2] Other actions on adjacent organs will be discussed in the part on Complications below.

In the majority of the unilateral folliculomas the *contralateral ovary* remains normal. In some cases, however, there is compensatory atrophy of the opposite ovary.[3] This is not surprising since animal experiments proved that chronic overdosage with folliculoids causes involution of the ovary (see chapter dealing with the effect of folliculoids on the ovary; Sect. IV, Vol. IV).

FOLLICULOMAS IN COMBINATION WITH *OTHER OVARIAN TUMORS:* Folliculomas are not infrequently combined with a variety of different ovarian tumors, which may develop either in the same or in the contralateral ovary. Thus, simultaneously with folliculomas, *dermoids and teratomas*[4] have been observed. Indeed in one instance a granulosa cell tumor was claimed to have arisen in the wall of an ovarian dermoid;[5] this case is particularly noteworthy since normal gonadal tissue is consistently lacking even in the most complete embryomas

The occasional occurrence, within folliculomas, of *cartilaginous* islets,[6] *struma* tissue[7] or *chorionepithelioma*-like *growths*[8] may also be interpreted as a combination of the follicle tumor with teratoid blastomas.

Not infrequently, we encounter the combination of folliculoma and *arrhenoblastoma.*[9] In some instances such morphologic pictures may have been confused with mixed folliculoid-tubular folliculomas, yet in others signs of virilization proved the bisexual nature of the ovarian blastoma.

The combination of folliculoid folliculomas with *seminomas* is rare.[10]

One blastoma[11] has been considered to be a mixture of a folliculoma with a *luteoma,* but it would appear preferable perhaps to regard tumors of this type as instances of "folliculome lipidique" with partial luteinization.

Folliculomas also occur in combination with *fibromas,*[12] *papillary cystomas,*[13] *pseudomucinous cysts*[14] and even "*Krukenberg tumors*".[15]

In one particularly interesting case a folliculoma occurred in combination with an *endometrioma* of the ovary and the latter underwent active proliferation, apparently under the influence of the folliculoid hormones produced by the former.[16]

FOLLICULOMAS IN COMBINATION WITH EXTRAOVARIAN TUMORS: In a comparatively large number of cases, especially in those of the carcinomatous type, *metastases* have been found in various organs.[17] One author[18] estimates that about 5-10% of the folliculomas tend to metastasize and recur after operation. In another series[19] 3 out of 33 patients died from metastases and 2 from postoperative recurrences. In a third series of 80 patients[3] 5% suffered from metastases or post-operative recurrences. If the papillary serous cystadenocarcinoma is to be included among the folliculomas (for rationale see above), the percentage of metastases must be regarded as even higher since these are rather malignant tumors.

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[10]cont'd A93763/36, *Iwanow* A95263/37, *Higuchi and Yamashita* A97150/38, *Diaz Colodredo* A97143/38, *Holland and McHugh* A97281/38, *Bernhart* A32090/39, *Nunes* A97428/39, *Shaw and Gluckman* A97591/39, *Mitra* A96634/40, *Delascio* A97789/40, A97539/41, *Kimura and Higuti* A97555/41, *Osorio Gil* A97817/41, *Peralta Ramos and Colmenarez* A96934/42, A96933/42, *Mackey* A97810/42, *Holmes and Hauck* A97802/42.

[1]*Voigt* A93785/38.

[2]*Miller* A18279/37.

[3]*Klaften* A62933/32.

[4]*Spalding* A76547/19, *Plate* A61890/32, *Klaften* A52117/34, *Bach and Montgomery* A36705/41, *Murray et al.* A55811/42.

[5]*Vasek* A97189/38.

[6]*Jung* A70546/04, *Schiller* A64834/34, *Solomons and Dockeray* A35157/40.

[7]*Frankl* A65149/31, *Murray et al.* A55811/42.

[8]*Klaften* A52117/34.

[9]*Meyer* A64437/30, A64798/30, A64174/31, *Amati* B234/32, *Novak and Long* A61572/33, *Brauer* 5536/33, *Schiller* A62173/35, *Solomons and Dockeray* A35157/40.

[10]*Föderl* A96495/38, *Sailer* A34954/40.

[11]*Vayssiere et al.* A64859/36.

[12]*Meyer* 4508/25, *Babes* A64729/28, *Habbe* A65156/31, *Klaften* A28157/35, *McGoldrick and Lapp* B6256/44.

[13]*Mayer* A64796/18, *Müller* A64810/34, *Tyrone and Weed* A36891/41, *Froldi* A98116/41.

[14]*Edwards* A79273/32, *Schiller* A64834/34.

[15]*Gobbi* A93811/34.

[16]*Novak and Brawner* A64816/34.

[17]*Soltmann* 5537/32, *Holmer* A61408/33, A53041/34, *Varangot* 68667/37, *Seegar and Jones* A32004/39, *McCartney* A32575/40, *Froldi* A98116/41, *Harris* A62912/42.

[18]*Novak* A61968/33.

[19]*Meyer* A65111/31.

Typical folliculomas have been observed to metastasize in the lymph nodes, uterus, vagina, peritoneum, liver, adrenal, appendix, lung, vertebrae and ribs.[1]

CHEMICAL COMPOSITION

The chemical composition of folliculomas has not been studied in any detail but it is known that they contain large quantities of cholesterol phospholipids and neutral fats.[2] In one carefully analyzed thecoma the total lipid content was 17%, the cholesterol content 3% and the phosphatid content 0.4%.[3]

INCIDENCE

The incidence of folliculomas is difficult to estimate because of the different interpretation given by various authors to the folliculoma concept. One author[4] claims to have collected as many as 50 cases in a group of 251 primary ovarian carcinomas. However, re-examination of this same material by another author[5] revealed that there is considerable doubt concerning the identity of many blastomas and the latter investigator accepts only 16 clinically benign and 8 malignant tumors of this series as folliculomas.

Among 76 ovarian carcinomas collected by one author during a period of 3 years 8 were folliculomas.[6] Another worker[7] diagnosed 10 of 47 ovarian carcinomas as deriving from the granulosa. On the other hand, in one series or 139 ovarian carcinomas only 9 folliculomas were found.[8] Perusal of several other pertinent series of observations revealed the following incidence rates: 6 folliculomas out of 506,[9] 6 out of 302,[10] 2 out of 77,[11] 10 out of 180[12] and 7 out of 327[13] ovarian neoplasms.

In a carefully examined series of 300 ovarian carcinomas[14] 42 were shown to be folliculomas. Later Novak[15] collected 68 cases and expressed the view that about 10% of all primary ovarian carcinomas belong to this group. Among 400 solid ovarian neoplasms studied by another worker[16] 30 were diagnosed as granulosa cell tumors. These figures clearly indicate that the folliculoma is not as rare as was previously thought; yet definite statistical calculations would be premature on the basis of the existing literature in which the definition of this tumor is not uniform.

Folliculomas may occur at any *age*. Probably the youngest patient ever observed to suffer from this tumor was 14 weeks old.[17] The age in other carefully investigated instances of folliculomas in children was 14 months,[18] 17 months,[19] 2 years,[20] 3 years,[21] 4 years,[22] 5 years,[23] 7 years,[24] 9 years,[25] 11 years[26] and 12 years.[27] Many other cases have been observed in children[28] and it is well known that most of these tumors tend to produce precocious pseudopuberty. It is highly probable that the majority, if not all of the cases recorded in the early literature as ovarian sarcomas of carcinomas conducive to precocious pseudopuberty, also belong to the folliculoma group.

On the other hand, folliculomas have also been described in elderly women whose age varied between 63 and 71 years;[29] occasionally such growths even occurred in women 80[30] and 92 years.[31]

It has been claimed that thecomas tend to occur later in life than other folliculomas,[32] but more statistical data will be necessary before this statement can be definitely accepted. Many of the folliculomas found in young children are very undifferentiated and of the sarcomatoid type. The papillary granulosa cell carcinoma, on the other hand, usually occurs at, or after, the menopause.[33] Considering all types of folliculomas conjointly as a single group, the age incidence recorded by the various investigators may be summarized in the following table:

[1] *Miller* A18279/37.
[2] *Traut et al.* A33606/39, *McIlroy* A34556/39, *Stabler and Thomson* A33350/40.
[3] *Morales and Boggino* 84014/43.
[4] *Kermauner* A64880/32.
[5] *Schiller* A64834/34.
[6] *Fauvet* A61750/32.
[7] *Klaften* A62933/32.
[8] *v. Szathmary* A61900/33.
[9] *Adrian* A64722/35.
[10] *Lynch* A59465/36.
[11] *Shaw* A61532/32, A61896/33.
[12] *Pund* A32330/39.
[13] *Meigs* 33256/35.
[14] *Novak and Gray* A61851/36.
[15] A83009/38.
[16] *Dockerty* A31809/39.
[17] *Zemke and Herrell* A37341/41.
[18] *Eerland* A61747/32, A79275/32, A79276/34.
[19] *Fuller and Smith* A37138/41.
[20] *Astner* A93851/36, *Sein* A30779/38, *Gross* A97376/40.
[21] *Eastlake* A64218/31, *Zikmund* 36746/36.
[22] *Anderson and Sheldon* A95051/37, A93792/39, *Mannheimer* A96512/38, *Wyatt* A34533/39.
[23] *Rummeld* A65175/31, *Görög* A93854/38, *Wyatt* A93861/39.
[24] *Klaften* A53045/34, A53046/34.
[25] *Pahl* A66185/31.
[26] *White* A34535/39, A93862/39.
[27] *Tesoriere* A96645/41.
[28] *Pahl* A66185/31, *Novak* A61968/33, *Bland and Goldstein* A79253/34, *Klaften* A53046/34, A53045/34, *Witzberger and Agerty* A95127/37, *Hare* A93855/37, *Harms* A79291/37, *Parks* A93858/38, *Cornil and Schachter* A98148/41.
[29] *v. Szathmary* A28075/35, *McIlroy* A34556/39, *Russell* A36410/40.
[30] *Stabnick* A93868/40.
[31] *Patterson and McCullagh* A70204/36.
[32] *Henderson* A37766/42.
[33] *Seegar and Jones* A32004/39.

Investigator	No. of Cases	Decade								
		I	II	III	IV	V	VI	VII	VIII	Doubtful
Habbe[1]	33	1	1	1	5	8	7	4	4	2
v. Szathmary[2]	120	3	6	10	26	22	33	20	—	—
Novak and Brawner[3]	36	5	1	5	8	13	3	1	—	—
Bland and Goldstein[4]	150	8	7	12	23	30	41	29	—	—
Varangot[5] (Review)	250	12	6	24	53	59	55	29	12	—
Miller[6] (Review)	128	10	8	17	18	36	21	10	2	6

It will be seen from the above table that the highest incidence is at or after the menopause, although cases have occurred at any age. A review of 53 folliculomas collected by the Society of Gynecological Pathologists of New York[7] indicates that nearly 70% had occurred prior to, or during the menopause, and 30% after its advent. The highest incidence was between 30 and 50 years.

Insufficient data are available to make any general statement concerning the *racial incidence* of folliculomas. The vast majority of the published cases occurred in white females, but the disease is certainly not limited to this race since folliculomas have also been noted in Javanese,[8] Burmese[9] and Negro patients.[10]

It has been claimed that "constitutional *stigmata*" are common in patients who develop folliculomas[11] but this view requires confirmation.

The *pregnancy incidence* of folliculomas is undoubtedly very low. One instance[12] of a large theca cell tumor and[13] of a granulosa cell neoplasm in one pregnant women are on record. There are also two instances of adenoma-like hyperplasia of the theca in pregnant women[14] and it is well established that the theca and the ovarian Leydig cells tend to hypertrophy during gestation (see Sect. IV, Vol. IV). It may be stated, however, that although many ovarian tumors proliferate actively in pregnant women, folliculomas are comparatively rare at this time. In this connection it is well to bear in mind that the hyperfolliculoidism caused by these tumors would be incompatible with subsequent conception.

PATHOGENESIS

Little is known about the *histogenesis* of folliculomas. It has been pointed out[15] that even during their earliest development these tumors resemble the *granulosa epithelium*. v. Werdt[16] expressed the view that they are derived from *Walthard's cell nests*, which in turn are granulosa-like formations originating in the germinal epithelium. It has been claimed[17] that these tumors are formed from fully developed granulosa cells, but this view was firmly rejected[18] on the basis of evidence suggesting that fetal granulosa precursors and not completely differentiated cells are the matrix of such tumors. Experimental work (see chapter on Folliculomas in Animals), on the other hand, gives some support to the concept that even mature granulosa cells are capable of neoplastic transformation.

It will be recalled that the same embryologic primordia form both the granulosa and the theca cells, hence it is perhaps not too far-fetched to assume that they may produce tumors in which either of these two potentialities can become manifest. It has been said[19] that the granulosa develops from the mesenchyme of the ovary rather than from the germinal epithelium. If we accept this view, the development of sarcomatoid tumors and fibroma-like theca cell growths is readily understandable.

Attention has been called to the fact[20] that the metastatic Krukenberg tumors of the ovary exhibit a definite tendency to grow in a fibroma- or sarcoma-like manner and that their carcinomatous nature was not recognized until quite recently; it is curious that in the case of the folliculomas, (which were originally considered to be epithelial growths) our views appear to develop in the opposite direction.

The great similarity between the typical *basal cell carcinomas* of the skin and mucous membranes and the granulosa cell tumors has also been emphasized.[20] Perusal of Krompecher's[21] classical monograph on

[1]A65156/31.
[2]A61900/33.
[3]A64816/34.
[4]A27987/35
[5]68667/37.
[6]A18279/37.
[7]*Traut and Marchetti* A33420/40.
[8]*Eerland* A79276/34, A79275/32.
[9]*Sein* A30779/38.
[10]*Novak* A61968/33, *McDonough* A95284/37.
[11]*Aschner* A64727/22.
[12]*Kusuda* A82387/25.
[13]*Slamova* A96549/37.
[14]*Dubreuil* A38140/41.
[15]*Meyer* A76843/12.
[16]A64866/14, 79417/14.
[17]*Robinson* A67262/30.
[18]*Meyer* A65111/31.
[19]*Fischel* A53999/30.
[20]*Miller* A18279/37.
[21]A79314/03.

the carcinomas which now bear his name, reveals many similarities between the basal cell tumors and the granulosa cell carcinomas, although the relationship between the two is still not understood. We must not disregard the possibility that the celomic basal cell may give rise to the granulosa cell tumors,[1] although there is no definite evidence to support this view.

We have no definite information concerning the *functional pathogenesis* of folliculomas. The high incidence at, or just preceding, the menopause and the occasional occurrence of theca adenomas during pregnancy, imply that such pronounced *changes in the hormonal equilibrium* (increased gonadotropic hormone production?) as occur during these phases of life may play an etiologic role. Yet the fact that folliculomas can develop at any age indicates that such predisposing factors as menopausal and pregnancy changes are of only limited significance.

Some workers[2] claim to have produced folliculomas in intrasplenic ovarian transplants of spayed rats due to the excessive gonodotropic hormone production of such animals. But it is not certain that these growths were true blastomas (see also chapter on Folliculomas in Animals).

CLINICAL COURSE

As stated in the section on the pathologic anatomy of folliculomas, these tumors exhibit a remarkable degree of morphologic polymorphism. The histologic characterization of the various types need not be recapitulated here, but it is important to emphasize that the hormonal dysfunction caused by folliculomas, if any, is that of pure hyperfolliculoidism irrespective of histologic structure. Thus, benign granulosa and theca cell tumors, as well as granulosa cell carcinomas and sarcomatous growths of the folliculoma group, produce essentially similar endocrine disturbances.

The accessory sex organs exhibit signs of excessive stimulation. These are particularly striking if the tumors develop in very young children, in whom they produce the symptom complex of *precocious pseudopuberty*. There is a premature development and sometimes colostrum formation in the *breasts* which may become painful and tender to touch. The *labia and clitoris* are enlarged, there is premature growth of *pubic hair* and frequently precocious *uterine bleeding*[3] (see also passage on Age Incidence above).

The most striking changes occur in the *uterus* which tends to be enlarged and in children precociously developed. Metrorrhagias due to *metropathia hemorrhagica* are an almost constant finding in any age group. This may be accompanied by the formation of *endometrial polyps, endometriosis* and *uterine fibroids*.[4]

Even the metastases of folliculomas may stimulate the uterus, as shown by the case of a patient who developed metrorrhagia and a decidual endometrium (luteinization?) 20 years after ovariectomy for a granulosa cell cancer, at the time when generalized carcinomatosis ensued.[5]

In *post-menopausal* women, folliculomas usually elicit irregular *bleeding* which frequently gives rise to the erroneous diagnosis of endometrial carcinoma.[6] In one 63-year-old woman *pyometra* developed in conjunction with a granulosa cell tumor.[7]

It is claimed[8] that many tumors, hitherto classified as papillary serous cystadenocarcinomas, are in reality papillary granulosa cell carcinomas. If we accept this view, a large number of post menopausal metrorrhagias must be ascribed to hormone overproduction by growths of the folliculoma group. This view is supported by the observation that in older women these ovarian carcinomas are often accompanied by endometrial hyperplasia and painful breast engorgement. As we shall see in the passage dealing with the clinical manifestations of ovarian carcinomas, there is good evidence that many carcinomas—hitherto not considered to be related to the ovarian follicle—are hormonally active and can be the cause of secondary changes in the accessory sex organs.

[1] *Miller* A18279/37.
[2] *Biskind and Biskind* A69381/44.
[3] *Eastlake* A64218/31, *Novak* A61968/33, *Novak and Long* A61572/33, *Klaften* A53045/34, A53046/34, *Bland and Goldstein* A52086/34, A27697/35, *Zikmund* 36746/36, *Verebely* A9218/37. *Traut and Butterworth* 78785/37, *Sein* A30779/38, *Mannheimer* A96512/38, *Schattenberg and Harris* A32319/39, *White* A34535/39, *Wyatt* A34533/39, *Gross* A97376/40, *Fuller and Smith* A37138/41, *Lull* A36030/41.
[4] *Aschner* A79241/20, *Konschegg* A79313/23, *Babes* A79243/24, A79244/27, *Neumann* A79350/25, *Meyer* 4508/25, *Isbruch* A64772/26, *Schiffmann* A64831/26, *Scheyer* A64829/27, *King* A68133/29. *Hamant and Mosinger* A79290/29, *TeLinde* A64448/30, A65187/30, *Arnold and Mathias* A43354/30, *Schuschania* 2647/30, *Massazza* A79328/31, *Frankl* A65149/31, *Klaften* A62933/32, *Brewer and Jones* A61456/33, *Kleine* A53171/33, A79312/35, *Lellbach* A61760/33, *Novak* A51974/34, *Stürmlinger* A93984/34, *Cannon* A52089/34, *Opitz* A28066/35, *v. Szathmary* A28075/35, A79402/36, *Meigs* 33256/35, *Dreyfus* A59684/36, *Rockstroh* A62171/36, *Varangot* 71521/37, *Dockerty* A31809/39, A32558/40, *Traut et al.* A33606/39, *Dockerty and MacCarty* A31395/39, *McCartney* A32575/40, *Powell and Black* A34642/40, *Ragins and Frankel* A34641/40, *Barnes and Barnes* A34219/40, *Sailer* A34954/40, *Fallas and Rosenblum* A33798/40, *Bach and Montgomery* A36705/41, *Henderson* 83191/41, *Curtis* A38063/41, *Wolfe and Neigus* A36880/41, *Porter and Bramhall* A37837/41, *Danforth* A37764/42, *Harris* A62912/42, *Morales and Boggino* 84014/43, *Pastorini and Schlossberg* A98006/43, *McGoldrick and Lapp* B6256/44.
[5] *Arnold and Mathias* 43354/30.
[6] *Brakemann* A79258/29, *Huber* A96043/37, *Draganic* A97610/39, *Treite* A97719/40, *Reich et al.* 85466/44.
[7] *v. Szathmary* A95114/36.
[8] *Seegar and Jones* A32004/39.

It is of special importance to realize that in a significant number of folliculomas the hormonal stimulation of the endometrium by the excessive amounts of folliculoids was so pronounced that *uterine carcinomas* developed.[1] Indeed in one case an "adenoma malignum" of the endometrium regressed following removal of a granulosa cell tumor.[2]

In one case a bilateral tumor purported to be a folliculoma, caused slight uterine enlargement in a postmenopausal patient but *no bleeding or other signs of hyperfolliculoidism;*[3] however, in our opinion there may be some doubt concerning the true nature of this tumor.

A rare instance of a granulosa cell carcinoma led to *amenorrhea.*[4] Cases of this type are reminiscent of the virilizing folliculomas (see below) which are frequently accompanied by cessation of the menstrual flow.

It has been stated that folliculomas may render children *prematurely fertile.*[5] Perusal of the original articles, upon which this statement was based, reveals, however, that in these instances of pregnancy in children there was no evidence of a folliculoma. We therefore regard these cases as being due to true precocious puberty. In the light of contemporary endocrinology it is very difficult to believe that folliculomas could render children prematurely fertile since such tumors merely produce an excess of folliculoid hormones and are not accompanied by precocious ovogenesis or corpus luteum formation.

In one case of microcystic degeneration of the ovaries with marked luteinization of the theca interna, as well as some luteinization of the ovarian stroma,[6] the resulting syndrome was characterized *by virilization* indicating that testoid hormones may also be produced by theca cells (see also chapter on Testoid Hyperthecosis). Although strictly speaking these cases do not belong to the folliculoma group, they are mentioned here because of the thecal involvement. A masculine type of hirsuties occasionally accompanied by amenorrhea, deepening of the voice and a somewhat virile appearance is rather exceptional in typical folliculomas.[7] These symptoms are difficult to explain, especially since they do not necessarily subside after ablation of the tumor.[8]

In a pseudohermaphrodite with male external and female internal genitalia a gonadal tumor of folliculoma or sarcoma-like character was found.[9] Since in this case the anomaly of the accessory sex organs was congenital, a hereditary predisposition for the abnormal development of the gonad may be suspected.

Several investigators commented on *psychologic changes* in patients suffering from folliculomas. In children there may be a precocious development of libido.[10] In a woman aged 67 there were erotic delusions which, however, were regarded as an incidental accompaniment of the folliculoma.[11]

Development of *carcinomas* in the pancreas[12] and urinary bladder[13] have also been reported in bearers of folliculomas. It remains to be established whether these should be regarded as secondary to the production of carcinogenic substances by the ovarian growth.

Excessive *somatic growth* has been reported in some children.[14]

The *basal metabolic rate* is sometimes slightly above normal.[15]

There may be *ascites*[16] and a folliculoma of the theca cell-type may even produce both ascites and pleural effusions.[17] In one instance[18] a granulosa cell tumor was associated with hemoperitoneum and hemothorax which were not due to carcinomatosis or any other obvious cause. The question arises whether there could be any relationship between these cases and the well known "Meigs' syndrome" of ovarian fibromas with ascites and hydrothorax.

COMPLICATIONS

The clinical course of the syndrome produced by folliculomas may be complicated by torsion of the tumor, hemorrhage, metastases, or invasion into neighboring organs. A discussion of these factors, as well as the influence of age, pregnancy, and race will be found in the passage devoted to the pathologic anatomy of folliculomas.

DIAGNOSIS

As a rule, the diagnosis of folliculomas is not very difficult because of the typical coexistence of *local signs* characteristic of an ovarian tumor with *general*

[1] *Schröder* A64836/22, *Tietze* A79409/27, *Russell* A36410/40, *Dockerty and MacCarty* 77976/40, *Tyrone and Weed* A36891/41, *Elton* A98110/42, *Henderson* A37766/42, *Kirshbaum* A63370/43, *Ingraham et al.* B7051/44.
[2] *Stohr* A55557/42.
[3] *McDonough* A95284/37.
[4] *Gianella* A93798/38.
[5] *Schattenberg and Harris* A32319/39.
[6] *Turner* A61334/43.
[7] *Klaften* A63164/30, *Kermauner* A73104/32, *Schiller* A64834/34, A62173/35.
[8] *Robinson* A64827/23.
[9] *Bauer* A79441/33.
[10] *v. Verebely* A9218/37.
[11] *Russell* A36410/40.
[12] *Dockerty and MacCarty* 77978/39.
[13] *Opitz* A28066/35.
[14] *Varangot* 68667/37, *v. Verebely* A9218/37.
[15] *Klaften* A65164/32, A28157/35.
[16] *Schmelz* A79385/27, *v. Szathmary* A61900/33, *Klaften* A53046/34, *Morales and Boggino* 84014/43.
[17] *Perlmutter* A71795/44, *Rubin et al.* B6263/44.
[18] *Vogt* A34640/40.

manifestations of folliculoid hormone overdosage. In prepubertal girls, this endocrine disturbance causes precocious pseudopuberty, while in adults, metropathia hemorrhagica, with the accompanying irregular bleeding, are the prominent features.

Early investigators devoted a great deal of attention to possible diagnostic signs permitting the clinical differentiation of hyperfolliculoidism due to folliculomas from that due to "sarcomas", "alveolar carcinomas" and other ovarian tumors. In view of the great histologic polymorphism of folliculomas, it appears highly questionable whether it is necessary to assume that tumors other than those of the folliculoma group can elicit this same clinical syndrome.

Within the folliculoma group there is no very close relationship between the histologic type of the growth and its hormone-producing ability, hence it is impossible to foretell the morphologic structure of a folliculoma from its clinical manifestations. It should be kept in mind, however, that the sarcomatoid type is frequent in children and usually develops very rapidly.

The flooding of the organism with *folliculoid hormones,* accompanied by a diminution in the formation of *gonadotropic hormones,* may be directly determined by estimating their concentration *in the blood and urine.* The relevant literature—as well as that concerned with the hormone content of the tumor itself—has been discussed in the volumes on Ovarian and Hypophyseal Hormone Metabolism respectively (Sect. IV, Vol. V and Sect. III, Vol. V).

From a differential diagnostic point of view it is important to remember that simple *follicle retention cysts* and *small-cystic degeneration* of the ovaries may cause the same type of hyperfolliculoidism as is produced by folliculomas. This is probably also true of certain tumors hitherto classified as *common ovarian carcinomas* especially of the serous papillary type (see chapter on Common Carcinomas).

Occasionally folliculomas have also been confused with *ectopic pregnancy.*[1] The past history of the patient, gonadotropic hormone estimations in the urine, and the absence of deciduomatous changes in the endometrium, will usually permit correct diagnosis. These same characteristics will also help to avoid confusion with *normal gestation,* an error which occurred only in a few cases.[2]

Precocious pseudopuberty due to the *adrenogenital syndrome* may also be the cause of confusion but it will be remembered that, unlike folliculomas, adrenal tumors tend to produce marked signs of virilism and are accompanied by an increased 17-ketosteroid excretion. For differentiation from other types of precocious pseudopuberty and true precocious puberty, see the chapters devoted to these latter conditions.

In post-menopausal women continuous bleeding must always raise the question of a possible uterine carcinoma, polyps, submucous fibroma, senile endometritis etc. The diagnosis of these conditions will be facilitated by endometrial biopsies, hysterosalpingography and the general clinical history.

It is especially noteworthy that in a few cases typical *folliculoid carcinomas were observed to cause no signs of hormone overproduction,*[3] probably because their cells were too immature to be functional.

PROGNOSIS

The course of the folliculomas is extremely variable. In some patients the tumors grow very slowly, while in others they enlarge at a rapid rate. In the great majority of these patients, the tumor is removed as soon as it is recognized, hence few recorded instances are suitable for the formulation of the prognosis in untreated cases. It should be kpet in mind, however, that highly differentiated types of granulosa and theca cell tumors grow slowly and have little tendency to metastasize, while malignant folliculoid carcinomas and sarcomas are likely to grow rapidly, to infiltrate into neighboring organs, and to metastasize. In some granulosa cell carcinomas removal of the growth effects an apparently permanent cure;[4] in other instances recurrences were noted.[5]

A statistical analysis of the follow-up records of 20 operated cases[6] is summarized in the following table:

No. of Cases	State at time of Last Follow-up	Duration of Follow-up
5	Alive and well	7-12 years
6	Alive and well	4-6 years
7	Alive and well	1-3 years
1	Died post-operative	21 days
1	Died from recurrence	3 months

[1]*Hörmann* A64769/28, *Stefanczik* A79397/32, *Schiller* A64834/34 *Bach and Montgomery* A36705/41.
[2]*Schiller* A64834/34, *Novak and Brawner* A64816/34.
[3]*Daily* A61922/33, *Wolfe and Kaminester* A62129/33.
[4]*Gross* A97376/40.
[5]*Schultze* A95321/37, *Countiss* A92243/38.
[6]*Henderson* 83191/41.

The data on 30 patients observed at the Mayo Clinic between 1910—1937[1] may be summarized as follows:

Age	Symptoms	Duration Symptoms	Operative procedure	Pathologic findings		Outcome
				Fibroid	Cystic Endometrium	
37	Amenorrhea Tumor	12 years 8 years	Local*	0	—	Living 19 years
31	Amenorrhea	2 years	Local	0	—	Living 15 years
39	Amenorrhea Constant flow	18 months 2 months	Local	0	+	Living 9 years
33	Amenorrhea Menorrhagia	2 years 1 year	Local	—	—	Died 3 days post-operative
38	Amenorrhea and menorrhagia	5 years	Total△	0	+	Living 9 years
25	Amenorrhea Metrorrhagia	18 months 3 months	Total	+	+	Living 9 years
17	Amenorrhea	1 year	Local	—	—	Living 2 years
26	Constant flow	1 year	Local	—	—	Living 20 years
48	Menorrhagia	5 years	Local	—	—	Not traced
50	Menorrhagia	1 year	2 local operations	—	—	Recurrence?
40	Amenorrhea	1 year+	Total	0	+	Living 8 years
47	Amenorrhea and menorrhagia	2 years	Total	+	+	Living 5 years
51	Periodic bleeding	2 years	Total	0	+	Living 5 years
63	Periodic bleeding	10 years	Total	+	+	Living 6 years
72	Bleeding	2 weeks	Total	0	+	Died, 5½ years later*△
60	Periodic bleeding	3 months	Total	+	+	Living 6 years
60	Periodic bleeding	3 months	Total	0	+	Living 8½ years
70	Periodic bleeding	4 years	Total	0†	+	Living 4½ years
58	Continuous bleeding	6 months	Total	+	+	Living 10 years
61	Irregular spotting	20 years	Total	+	+	Living 3½ years
51	Periodic bleeding	1 year	Total	+	+	Living 9 years
55	Periodic bleeding	4 years	Total	+‡	+	Died 10 months later
62	Periodic spotting	5 years	Total	0	+	Died 10 days later
59	Irregular bleeding	5 years	Total	0†	+	Living 7 years
58	Irregular and periodic bleeding	4 years	Total	0	+	Living 17 years
56	Menorrhagia and metrorrhagia	1 year	Total	0	+	Not traced
69	Slight irregular bleeding	3 years	Total	0	+	Living 15 years
77	Bronchial pneumonia	1 week	No operation	0	+	Necropsy
61	Bleeding	1 month	Total	0	+	Living 10 years
62	Recurrent periodic bleeding	8 months	Total	+	+	Living 11 years

**Operative resection of tumor only.*
△Total abdominal hysterectomy and bilateral salpingo-oophorectomy.
**△Died of unknown cause.*
†Carcinoma of fundus of uterus.
‡Died of cerebral hemorrhage.

[1]*Dockerty* A31809/39.

THERAPY

In all cases of folliculoma the therapy should be *surgical* whenever possible. Some surgeons try to perform a simple ovariectomy whenever there is no reason to suspect infiltrative growth into the neighboring organs. Others remove both ovaries and the uterus as a matter of routine, irrespective of the nature of the tumor. The technical and theoretical considerations which may influence one's choice have been discussed in some detail by those who practice these operations for the removal of folliculomas.[1] In general, it may be stated that if the tumor is very small, limited to one ovary and apparently benign, simple ovariectomy is the operation of choice. This is true especially in young women and children, while with bilateral folliculomas if there is any cause to suspect ovarian malignancy and especially in elderly women, simultaneous hysterectomy is clearly preferable in view of the comparatively common association of folliculomas with uterine cancer. (For follow-up records of surgically treated cases, see part on Prognosis). After the operation, the signs of hyperfolliculoidism disappear rapidly and in children the excessively developed accessory sex organs return to the infantile condition. If there is any reason to suspect metastases, and especially if these have actually developed, X-ray treatment should be applied after the operation.

Folliculomas, and particularly those of the granulosa cell type, have been claimed to be especially sensitive to *X-rays*.[2] Even a folliculoma, which recurred after operation, appears to have been successfully treated by roentgen irradiation.[3] In general it must be admitted, however, that the reports concerning X-ray treated cases give little hope of a permanent cure, although there is frequently an initial period of transitory *involution*.[4] In fact in one unusual case[5] a granulosa cell carcinoma developed after X-ray castration for myoma and endometrial hyperplasia. While it is possible that in this case the uterine changes were the consequence of a latent, but pre-existent folliculoma, the fact remains that growth of the tumor occurred after X-ray castration.

The few instances in which *radium* treatment was attempted are likewise not very encouraging, although transitory benefit may be obtained.[6]

In conclusion it may be said that the available evidence certainly gives first choice to surgical treatment; radiation therapy should not be employed except in patients with widespread, inoperable, malignant folliculomas or in those in whom metastases and recurrences following an operation make additional surgical interventions impossible.

[1] *Delepine and Augier* A79265/03, *Eastlake* A64218/31, *Dreyfus* A59684/36, *White* A34535/39, *Wyatt* A34533/39, *Bernhart* A32090/39, *Russell* A36410/40, *Dockerty and MacCarty* 77976/40, *Stabler and Thomson* A33350/40, *Henderson* A36837/41, 83191/41, *Lull* A36030/41, *Fuller and Smith* A37138/41, *Stohr* A55557/42.

[2] *Kleine* A61566/33.

[3] *Walthard and v. Werdt* A79415/22.

[4] *Schulze* A79390/33, *Wolfe and Kaminester* A62129/33, A62330/36, *v. Szathmary* A61900/33, *Opitz* A28066/35, *Herrmann* A93769/35, *Traut and Marchetti* A33420/40, *Dockerty and McCarty* A97401/40, *Henderson* A36837/41, *Fallas* A56094/42.

[5] *Scheyer* A64829/27.

[6] *Studdiford* A93778/37.

OVARIAN FOLLICULOMAS IN ANIMALS

Typical granulosa cell tumors may occur spontaneously in animals[1] although they appear to be much less frequent among the lower mammals than they are in women.

While studying the effect of X-rays on the incidence of ovarian tumors in *mice* it has been found that among animals kept to senility, X-ray treatment increases the incidence of ovarian tumors to about 15 times that in control stock.[2] A histologic analysis of these neoplasms revealed that a large number of them are granulosa cell tumors. They are apparently derived from surviving elements in the cell nests formed from normal follicles, after most of the granulosa cells and the ova degenerated under the influence of the X-rays.[3] The tumors have been successfully grafted to related mice.[4] A subsequent detailed study of this subject revealed that in the ovaries of X-rayed mice, the granulosa cell tumors tend to become the site of lipid deposition and thus resemble the so-called "folliculome lipidique of Lecène". These luteinized ovarian tumors are apparently derived from undifferentiated parenchyma. While the theca cells participate in the early proliferation and luteinization, mature granulosa cells appear to play no role in the genesis of these neoplasms. The fact that the luteinized granulosa cells of the neoplasms are hormonally active is clearly shown by the proliferative changes which take place under their influence in the endometrium and vaginal mucosa (cystic hyperplasia of endometrium and cornification of the vagina).[5]

In mice of the CBA strain a spontaneous, malignant, papillomatous granulosa cell tumor was observed. It was readily transplantable and produced signs of hyperfolliculoidism.[6]

[1] *Baumann* A79248/35, *Weyel* A79419/36.
[2] *Furth and Furth* A64757/36.
[3] *Furth and Butterworth* A59927/36, *Traut and Butterworth* 78785/37.
[4] *Furth and Boon* B144/45.
[5] *Geist et al.* A33605/39.
[6] *Strong and Hill* 68575/37, *Strong et al.* 68576/37, 83148/38.

PLATE V

FOLLICULOMAS

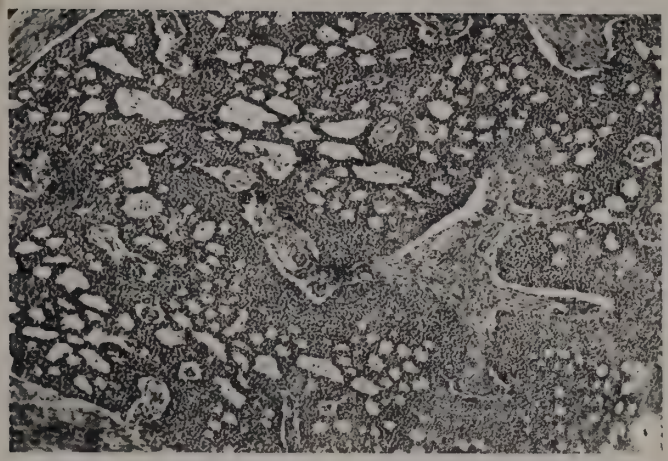

Fig. 1. FOLLICULOID GRANULOSA CELL TUMOR (courtesy of Dr. H. T. Karsner). Characteristic folliculoid pattern in a prevailingly epithelial field. Some of the small follicle-like cavities contained coagulated fluid and cell debris, remotely resembling degenerating ova.

Fig. 2. FOLLICULOID GRANULOSA CELL TUMOR. Another field of the tumor shown in Fig. 1. Note that here epithelial and stroma elements are about equally represented.

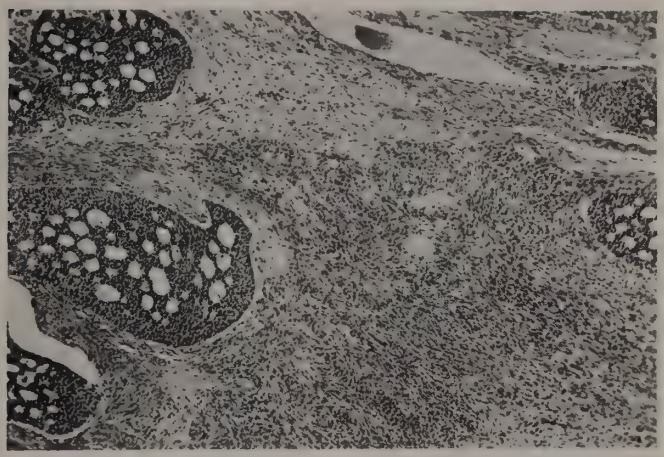

Fig. 3. FOLLICULOID GRANULOSA CELL TUMOR. Yet another field of the neoplasm illustrated in Figs. 1 and 2. Note that here stroma elements definitely predominate and assume a fibroma, or thecoma-like appearance.

Fig. 4. DIFFUSE GRANULOSA CELL TUMOR (courtesy of Dr. H. T. Karsner). Higher magnification of a typical field in a diffuse granulosa cell tumor. Some of the cells are oblong, almost spindle-shaped. In such instances, differentiation from thecomas may be difficult.

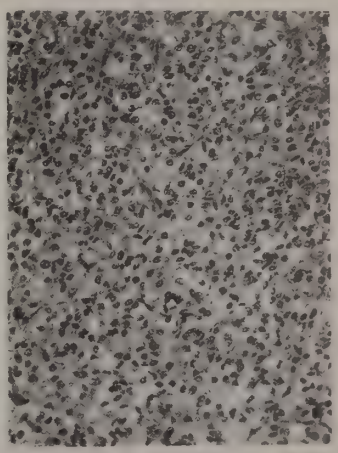

Fig. 5. "FOLLICULOME LIPIDIQUE" OF LECENE (courtesy of Dr. H. T. Karsner). Partially-luteinized region in a granulosa cell tumor. On purely histologic grounds this type is often difficult to differentiate from luteomas; indeed, it is quite possible that this neoplasm represents a transition between the pure granulosa cell tumor and the luteoma.

Fig. 6. THECOMA (courtesy of Dr. H. Karsner). Characteristic fibroma-like structure of a typical, pure thecoma.

Fig. 7. RETROGRESSIVE CHANGES IN THECOMA. Another region of the tumor illustrated in Fig. 6. Note intercellular edema (left part of field) and extensive hyaline plaques (right side of field) both representing retrogressive changes commonly observed in thecomas.

PLATE VI
FOLLICULOMAS

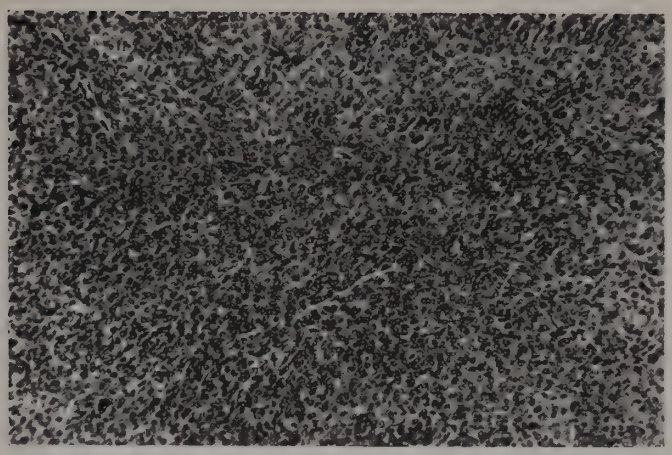

Fig. 1. DIFFUSE GRANULOSA CELL TUMOR (courtesy of Dr. L. Berger). The entire field consists of closely packed typical granulosa cells. The patient was 48 years old; her menstrual cycles were irregular during the last year and there was hypermenorrhea and dysmenorrhea. The former was so severe that secondary anemia ensued. The endometrium was atrophic but showed small, cystically-dilated glands.

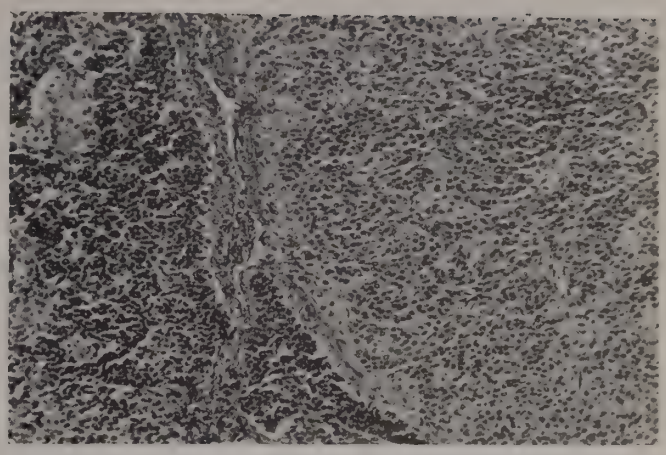

Fig. 2. PARTIALLY LUTEINIZED GRANULOSA CELL TUMOR (courtesy of Dr. L. Berger). Typical diffusely arranged granulosa cells (left side of field) and partially luteinized cells (right side of field) are seen side by side within the same tumor. 54-year-old patient who never underwent a typical menopause but had irregular menstrual bleeding with hypermenorrhea during the two previous years; the bleeding periods lasted 15 to 21 days as a rule.

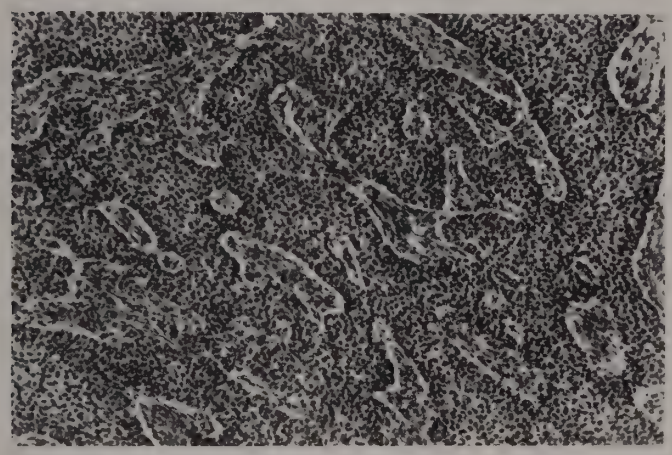

Fig. 3. TRABECULAR GRANULOSA CELL TUMOR. Another region of the neoplasm shown in Fig. 2. Note that here the cell arrangement follows a coarse trabecular pattern.

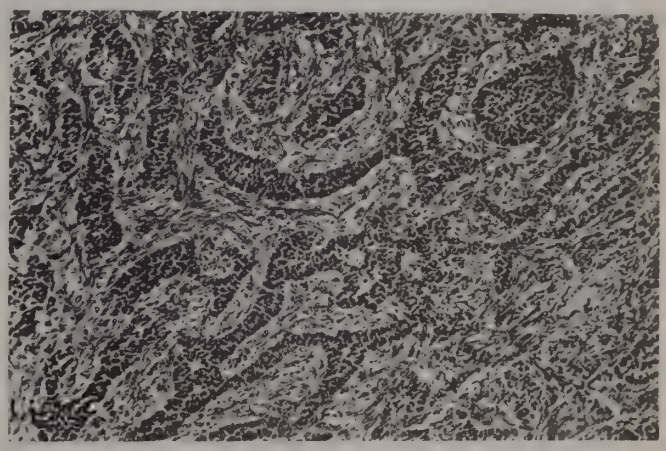

Fig. 4. PLEXIFORM GRANULOSA CELL TUMOR (courtesy of Dr. L. Berger). Granulosa cell tumor in which the epithelial components are arranged in a plexiform pattern, consisting of solid, narrow, interlacing and anastomosing trabeculae. Note the thecalization of the stroma cells. The patient was 44 years old and suffered from repeated severe menorrhagias.

Fig. 5. GYRIFORM GRANULOSA CELL TUMOR (courtesy of Dr. L. C. Simard). Note the characteristic gyriform arrangement of the granulosa cells. The epithelial columns are almost invariably two cells deep and thus resemble narrow tubules but there is no distinct central lumen.

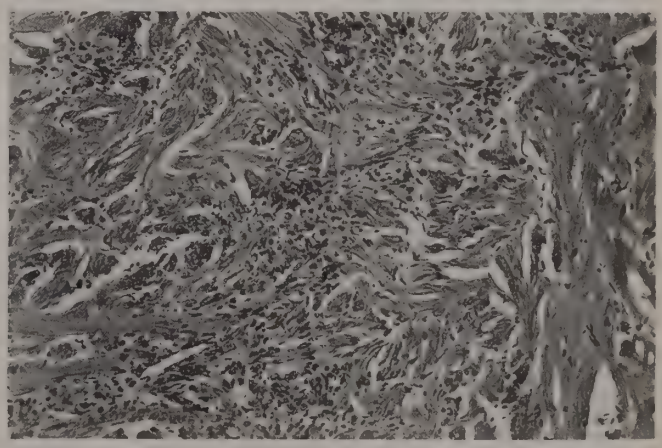

Fig. 6. HYALINIZED THECOMA WITH EPITHELIOID CELLS (courtesy of Dr. L. Berger). This roundish tumor measured about 2 inches in diameter and exhibited the same pattern throughout. Note the extremely dense fibrous tissue stroma with irregular islets of "epithelioid" cells. The 42-year-old patient suffered from polymenorrhea (bleeding every 18 days) and hypermenorrhea (duration of bleeding 8 days). Special stains revealed that the epithelioid cells are rich in fat granules.

PLATE VII

FOLLICULOMAS

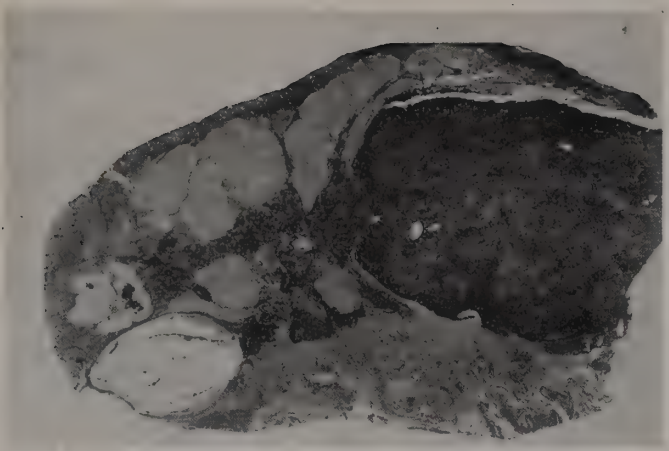

Fig. 1. SMALL SUBCAPSULAR THECOMA (courtesy of Dr. L. Berger). General view of an ovary containing a small subcapsular thecoma. The patient was 64 years old and suffered from occasional slight post-menopausal metrorrhagias during the last 2 years. The endometrium showed only slight metropathia hemorrhagica but there was extensive internal endometriosis.

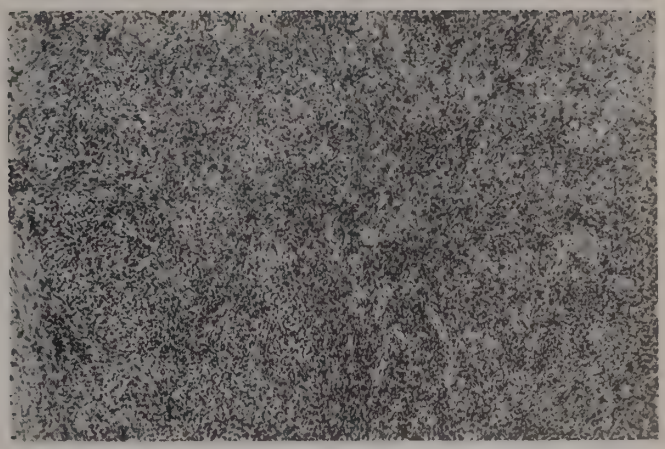

Fig. 2. THECOMA. Higher magnification of an area in the thecoma shown in Fig. 1. The tumor consists partly of typical, spindle-shaped thecal cells and partly of "epithelioid" cells. The latter (mainly in right side of field) are very reminiscent of diffuse granulosa cell tumors.

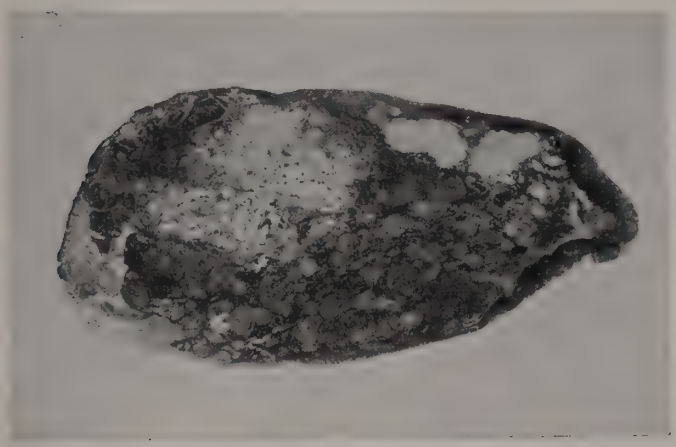

Fig. 3. SMALL SUBCAPSULAR, PARTLY PAPILLARY GRANULOSA CELL TUMOR (courtesy of Dr. P. Masson). General view of an ovary with an extremely polymorph granulosa cell tumor, containing irregular cystlets with pseudopapillary excrescences (visible even at this low magnification). The patient was 62 years old and suffered from a cancerous polyp of the corpus uteri.

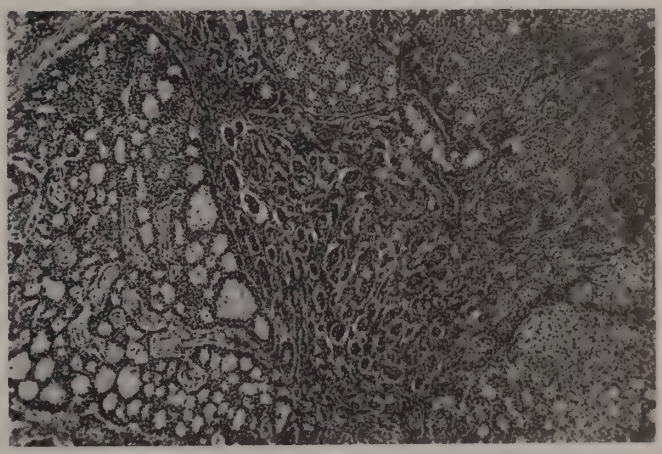

Fig. 4. POLYMORPH GRANULOSA CELL TUMOR. Higher magnification of a field in the tumor shown in Fig. 3. Within the same field we see tubular (center of the field), diffuse (right side of the field) and microcystic (left side of the field) cell arrangements.

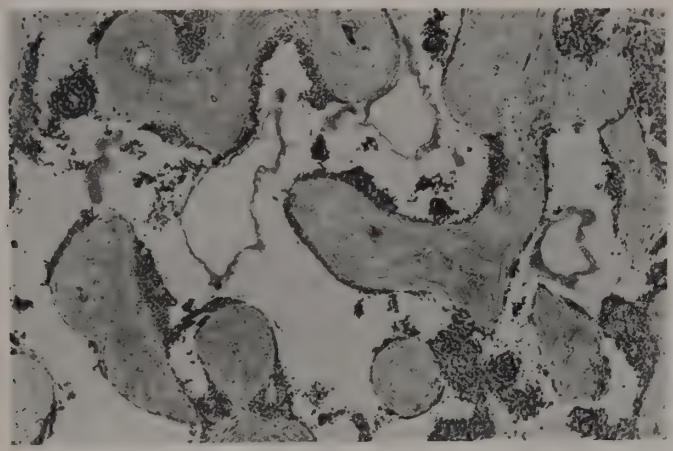

Fig. 5. POLYMORPH GRANULOSA CELL TUMOR. Another region of the growth illustrated in Figs. 3 and 4. Note "pseudopapillary" formations, consisting of dense hyalinized, connective tissue trabeculae, surrounded by irregular layers of granulosa cells. The pseudopapillary appearance is due to degeneration of diffusely-arranged granulosa cells between the branching, connective tissue septa. In some regions the latter are devoid of a lining, in other places they are covered by a few granulosa cell layers.

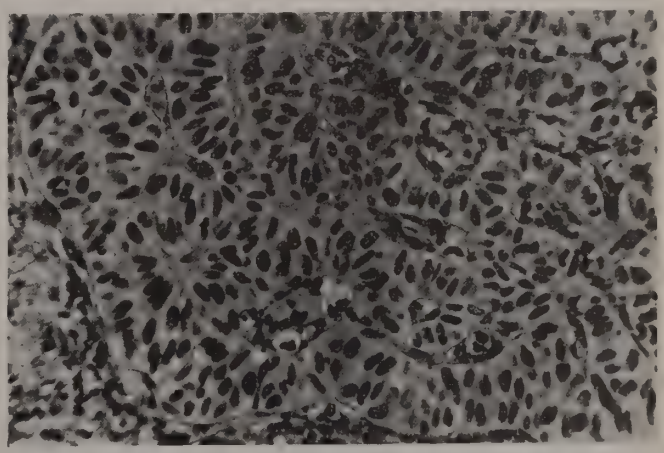

Fig. 6. "GYRIFORM" GRANULOSA CELL TUMOR (courtesy of Dr. P. Masson). High magnification of a field illustrating the "pseudotubular" cell arrangement, characteristic of gyriform granulosa cell tumors. The individual epithelial cell columns consist of a single cell layer arranged around a central axis but without detectable lumen formation.

PLATE VIII

FOLLICULOMAS

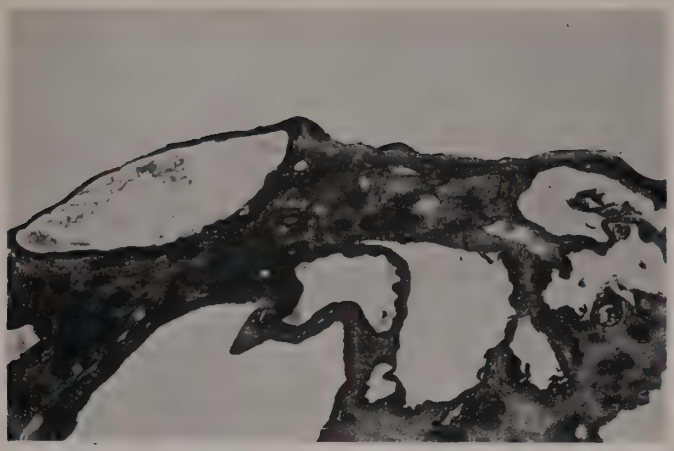

Fig. 1. CYSTIC GRANULOSA CELL TUMOR (courtesy of Dr. P. Masson). Folliculoma with comparatively large cystic cavities. The patient was 58 years old and suffered from metropathia hemorrhagica.

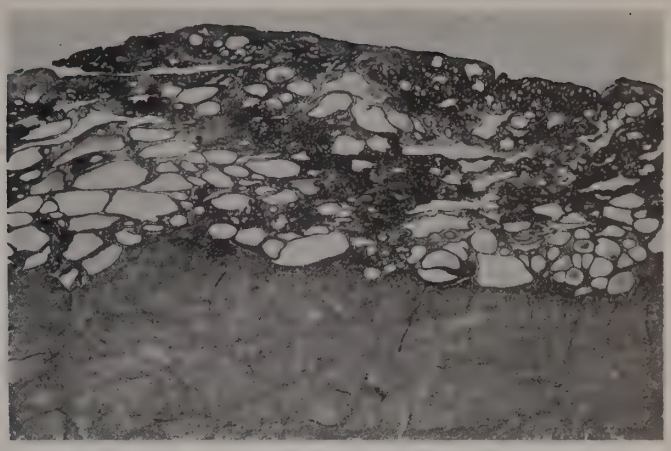

Fig. 2. METROPATHIA HEMORRHAGICA. Uterus of the patient whose cystic folliculoma is illustrated in Fig. 1. Note the typical "Swiss Cheese" aspect of the endometrium.

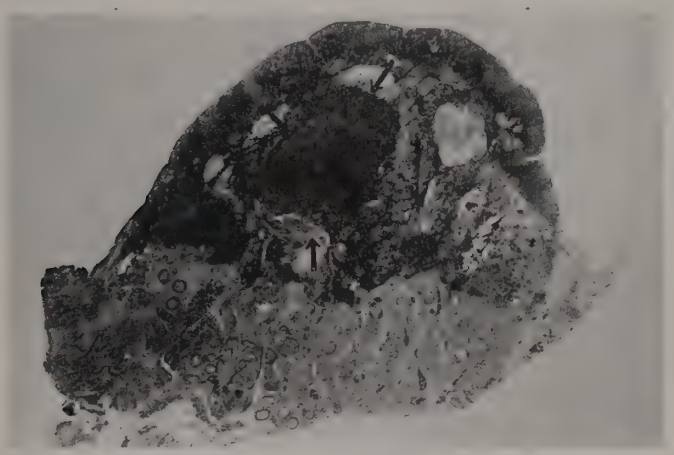

Fig. 3. SMALL THECOMA IN THE MIDDLE OF THE OVARY. General view of a cross section through an ovary with a small thecoma in the middle of the organ (homogeneous, dark grey area marked by arrows). The patient was 66 years old and suffered from comparatively slight post-menopausal metrorrhagia (with passing of blood clots) twice during the last year.

Fig. 4. THECOMA. Higher magnification of a small area in the tumor shown in Fig. 3. Note partly "epithelioid" aspect of the cells (especially, in the right part of the field) which form strands among the otherwise typical, spindle-shaped theca cells.

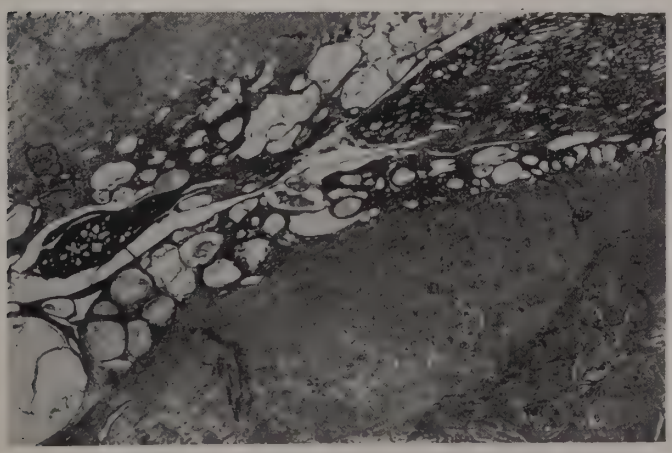

Fig. 5. METROPATHIA HEMORRHAGICA. Uterus of the patient whose thecoma is represented in Figs. 3 and 4. Typical "Swiss cheese" endometrium with small polypoid excrescences and some fairly large endometrial cysts, especially in the left part of the field.

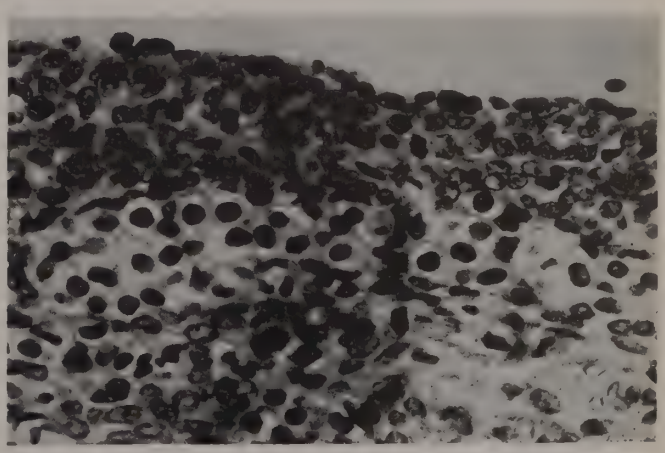

Fig. 6. GRANULOSA CELL TUMOR (courtesy of Dr. P. Masson). High magnification of the wall of a small cyst in a typical granulosa cell tumor. Note large, light, lipid-containing theca cell-like elements underneath the surface.

PLATE X

FOLLICULOMAS

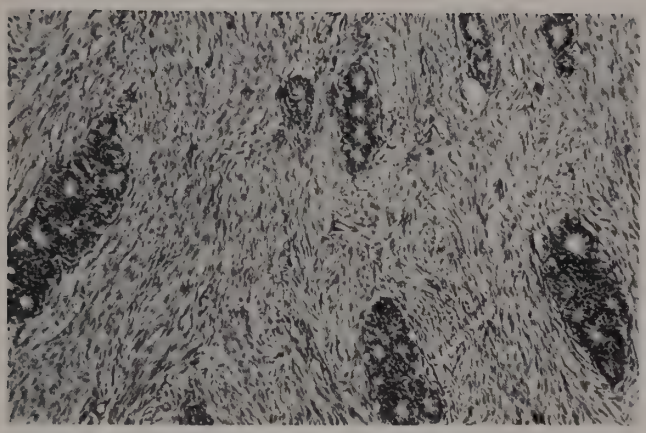

Fig. 1. TUBULAR GRANULOSA CELL TUMOR. Note that tubules contain well defined lumina and are quite reminiscent of those seen in virilizing tubular adenomas. Stroma is dense, fibroma-like.

Fig. 3. GRANULOSA CELL TUMOR WITH PRECOCIOUS PSEUDOPUBERTY (after Mannheimer A96512/38). Photograph of a four year old girl whose granulosa cell tumor produced precocious menstruation, breast development, increased skeletal growth and early ossification of bones. The tumor was removed a few days after the first picture was taken. The second pair of pictures is taken three months, the third pair, thirteen months after operation. Note regression of the breasts and the more immature outlines of the face and pelvis following the operation. Menstruation did not occur after removal of the tumor.

Fig. 4. GRANULOSA CELL TUMOR WITH PRECOCIOUS PSEUDOPUBERTY (after Bland and Goldstein A52086/34). Child aged seven with precocious sexual development (pubic hair growth, breast enlargement) and distension of the abdomen, due to a large, nodular, bilateral, granulosa cell carcinoma which recurred after operation.

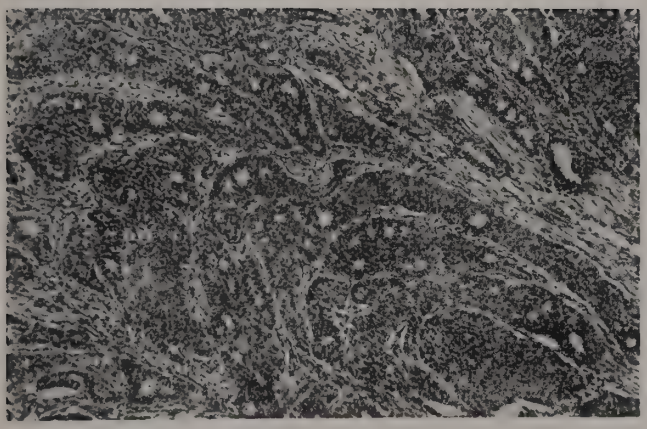

Fig. 2. FOLLICULOID REGION IN TUBULAR GRANULOSA CELL TUMOR. Predominantly parenchymatous and follicular portion of the tumor shown in Fig. 1. Another example of a polymorph folliculoma.

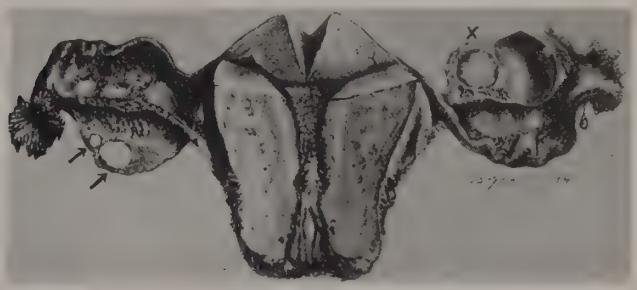

Fig. 5. GROSS APPEARANCE OF SMALL THECOMA OF OVARY WITH ADNEXA (after Novak B109/44). Note small thecoma (X) and cyst in one ovary and two small fibromas in contralateral gonad (marked by arrows). Uterus enlarged, endometrium hyperplastic.

OVARIAN CORPUS LUTEUM CYSTS

SYNONYMS: Persistent cystic corpora lutea, luteoma cysticum.

REVIEWS

ENGLISH: Israel A55802/42, *Geist B6672/42.*

FRENCH: Keller A92418/22, A92419/25, *Portes* A95313/36, *ten Berge* A97038/38, *Weil and Ginsbourg* B5049/40.

GERMAN: v. Oettingen A93573/22, *Iseki* A92417/24, *Magalaschwili* A94118/29, *Miller* A18279/37.

ITALIAN: Patellani-Rosa A81285/04, *Docimo* B5923/29, *Motta* A59471/36, *Giampalmo* A97144/38, *Guercio* A97065/38.

RUSSIAN: Bielov A96065/11, *Osiakina* A92425/24.

DEFINITION

Corpus luteum cysts are transformation products of corpora lutea resulting from excessive accumulation of fluid in the central cavity. Their life span is usually longer than that of the normal corpus luteum of menstruation but the luteal tissue, which lines their wall, is not capable of the unlimited growth characteristic of true blastomas. They are usually simple cysts and should be distinguished from the multiple cystic corpora lutea found in the ovaries of women who suffer from hydatidiform mole, or chorionepithelioma.

HISTORY

Hewitt[1] described "ovaries showing false corpora lutea with commencing cystic disease"; yet v. Rokitansky[2] is generally credited with having first characterized the corpus luteum cyst as a specific pathologic entity in 1859. Halban,[3] Fraenkel[4] and v. Oettingen[5] called attention to the clinical syndrome resulting from the excessive production of hormones by persistent cystic corpora lutea. Later more light was shed on the endocrine mechanism responsible for the development of large cystic corpora lutea by experiments showing that in the rat these structures may be produced at will by simultaneous treatment with gonadotropic and folliculoid hormones.[6]

PATHOLOGIC ANATOMY

The histologic structure of corpus luteum cysts is comparatively simple. It resembles that of a large corpus lutuem whose cavity is greatly distended by fluid. The wall consists of more or less typical, lipid-containing (macroscopically yellow) corpus luteum cell tissue which may be either in direct contact with the central fluid accumulation, or separated from it by a simple epithelial lining or a band of connective tissue. It has been claimed that the persistent corpus luteum resembles that of gestation inasmuch as it is comparatively poor in lipid granules and rarely contains a central hemorrhage.[7] Comparatively few corpus luteum cysts have been described in the literature, although clinical evidence indicates that they are more frequent than is generally suspected. It is probable that many relevant instances which have come to the attention of gynecologists have not been the subject of special publications, while some of the published cases may not have been true corpus luteum cysts. Special attention must be called to the fact that lipid-containing "pseudoxanthoma" cells in the walls of ovarian endometriomas, abscesses or infected ovarian cysts may be mistaken for corpus luteum cysts. The former may resemble the latter even with regard to some of the clinical manifestations, since both these conditions tend to produce lengthy periods of amenorrhea. "Corpus luteum cysts" which contained pseudomucinous papillae[8] or a serous papilloma in their cavity[9] and "tarry corpus luteum cysts with heterotopic epithelial lining"[10] may have been cases in point.

Additional data concerning the structure of corpus luteum cysts will be found in many of the relevant *case reports.*[11]

INCIDENCE

According to one author[12] about 55% of the patients, suffering from menstrual disturbances accompanied by detectable morphologic lesions in the ovaries, have corpus luteum cysts. Another worker who examined 100 pairs of ovaries gathered from unselected autopsy material found corpus luteum

[1]A81573/857-8.
[2]A80030/859.
[3]A3228/15.
[4]A26969/22.
[5]A93573/22.
[6]*Selye et al.* 32001/35.
[7]*Meyer* B8489/20.
[8]*Shaw* A77095/27.
[9]*King* A68133/29.
[10]*Shaw* B7184/27.
[11]*Shattock* A45109/887-8, *Fränkel* A90203/894, A81177/894, A26968/898, A93558/898/9, *Mikhalson* A90208/896, *Orthmann* A81212/897, *Oliva* A93574/01, *Alcock* A93551/02, *Diepgen* A80973/03, *Santi* A93577/04, *Patellani-Rosa* A81285/04, *Calmann* A69559/05, *Gruzdeff* A69597/05, A93561/06, *Cornil* A80942/05, *Engelhard* A93557/08, *Bazterrica and Bello* A93552/10, *Walter* A93582/15, *Schwarz* A93579/19, *Trancu-Rainer* A81113/21, *Mueller* A26777/22, *v. Oettingen* A92424/24, *Schröder* A92427/25, *Tiesenhausen* B6645/25, *Wolkowinski* A92432/28, *Portarsky* A94120/29, *Cahen* A62289/32, *Keller and Cikowski* A62306/32, *Reeb* A61433/33, *v. Probstner* A29211/35, *Colanori* A94776/37, *ten Berge* A97039/38, *Viana* A97190/38, *Wheelon and Wilson* A97220/39, *Henthorne* A97710/40.
[12]*v. Fekete* A79279/27.

cysts in 9% of his cases.[1] These estimates are certainly excessive, however, probably because normal corpora lutea (which also contain an antrum in women) have been included.

The high incidence of multiple corpus luteum cysts during normal and pathologic *pregnancy* has already been mentioned above.[2] In one series of 30 pregnant women with ovarian cysts there were 7 (26.9%) cases of corpus luteum cysts.[3]

PATHOGENESIS

The etiology of corpus luteum cysts is still insufficiently known in spite of the numerous publications concerned with this subject.[4] It is well established that in women suffering from tumors which produce an excessive amount of hypophysoid gonadotropic hormones, the ovaries almost invariably contain a large number of cystic corpora lutea (see chapters on ovarian changes in chorionepithelioma, hydatidiform mole and pituitary tumors in Sect. IV, Vol. VI). It is known, furthermore, that treatment with gonadotropic hormones produces "mulberry ovaries" in various species of laboratory animals. As mentioned above, unusually large cystic corpora lutea can be produced in the rat by simultaneous treatment with gonadotropic and folliculoid hormones.[5] Similar hormonal factors are likely to be the cause of multiple corpus luteum cysts in patients suffering from tumors of placental origin; they may also explain the comparative frequency of corpus luteum cysts in normal and in ectopic pregnancy as well as immediately following incomplete abortion (see chapters on ovarian changes in normal and ectopic pregnancy in Sect. IV, Vol. IV). In all these instances the simultaneous production of gonadotropic and folliculoid hormones may well be the cause of the ovarian change. It remains to be shown, however, whether the typical, usually single corpus luteum cyst is due to a similar pathogenic mechanism, and if so, what determines the number of corpora lutea which undergo cystic change. It is probable that separate hormonal factors are responsible first for the formation of corpora lutea and subsequently for their persistence and transformation into cysts. The first of these two factors might well determine whether one or many corpora lutea will be present in the ovary when the stimulus for cystic transformation becomes effective.

It has been stated[6] that a number of conditions, which can cause pelvic hyperemia, may lead to the formation of cystic corpora lutea, since such cysts are reputedly common in women who suffer from salpingitis with pelveoperitonitis or carcinoma of the uterus. Further evidence will be required, however, to prove definitely that local conditions are of pathogenic importance.

CLINICAL COURSE

The most important clinical manifestation of corpus luteum cysts is their tendency to cause persistent *amenorrhea*. Halban[7] was the first to emphasize the clinical similarity between corpus luteum cysts and tubal pregnancies. He found that women with corpus luteum cysts complain of amenorrhea and frequently believe themselves to be pregnant. Palpation reveals an enlarged uterus and a soft mobile tumor in the region of one of the adnexa. Many other investigators have commented on the frequency of amenorrhea in women with corpus luteum cysts[8] and it is noteworthy that the clinical syndrome is that of pseudopregnancy.[9] Of course, in view of the frequency of corpus luteum cysts in true and ectopic gestation, the possibility of pregnancy as the cause of the cyst must always be borne in mind.

The characteristic amenorrhea is usually due to the persistent *progestational transformation* of the endometrium which fails to break down in monthly intervals.[10]

Occasionally severe *metrorrhagias* occur[11] after a period of amenorrhea presumably due to a variation in ovarian hormone production or to the eventual breakdown of the corpus luteum cyst.

It has been claimed that in 3.2% of the cases persistent corpora lutea are associated with internal or external *endometriosis*[12] and that sometimes they may even cause *metropathia hemorrhagica*-like changes in the endometrium.[13] One author[14] goes so far as to claim that 14% of his patients with "functional uterine bleeding" exhibit a secretory, not a proliferative, endometrium. Among these corpus luteum cysts were commonly demonstrable. The pathogenesis of these changes is not fully understood, although certain animal experiments indicate that progesterone may produce a "Swiss cheese" endometrium if the uterus is subjected to trauma while under

[1] *Bufe* A96007/37.
[2] *Arenas et al.* A97333/40, *Cotte* A97475/41, *Leon* A96921/43, A96923/43, A96922/43.
[3] *Watts and Adair* B7320/44.
[4] *Brown* A93554/11-3, *v. Oettingen* A93573/22, *Vogt* A92431/23, *Cattaneo* A99139/40.
[5] *Selye et al.* 32001/35.
[6] *Cohn* 39787/09.
[7] A74963/15, A3228/15, A93562/15.
[8] *Wagner* 39581/28, *Davanzo* A65067/30, *Cotte* A67289/30, A65066/31, A97475/41, *Reeb* A61433/33, *van Tongeren* A92430/36, *Motta* A59471/36, A95071/37, *Rockstroh* B20157/38, *Zacharin* B15172/38.
[9] *Wagner* 39581/28, *Reeb* A61433/33, *van Tongeren* A92430/36.
[10] *Meyer* B8489/20, *Bickers* 85346/44.
[11] *Macfarlane* A92423/17, *Ochsner* A93648/19, A93649/19, *v. Oettingen* A93573/22, *Fraenkel* A26969/22, *Reinhart* A95037/35, *Motta* A95071/37.
[12] *Fallas and Rosenblum* A33798/40.
[13] *Pischzek* A76296/24.
[14] *Jones* B20206/38.

the influence of the hormone.[1] (See also chapter on Metropathia Hemorrhagica).

As in pregnancy the *breasts* are enlarged and may secrete colostrum.[2]

Upon *pelvic examination* a corpus luteum cyst reveals itself as an approximately walnut-sized, smooth, somewhat mobile, adnexal tumor[3] which may be painful.[4] In one patient[5] there was no menstrual anomaly, but periodic swelling of the ovaries, which at autopsy proved to be due to corpus luteum cyst formation. It should be kept in mind that these cysts rarely reach a diameter of more than about 2½ inches and many of the large tumors described as corpus luteum cysts are in reality abscesses with a lipid-containing lining.

Occcasionally corpus luteum cysts may be associated with *acetonuria,*[6] but this finding has not been checked in a sufficiently large number of cases.

COMPLICATIONS

The most frequent complications of corpus luteum cysts are due to the fact that their walls are thin and fragile and hence readily subject to *rupture.*[7] Even careful pelvic examination may suffice to rupture corpus luteum cysts.[8]

Another common complication is *hemorrhage,* either into the cavity of an intact cyst or into the peritoneum, following rupture of the wall. This complication, as well as the extremely rare occurrence of *torsion,* is discussed in the corresponding chapters of Sect. IV, Vol. VI.

DIAGNOSIS

The clinical diagnosis of corpus luteum cysts, though carefully studied by many investigators[9] is usually impossible.

Most relevant cases are operated upon under the diagnosis of *ectopic gestation* because almost all the symptoms and signs of these two conditions are identical.[10] The similarity goes so far that even the gonadotropic hormone excretion in the urine may be augmented in the presence of corpus luteum cysts as it is in pregnancy.[11] This fact gives further support to the view that hypophysoid hormones play an important role in the pathogenesis of these cysts.[12] Since ectopic pregnancy not infrequently fails to elicit a marked increase in urinary gonadotropins, even a negative A-Z test[13] is of little diagnostic value (see section on gonadotropic hormone in urine). Systematic pregnanediol determinations in the urine of women with corpus luteum cysts have not as yet been made but would probably give helpful information.

PROGNOSIS

In many cases corpus luteum cysts persist for a very long time and tend to recur, as jugded by the menstrual histories. Spontaneous and permanent cures may occur.[14] The otherwise favorable prognosis is somewhat darkened by the ever existing possibility of a severe, potentially fatal, peritoneal hemorrhage.

THERAPY

The usual therapy of corpus luteum cysts is *surgical* excision of the cyst itself, leaving the remaining ovarian tissue intact. This leads to a withdrawal hemorrhage after which the menstrual cycles may become normal owing to the re-establishment of a physiologic relationship between the ovaries and the pituitary.[15] On the other hand, if the primary cause of the condition is entirely extraovarian, there is no guarantee of a permanent cure following removal of the cyst. Could the condition be recognized with certainty, the advisability of a surgical intervention would be very doubftul, especially since complications, such as serious ovarian or uterine hemorrhages, are rare. Most cases are recognized only on the operating table, however, and then removal of the cystic corpus luteum is certainly justified.

In one case X-rays were applied to the hypophyseal region of a woman suffering from a corpus luteum cyst associated with symptoms of a benign pituitary adenoma, but no very beneficial results were obtained.[2]

[1] *Selye et al.* A36609/42.
[2] *Wagner* 39581/28.
[3] *Wagner* 39581/28, *Israel* A55802/42.
[4] *Molin et al.* A67248/30.
[5] *Ries* A83443/13.
[6] *Novak* A83002/15.
[7] *Hitzanides* A81397/25, *Soimaru* A81413/25, *Grünstein* A71396/28.
[8] *Halban* A3228/15, *Crousse* A92413/24, *Israel* A55802/42.
[9] *v. Stephanowich* A92428/23-4, *Cuizza* A97236/39.
[10] *Dorman* A93556/13, *Hitzamides* A81397/25.
[11] *do Amaral Silva* B15181/37, *Israel* A55802/42, *Bickers* 85346/44.
[12] *Israel* A55802/42.
[13] *Taylor* A59480/36.
[14] *Cambon* A61371/33.
[15] *Halban* A3228/15, *Taylor* A59480/36, *Israel* A55802/42, *Bickers* 85346/44.

OVARIAN CORPUS LUTEUM CYSTS IN ANIMALS

Cystic and persistent corpora lutea are especially common among *cattle*.[1] In this species they are of some practical importance, since the continued pseudopregnancy, which results from the excess production of luteoid hormones, renders the cows sterile. In some such instances, manual rupture of the cyst through the vagina or the rectum, is occasionally practiced by veterinarians, with the view of destroying the persistent corpus luteum and restoring fertility. In one cow a purulent endometritis was seen in association with a persistent corpus luteum.[2]

[1]*Tassi* A64020/31, *Clark* A94268/35, *Orlandini* A94301/35.

[2]*Frei* 38720/35.

OVARIAN CORPUS ALBICANS CYSTS

Cysts apparently due to fluid accumulation in the center of a corpus albicans have repeatedly been described.[1] They originate as a result of hyalinization of cystic corpora lutea and are of little clinical significance since they do not produce hormones and rarely reach a size which could in itself produce disturbances of a mechanical nature. As in the case of some so-called "giant corpus luteum cysts" the very large corpus albicans cysts of the literature are probably abscesses whose walls have a misleading histologic structure. Intense hyalinization and sclerosis of the abscess wall may lead to structures very similar to corpus albicans cysts, especially if the pus of the central cavity is gradually replaced by limpid fluid.[2]

[1]*Koebner* A81191/08, *Novak and TeLinde* A80029/23.

[2]*Miller* A18279/37.

OVARIAN LIPID CELL TUMORS IN GENERAL (INCLUDING HYPERNEPHROMAS AND LUTEOMAS)

SYNONYMS: Luteoma, luteinoma, luteoblastoma, carcinoma of the corpus luteum, struma ovarii luteinocellulare maligna, hypernephroma, malignant hypernephroma, Grawitz tumor of the ovary, adrenal cortical carcinoma, struma suprarenalis aberrata, masculinovoblastoma, leydig cell tumor of the ovary, sympathicotropic or hilus cell tumor of the ovary, yellow tumors of the ovary, lipid cell tumors of the ovary.

It will be noted that some of these terms were not meant to be synonymous yet they will be considered as a single entity until proven otherwise.

One author[1] designates as "*arrhenoma*" all testoid-producing and as "*theloma*" all folliculoid-producing tumors, irrespective of structure.

REVIEWS

Traut and Butterworth 78785/37, *Varangot* 68667/37, *Miller A18279/37, Saphir* A83013/39, *Kirk and Edwards* A33076/39, *Schattenberg and Harris* A32319/39, *Geist B6672/42.*

DEFINITION

The lipid cell tumors constitute a group of ovarian neoplasms characterized mainly by the fact that they consist of endocrine cells containing many lipid granules and resembling those of the corpus luteum, the adrenal cortex, the theca folliculae, or the Leydig cells. They are usually virilizing growths. In my opinion it is impossible with the methods now available to determine the origin of these tumors with certainty. Therefore, without excluding the possibility that they are morphogenetically heterogeneous, they will be discussed conjointly under the non-committal heading of lipid cell tumors. The common corpus luteum cysts, and the adenomatous proliferation of theca lipid cells or ovarian Leydig cells are discussed in special chapters merely because their identity is more clearly established than that of the ovarian hypernephromas and solid luteomas. Hence only these last mentioned neoplasms will be treated in conjunction with the debatable and obscure case reports in the present chapter on Lipid Cell Tumors in General.

HISTORY

v. Rokitansky[2] was probably the first to describe in 1859 a lipid cell tumor in the ovary of a woman aged 65. This growth was about the size of a child's head and composed of lipid-containing cells. Peham,[3] however, in 1899 appears to have first attempted to analyze such a case in any detail both from the clinical and morphologic point of view. He emphasized the resemblance of the growth to the zona glomerulosa of the adrenal cortex and called attention to the high glycogen content of its cells. Hence he termed the growth "hypernephroma of the ovary". A four-year-old girl, in whom a similar tumor caused signs of precocious pseudopuberty, was described in 1907 by Debeyre and Riche.[4]

PATHOLOGIC ANATOMY

Macroscopically the lipid cell tumors of the ovary are usually more or less irregular in outline and comparatively solid growths which can readily be distinguished from the simple corpus luteum cysts discussed in the previous section. They rarely reach a size of more than about 6 inches in diameter while the smallest examples are minute nodules which can hardly be distinguished from the non-blastomatous adrenal rests. Perhaps their most characteristic macroscopic feature is the bright yellow color which strikingly resembles that of the corpus luteum or adrenal cortex. Occasionally multiple hemorrhages—such as are characteristic of the Grawitz tumor—give a rather mottled appearance to these growths. Their consistency is usually soft, almost brain-like, but in some cases they are quite hard.[5]

Not infrequently lipid cell tumors develop *bilaterally*[6] and many of them are found *within the mesovarium or in the broad ligament* (see chapter on Para-Ovarian Lipid Cell Tumors). The latter, of course, are not true ovarian neoplasms; we mention them here merely because, if the adrenal rest theory is correct, there is no essential difference between a hypernephroma developing from an accessory adrenal within the ovarian tissue and one originating at some distance from the gonad in the broad ligament.

Microscopically the appearance of the lipid cell tumors is extremely variable. They usually consist of more or less irregular bands or islets of vacuolated, large, polyhedral cells which imitate the structure of the corpus luteum or adrenal cortex. In vivo the vacuoles are filled with lipid granules and in some cases they also contain considerable quantities of glycogen. Several investigators consider the high-glycogen content as a characteristic feature of tumors derived from the adrenal cortex, which permits the

[1] *Burrows* A71758/43.
[2] A80030/859.
[3] A5145/899.
[4] A79961/07.
[5] *Miller* A18279/37.
[6] *Funccius* A79967/05, *Scudder* A80004/05, *v. Rosthorn* A79999/09, *Komocki* A79978/28, *Neumann* A42640/29, 79991/35, 35119/36, *Miller* A18279/37.

differentiation of these growths from those of the corpus luteum.[1] The fuchsinophilic granules, which are considered characteristic of the adrenals in the adrenogenital syndrome, were present in some,[2] but not in all[3] lipid cell tumors of the ovary examined for them. Several tumors were diagnosed as "luteomas" because they contained pigment cells,[4] yet pigment cells are not characteristic constituents of corpora lutea.

In some cases at least certain portions of the growths may exhibit the aspect of an alveolar sarcoma, a medullary, papillary or a scirrhous carcinoma; they may contain spindle-shaped or giant cells and it is difficult to make generalizations concerning the structure of these polymorph tumors. Hence, many relevant cases have been described as carcinomas, endotheliomas, peritheliomas, sarcomas, etc. From this histologic description it is quite evident that at least in many, if not all, of these blastomas even a guess concerning their derivation (from the corpus luteum or the adrenal cortex rests respectively) would be entirely unfounded. Consequently we shall not go into the numerous suggestions that have been made concerning criteria which could make such a diagnosis possible.

In view of these diagnostic difficulties it is noteworthy that without any very definite reason some lipid cell tumors have been described as *corpus luteum tumors* or luteomas,[5] others as *carcinomas of the corpus luteum*[6] and still others as ovarian *hypernephromas*.[7] In a few instances the general appearance of the tumor was of a *sarcomatous* type.[8] These have been interpreted as sarcomas of the corpus luteum or of adrenal rests, and in some cases they have been merely designated as ovarian sarcomas without indicating the structure from which their lipid-containing cells might have originated. The "*sarcomas of the interstitial cells*" of the ovary[9] are very reminiscent of dysgerminomas as judged by the published illustrations.

The fact that certain granulosa cell tumors may become partially luteinized and assume the aspect of the "*folliculome lipidique*" of Lecène has been emphasized in the chapter on folliculomas. It is obvious that if this process of luteinization goes far enough, transitional types will result which are difficult to classify.[10] It must be borne in mind that luteinized granulosa cell tumors and corpus luteum tumors are so closely related that it would be difficult to make even a theoretical distinction between them.

Invasive growth of lipid cell tumors into neighboring organs is comparatively rare, but it may occur.[11] Secondary complications are likewise uncommon since these growths do not tend to undergo *suppuration, torsion* or *rupture*. Small *necrotic foci* and partial liquefaction which leads to cyst formation may occur in these growths, however, and they may also be the site of small *hemorrhages*.[12]

Ovarian *metastases* of extragenital hypernephromas may lead to secondary ovarian lipid cell tumors.[13] Conversely, primary lipid cell tumors of the ovary may metastasize in other organs.[14]

Combination of lipid cell tumors with other ovarian blastomas, such as dermoid cysts[15] or serous cystomas,[16] has been noted in the same ovary, and in one case[17] a lipid cell tumor on one side co-existed with a serous cystoma of the contralateral ovary.

CHEMICAL COMPOSITION

The chemical composition of lipid cell tumors received special attention only by one author[17] who

[1]*Sternberg* A80005/06, A64845/26, *v. Rosthorn* A79999/09, *Glynn* 6810/21, *Benda and Kraus* A52254/34.
[2]*Bauer* A83005/39, *Blackmun* A83006/42, *Kepler et al.* A71597/44.
[3]*Rottino and McGrath* A83012/39.
[4]*Michelazzi* A80028/02, *Gruzdeff* A80019/03, *Greggio* A77527/08.
[5]*Selhorst* A80034/00, *Michelazzi* A80028/02, *Gruzdeff* A80019/03, *Santi* A80031/04, *Markovitch* A80023/13, *Massabuau and Etienne* A80024/13, *Tuffier* A6612/14, *Lino* A80020/22-3, *Massazza* A64988/23, *Novak and TeLinde* A80029/23, *Bingel* A15916/24, *Wolfe* A64869/27, *Cosacesco et al.* A64215/31, *Cramarossa* A79959/35, *Decoulx and Bastien* A28084/35, *Cutler* A27994/35, *Bourg and Rocmans* A95234/37, *Saphir* A83013/39, *Traut et al.* A33606/39.
[6]*Savage* A80033/09, *Christian* A64746/10, *Tiesenhauser* B6645/25, *Cattaneo* A71388/28, *Curtis* A79960/28, *Lissowetzky* A66131/31, 5588/33, *Nixon and Hartman* A27713/35, *Gallo and Gallo* A59687/36.
[7]*Eastwood* A992/02, *Scudder* A80004/05, *Sternberg* A80005/06, *Lihotzky* A79981/06, *Santi* B13364/07, *Gardner and McCleary* A79969/08, *Gaudier* A79970/08, *v. Rosthorn* A79999/09, *Pick* A78832/10, *Vonwiller* A25514/11, *Saltykow* A80000/11, *Alamartine and Maurizot* A79952/12, *Murray* A79987/19, *Gordon* A21248/19, A79973/19, A79974/20, *Nicholson* A79993/23, *Albrecht* A77958/23, *Lévy-Du Pan* A79980/24, *Muller* A79986/25, *Sellheim* 24793/25, 28307/26, *Orrù and Volpe* A79994/26, *Schwörer* A80003/27, *Lastra and Colillas* A79979/28, *Neumann* A79990/28, A79991/35, *Hochloff* A68230/29, *Gough* A79975/29, *Reiners* A79997/29, *Naeslund* A79988/30, *Kleemann* A79977/32, *Mathias* A79983/32, *Büttner* A79957/34, A79958/35, *Witzberger and Agerty* A95127/37, *Turcò* A83039/37, *Stadiem* A95111/37, *Novak* A83009/38, *Giacchè* A94714/38, *Reis and Saphir* A15258/38, *Schattenberg and Harris* A32319/39 *Kreutzmann* A97691/39, *Kleine* A95445/39.
[8]*Santi* A93576/02, A80032/05, *Michelazzi* A80028/02, *Gruzdeff* A80019/03, *Greggio* A77527/08, *Ishikawa* A77565/21, *Massazza* A64988/23, *Vallone* A77866/24, *Schiffmann and Szamek* A80002/26, *Ewing* A64873/28-42.
[9]*Klemperer* A77591/13, A77592/14.
[10]*Benda and Kraus* A52254/34, *v. Numers* A57989/40, *Henderson* A37766/42.
[11]*Alamartine and Maurizot* A79952/12.
[12]*Miller* A18279/37.
[13]*Brüchanow* 6740/899, *Funccius* A79967/05, *Santi* A80001/06, *Wahl* A80008/30, *Kannerstein et al.* A61333/43.
[14]*Pick* 7097/01, *Scudder* A80004/05, *Sternberg* A80005/06, A64845/26, *Meyer* A79984/08, *Downes and Knox* A79965/24.
[15]*Komocki* A79978/28.
[16]*Peham* A5145/899.
[17]*Hochloff* A68230/29.

demonstrated the presence of cholesterol and lecithin by qualitative tests. It has been mentioned above that glycogen and neutral fats are often abundant in these growths as judged by histochemical studies.

INCIDENCE

The *general incidence* of lipid cell tumors is difficult to estimate, but it is certainly correct to say that they are very rare growths.

These blastomas may appear at any *age*. Several cases have been described in children[1] in whom these growths tend to produce a syndrome of precocious pseudopuberty. The majority of the cases occurred in adult women and frequently after the menopause. One typical instance[2] was observed in a woman aged 62, another[3] in one aged 69, and a third[4] in a patient aged 74.

Almost all lipid cell tumors were observed in the white *race*, only one having been noted in a colored woman.[5]

PATHOGENESIS

It is debatable whether solid lipid cell tumors can develop from fully formed corpora lutea, in spite of the many reports on so-called "luteomas". It must be clearly stated that in most cases no reason is given by authors for their designation of a growth as "luteoma" rather than hypernephroma and vice versa. The theory now generally accepted is that at least the majority, if not all, of these growths are hypernephromas derived from adrenal cortical remnants or so-called Marchand's[6] rests. This view is supported by the previously mentioned fact that many lipid cell tumors occur in the broad ligament where Marchand's rests are particularly common (see Sect. on adrenal malformations). It has been stated[7] that Marchand's rests are not found in the parenchyme of the ovary itself, but Meyer[8] described a typical nodule of this type within the ovary of a fetus and several other investigators expressed the view that adrenal rests may occur in the ovary.[9] It is true that in some cases the identity of such nodules may be questionable, as small corpora atretica could be mistaken for Marchand's rests, but even if true adrenal remnants were invariably at a little distance from the ovary, their blastomatous growth would secondarily bring them into such close contact with the gonad that they would be indistinguishable from primary ovarian tumors. Hence we must agree with those investigators[10] who derive most of these tumors from adrenal cortical remnants. Nevertheless the possible origin of certain virilizing growths from the Leydig cells, or even from corpora lutea, is not denied.

CLINICAL COURSE

In addition to the usual local manifestations of an ovarian tumor, the lipid cell growths—if hormonally active at all—are mainly characterized by signs of *virilization* which frequently are so pronounced that one may well speak of pseudohermaphroditism. There may be marked hirsuties of the trunk and extremities, as well as beard growth, enlargement of the clitoris, deepening of the voice, amenorrhea, atrophy of the breasts and a general masculinization of the habitus.[11]

In children, lipid cell tumors cause *precocious pseudopuberty* with premature growth of the breasts (unlike in adults!), the pubic hair and occasionally premature development of libido. In the cases published up to the present time these signs were not accompanied, however, by manifestations of pseudohermaphroditism.[12]

As mentioned above, most of these cases are accompanied by amenorrhea and other signs of pseudopregnancy[13] but occasionally the *menstrual cycle* remains normal[14] and there may even be severe metrorrhagias.[15] In some instances the condition was accompanied by uterine fibroids,[16] or general enlargement of the uterus,[17] but this is comparatively rare.

It is of special interest that in many patients with lipid cell tumors of the ovary there were also other symptoms of the adrenogenital syndrome (or Cushing's syndrome) such as *hypertension, poly-*

[1] *Debeyre and Riche* A79961/07, *Riche* A79998/07, *Downes and Knox* A79965/24, *Delfourd and Lucien* A26965/25, *Nekrassov* A79989/26.
[2] *Maxwell* A83008/37.
[3] *Giordano and Haymand* A71813/44.
[4] *Kermauner* A64880/32.
[5] *Greene and Lapp* A71598/44.
[6] A79982/891.
[7] *Bovin* 6735/08.
[8] A65111/31.
[9] *Varaldo* A6016/04-5, B9108/04, *Downes and Knox* A79965/24, *Sternberg* A64845/26.
[10] *Weiss* A6147/898, A80009/898, *Miller* A18279/37, *Schiller* A83014/39.
[11] *Bovin* 6735/08, *Bingel* A15916/24, *Sellheim* 24793/25, 28307/26, *Orru and Volpe* A79994/26, *Hochloff* A68230/29, *Gough* A79975/29, *Cosacesco et al.* A64215/31, *Veil* 43485/32, *Kolodny* A6538/34, *Saphir and Parker* A36819/36, *Maxwell* A83008/37, *Novak and Wallis* A83010/37, *Reis and Saphir* A15258/38, *Bauer* A83005/39, *Rottino and McGrath* A83012/39, A58771/43, *Blackmun* A83006/42, *Mayer* A96926/42, *Greene and Lapp* A71598/44, *Kepler et al.* A71597/44.
[12] *Debeyre and Riche* A79961/07, *Gaudier* A79970/08, *Downes and Knox* A79965/24, *Nekrassov* A79989/26.
[13] *Torres* A95122/37.
[14] *Lissowetzky* 5588/33.
[15] *Gaudier* A79970/08.
[16] *Sellheim* 24793/25.
[17] *Blackmun* A83006/42.

cythemia, obesity, cutaneous striae and *diabetes.*[1] These manifestations are clearly reminiscent of adrenal hyperfunction and strongly suggest that the lipid cell tumors can imitate adrenal growths with regard to all three main pharmacologic types of steroid hormones produced by the cortical cell, namely, the testoids, the salt-active, and the carbohydrate-active corticoids. In one interesting case, beard growth and diabetes developed concurrently with metrorrhagias in a 62-year-old woman. Ovariectomy and panhysterectomy were performed; the adrenals proved greatly enlarged as judged by palpation. One ovary contained a lipid cell tumor interpreted as a luteoma and the uterus was hypertrophic with a large fibroid. In this case it is difficult to decide whether the symptoms were due to the adrenal enlargement or the ovarian tumor.[2] The possibility of an etiologic relationship between the ovarian and adrenal lesions must also be considered since both may have resulted from a common (pituitary) cause.

Psychic changes, such as severe depression, emotional instability, etc. are not uncommon[3] and in most patients there is diminution of libido.[4]

A peculiar type of diffuse papillomatosis with bronze discoloration of the *skin* was noted in one case.[5] Since these manifestations disappeared following ablation of the ovarian tumor, the author regarded them as a consequence of some activity on the part of the blastoma. Keratosis pilaris and acne vulgaris are more common.[6] It should also be emphasized that, as part of the virilization syndrome, at least partial *baldness* is not infrequent with lipid cell tumors.[7] In these patients hair is lost from the scalp while beard and body hair grows excessively.

If a malignant lipid cell tumor obstructs blood and lymph vessels in the pelvis, extensive *edema of the lower extremities* may result.[8]

DIAGNOSIS

The clinical diagnosis of lipid cell tumors is extremely difficult as shown by the fact that only in one case was at least a probable diagnosis of "adrenal cortical tumor of the ovary" made on the basis of clinical evidence.[6] Such a diagnosis would appear warranted in patients in whom signs resembling the adreno-genital syndrome or Cushing's syndrome develop simultaneously with an ovarian tumor. From the differential diagnostic point of view, Cushing's disease and primary adrenal cortical tumors have to be eliminated on the basis of the usual local symptoms pointing to a tumor in the adrenal or pituitary region. It is well to remember that hypophyseal tumors may secondarily cause luteinization of the ovaries and subsequently lead to virilization of the testoid hyperthecosis type. In a typical relevant case[9] there was marked virilization with abundant beard growth and hypertension, yet the menses were normal and the A-Z reaction in the urine remained negative. The patient died shortly after removal of bilateral small-cystic ovaries which showed marked thecal luteinization. At autopsy a basophilic adenoma of the pituitary and hyperplasia of the adrenal cortex were evident. Another case[10] was rather similar as regards ovarian histology. The patient survived operation and no autopsy was performed, yet it is evident that neither the masculinization nor the hypertension were primarily of ovarian origin since these manifestations did not subside following ovariectomy. The existence of severe headache in this case strongly suggests the possibility of a concurrent hypophyseal adenoma.

Hormonal studies may also be of some diagnostic value. In one case[6] the urinary excretion of 17-ketosteroids was 54.6 mg. by Callow's colorimetric method (normal range 6-17 mg.), while the folliculoid and gonadotropic hormone content of the urine remained unchanged. On the other hand, in a second case[11] there was an unusually high titer of urinary folliculoids, while in most other cases these were normal or subnormal.

No urinary corticoid assays have as yet been reported in such cases although these might be of diagnostic interest. In view of the great variability of the hormonal findings the diagnosis must still rest on clinical symptoms and signs since the only apparently constant factor in the hormone analysis is the increase in urinary 17-KS which is merely a biochemic confirmation of the clinically manifest virilization.

PROGNOSIS AND THERAPY

It is hardly likely that any lipid cell tumor would improve and regress spontaneously, but the results following surgical ablation of such growths are very encouraging. From a statistical survey[6] it is evident that if the patient survives the operation, the symptoms almost invariably vanish. There are exceptions, however, which show that ablation of a virilizing "lutein cell tumor" is not necessarily

[1] *Bingel* A15916/24, *Saphir and Parker* A36819/36, *Novak and Wallis* A83010/37, *Maxwell* A83008/37, *Rottino and McGrath* A83012/39, A58771/43, *Blackmun* A83006/42 *Kepler et al.* A71597/44.
[2] *Tuffier* A6612/14.
[3] *Hochloff* A68230/29, *Bergstrand* A80125/34, A27534/34, *Kepler et al.* A71597/44.
[4] *Rottino and McGrath* A83012/39.
[5] *Albrecht* A77958/23.
[6] *Kepler et al.* A71597/44.
[7] *Bingel* A15916/24, *Sellheim* 24793/25, 28307/26, *Cosacesco et al.* A64215/31, *Maxwell* A83008/37.
[8] *Alamartine and Maurizot* A79952/12.
[9] *Bergstrand* A80125/34, A27534/34.
[10] *Rottino and McGrath* A58771/43.
[11] *Saphir and Parker* A36819/36.

followed by the disappearance of the pseudohermaphroditic traits.[1]

The reason for the comparatively high mortality rate after operation is perhaps that a sudden drop in the corticoid hormone content of the blood and tissues, such as would be occasioned by extirpation of an adrenal cortical growth, is likely to produce a transitory adrenal cortical hormone deficiency. It is quite possible that hypernephromas of the ovary, just as those of one adrenal, could cause compensatory atrophy of the nonblastomatous remaining cortical tissue. In this event some time would be necessary before the normal adrenal cortex could resume adequate hormone production. With this in mind pretreatment with NaCl and corticoid hormones before operation has been recommended for patients in whom a tentative diagnosis of ovarian hypernephroma is possible before intervention.[2]

[1]*Fournier* A3213/23.

[2]*Kepler et al.* A71597/44.

PARA-OVARIAN LIPID CELL TUMORS

Leydig cell proliferations may occur in the ovarian hilus or at some distance from it in the mesovarium. These will be discussed conjointly with testoid hyperthecosis in the next chapter.

Neoplasms with a structure resembling the adrenal cortex have been described—under the designation of Ovarian Hypernephromas—in the preceding chapter on the Lipid Cell Tumors of the Ovary. It is very probable that these neoplasms originate from accessory adrenals and adrenal remnants in the broad ligament and the immediate vicinity of the normal gonad. Depending upon whether such a tumor arises from an adrenal remnant contiguous with the ovary, or whether it arises from a similar vestige at some distance from the gonad, the resulting tumor will be an ovarian hypernephroma or a para-ovarian hypernephroma, respectively. For this reason it does not appear profitable to discuss the para-ovarian hypernephromas separately from the corresponding ovarian tumors. Suffice it to say that adrenal remnants may occur throughout the *broad ligament* and numerous instances of para-ovarian hypernephroid growths can be found in the literature.[1] It has even been claimed that hypernephroid tumors can occur in the *uterus*[2] and one author describes lutein-like changes in the oviduct[3] (pseudoxanthoma cells?). In many of these cases it is rather difficult to distinguish between the adenomas of accessory adrenals and the accessory adrenals themselves. Evidently, a group of adrenal cortical cells within the broad ligament may be regarded merely as an accessory adrenal cortex or as an adenoma of the same, as long as the growth rate of the tissue is comparatively slow. Similarly, in the case of hypernephromas situated in the immediate vicinity of the ovary, it is difficult to distinguish between ovarian hypernephromas and primarily para-ovarian hypernephromas which came into contact with the gonad secondarily as a result of their expansion. For this reason, some of the case reports quoted in the present chapter are identical with those listed under accessory adrenal cortices and ovarian hypernephromas respectively.

From a *clinical* point of view, the para-ovarian hypernephromas are similar to those found in the ovary proper, hence we need not discuss them here again.

[1]*Hartmann* B6638/, *Marchand* 5920/883, 6918/891, *Chiari* 39723/884, *Pilliet* B6641/891, *Pilliet and Veau* A5231/897, *Weiss* A6147/898, A80009/898, *Rossa* 39068/898, *Meyer* A4753/898, B6640/01, A79984/08, *Peham* A5145/899, *Warthin* B6642/00, *Pick* 7097/01, *Albarran and Cathelin* B6634/01, *Eastwood* A992/02, *Hartmann and Lecène* B6637/06, *Fuchs* A79966/07, *Gompil* B6636/07-8, *Gardner and MacCleary* A79969/08, *Meyer* A79984/08, A79985/08, *Amann* A73196/08, *Delore and Alamartine* B6635/10, *Kostenko* B6639/11, *Alamartine and Maurizot* A79952/12, *Dietl* A79964/22, *Desnoyers et al.* A79963/33.

[2]*Piersanti* B21759/27, *Hochgesand* B7711/38.

[3]*Strassman* B13263/06.

OVARIAN TESTOID HYPERTHECOSIS

Experimental work and perusal of many clinical case reports lead me to believe that hyperplasia and hypertrophy of luteinized theca cells may cause a type of virilism which has hitherto not been clearly recognized as a special disease entity. Thus Stein and Leventhal[1] and Stein and Cohen[2] in their study of the "polycystic ovary" incidentally mention in their case reports that in some women this condition is accompanied by signs of virilism and especially by hirsuties. At the same time the ovaries reveal a tendency toward *theca luteinization.* Additional probably relevant cases have been described.[3]

Under the name of "hyperthecosis" Fraenkel[4] described a syndrome of virilization elicited by diffuse *hyperplasia of the theca cells.* He apparently considered the theca proliferation as truly blastomatous since occasionally he referred to it as "thecomatosis". In order to distinguish these cases from the thecomas which cause hyperfolliculoidism the term "testoid hyperthecosis" will be used here.

In a relevant case[5] virilization due to diffuse theca cell hyperplasia was combined with small cystic degeneration of the ovaries. In most of these women ovariectomy was followed by at least partial disappearance of the pseudohermaphroditic traits. Yet the ovarian origin of the clinical symptoms is subject to doubt in some cases. One author[6] observed a bearded woman with normal menses but a typical Cushing Syndrome. The ovaries were greatly enlarged due to small-cystic degeneration with theca luteinization. She died from pulmonary embolism shortly after removal of her ovaries and autopsy revealed a basophilic pituitary adenoma and adrenal cortical hyperplasia. In another[7] case the clinical manifestations and the ovarian changes were very similar. Ovariectomy led only to temporary regression of the virilism (depression of testoid production during alarm reaction?). Since the patient survived, the presence of a primary pituitary lesion could not be checked. It is suggestive, however, that she suffered from bad headaches.

Further work will have to be done before the pathogenesis of this syndrome is understood, but attention is drawn to the fact that theca luteinization induced by gonadotropic hormone treatment causes virilism in animals (see Sect. IV, Vol. IV). Thus we have both clinical and experimental evidence indicating that the theca cells can produce both folliculoid and testoid hormones. The possibility of simultaneous adrenal cortical hyperactivity in cases with primary hypophyseal hyperfunction must also be kept in mind.

The relationship of the theca cells to the so-called hilus cells, sympathicotropic cells or Leydig cells of the ovary is rather problematic in spite of their superficial morphologic similarities; it is certain, however, that they bear a striking resemblance to the Leydig cells of the testis and to the so-called extratesticular Leydig cells found in the capsule of the male gonad and in the funiculus spermaticus. In connection with testoid hyperthecosis it is pertinent to mention that *hyperplasia and the formation of small adenomas in Leydig cells of the hilus* are also conducive to virilism.[8] These cells are not known to give rise to large or malignant tumors and the resulting virilism is usually also rather moderate. There is usually some growth of the clitoris, deepening of the voice, hirsuties and breast atrophy, but the menstrual cycle may continue normally. In many cases the cause of such changes remains unknown; perhaps hilus cell hyperplasia would prove to be more common than is generally assumed if these cells were examined in all cases of inexplicable virilism.

The *diagnosis* of testoid hyperthecosis or of Leydig cell hyperplasia is impossible with our present-day methods, unless biopsy specimens of the ovary can be procured. From the differential diagnostic point of view arrhenoblastomas, adrenal tumors, congenital true and pseudohermaphroditism and virilizing folliculomas will have to be considered.

It will be kept in mind that, although theoretically high gonadotropic titers should be expected in patients with testoid hyperthecosis due to Cushing's disease in one relevant case,[6] the A-Z reaction in the urine was negative yet autopsy confirmed the presence of a basophil adenoma.

The *therapy* must be ovariectomy whenever the symptoms are sufficiently severe to justify such a drastic intervention..

[1] 78805/35.
[2] A33592/39.
[3] *Schiller* A62173/35.
[4] A69401/41, A63355/43.
[5] *Turner* A61334/43.
[6] *Bergstrand* A80125/34, A27534/34.
[7] *Rottino and McGrath* A58771/43.
[8] *Lewin* 26049/26, *Petit et al.* B6619/26, *Berger* A55382/42, *Simard* A55385/42, 83003/42, *Simard and Simard* B6691/44.

PLATE XI

CORPUS LUTEUM CYSTS AND SOLID LIPID CELL TUMORS

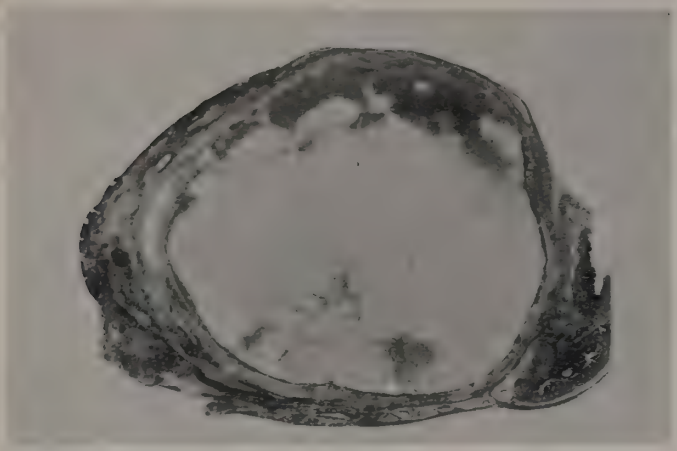

Fig. 1. CORPUS LUTEUM CYST (courtesy of Dr. L. C. Simard). General aspect of an ovary which contains an unusually large, thin-walled corpus luteum cyst.

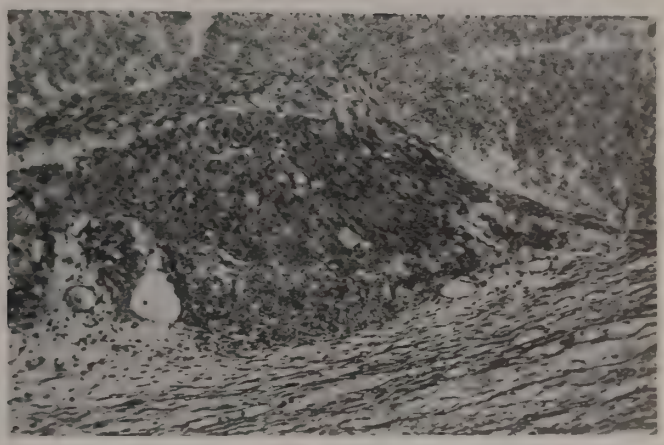

Fig. 2. CORPUS LUTEUM CYST. Higher magnification of the wall of the corpus luteum cyst shown in Fig. 1. Note that a stratified lining of well-developed corpus luteum cells is distinctly visible in the left part of the field but tapers off towards the right. Perusal of the entire cyst wall shows irregular patches of such corpus luteum cells in some places, while other regions consist of the connective tissue capsule only and are denuded of epithelial cells.

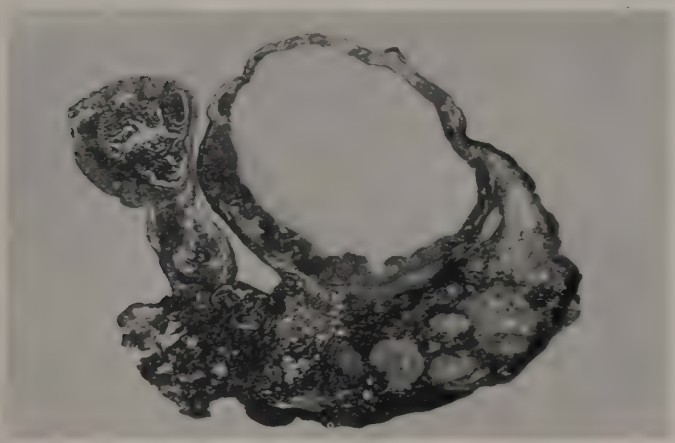

Fig. 3. CORPUS LUTEUM CYST (courtesy of Dr. L.C. Simard). Low magnification of an ovary containing a medium sized corpus luteum cyst. The cyst wall is lined by an irregular, but in general fairly high, corpus luteum cell border. The latter is thinnest near the upper pole and thickest in the lower left section of the cyst. The mesosalpinx and a cross-section through the oviduct are seen to the left of the cyst.

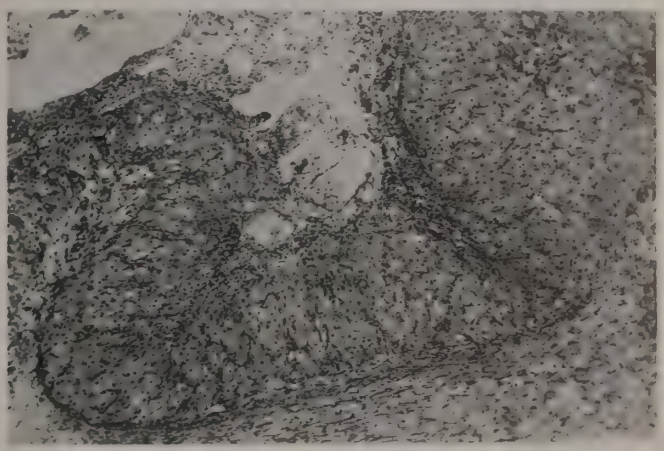

Fig. 4. CORPUS LUTEUM CYST. Higher magnification of the wall of the corpus luteum cyst shown in Fig. 3. Note the typical corrugated appearance of the corpus luteum lining which forms a stratified, fairly thick epithelial layer. The cell borders and nuclei are of normal appearance.

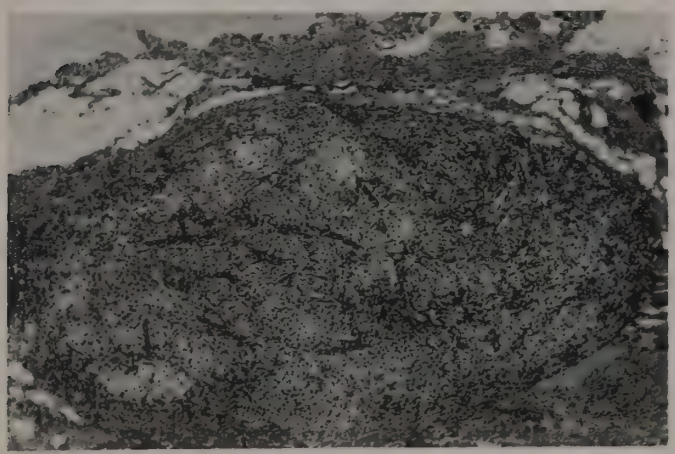

Fig. 5. ACCESSORY ADRENAL CORTEX (courtesy of Dr. L. Berger). Typical adrenal cortical tissue in the broad ligament of a 46-year-old woman. Note the lipid-containing "foam" cells characteristic of the normal adrenal cortex (some marked by arrows). Unlike the sympathicotropic or Leydig cells of the ovary, the accessory adrenal cortical elements do not follow nerve tracts and contain no crystalloids.

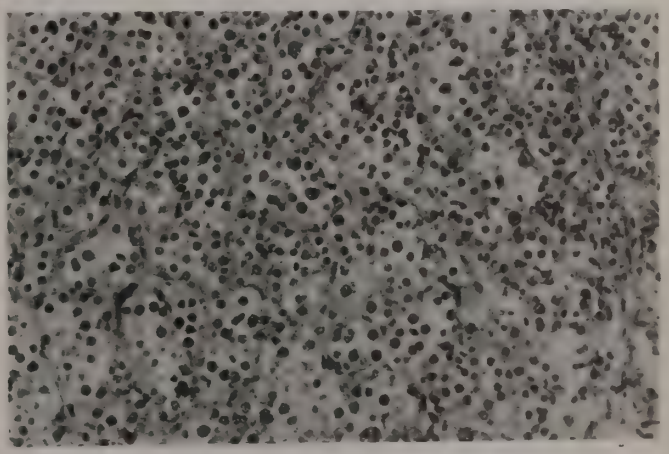

Fig. 6. HYPERNEPHROMA OF THE OVARY (courtesy of Dr. H. T. Karsner). Adrenal cortical cells similar to those in the accessory adrenal shown in Fig. 5. At this higher magnification the cell details are evident. The tumor appears to be benign and would be difficult to differentiate from an ordinary accessory adrenal.

PLATE XII

LIPID CELL TUMORS

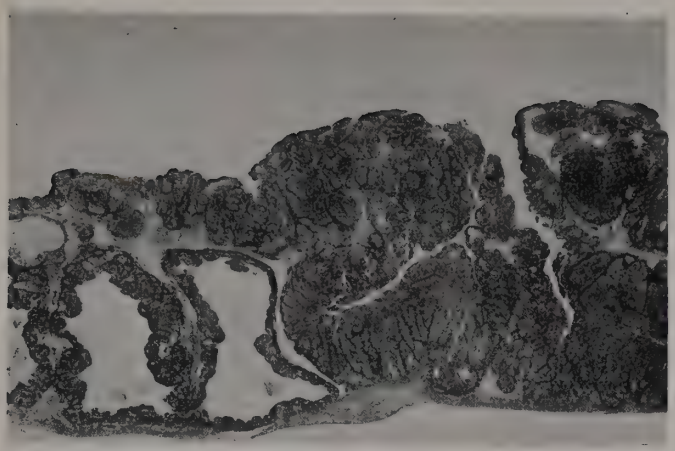

Fig. 1. CARCINOMA OF THE CORPUS LUTEUM? (courtesy of Dr. P. Masson). Very low magnification of the tumor wall. Note greatly corrugated surface which resembles the wall of a corpus luteum cyst. In left lower corner several independent cystlets developed; their walls are similar to that of the main cavity but somewhat thinner.

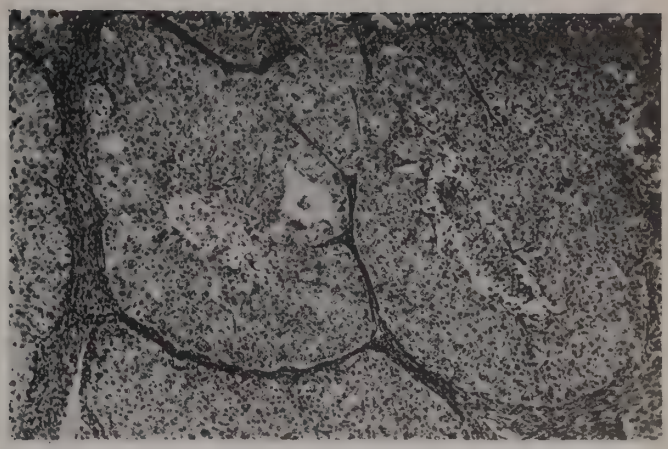

Fig. 2. CARCINOMA OF THE CORPUS LUTEUM? Medium magnification of a region in the tumor illustrated in Fig. 1. The cell arrangement is reminiscent of a corpus luteum but much more irregular. Even at this comparatively low magnification several mitoses and the irregularity of the nuclei are clearly distinguishable.

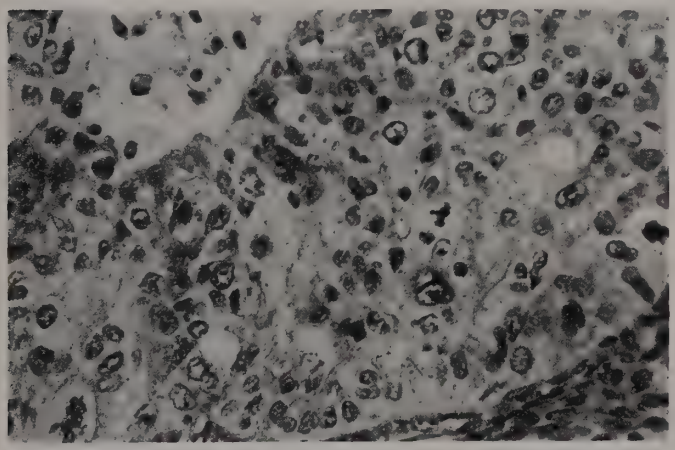

Fig. 3. CARCINOMA OF THE CORPUS LUTEUM? High magnification of a region in the tumor illustrated in Figs. 1 and 2. Note the numerous atypical mitotic figures, as well as the great irregularity in the size and shape of the nuclei, which suggest malignancy. Otherwise, the cells resemble those of the corpus luteum, but the exact nature of this tumor cannot be determined with certainty.

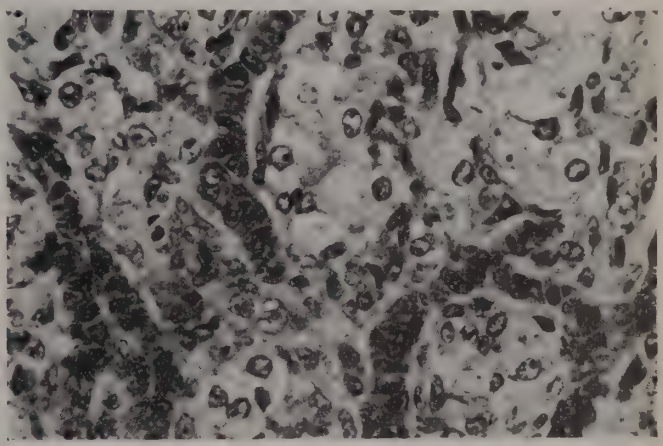

Fig. 4. ARRHENOBLASTOMA WITH LEYDIG CELLS? (courtesy of Dr. P. Masson). This tumor was originally described as a "luteinoma" by Cosacesco et al. A64215/31. Sections of it were kindly placed at our disposal by Professor P. Masson who obtained specimens from the authors. Regions, such as this, are definitely suggestive of the trabecular type of arrhenoblastoma or tubular adenoma (dark cells) with lipid-containing (light) Leydig cells between the cords.

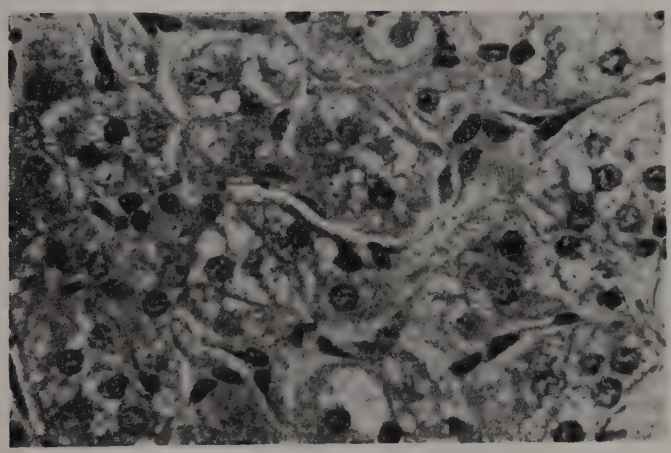

Fig. 5. ARRHENOBLASTOMA WITH LEYDIG CELLS? Another region of the neoplasm shown in Fig. 4. Note that here only lipid-containing cells are visible.

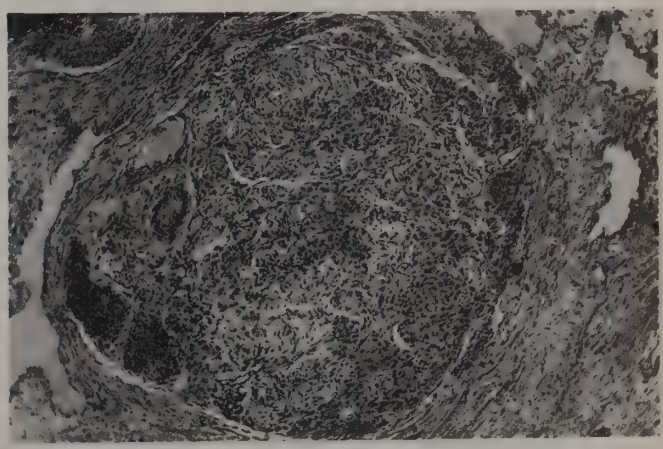

Fig. 6. LEYDIG CELL HYPERPLASIA (courtesy of Dr. L. Berger). Note the extensive hyperplasia of epithelial cells within nerve tracts. These ovarian Leydig cells may contain Reinke crystalloids and resemble in every respect the Leydig cells of the testis. In this particular woman of 45 years, no obvious clinical manifestations resulted from this comparatively small cell proliferation.

PLATE XIII

LIPID CELL TUMORS

Fig. 1. VIRILIZATION DUE TO LIPID CELL TUMOR (HYPERNEPHROMA?) (Novak and Wallis A83010/37). Note masculine facial expression and body build, atrophy of breasts, excessive hair growth on abdomen and arms. The 32-year-old patient suffered from secondary amenorrhea, polycythemia (6,600,000 erythrocytes), slight hypertension slight hyperglycemia and excessive development of the clitoris. She lost much of her scalp hair, especially in the temporal region but grew a light beard. After removal of a unilateral, lipid cell tumor (interpreted as a lutein cell tumor), the menses returned and all other symptoms and signs disappeared.

Fig. 2. VIRILIZATION DUE TO LIPID CELL TUMOR (HYPERNEPHROMA?). Same patient as that shown in Fig. 1. Note marked acne and beard growth as well as slight temporal baldness.

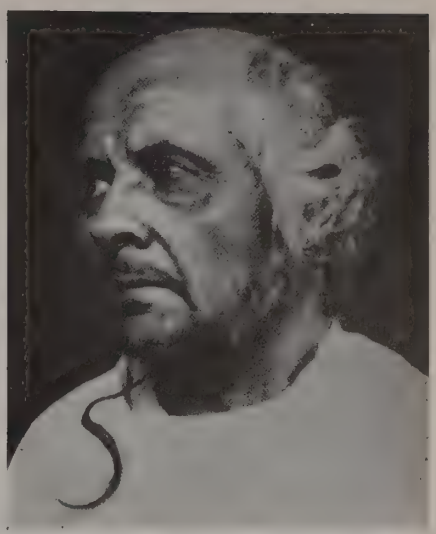

Fig. 3. VIRILIZATION CAUSED BY ARRHENOBLASTOMA (after Büttner 5587/32). 66-year-old woman with marked virilization. Note pronounced beard growth, baldness and coarse, masculine facial expression. The ovary contained a partly tubular, partly papillary tumor with occasional giant cells. The tubular portion resembled the common, tubular adenoma but the neoplasm was not very typical.

Fig. 4. VIRILIZATION DUE TO TUBULAR ADENOMA (after Strassmann A68123/29). This 24-year-old patient suffered from amenorrhea with an abdominal tumor, erroneously diagnosed as pregnancy. Her facial expression became masculine and she developed some beard and moustache growth so that she had to shave every three days. Her libido was increased. Following removal of a roundish tumor (about 6 inches in diameter) the symptoms disappeared and the menses reappeared. Histologically, the tumor was a tubular adenoma with sarcomatoid stroma.

Fig. 5. CURE OF VIRILIZATION DUE TO TESTICULAR ADENOMA (after Strassmann A65185/31). Same patient as that shown in Fig. 4, but following ablation of her virilizing tumor. The facial appearance of the patient became feminine again, the menses reappeared and two years after ablation of the tumor, she became pregnant. She is shown here with her child.

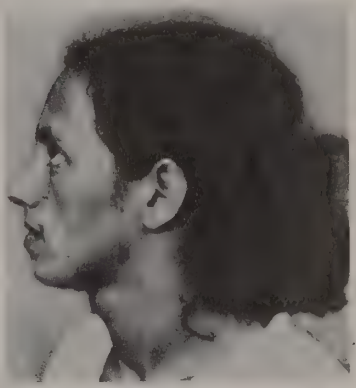

Fig. 6. VIRILIZATION DUE TO TUBULAR ADENOMA (after Schiller A62173/35). 17-year-old patient with primary amenorrhea (only occasional irregular spotting), marked hirsutism and masculine facial expression. Her libido was normal. Following removal of a rather irregular, partly trabecular and partly tubular adenoma with fat-containing interstitial cells, the menses became normal and most of the facial hair was lost.

Fig. 7. CURE OF VIRILIZATION DUE TO TUBULAR ADENOMA. Same patient as that shown in Fig. 6, six months after operation. Note loss of beard and beginning feminization of facial expression.

OVARIAN TUBULAR ADENOMAS

SYNONYMS: Arrhenoblastoma, andreioblastoma, adenoma testiculaire of ovotestis, adenoma tubulare ovarii testiculare, adenoma testiculi ovotestis, adenoma of rete ovarii, masculinoma, tubular hamartoma of ovary.

The terms *arrhenoblastoma* and *arrhenonoma* are somewhat confusing, since they are used to designate all masculinizing ovarian tumors irrespective of structure. Not all tubular adenomas of the ovary are masculinizing and conversely, some masculinizing tumors (e.g. lipid cell tumors) are not tubular adenomas (see passage on Definition).

The term *gynandroblastoma* has been suggested for tumors containing tubular adenoma as well as granulosa cell tissue and presumably producing both testoid and folliculoid hormones.

REVIEWS

ENGLISH: Popoff A65626/30, *Novak and Long* A61572/33, *Geist* A79284/35, A28064/35, *Schiller* A64891/36, *Schattenberg and Harris* A32319/39, *Robertson* A97586/39, *Dudman* A97270/39, *Dockerty* A31813/39, A96679/41, *Kanter and Klawans* A37670/40, *Boltuch* A33972/40, *Kanter and Ragins* A37840/41, *Krock and Wolferman* A36913/41, *Geist* B6672/42, *Novak* A58770/43, A59426/43.

FRENCH: Bélot A64732/37, *Varangot* 68667/37.

GERMAN: Halban A26279/25, *Bumm* A73149/25, *Neumann* 42643/25, *Meyer* A65042/30, A65111/31, *Büttner* 5587/33, *Mathias* 5535/33, *Fauvet* A95252/36, *Benecke* A95232/37, *Miller A18279/37, Westman* A34211/39.

HUNGARIAN: Szathmary A80142/34, *Fonyo* A97273/39.

ITALIAN: Amati A62282/32, *Cagnetto* A97258/39.

POLISH: Sedlis A61895/32.

PORTUGUESE: Escobar Pires A96493/38, Althabe et al. A97346/40.

SPANISH: Usandizaga and Oliva A97832/42.

DEFINITION

In this Encyclopedia the term tubular adenoma of the ovary will be used to designate any ovarian tumor whose epithelial components consist prevailingly of narrow, gland-like tubules, the cells of which are free of mucin. The rather rare malignant varieties of this neoplasm are interpreted as carcinomatous tubular adenomas. Attention is drawn to the fact that frequently, but not invariably, these tumors are conducive to clinical signs of virilization or at least "defeminization."

The serous "Wolffian adenomas", "rete adenomas", and some of the so-called "parvilocular cystadenomas" are so closely related to the typical tubular adenomas that it is difficult, if not impossible, to delimit them from each other. Such a distinction would be far too dependent upon subjective interpretation to serve as a basis for a strict subdivision. For a survey of the characteristics associated with these latter growths the reader is referred to the chapter on Common Cysts.

An attempt has been made to define as "arrhenoblastomas" or "andreioblastomas" all those neoplasms which are "masculinity tumors" (Männlichkeitsgeschwülste) without distinguishing between growths which are "masculine" because of testoid production and those which morphologically imitate the male gonad.[1] Other investigators regard all clinically masculinizing tumors as arrhenoblastomas irrespective of their histologic structure. Such definitions are inconvenient and confusing since they group together a number of essentially different tumors (e.g. tubular adenomas, lipid cell tumors etc.). Occasionally pseudohermaphroditic traits have even been seen in women whose ovaries contained various types of sarcomas, carcinomatous serous papillomas, Krukenberg tumors and other neoplasms. These are much more suitably classified on the basis of their clear-cut and indisputable histologic characteristics, especially since in many of the pertinent cases the causal connection between the neoplasm and the associated virilism is in doubt.

On the other hand, it is also inadmissible to separate strictly the tubular adenoma without virilization from the arrhenoblastoma by defining the latter as histologically similar to the former, but always associated with pseudohermaphroditic traits. It is true that some prominent authorities[2] discuss these groups in separate chapters, frequently citing border-line cases in both; however this separation on purely functional grounds is not acceptable, at least until much more is known about the pathologic physiology of these neoplasms. Such a distinction would be no more justified than the assumption that a struma ovarii which produces Graves' disease is a neoplasm essentially different from one which does not elaborate enough thyroid hormone to cause detectable signs of hyperthyroidism. It is quite possible that the degree of Leydig cell development within the tubular adenomas could account for the virilization seen in some cases, but this has not been proven as yet.

The relationship of the tubular adenoma to the seminoma of the ovary is not fully clarified; there is good reason to believe, however, that both these neoplasms develop from a failure of complete sexual differentiation into the female type. Some of the rete adenomas[3] appear to be merely a slight exaggeration of the normal "male" part of the ovary,

[1] *Meyer* A64436/30, A64798/30. [2] *Miller* A18279/37. [3] *Weishaupt* A68501/15-6.

while in other cases the tubular structures imitate testis tissue so closely that the ovaries which contain it were described as true hermaphroditic ovotestes. The difficulty of accurate differentiation is well illustrated by the fact that one of the famous relevant cases was first described as an ovotestis[1] and later reclassified as an arrhenoblastoma.[2] The seminoma or dysgerminoma is listed as a separate blastoma type because its characteristic morphologic appearance clearly distinguishes it from the tubular adenoma; yet there is no reason to disregard the possibility that the seminoma is merely a particularly anaplastic type of the "male" part of the ovary, while the tubular adenoma is more differentiated. Should this interpretation prove to be correct, the tubular adenoma and the seminoma could be regarded as closely related to each other.

HISTORY

Tubular adenomas of the ovary, frequently associated with virilism, have been known to pathologists for a long time.[3] In 1905 Pick[4] described them under the name of "adenoma tubulare testiculare ovarii". Meyer[5] first referred to them as "adenoma tubulare ovarii", subsequently as "andreioblastomas", and still later as "arrhenoblastomas". He deserves much credit for having clarified many points concerning their morphology and pathogenesis. Probably the first relevant report in the American literature was that of Moots[6] who in 1921 described a case as a "fibroblastic sarcoma of embryonic testis".

CLASSIFICATION

The classification of the tubular adenomas may be based on functional or morphologic criteria. From a functional point of view it is advisable to separate the virilizing from the hormonally inert neoplasms. It is not definitely established whether tubular adenomas may remain functionally inactive in spite of containing significant number of interstitial cells. There is good evidence (see other sections of this Encyclopedia) that the interstitial cells are the main, if not the only source of testoids in the male gonad; hence it is tempting to assume that in the tubular adenoma, virilization depends upon these same structural elements. It is difficult to be certain that any given tubular adenoma is free of Leydig cells since these may readily be missed if they are present merely as localized accumulations in a circumscribd area of the tumor. Further work will be necessary to correlate the degree of virilization with the development of interstititial cells in the tubular adenomas, but if such a correlation can be demonstrated, the functional sub-division into two groups will have its tangible, morphologic counterpart.

On a purely histologic basis the tubular adenomas, as defined in these pages, may be subdivided into the following groups:

1) *Rete adenomas.* These consist mainly of rather regular narrow tubules generally localized in the rete region and bearing a striking resemblance to the normal rete tubules. Such adenomas are comparatively common, usually of small size, and not conducive to clinical symptoms.[7]

2) *Typical tubular adenomas.* These are often difficult to distinguish from the rete adenomas. They are claimed to originate, not from the rete tubules, but from medullary cords, that is, structures corresponding to the seminiferous tubules of the testis. In these neoplasms, the stroma and the interstitial cells tend to be more developed than in the rete adenomas and the growths may reach a greater size. In some instances the tubular lumen is not noticeable and the epithelial components exhibit a trabecular aspect.[8] A very large number of them are distinctly virilizing.[9]

3) *Partly tubular and partly diffuse adenomas.* In these comparatively orderly tubules are seen in some regions, while other portions of the growth contain epithelial cells more or less irregularly arranged.[10] Certain areas may be cylindromatous[11] or resemble sarcomas.[8]

4) *Entirely atypical tubular adenomas.* In these the tubular elements are so irregular that in most cases they cannot be distinguished with certainty and the diagnosis is based partly upon the clinical manifestations of virilization.[12] Many relevant cases have been diagnosed as solid carcinomas or sarcomas of the ovary. It is not unlikely that most, if not all of the solid carcinomas sarcinosarcomas and sarcomas purported to have elicited signs of pseudohermaphroditism, actually belong to this blastoma type (see chapters on Common Carcinomas and Common Sarcomas).

The comparatively large number of *malignant or carcinomatous tubular adenomas* may also be regarded as belonging to this group, although in some of them the tubular formations remain fairly distinct,

[1]*Polano* 12215/20.
[2]*Novak* A74246/35.
[3]*Marchand* A70821/880, *Pick* A10566/05, A10565/05, *Kraus* A73152/11.
[4]A10566/05, A10565/05.
[5]A73153/14, A73154/14, A73155/14, A68492/15, A64796/18, A10553/25, A73159/25, A64436/30, A64798/30.
[6]74100/21.
[7]*Weishaupt* A68501/15-6, *Wallart and Scheidegg* A52194/34.
[8]*Benecke* A80124/34.
[9]*Pick* A10566/05, A10565/05, *Mallory* B81/39.
[10]*Kleine* A52268/34, A79312/35.
[11]*Peyron* 13364/22, A79333/24.
[12]*Krock and Wolferman* A36913/41.

at least in certain areas of the tumor.[1] Transitional types between these main groups are not uncommon. Special emphasis must be laid upon the fact that in the case of groups 3 and 4, the co-existence of diffusely arranged cells and tubulo-alveolar formations may give the growth an appearance very similar to that of granulosa cell tumors. It will be recalled that among the folliculomas there also exist neoplasms in which the cell arrangement is rather diffuse, with only a few recognizable tubular or alveolar formations. Prevalence of more or less anaplastic theca cells in the stroma of granulosa cell tumors may further emphasize their resemblance to some of the partly fibrous or sarcomatoid tubular adenomas. For these reasons, strict differentiation between folliculomas and tubular adenomas is often difficult, if not impossible. This fact was pointed out repeatedly[2] and may perhaps account for the description of purportedly virilizing folliculomas (see chapter on Folliculomas).

PATHOLOGIC ANATOMY

Macroscopic Characteristics: Upon naked eye inspection most tubular adenomas prove to be medium-sized, round or ovoid, solid growths whose surface is either smooth or slightly nodular. Their color, as viewed from the surface, is grayish-white and their consistency rather firm.[3] On the cut surface many of these neoplasms reveal a very characteristic bright yellow color.[4] This is probably due to the presence of lipid-containing interstitial cells; yet in some instances the cut surface is pinkish[5] and there are no definite data concerning the correlation between macroscopic color and degree of Leydig cell development.

The tubular adenomas are almost invariably surrounded by a fairly dense fibrous *capsule* from which connective tissue trabeculae invade the stroma, thus subdividing it into small lobules.[6]

The tumor is found in the left and right ovary with approximately equal frequency.[7]

Multiple tubular adenomas are exceedingly rare but in one case the ovary contained four distinct tumors of this type, all about 1.0 cm. in diameter, which could easily be shelled out of the gonad as they were enclosed in separate capsules.[8] *Bilateral* tubular adenomas are likewise exceptional.[9] Although the tubular adenoma is a rare tumor, careful perusal of the literature reveals several hundred relevant *case reports*.[10]

Microscopic Characteristics: The histologic structure of tubular adenomas has already been briefly discussed in the section concerned with their classification. Suffice it to mention here that in the typical blastomas the prevailing structures are epithelial *tubules* lined by serous cells which tend to resemble the Sertoli cells of the testis.[11] Occasionally solid trabeculae and irregular groups of cylindric cells are found between the characteristic tubules: these may give a carcinoma-like appearance even to otherwise benign tumors.[12] Mature spermatozoa are never found in the tubules of these tumors and indeed they do not occur even in testes if these are located within the peritoneal cavity. The possibility of immaculate conception in women with tubular adenomas of the ovaries—enthusiastically defended by Timme[13]—has therefore hardly ever been a cause for serious anguish to us.

In some publications undue emphasis is placed upon the *cytologic details* of the epithelial cells and their arrangement with respect to each other; these will not be discussed here since none of the criteria mentioned are absolutely characteristic for this particular tumor type.

Among the less constant histologic features, the formation of epithelial giant cells of a syncytial or plasmodial character is of some importance,[14] since it may indicate a certain relationship to the seminoma in which giant cells are common. Indeed there are tumors which appear to be intermediate between the

[1] *Meyer* A73155/14, A73153/14, A68492/15, *v. Szathmary* 95115/37, *Novak* A83009/38, A59426/43, *Norris* A96525/38, *Soetidjo Hardjosockatmo* A97441/39, *Dockerty and MacCarty* A33066/39, *Dockerty* A31813/39.
[2] *Novak and Long* A61572/33, *v. Szathmary* A80142/34, *Miller* A18279/37.
[3] *Miller* A18279/37.
[4] *Pick* A10566/05, A10565/05, *Neumann* A73165/28, *Gnassi* A62068/36.
[5] *Popoff* A65626/30.
[6] *Pick* A10566/05, A10565/05, *Schickele* A73170/07, *Neumann* 42643/25, A73164/27.
[7] *Krock and Wolferman* A36913/41.
[8] *Gnassi* A62068/36.
[9] *Neumann* A73165/28.
[10] *Schickele* A73170/07, *Hofbauer* A80132/09, *Meyer* A73154/14, A64796/18, A10553/25, A73159/25, A65042/30, A64437/30, A64436/30, A64798/30, A80137/30, *Polano* 12215/20, *Thaler* A73172/22, *Aubert* A64728/24, *Orru* A80139/26, *Berner* A10468/26, A64414/30, *Neumann* 42639/27, A73164/27, A80138/33, *Heesch* A73151/28, *Goldberg* A80131/28, *Geisler* A80130/28, *Rössle* A80140/30, *Wagner* A64451/30, A80145/30, *Wallart* A65118/31, *Bohne* A73148/31, *Sedlis* A66205/32, *Putschar* A80141/32, *Spielman* A61897/33, *Wüthwein* A80146/33, *Krock* A80136/33, *Bergstrand* A53146/33, A53147/34, A80125/34, *Taylor et al.* A61813/33, *Phelan* A53060/34, *Kleine* A52268/34, A971552/38, *Eerland* A80128/34, *Derichsweiler* A53156/34, *Krediet* A80135/34, *v. Szathmary* A52308b/34, *Benecke* A80124/34, A28144/34, *Behrend* A73145/35, *Tragermann* A80144/35, *Baldwin and Gafford* A62054/36, *Behrend and Levine* A59876/36, *Haffner* A95260/37, *Föderl* A95255/37, *Miller* A95064/37, *Correa da Costa* A97173/38, *Anderson* A95376/37-8, *Aburel et al.* A97572/39, *Sarkar and Tribedi* A97590/39, *Ekers and Harstad* A97271/39, *Dockerty* A97268/39, *Luzuy* A97291/39, *Kny* A96694/40, *Felicissimo de Paula Xavier and Junqueira* A97422/40, *Collins et al.* A56015/42.
[11] *Novak* A59426/43.
[12] *Bell* A80123/20.
[13] B80/34.
[14] *Bell* A80123/20, *Neumann* A73165/28, *Berner* A64414/30, *Büttner* 5587/32, *Miller* A18279/37.

seminoma and the tubular adenoma,[1] but these are rare.

The occurrence of *papillomatous regions* within otherwise typical tubular adenomas[2] is noteworthy though unusual. It will be recalled that certain carcinomatous serous papillomas have been considered to develop from the rete,[3] and since classical masculinizing tubular adenomas may be lodged in the wall of apparently common cystomas,[4] it is quite possible that virilization due to supposedly common cystomas and papillomas (see chapter on Common Cystomas) is due to the formation of small tubular adenomas in one region of the blastoma where it is not discovered.

The *stroma* may be scanty or excessively developed and within the stroma areas of hyalinization[5] or mucoid degeneration[6] are common. The mucoid connective tissue of the tubular adenoma stroma resembles Wharton's jelly and is very reminiscent of that experimentally produced in the oviduct and mesosalpinx of very immature rats treated with testosterone.[7] In one case a virilizing tumor described as an arrhenoblastoma consisted partly of tubular structures and partly of fibrous tissue with diffuse inclusions of "round laminated basophilic bodies",[8] but such formations are rare.

Interstitial cells are comparatively common; they may form small islets between the tubules or distant, adenoma-like, large accumulations. They are sudanophilic and their cytologic characteristics are generally similar to those of the Leydig cells in the testis.[9] Like the extratesticular Leydig cells in the male gonad and the interstitial or sympathicotropic cells in the normal ovary, the interstitial cells in tubular adenomas may show close topographic relations to nerves.[10] Attention has been called to the fact that these interstitial cells are more readily recognized if examined under the fluorescence microscope.[11]

In one virilizing tubular adenoma examined for fuchsinophilic material, the reaction was negative.[12] Further observations will have to show, however, whether there is any constant difference between these neoplasms and the virilizing adrenal growths with regard to fuchsinophilic granule content.

Secondary Changes in Tubular Adenomas and in the Remaining Ovarian Tissue: Adhesions may connect tubular adenomas with other peritoneal organs,[13] but they are rare.

Among the *secondary changes* within the tumor the myxomatous and hyaline degeneration of the stroma have been mentioned above and the possibility of secondary carcinomatous transformation has also been emphasized. Other secondary changes, such as widespread necrosis or hemorrhagic infarction of tubular adenomas, are rather exceptional.[14]

The neighboring organs are usually not affected by the tubular adenomas as these neoplasms rarely exhibit any great tendency towards *invasive growth.*

The *ovarian remnant* is often completely destroyed by the tumor; yet in some cases parts of it remain detectable.[15] As a rule, tubular adenomas tend to originate in the hilum region of the ovary, which is in agreement with the view that they develop from the "male" part of the female gonad. It is rather difficult to explain the exceptional case of a tubular adenoma attached to the cranial part of the ovarian surface.[16] The *contralateral ovary* is frequently atrophic, perhaps as part of the "virilization" syndrome.

Combination of Tubular Adenomas with Other Ovarian Tumors: Teratoid elements including cartilage, mucous cysts etc., may be detected in certain parts of otherwise typical tubular adenomas[17] as mentioned above; in other cases—sometimes referred to as "gynandroblastomas"—part of the growth resembles a granulosa cell tumor.[18]

The contralateral ovary may contain a *common cyst,*[19] or a *fibroma*[20] (see also corresponding passages in chapters devoted to other tumors).

INCIDENCE

With regard to the *general incidence* of tubular adenomas, it may be said that most investigators refer to them as one of the rarest types of ovarian tumors.[14] It is undoubtedly true that these tumors are not common; it must be borne in mind, however, —as we have stated above—that many instances of virilization purportedly due to solid carcinomas, sarcomas and even granulosa cell tumors, probably belong to this category. The general incidence of

[1] *Mallory* B82/37.
[2] *Büttner* 5587/32.
[3] *Wallart and Scheidegg* A52194/34.
[4] *Wijsenbeek and Plate* A33564/40.
[5] *Büttner* 5587/32, *Varangot* 68667/37.
[6] *Krock and Wolfermann* A36913/41.
[7] *Selye* A19982/40.
[8] *Canelo and Lisser* A30063/39.
[9] *Neumann* A73165/28, *Gnassi* A62068/36, *Novak* A83009/38, *Luzuy* A30682/39, *Mallory* B81/39, *Boltuch* A33972/40.
[10] *Novak* A59426/43.
[11] *Kanter and Ragins* A37840/41.
[12] *Broster* 69563/37.
[13] *Orrù* A80139/26, *Taylor et al.* A61813/33.
[14] *Miller* A18279/37.
[15] *Pick* A10566/05, A10565/05, *Schickele* A73170/07, *Berner* A64414/30, A65145/30, *Popoff* A65626/30.
[16] *Neumann* A73165/28.
[17] *McLester* A61846/36, *Kanter and Klawans* A37670/40, *Krock and Wolferman* A36913/41.
[18] *Plate* A96533/38, *Mechler and Black* A67077/43.
[19] *Berner* A65145/30, A64414/30.
[20] *Mallory* B81/39.

tubular adenomas is difficult to estimate. In a series of 400 solid ovarian neoplasms removed surgically at the Mayo Clinic between 1910 and 1937, 4 tubular adenomas were found.[1] Within the group of solid ovarian tumors their incidence may hence be placed at approximately 1%.

Reliable statistical data concerning the *age incidence* of tubular adenomas are likewise not available. One such tumor was found in a 14-day-old infant[2] and most other instances were reported in young women between 20 and 35 years of age.[3] Even in post-menopausal women, however, tubular adenomas may occasionally occur.[4]

The *pregnancy incidence* is of interest mainly because it shows that virilizing ovarian neoplasms are not incompatible with the maintenance of gestation and because in relevant cases virilization of both mother and offspring is sometimes manifest.[5]

Not much can be said regarding the *racial incidence* of this rare neoplasm. That most cases reported in the literature occurred in the Caucasian race may well be due to the fact that white women predominate among the patients of the large hospitals in which these tumors would usually be diagnosed and published. It may be mentioned, however, that a typical case has been noted in a Javanese woman.[6]

PATHOGENESIS

Histogenesis: The striking resemblance of tubular adenomas to the corresponding neoplasms of the male gonad, their histologic structure, their frequent occurrence in the "male" hilus region of the ovary, as well as their ability to produce testoid hormones, has led to the almost universal acceptance of the theory that they are derivations of *"male" gonadal elements in the ovary.* There are minor differences of opinion concerning the specific point of origin within this region. While some derive these tumors from the rete itself, others believe they originate from the medullary cords or even from the seminiferous tubules of a congenitally truly hermaphroditic gonad.[7] The assumption according to which tubular adenomas are derived from the "male" part of the ovary has much in its favor, but it appears unjustified to go any further and designate the exact cell type within this region from which these neoplasms develop. It should be kept in mind that these theories are based purely on histologic evidence and that the extremely varied appearance of these neoplasms does not justify any far-reaching conclusions concerning their specific resemblance to rete tubules, medullary cords or atrophic seminiferous tubules respectively. The existence of intermediate types between seminomas and tubular adenomas suggests close pathogenic correlations between these two "male" ovarian tumors.

In connection with these histogenetic considerations surprisingly little attention has been given to the common occurrence of *interstitial cells* within the stroma of tubular adenomas. These "Leydig cells" are strikingly similar to those found in the normal testis and in the hilus region of the normal ovary. In tubular adenomas these may proliferate not only in the form of individual cell groups between tubules, but even as distinct lipid cell adenomas. Such cases may be regarded as intermediate between the pure (interstitial cell free) tubular adenomas and the pure Leydig cell tumors (as described in the chapter Testoid Hyperthecosis). Since the Leydig cells probably play a prominent part in the functional activities of tubular adenomas, their histogenesis deserves special attention. A study of the case reports quoted in this Encyclopedia leaves us with the impression that tubular adenomas probably arise in individuals who are hereditarily more ambisexual than normal females and in whom the entire hilus region, including both tubular and interstitial cells, is subjected to a strong stimulus in the direction of sex reversal or male differentiation.

The rare but much quoted cases in which small, circumscribed tubular adenomas originate at a distance from the ovarian hilus[8] are admittedly difficult to explain on the basis of the above hypothesis, but they hardly suffice to reject it. It has been stated that tubular adenomas may originate from invaginations of the *surface epithelium*[9] and perhaps the cases in which certain regions of tubular adenomas exhibited a papillomatous aspect (see above) should be interpreted as supporting this concept. This histogenetic hypothesis could explain the rare cases of tubular adenomas on the ovarian surface, but it is hardly applicable to the majority of these tumors since it could not explain either their histologic structure (e.g. Leydig cells) or their functional potentialities.

The view that the tubular adenomas are one-sided *teratoid* tumors deserves more serious attention. They have been regarded as "tubular hamartomas".[10] The cases in which tubular adenomas developed within otherwise typical teratoids (containing cartilage, bone, mucous cysts, etc.) have also been quoted in support of this theory.[11]

[1] *Dockerty* A31813/39.
[2] *Neumann* 42643/25.
[3] *Miller* A18279/37.
[4] *Büttner* 5587/33, *Behrend* A73145/35.
[5] *Berner* A65145/30, *Felicissimo de Paula Xavier and Junqueira* A96494/38.
[6] *Eerland* A61748/33.
[7] *Pick* A10566/05, A10565/05, *Meyer* A73154/14, A73155/14, A10553/25, A73159/25, *Popoff* A65626/30, *Wallart* A65118/31, *Dockerty and MacCarty* A33066/39.
[8] *Pick* A10566/05, *Neumann* A73165/28.
[9] *Meyer* A10553/25.
[10] *Neumann* 42643/25, A73165/28, *Popoff* A65626/30.
[11] *McLester* A61846/36, *Krock and Wolferman* A36913/41, *Mechler and Black* A64077/43.

FUNCTIONAL PATHOGENESIS: Heredity plays an important rôle in the causation of tubular adenomas. Thus tubular adenomas have been noted in two sisters, both of whom also suffered from partial aplasia of the internal sex organs.[1] The comparative frequency of congenital malformations in patients with tubular adenomas (see part on Clinical Course) likewise stresses the importance of hereditary factors. In this connection it should also be remembered that, from the histologic point of view, there is an almost insensible transition between the ovotestis of the true hermaphrodite and an ovary with a highly differentiated tubular adenoma.

Only few data are available which could give us information concerning the functional stimulus directly responsible for eliciting these neoplasms. It seems rather probable, however, that even in hereditarily predisposed individuals an additional growth impulse is necessary to elicit neoplastic proliferation in the ovary at one particular period of post-embryonic life. Unlike the patients with seminomas, those with tubular adenomas rarely exhibit congenital pseudohermaphroditic traits. Signs of mild virilism are common in normal women during pregnancy and after the menopause when the rete tubules and Leydig cells in the ovary tend to proliferate (see chapters on Ovarian Changes during Pregnancy and Old Age in Sect. IV, Vol. IV). It would be futile at this time to speculate on the exact nature of the pathogenic mechanisms responsible for the development of "pseudohermaphroditic traits" during pregnancy and old age; yet it is rather tempting to look upon the virilizing tubular adenoma as an abnormal exaggeration of the same processes. It is of interest in this connection that during embryonic life treatment with *testoid hormones* can cause almost complete sex reversal in female birds, with the development of functional seminiferous tubules in genetically female gonads (see chapter on Ovarian Changes due to Testoid Hormone Administration in Sect. IV, Vol. IV). In mammalian embryos such marked degrees of virilization cannot be obtained. Even during early post-embryonic life, however, overdosage with testoids causes pronounced inhibition in the development of the uterus and vagina, as well as adenomatous proliferation of the rete tubules.[2] It is quite possible, therefore, that in women, the immediate stimulus which elicits both the formation of "defeminizing and virilizing" tubular adenomas and the occasionally co-incident malformations of the Müllerian duct derivatives is also humoral.

In the part on Diagnosis several instances are mentioned in which patients with Cushing's disease or adrenal hyperplasia developed a tubular adenoma of the ovary. Such cases suggest a possible pathogenic relationship between excess production of pituitary and adrenal cortex hormones and the formation of tubular adenomas of the ovary. Many additional cases will have to be studied, however, before this possible interrelation can be more clearly formulated.

CLINICAL COURSE

In the majority of women with tubular adenomas of the ovary *local signs* are not particularly prominent (see part on Diagnosis).

The most striking manifestations of these neoplasms are due to the production of excessive quantities of testoid hormones; indeed, in the so-called "silent" varieties of these tumors the clinical course has no characteristic features. Among the symptoms and signs due to testoid hormone over production, *virilization* and *defeminization* are conspicuous. Most patients state that their sexual development, and even their menstrual cycle, was normal until the beginning of the illness. Then gradually excessive hair growth on the upper lip, chin, arms, legs and buttocks becomes evident; the scalp hair may fall out, so that these bald women resemble middle-aged men. Acne may appear, the voice assumes a low pitch and is often hoarse, the clitoris is enlarged, there is amenorrhea and the uterus, as well as the breasts, become atrophic. There is often a marked loss of libido. Usually neither the blood pressure nor the blood count show any conspicuous change, but in some cases there is a definite tendency to put on weight as the tumor develops.[3]

Whether tubular adenomas may be the cause of *metrorrhagias* is somewhat doubtful since the cases in which this sign was evident may belong to the granulosa cell group.[4]

Ascites is not a characteristic accompaniment of tubular adenomas although it occurs occasionally.[5]

Studies concerning the *metabolism* and the chemical composition of blood and urine in patients with tubular adenomas revealed no characteristic changes.[6]

Carcinomatous transformation of tubular adenomas has been mentioned in the section on pathology. From the clinical point of view the carcinomatous tubular adenoma does not differ essentially from other primary ovarian cancers except for the accompanying signs of pseudohermaphroditism.

[1] *Novak* A58770/43.
[2] *Selye* A19982/40.
[3] *Schickele* A73170/07, *Neumann* A73165/28, *Büttner* 5587/33, *Plate* A96533/38, *Mallory* B81/39, *Boltuch* A33972/40, *Kanter and Ragins* A37840/41.
[4] *Büttner* 5587/33.
[5] *Orru* A80139/26, *Taylor et al.* A61813/33, *Eerland* A80128/34, *Kleine* A52268/34, A79312/35.
[6] *Canelo and Lisser* A30063/39, *Kanter and Klawans* A37670/40.

COMPLICATIONS

The clinical course of tubular adenomas is but rarely complicated by *torsion* and *hemorrhage* into the tumor, or *herniation* of the affected ovary (see Sect. IV, Vol. VI).

DIAGNOSIS

In the diagnosis of tubular adenomas *local signs* rarely play a conspicuous role since usually these blastomas are of moderate size and exhibit no great tendency towards invasive growth. In certain cases, however, the pelvic findings are of great importance; if the tumor is virilizing they help the differential diagnosis between an ovarian and adrenal-cortical neoplasm and if there are no pseudohermaphroditic traits, the local signs may be the only detectable manifestations of the tubular adenoma. The usually smooth surface and firm consistency of these growths may be of some diagnostic value, but it must be admitted that the pre-operative diagnosis of these tumors is usually impossible. During the operation the often (but not invariably) bright yellow color of the cut surface may help the recognition of the neoplasm. It must be kept in mind, however, that other virilizing tumors (especially the hypernephromas and Leydig cell tumors) as well as corpus luteum tumors and lipid containing folliculomas may have the same color.

The signs of *defeminization* (atrophy of breasts and uterus, amenorrhea, loss of libido etc.) and *virilization* (hirsutism, growth of the clitoris, deepening of the voice, loss of scalp hair etc.) should always raise the suspicion of a tubular adenoma. From a *differential diagnostic* point of view adrenal-cortical tumors (of the adrenal itself or of adrenal rests in the ovary) and Cushing's disease can often be excluded, since in most tubular adenomas there is no special tendency towards the development of plethora, hypertension, diabetes, abdominal striae or the characteristic "moon face". A search for specific local signs in the adrenal and pituitary region is always indicated, however, in such cases. In one rather unusual instance a tubular adenoma of the ovary caused not only virilization, but also hypertension, polycythemia, diabetic glucose tolerance curve and a B.M.R. of plus 39% and yet was diagnosed as an arrhenoblastoma.[1] In this patient the correctness of the diagnosis was confirmed by the histologic structure of the tumor, and by the disappearance of her symptoms following its ablation. In another similar case heterosexual hypertrichosis was accompanied by increase in weight, abdominal striae, headaches and slight enlargement of the sella turcica. Although the blood pressure was normal, it was diagnosed as Cushing's disease and the pituitary was partially removed. The patient finally died and autopsy revealed no hyaline changes in the basophiles of the anterior lobe, but there was a cyst in the pituitary. The ovary contained a more or less typical tubular adenoma. In this case the possible participation of the pituitary in the syndrome cannot be excluded with certainty. In another patient with a virilizing tubular adenoma of the ovary, one adrenal was found markedly enlarged at operation and the pseudohermaphroditic traits did not disappear completely after removal of the ovarian tumor.[2]

Such borderline cases are not very common, however, and in the majority of the patients suffering from masculinizing tubular adenomas, signs of Cushing's syndrome are not manifest except for the virilization.

Urinary *hormone determinations* (17-KS., folliculoids or gonadotropic, hypophysoid hormones) have not been carried out in a sufficiently large number of cases to be of real diagnostic value. The few reported data do not reveal any great deviation from the normal.[3]

Although the tentative diagnosis of tubular adenoma has frequently been made in cases of virilizing ovarian tumors, it is hardly surprising, in view of the rather uncharacteristic symptomatology, that only few instances have definitely been diagnosed as such prior to operation.[4]

PROGNOSIS

The prognosis of tubular adenomas is generally good if the tumors are completely removed. Since these neoplasms tend to occur in young women, before or during the child-bearing period, and since they are usually not malignant or bilateral, conservative operations appear justified. Following removal of the growth the menstrual cycles tend to re-appear in previously amenorrheic patients while most of the pseudohermaphroditic traits disappear. The loss of the excessive body and facial hair is particularly striking and becomes noticeable a few weeks after the operation. The libido also tends to return within a short period, and the previously atrophic breasts become full again. The regression of the enlarged clitoris is generally more time-taking. Although some slight virilization may persist, *in general the manifestations of testoid hormone over-*

[1] *Maxwell* A83008/37.
[2] *Westman* A34211/39.
[3] *Szathmary* A95115/37, *Mallory* B81/39, *Dockerty and MacCarty* A33066/39, *Wijsenbeek and Plate* A33564/40, *Kanter and Klawans* A37670/40.
[4] *Maxwell* A83008/37, *Boltuch* A33972/40.

dosage are effectively cured by the removal of the neoplasm.[1]

After the tumor is removed and the patient "refeminized", normal *pregnancies occur* in a fairly large number of cases.[2]

Recurrences after the operation are comparatively rare since the tumors are generally of a low grade malignancy.[3] In some cases, however, local recurrences or post-operative growth of metastases led to a second period of virilization some time after the original tumor was removed and such recurrences often proved fatal.[4] If the tumor recurs at all, this is usually obvious within the first few years after the operation, but in one rare instance a recurrence was noted 16 years after ablation of the original growth.[5]

THERAPY

The therapy of tubular adenomas must always be surgical. No data are available concerning the efficacy of X-ray therapy and in view of the excellent results obtained by conservative surgical interventions, experimentation along these lines would hardly be justified.

The excellent functional results of conservative surgery have been discussed in the preceding chapter in connection with the prognosis. Suffice it to mention here that following removal of (the usually atrophic) ovaries containing the tubular adenomas, severe menopause-like deficiency symptoms may be noted in exceptional cases.[6] This could be due to withdrawal of the hormone produced by the tumor itself.

[1]*Moots* A74100/21, *Bell* A80123/20, *Goldberg* A80131/28, *Strassmann* A68123/29, A65185/31, A65186/31, *Meyer* A80137/30, *Neumann* A80138/33, *Eerland* A61748/33, A80128/34, *Taylor et al.* A61813/33, *Benecke* A80124/34, *v. Szathmary* A80142/34, *Schiller* A62173/35, *Gnassi* A62068/36, *Broster* 69563/37, *Novak* A83009/38, *Mallory* B81/39, *Westman* A34211/39, *Boltuch* A33972/40, *McIntyre* A55678/42.

[2]*Davis* A7006/00, *Stübler and Brandess* A76588/24, *Neumann* A73165/28, *Popoff* A65626/30, *Strassmann* A65186/31, *Mathias* 5535/33, *Phelan* A53060/34, *Dockerty* A31813/39, *Lisser et al.* A97806/42.

[3]*Dockerty and MacCarty* A33066/39.

[4]*Davis* A7006/00, *Goldberg* A80131/28, *Meyer* A80137/30, A64798/30, *Krock and Wolferman* A36913/41.

[5]*Terrades* A80143/29.

[6]*Novak* A58770/43.

OVARIAN TUBULAR ADENOMAS IN ANIMALS

Tubular adenomas, or arrhenoblastomas, are apparently quite common among the lower vertebrates. In general it is difficult, however, to distinguish the true neoplastic variety of tubular growths from the hermaphroditic development of testis tissue within the ovary.

In the *turtle (Malaclemmys centrata)* a medullary tumor of the "arrhenoblastoma" or tubular adenoma type has been observed, but the animal was obviously ambisexual.[1]

In the *fowl* removal of the left ovary, or injection of gonadotropic preparations, may cause marked proliferation of the normally vestigial right gonad. In such instances the proliferating gonadal tissue may be indistinguishable from fetal or even adult testes or arrhenoblastoma tissue. It is obvious that destruction of the left gonad by disease may act in a similar manner and cause proliferation of the potentially ambisexual right gonad.

In a number of hens in which spontaneous sex reversal occurred, there was marked atrophy or complete destruction of the left ovary. In its place a mass was found which, for want of a better description, was called "tumorous". The histologic structure of this growth was essentially identical with that of testicular tissue in various phases of differentiation; hence it was concluded that: "the pathology of certain of these hen tumors distinctly resembles that of the arrhenoblastoma of women".[2] As has been stated in the chapter on Tubular Adenomas of the Human Ovary (see above), as well as in the chapter on Ambisexuality (see Sect. IV, Vol. VI.), it is impossible to differentiate between testicular tissue in the ovary (as it occurs in cases of true hermaphroditism) and the highly differentiated mature types of ovarian tubular adenomas. In hermaphrodites testis tissue within the ovary in the abdominal cavity would normally remain immature in any case just as cryptorchid testes do in men. In the bird, on the other hand, testicular tissue normally matures and forms sperm while in the peritoneal cavity; hence it is not surprising that ambisexually developed gonads tend to reveal more advanced stages of spermatogenesis, often reminiscent of unusually mature seminomas (see chapter on Seminomas).

In the *mouse* tubular adenomas of the ovary tend to develop under the influence of X-rays.[3]

[1]*Risley* 79786/41.

[2]*Friedgood and Uotila* A36456/41, *Friedgood* 80844/41.

[3]*Furth and Furth* A64757/36, *Furth and Butterworth* A59927/36, *Geist et al.* A33605/39.

PLATE XIV

TUBULAR ADENOMAS

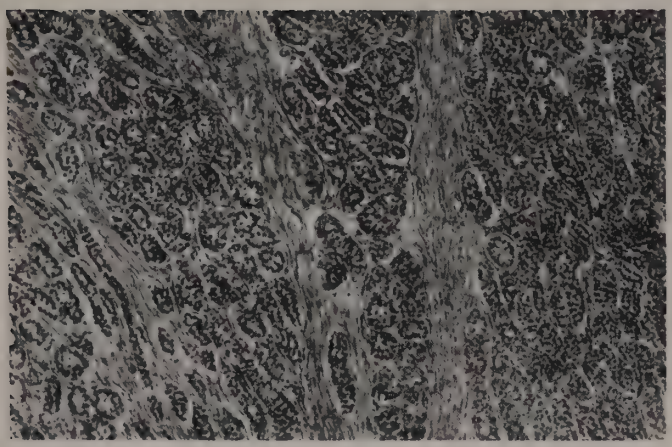

Fig. 1. TUBULAR ADENOMA (courtesy of Dr. H. T. Karsner). Tubular adenoma ("arrhenoblastoma") as seen under low magnification. Note the numerous glandular tubules which in some areas are separated only by very fine connective tissue septa, while in other regions they are subdivided by dense connective tissue trabeculae.

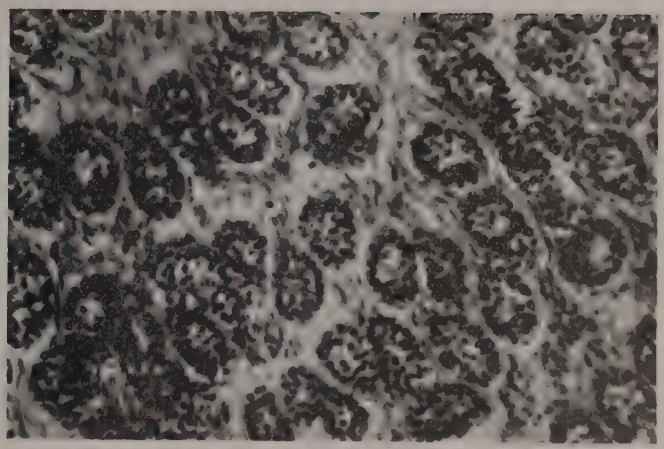

Fig. 2. TUBULAR ADENOMA. Higher magnification of a region in the tumor illustrated in Fig. 1. Note the great resemblance of the tubules to those seen in fetal testicular tissue. The "spermatogenic" epithelium shows no great tendency towards maturation and differentiation but is stratified and in some places tubular lumina are distinguishable. In this region, the stroma consist of ordinary connective tissue without well-defined Leydig cells.

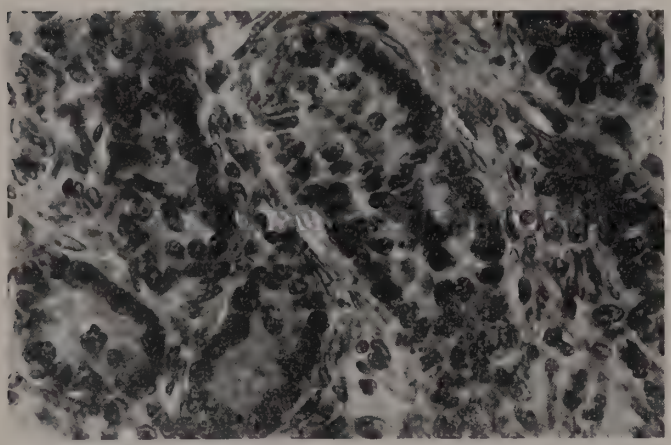

Fig. 3. TUBULAR ADENOMA (courtesy of Dr. P. Masson). High magnification of the tubules illustrating cell details. Note the complete absence of tubular lumina. Regions such as this bear a certain resemblance to the tubular type of the granulosa cell tumor.

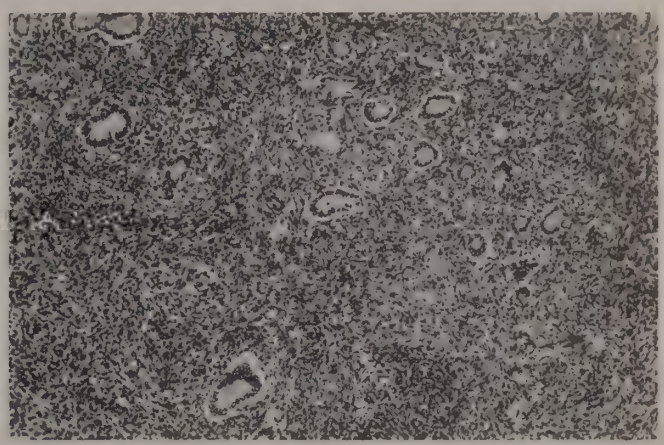

Fig. 4. TUBULAR ADENOMA (courtesy of Dr. H. T. Karsner). Mixed sarcomatoid and tubular type.

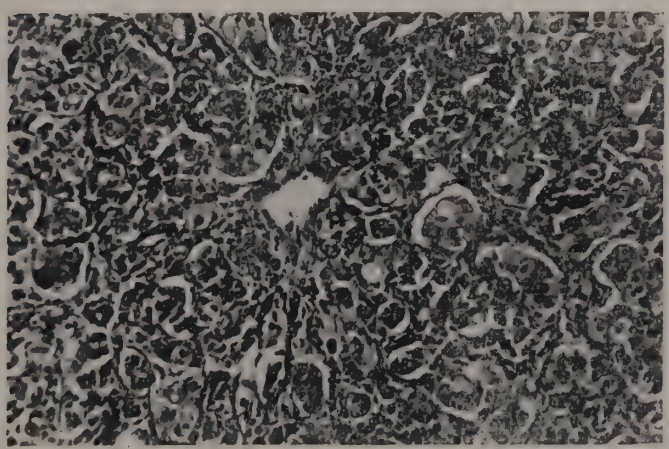

Fig. 5. TUBULAR ADENOMA (courtesy of Dr. H. T. Karsner). The tubular arrangement of epithelial cells is extremely indistinct in this neoplasm but large, epithelioid Leydig cells are clearly distinguishable among the narrow and irregular tubules.

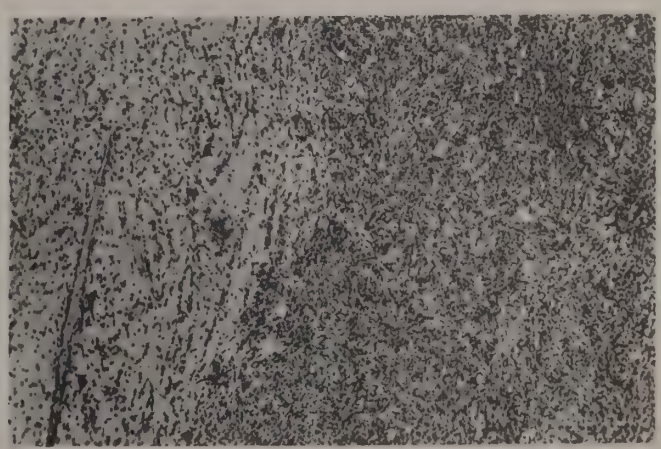

Fig. 6. "SARCOMATOID ARRHENOBLASTOMA" (courtesy of Dr. H. T. Karsner). Pure sarcomatoid cell arrangement resembling the stroma of the tumor illustrated in Fig. 4. Note intercellular edema in the left part of the field.

OVARIAN SEMINOMAS

SYNONYMS: Dysgerminoma, disgerminoma, embryonic carcinoma, encephaloid of ovary, large-cellular medullary carcinoma of ovary, carcinoma ovarii puellarum, solider Rundzellenkrebs des Eierstockes, solides grosszelliges Keimepithelblastom, grosszelliges solides Karzinom der Jugendlichen und der Scheinzwitter, tumeur de l'ovaire des fillettes.

The terms "Epithelioma chorio-ectodermale (Pick)" and "Alveolar round cell sarcoma" of the ovary are not synonymous but have repeatedly been used to designate seminomas by authors who failed to recognize their true nature.

REVIEWS

CZECH: Pazourek A79518/33, *Klaus* A59910/36, *Matousek and Vojta* A97597/41.

ENGLISH: Geist A79284/35, A28064/35, B6672/42, *Novak and Gray* A96528/38, *Russel* A96541/38, *Innes et al.* A94672/38, *Robertson* A97586/39, *Dudman* A97270/39, *Schattenberg and Harris* A32319/39, *Karsner* A32285/40, *Dockerty* A96679/41, *Novak* B109/44.

FRENCH: Thélin A79532/25, *Hoche* A79475/29, A64425/30, *Béclère* A49974/34, *Christidi and Fagarasanu* A95387/38.

GERMAN: Sternberg A64845/26, *Döderlein* A59881/36, *Miller A18279/37, Kleine* A97152/38, *Föderl* A96495/38, *Hüssy* A96919/42, B10134/43.

ITALIAN: Amati A62282/32, *La Manna* A94674/39.

RUMANIAN: Lazarescu and Platareanu A79492/30-1, A79493/30-1.

SPANISH: Jorge and Moreno A95402/37, A95264/37, *Sardi and Ahumada* A97589/39.

DEFINITION

The seminoma of the ovary is a malignant neoplasm characterized by the presence of medium sized, round or polyhedral, lightly staining cells diffusely arranged in a loose stroma. The epithelial elements may contain large amounts of glycogen and sometimes form multinuclear giant cells; the stroma is infiltrated with lymphocytes. This tumor often develops in children and in pseudohermaphroditic individuals. Histologically it strikingly resembles the seminoma of the testis but tends to be less malignant. It is not known to produce any hormones or obvious endocrine disturbances, although it may lead to increased urinary elimination of gonadotropic hypophysoid hormones.

HISTORY

The testicular seminomas were first described by Chevassu[1] in 1906. He recognized that, contrary to the opinion of earlier workers, these tumors are not alveolar sarcomas, but represent a distinct type similar only to certain ovarian neoplasms. Later, Chenot[2] separated this tumor from the large group of solid ovarian cancers, emphasizing their great resemblance to the testicular seminomas of Chevassu. The subsequent studies of Masson,[3] who described the growths as "seminomas of the ovary", and of Strong,[4] who spoke of them as "embryonal carcinomas", helped greatly to clarify our views regarding this neoplasm. The term dysgerminoma was proposed by Meyer[5] because he claimed that the tumors arise from the germinal epithelium which loses its "germinal" properties as a result of some derangement occurring before its differentiation into ovarian or testis tissue.

PATHOLOGIC ANATOMY

Macroscopically the *shape* of the ovarian seminomas is usually round or ovoid, occasionally kidney-like; their surface may be smooth or nodular and is often covered by a distinct capsule. In some cases the capsule is missing and the tumor is adherent to the adjacent tissues which it eventually invades.[6] Although their growth rate is rapid, seminomas are usually only of moderate size, due to the fact that before they reach considerable dimensions they are either removed or cause the death of the patient. In some cases, however, the tumors weighed anywhere between 12 and 15 lbs.[7]

The *color* of seminomas is generally yellowish or grey, sometimes with a bluish tinge. Occasionally red or brown patches are formed within the tumor due to small hemorrhages.[8]

The *consistency* of seminomas is commonly hard and elastic, but may be soft or brittle. In any case, these are invariably solid tumors.[9]

On the *cut surface* the seminomas exhibit an appearance somewhat reminiscent of testis tissue. They are usually greyish with a tinge of yellow and their parenchyme is subdivided by fine connective tissue trabeculae.[10] In comparatively small seminomas it is still possible to determine the exact point of origin and it appears that they arise most often in the hilus region.[11]

[1] 39718/06.
[2] A79442/11.
[3] A79498/12.
[4] A79527/19.
[5] A65042/30.
[6] *Miller* A18279/37.
[7] *Sarnoff* A64543/29, *Wallis* A61705/33.
[8] *Neumann* A67249/30, *Miller* A18279/37.
[9] *Wallis* A61705/33, *Bettinger* A79438/33, *Szathmary* A79528/33.
[10] *Chenot* A79442/11, *Daube* 50738/19, *Gery and Reeb* A68179/29.
[11] *de Mora* A79507/31, *Miller* A18279/37.

An unusually large number of seminomas are *bilateral*.[1] In one series of observations[2] seminomas occurred bilaterally in about 35% of the cases.

The general *microscopic* appearance of the seminomas was briefly outlined above in connection with their definition. It is of particular importance to emphasize that, contrary to common belief, these are not large cellular cancers, since the average *diameter of the epithelial cells* usually varies between 12 and 18 μ.[3] Yet in the old literature this neoplasm was consistently described as a large cellular growth because it was considered to be a round cell sarcoma and compared to these small cellular neoplasms its cells are fairly large. The irregular, roundish, loosely arranged epithelial cells, which constitute the parenchyme of the seminomas are certainly reminiscent of sarcomas, but it must be kept in mind that post-mortem decomposition very rapidly tends to influence the structure of these growths unless they are carefully fixed while still fresh. Among the post-mortem changes swelling of the cell body with the formation of vacuoles is particularly characteristic. Furthermore, the epithelial elements often shrink away from each other and from the connective tissue stroma.

In adequately fixed seminomas the epithelial cells regularly contain one or two prominent *centrosomes* in a dense area of the cytoplasm close to the nucleus.[4]

Not infrequently *polynuclear giant cells* are seen within the parenchyme of the seminoma. These have often been mistaken for Langhans cells of tubercles which led to much speculation concerning a possible causal relationship between tuberculosis and seminoma formation. This interpretation appears to be entirely unjustified, and perusal of the cases, in which polynuclear giant cells are described, leads us to regard them as modified foreign body giant cells.[5] These peculiar giant cells also led to other misinterpretations and induced some workers[6] to speculate upon a possible connection between seminomas and chorionepitheliomas, while others[7] spoke of a "tuberculoid reaction" which, according to one author,[8] is possibly due to the formation within the neoplasm of lipids similar to those elaborated by the tubercle bacilli. Attention should be called to the fact that in the testes of hypophysectomized animals, similar polynuclear giant cells are formed from the seminiferous epithelium during the involution resulting from gonadotropic hormone deficiency.[9]

The *glycogen* content of the blastoma cells is somewhat variable, but often rather high[10] and in suitably stained frozen sections, numerous minute *lipid* granules can frequently be demonstrated in the cytoplasm of seminoma cells;[11] occasionally even crystalloids are found.[4]

The *nuclei* are comparatively large and usually ovoid or round, sometimes distorted as a result of faulty fixation. There is a striking difference between the vesicular nuclei of seminoma cells and the dark nuclei of the granulosa cell tumors.[12] On the other hand, it has also been claimed that the nuclei are "hyperchromatic".[13] In view of the frequently pronounced post-mortem decomposition of seminomas, their nuclear structure is rarely of great diagnostic value. Generally 1-3 nucleoli are found.[3] The number of mitoses is extremely variable; in some cases they are numerous,[14] in others rare or absent.[15]

The presence of *lymphocytes* in the stroma has been mentioned above and it may be said that they constitute one of the most characteristic features of seminomas. Sometimes they form only light infiltrations, while in other cases the entire stroma is heavily invaded by lymphocysts and almost completely transformed into lymphoid tissue.[16] Lymph follicles, with distinct germinal centers, are rare, and if present contain no reticular fibrils.[17] It is also unusual to find leucocytes or plasma cells in the seminoma stroma.[3]

Sometimes folliculoid formations are found in otherwise typical seminomas. They lead to confusion with granulosa cell tumors[18] but this diagnostic error is easily avoided if the above mentioned characteristics of seminomas are kept in mind. As indicated in the chapter on Folliculomas, a seminoma may, however, also develop in combination with a true granulosa cell tumor.

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[1] *Eastman* A40889/883-4, *Neumann* A73164/28, *Bonnet* A79440/28, *L'Esperance* A79456/28, *Muller* A79510/31, *Vincent* A62956/32, *Krafft* A79489/32, A79490/34, *Bettinger* 5539/33, A79438/33, *Klaften* A27707/34, *Dworzak* A27996/35, *Long et al.* A38069/41.

[2] *Dockerty and MacCarty* 77977/39.

[3] *Miller* A18279/37.

[4] *Peyron* A79519/21.

[5] *Zimmermann* A79544/23, *Neumann* 42642/27, *Tirelli* A79535/29, *Schiller* A52279/34, A79525/34, *Frankl* A59887/36, *Novak and Gray* A96528/38, *Greenblatt and Pund* A96428/38, *Hansen* A94670/39, *Sailer* A34954/40, *Heller* A58779/43.

[6] *Meyer* A73159/25, *Pick* A80099/04, A80100/05, A80101/05.

[7] *Heller* A58779/43.

[8] *Schiller* A52279/34, A79523/34.

[9] *Collip et al.* 9728/33.

[10] *Chenot* A79442/11, *Matsner* A79499/23, *Hamant and Cornil* A79474/25, *Hoche* A79475/29, A64425/30, *Lissowetzky* A28117/35.

[11] *Thélin and Rosselet* A79533/27.

[12] *Chenot* A79442/11.

[13] *L'Esperance* A79456/28.

[14] *Chenot* A79442/11, *Zimmermann* A79544/23, *L'Esperance* A79456/28, *Parreira and Silva* A79517/28, *v. Szathmary* B12390/33.

[15] *Meyer* A64796/18, *Hamant and Cornil* A79474/25, *Dupont* A79452/25, A79451/25, *Neumann* 42642/27.

[16] *Desmarest and Masson* A79449/12, *Géry and Reeb* A79467/29, A79468/29, *Anderes* A77998/29, *Dworzak* A61378/32, *Blau* A61365/32, *Bettinger* 5539/33, A79438/33.

[17] *Klaften* A79305/33.

[18] *v. Werdt* A64866/14, *Massazza* A64386/31.

The numerous *case reports* in which seminomas are described yield a wealth of material concerning both their morphologic and clinical characteristics.[1]

SECONDARY CHANGES IN SEMINOMAS AND IN THE REMAINING OVARIAN TISSUE: Among the *secondary changes* which may affect the seminoma, hyalinization of the connective tissue is comparatively common.[2] There may also be some edema[3] and, following rupture of small blood vessels, hemorrhage into the tumor tissue.[4] Indeed, in certain cases the hemorrhages are very pronounced and conspicuous, so that the entire neoplasm is replete with hemorrhagic patches.[5]

As in many of the medullary neoplasms, the seminoma is rather subject to extensive necrosis in the event of vascular disturbances. This may transform large parts of the tumor into a brittle or soft, jelly-like, semi-fluid tissue and eventually liquefaction cysts can be formed within the tumor parenchyme.[6] Secondary calcification of the necrotic areas is comparatively rare.[7]

The *ovarian remnant* is usually not demonstrable in the seminoma mass, although in some cases part of the ovarian tissue is still sufficiently preserved to be detectable.[8]

The *contralateral ovary* may be normal or the site of a similar tumor formation since, as stated above, seminomas are frequently bilateral. Occasionally the contralateral gonad is hypoplastic[9] or affected by small cystic degeneration.[10] It may even contain an entirely independent second tumor, e.g. an adenocarcinoma.[11]

The *pedicle* may be thick and edematous,[12] or long and thin,[13] and it may become invaded by the malignant cells of the seminoma.[14]

In many cases there are dense *adhesions* between the neoplasm and the adjacent organs,[15] but in other cases the tumor is entirely free and mobile so that it can readily be removed by the surgeon with any time-taking dissection.[16]

SEMINOMAS IN COMBINATION WITH OTHER EXTRAOVARIAN AND OVARIAN TUMORS: Metastases into distant organs occur infrequently[17] but have been demonstrated in the abdominal wall,[18] the tibia,[19] the pleura,[20] the lungs,[21] the peritoneum,[22] or the lymphnodes,[23] the kidneys[21] and the liver.[21]

It is comparatively rare to find seminomas in combination with other ovarian tumors. In certain instances, however, the ovarian seminoma was accompanied by the simultaneous develpoment of *common cystomas*,[24] *dermoid cysts* and *teratomas*[25] or areas with characteristically folliculoid formations such as are found in *granulosa cell tumors*[26] (see also chapter on Folliculomas).

INCIDENCE

It is very difficult to estimate the *general incidence* of ovarian seminomas because of the comparative rarity of the tumor and the fact that so many relevant growths have been misdiagnosed as round cell sarcomas, medullary cancers, etc. In a series of 1101 cases of unselected benign and malignant, primary

[1] *Okinczyc and Renaud* A79516/20, *Peyron* A79519/21, 13364/22, A79520/22, A79333/24, *Ménétrier et al.* A79500/22, *Matsner* A79499/23, *Zimmermann* A79544/23, *Hamant and Cornil* A79474/25, *Dupont and Simard* A68509/25, *Delbet* A79448/27, *Neumann* 42642/27, *Béclère* A79432/27, A49974/34, *L'Esperance* A79456/28, *Bonnet* A79440/28, *Althabe and Colillas* A79425/28, A79426/28, A96761/28, *Jianu et al.* A79478/28-9, *Babes* A79430/29, *Géry and Reeb* A79468/29, A68179/29, *de Mora* A79507/31, *Frank* 58775/32, *Gruss* A79472/32, *Dworzak* A61378/32, A27996/35, *v. Szathmary* B12390/33, *Wallis* A61705/33, *Goldstine* A79471/33, *Daniel et al.* A79445/33, *Klaften* A27707/34, *Kleine* A52120/34, A79488/35, *Tunis* A52311b/34, *Bach* A79431/34, *Schiller* A79525/34, *Fauvet* A79458/34, A79459/34, A79457/34, *Frankl* A79461/34, A59887/36, *Hajek* A27703/35, *Lissowetzky* A28117/35, *Reifferscheid* A27715/35, *Wolfe and Kaminester* A27719/35, *Ahumada et al.* A62052/36, *Gentil* A61845/36, *Lazaresco* A95275/37, *Maruyama and Nakamura* A95289/37, *Greenblatt and Pund* A96498/38, *Seegar* A97157/38, *Blanchot and Goumain* A97171/38, *Dionisi* A95438/39, A97580/39, *Ibarbie* A97687/39, *Stoïa et al.* A33675/39, *Hohage* A96690/40, *Kramberg* A97387/40, *Nittono* A97499/41, *Antumes and Netto* A98095/41, *Arenas and Guglielmo* B10128/42, *Nordmeyer* A96928/42, *Fazio* A96844/43, *Orellana* A96930/43.

[2] *Meyer* A64796/18, *L'Esperance* A79456/28, *Neumann* A67249/30, A79514/30, *Tietze* A64203/31.

[3] *Zimmermann* A79544/23, *Anderes* A77998/29.

[4] *Matsner* A79499/23, *Hamant and Cornil* A79474/25.

[5] *Chenot* A79442/11, *L'Esperance* A79456/28.

[6] *Miller* A18279/37.

[7] *Bettinger* A79438/33.

[8] *L'Esperance* A79456/28, *Géry and Reeb* A68179/29, A79463/29, *v. Szathmary* B12390/33.

[9] *Dupont and Simard* A79453/25, *Meigs* 33256/35.

[10] *Matsner* A79499/23.

[11] *Reifferscheid* A27715/35.

[12] *Bonnet* A79440/28.

[13] *Chenot* A79442/11, *Thélin and Rosselet* A79533/27, *Géry and Reeb* A79468/29.

[14] *Hoche* A79475/29, A64425/30.

[15] *Demarest and Masson* A79449/12, *Matsner* A79499/23, *Neumann* A73164/28, *Parreira and Silva* A79517/28, *v. Szathmary* B12390/33.

[16] *Chenot* A79442/11, *Thélin and Rosselet* A79533/27, *Géry and Reeb* A79468/29, *Krafft* A79489/32, A79490/34.

[17] *v. Szathmary* A79528/33, *Long et al.* A38069/41.

[18] *Fauvet* A79458/34.

[19] *Krafft* A79489/32, A79490/34.

[20] *Müller* A78737/29.

[21] *Kirshbaum and Newman* A57477/43.

[22] *Dworzak* A61378/32, *Klaften* A62307/32, A61759/33.

[23] *Desmarest and Masson* A79449/12, *Matsner* A79499/23, *Thélin and Rosselet* A79533/27, *Muller* A78737/29, *Tronconi* A65087/30, *Dworzak* A61378/32, *Krafft* A79489/32, *Blau* A61365/32, *Klaften* A62307/32, A61759/33.

[24] *Chenot* A79442/11.

[25] *Akimoto* A64724/25, *Hoche* A79475/29, A64425/30, *Aitken* A61915/33.

[26] *Reifferscheid* A27715/35.

and metastatic ovarian tumors of any kind—examined at the Mount Sinai Hospital in New York during a period of 11 years—only 2 neoplasms were listed under this heading.[1] On the other hand, an analysis of 300 selected solid or solid-cystic ovarian tumors surgically removed at the Mayo Clinic in Rochester, yielded 9 examples of this neoplasm.[2]

The *age incidence* of the seminomas is especially interesting, because of the great predisposition of children and young women to the formation of this growth. Most other epithelial tumors (and especially the cancerous ones) tend to develop at, or after, the menopause, yet it is quite exceptional to find seminomas during this period of life. A review of 95 published cases showed the following age distribution:[3]

Years	No. of Cases
1-10	4
11-20	45
21-30	26
31-40	10
41-50	3
51-60	4
61-70	2
71 and over	1

Many additional case reports show the comparatively great frequency with which the seminomas tend to develop in prepubertal girls and in young women.[4]

The *pregnancy incidence* is comparatively high considering that so many of the patients who bear this tumor are children or sterile pseudohermaphrodites. The relevant case reports show that the progress of gestation is often not significantly influenced by the simultaneous development of a seminoma.[5] If pregnancy proceeds to term, the tumor may obstruct delivery, a complication which frequently necessitates caesarean section.[6] In one case an ovary with a seminoma had to be removed during the third month of pregnancy and this intervention did not interfere in any way with the subsequent development of gestation.[7]

The *puerperal incidence* of seminomas is extremely low, mainly because any relevant neoplasms which were sufficiently large to cause disturbances during puerperium would have been noticed before or at delivery. Yet in one case a seminoma was detected 8 days after delivery owing to the fact that it caused an intestinal occlusion.[8]

PATHOGENESIS

Histogenesis. With regard to the histogenesis of the seminomas, perhaps one of the most important leads is their testis-like structure and the fact that they develop from the hilus region of the ovary.[9] In view of the great immaturity and undifferentiated appearance of the seminoma cells, it is not improbable that they are derived from *remnants of the medulla of the embryonic gonad* and that the primary cause of their formation goes back to the earliest periods of prenatal life.[10]

Several cases are known in which seminomas developed outside the ovary and without involvement of the latter, e.g. in the myometrium[11] or the pelvic connective tissue.[12] In these cases the neoplasm may have originated in *undifferentiated ectopic gonadal parenchyme.*

One theory holds that these growths are derived from *abnormal placental Langhans* cells which tend to form syncytia.[13] This interpretation is consonant with the increased gonadotropic hormone production noted in some seminoma bearers. It has been refuted (see above), however, since the polynuclear giant cells—which gave rise to this interpretation—are more probably modified foreign body giant cells than placental cells. This same objection must be raised against the interpretation of these same cells as *Langhans cells of tubercles* and of the lesion as a modified type of tuberculosis (see passage on microscopic appearance of seminomas).

Functional Pathogenesis. Among the factors predisposing to the formation of seminomas, *heredity* plays an important part. Thus Bettinger[14] described seminomas in two sisters and according to a personal communication of the same author,[3] a third sister developed the same type of tumor a little later. In view of the comparative rarity of seminomas, this familial occurrence is noteworthy.

[1] *Bernstein* 81758/36.
[2] *Dockerty and MacCarty* 77977/39.
[3] *Miller* A18279/37.
[4] *Rössle* A70539/12, *Desmarest and Masson* A79449/12, *Ridout* A79338/19, *Rendu and Pouzet* A79336/26, *Mornard and Hirschberg* A79508/27, *Lombard* A79495/29, *Sarnoff* A64543/29, *Rosenberg* A64720/29, *Kleijn* A62094/35, *Gough* A97145/38, *Dockerty and Carpenter* 77977/39, *Long et al.* A38069/41, *Freedman* A71621/43, *Neves et al.* A96927/43.
[5] *Rochat* A79339/25, *v. Szathmary* A79528/33, A79529/33, A79531/33, *Dockerty and MacCarty* 77977/39.
[6] *Tirelli* A79535/29, *Cunningham* A34476/39, *Nyst* A32264/39, *Cunningham and McGrath* A55677/42, *Abernethy* A63374/43.
[7] *Lorber and Vesell* A33170/40.
[8] *Doubrère* A61924/33.
[9] *Hoche* A79475/29.
[10] *Chenot* A79442/11, *Meyer* A64796/18, A10553/25, *Neumann* A67249/30.
[11] *Schiller* A79525/34.
[12] *Horand and Fayol* A79477/12, *Goldstine* A79471/33.
[13] *Pick* A80099/04, A80100/05, A80101/05.
[14] 5539/33, A79438/33.

In this same connection, the occurrence of seminomas in combination with other apparently hereditary malformations, is of interest. Thus seminomas tend to develop in girls with virile, sometimes frankly *pseudohermaphroditic* traits, such as beard growth, masculine voice and skeleton, enlargement of the clitoris etc.[1] One author[2] estimates that 30% of the patients with seminomas show signs of pseudohermaphroditism. In some of these cases the pseudohermaphroditic features were noted at birth; they could be regarded as an associated abnormality which may have predisposed the patient to the formation of seminoma, but is not likely to have been its cause. This is especially true of the comparatively rare instances in which seminomas developed in *true (glandular) hermaphrodites* exhibiting both ovarian and testicular tissues.[3] In view of the great rarity of true hermaphroditism, it is certainly not coincidental that so many cases of seminomas were found among such individuals. In rare instances, following removal of the seminoma, a certain improvement in the symptoms of the patient is noted as far as the accessory sex organs are concerned.[4] This suggests some testoid hormone production by the neoplasm, but further observations will be required to clarify this point.

Another feature in the appearance of the patients, which may be interpreted as due to hereditary stigmatization, is the often pronounced *hypoplasia of the female accessory sex organs,* such as the uterus, vagina and breasts. In some cases there may even be a partial or complete aplasia of Müllerian duct derivatives.[5] These genital malformations may be merely associated manifestations of a primary common hereditary disturbance which also predisposes to seminoma formation. It is also possible, however, that the seminoma produces hormonal substances which secondarily influence the development of the accessory sex organs. Often, though by no means always, the abnormalities in the sex organs of seminoma bearers are congenital; yet it is possible that even during embryonic life substances may be produced outside the tumor which could exert a virilizing influence upon the sex organs. Attention is called in this connection to the pronounced effect of testoid substances in the embryo. As stated in Sect. IV, Vol. VI of this Encyclopedia, administration of testoid compounds during embryonic life—especially in birds—may cause the development of testicular tubules in the ovary, while it inhibits the development of Müllerian derivatives. It is not inconceivable that similar morphogenic influences are operative in women in whom seminomas develop.

The singular occurrence of a seminoma in an *achondroplastic dwarf*[6] may perhaps also be interpreted as indicating some hereditary predisposition for the formation of these tumors.

CLINICAL COURSE

Since seminomas are not definitely hormone-producing tumors, their clinical course reveals no manifest signs of endocrine disorder. It is rather characteristic of these neoplasms, however, that they frequently occur in pseudohermaphrodites and in women with genital hypoplasia (see part on Pathogenesis); it would be unjustified to disregard entirely the possibility that humoral influences may play a role in the genesis of these sexual malformations.

In cases with pronounced uterine hypoplasia or aplasia, it is not surprising to find primary *amenorrhea.* It is noteworthy, however, that even without any uterine malformation, amenorrhea is not common among patients suffering from seminomas.[7] In other cases the *menstrual period is irregular and sometimes painful;*[8] *leucorrhea* is rare.[9]

Precocious uterine bleeding is an unusual accompaniment of seminoma formation in children.[10] In one case the uterus was unusually large and returned to normal after ablation of the seminoma.[11]

In a large number of patients the *menstrual periods remain normal.*[12] The numerous instances of seminomas in pregnant women clearly indicate that sterilizing sexual disturbances are not a necessary accompaniment of these neoplasms (see passage on pregnancy incidence).

It is rather unusual to find much *ascites* although peritoneal fluid accumulations,[13] which are sometimes hemorrhagic,[14] have been noted in a few cases.

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[1]*Hall* A50578/898, *Keller* A79480/13, A79481/22, *Meyer* A64796/18, A10553/25, *Béclère and Siredey* A79436/21, *Ménétrier et al.* A79501/22, *Pol* A79334/24-5, *Neumann* A73164/28, A79514/30, A67249/30, *Cordes* A94705/28, *Cordea* A79444/28, *Hoche* A79475/29, *Klaften* A62307/32, *Bettinger* 5539/33, *Gough* A97145/38, *Long et al.* A38069/41.

[2]*Matsner* A79499/23.

[3]*Daube* 50738/19, *Reverdin* A79337/23, *Christophe et al.* A79443/27, *Lordy* A64433/30, *Moehlig* A55618/42.

[4]*Zimmermann* A79544/23, *Meigs* 33256/35, *Gough* A97145/38.

[5]*Horand and Fayol* A79477/12, *Matsner* A79499/23, *Zimmermann* A79544/23, *Dupont* A79452/25, A79451/25, *Dupont and Simard* A79453/25, *Neumann* 42642/27, *Parreira and da Graca Silva* A79517/28, *L'Esperance* A79456/28, *Babes* A79430/29, *Wallis* A61705/33, *Aitken* A61915/33, *Bettinger* A79438/33, 5539/33, *Kleine* A52120/34, *Meigs* 33256/35, *Dockerty and MacCarty* A77977/39, *Neves et al.* A96927/43.

[6]*Feeney* A34477/39.

[7]*Horand and Fayol* A79477/12, *Meyer* A64796/18, *L'Esperance* A79456/28, *Parreira and Silva* A79517/28.

[8]*Meyer* A64796/18, *Thélin and Rosselet* A79533/27, *L'Esperance* A79456/28, *Géry and Reeb* A79468/29.

[9]*Müller* A79510/31.

[10]*Rendu and Pouzet* A79336/26, *Tietze* A64203/31.

[11]*Mornard and Hirschberg* A79508/27.

[12]*Chenot* A79442/11, *Meyer* A64796/18, *Neumann* 42642/27, *Anderes* A77998/29, *Klaften* A61759/33, *Black and Heyns* A61911/43.

[13]*Matsner* A79499/23, *Wallis* A61705/33, *v. Szathmary* A79529/33, B12390/33, *Dworzak* A27996/35.

[14]*Chenot* A79442/11, *Géry and Reeb* A79468/29, *Klaften* A61759/33.

The exceptional development of nervous symptoms due to "toxic damage"[1] is merely mentioned as a curiosity since even its connection with the neoplasm is unproven.

In general, it may be said that the clinical course is notably devoid of any specific characteristics other than those due to the presence of a usually rapidly growing ovarian neoplasm which frequently shows malignant properties and tends to develop in young or pseudohermaphroditic individuals. Unlike patients with ovarian tumors, which elecit signs of virilism owing to their testoid hormone production, the women with seminomas usually have exhibited pseudohermaphroditic traits or genital hypoplasia since birth or at least for a long time before the neoplasm was noted.

COMPLICATIONS

Seminomas may cause the same complications as other malignant ovarian tumors. Thus in rare instances they may undergo *torsion, hemorrhage, necrosis* etc. (see Sect. IV, Vol. VI). The seminomas may also invade neighboring organs and metastasize, as stated in the part concerned with their pathology.

In exceptional cases a seminoma may cause intestinal occlusion due to mechanical interference with the gut.[2]

DIAGNOSIS

The pre-operative diagnosis of ovarian seminomas is next to impossible. The only clinical signs which may justify the suspicion that a seminoma is present, are those mentioned in the section dealing with the clinical course of these neoplasms; namely, their tendency to develop at an early age and often in individuals with marked signs of genital hypoplasia or pseudohermaphroditism.

Among the *local signs* we find none that are especially characteristic of this growth. In the majority of the cases, however, a firm roundish tumor is felt in the ovarian region. This tumor tends to be mobile as it does not usually become adherent to the adjacent tissues until late in the course of the disease. The frequently rapid growth rate of the neoplasm can be checked by repeated palpitation, but none of these physical criteria are very characteristic. The use of lipiodol to obtain a good X-ray picture of the internal sex organs may be of some value[3] especially in recognizing associated abnormalities in the Müllerian derivatives.

Bioassays for the presence of gonadotropic hormones in the urine have given very contradictory results.[4] In one case, in which the urine was assayed for folliculoid activity, none could be demonstrated.[5]

Among the diagnostic errors made in patients with seminomas the most frequent is confusion with other types of ovarian neoplasms. Less commonly the growth may be mistaken for a *uterine fibroid*[6] or a *pregnant uterus;*[7] but such errors can usually be avoided thanks to the specific symptomatology of these latter conditions.

PROGNOSIS

Seminomas are rapidly growing tumors; they may fill the whole pelvis within a few months after they have reached a size which makes them detectable by palpation.[8] In most cases their progress is rapid and lethal,[9] yet in some it is benign.[10]

One author[11] states that the cellular tumors, in which the connective tissue is poorly developed, have a particularly great tendency to infiltrate other organs and to metastasize. He also claims (on the basis of little evidence) that marked augmentation of luteinizing hormone in the urine is prognostically a bad sign.

Our own review of the literature leads us to believe that seminomas are much more malignant than is generally thought. It is true that in many cases the tumor does not recur following conservative operations; indeed a normal pregnancy may even ensue following unilateral ovariectomy for a seminoma.[12] We cannot share the view,[13] however, that "conservatism should be the rule and only the affected ovary should be removed", an opinion expressed in connection with a case of seminoma in which a right salpingo-oophorectomy was performed. The author comments that: "Had the diagnosis of disgerminoma been known at the time of the patient's second admission to the Hospital, she might have been spared the radical operation, since this tumor is not very malignant, especially when removed early. The patient would have been either treated expectantly, being watched for any further enlargement of the ovary or a biopsy and frozen section examination would have been made at time of operation and the ovary saved."

[1] *Tronconi* A65087/30.
[2] *Doubrère* A61924/33.
[3] *Vincent* A62956/32.
[4] *Wallis* A61705/33, *Kleine* A52120/34, *Fauvet* A62065/36, *Ricard and Accart* A95316/37.
[5] *Kleine* A52120/34.
[6] *Rouville and Madon* A79522/24.
[7] *Laffont and Bonafos* A28158/34.
[8] *Matsner* A79499/23.
[9] *Peyron* A79520/22, *L'Esperance* A79456/28, *Hoche* A79475/29, *Dworzak* A61328/32.
[10] *v. Szathmary* A79528/33.
[11] *Fauvet* A62065/36.
[12] *Meigs* 33256/35, *Dworzak* A27996/35, *Hückel* A95442/39.
[13] *Brody* 83811/38.

PLATE XV

SEMINOMAS

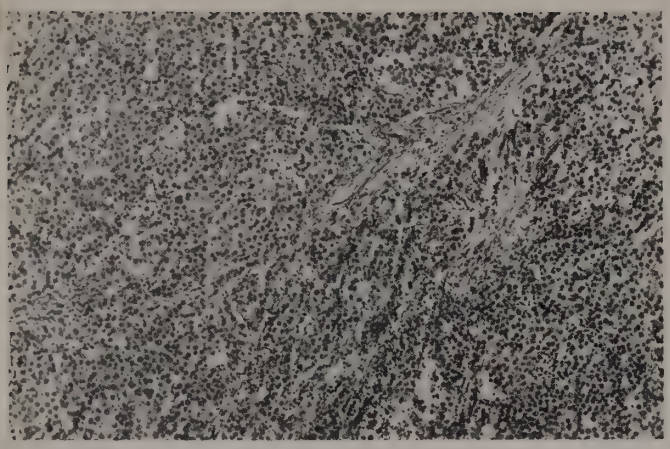

Fig. 1. PARENCHYMATOUS SEMINOMA (courtesy of Dr. H. T. Karsner). Note scarcity of connective tissue trabeculae and predominance of loosely-arranged roundish epithelial cells.

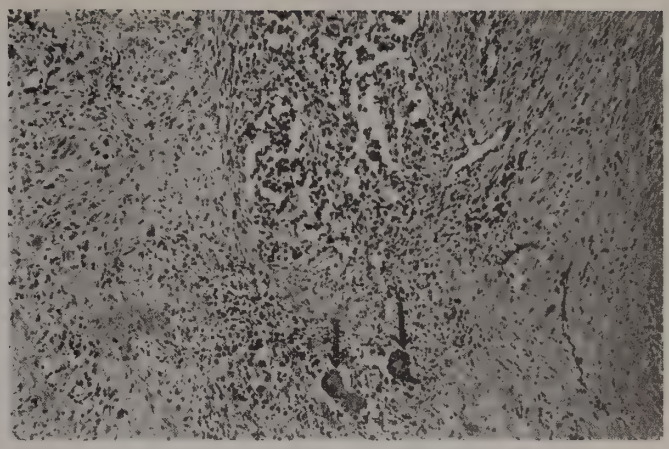

Fig. 2. SCIRRHOUS SEMINOMA (courtesy of Dr. T. R. Waugh). Note great predominance of dense, sclerotic, partly hyalinized stroma. Only the central portions of the field consist of epithelial cells. Two large giant cells are marked by arrows.

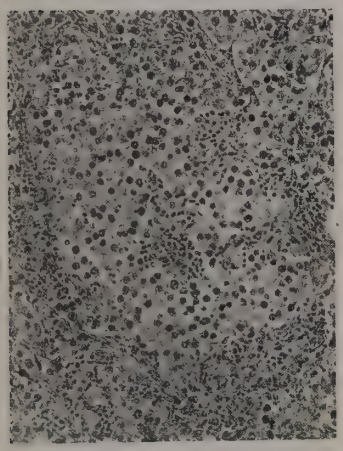

Fig. 3. SEMINOMA (courtesy of Dr. P. Masson). Note large, light cells (center of field) and darker small cells (periphery of field) as well as generalized lymphocytic infiltration. At this magnification, only the small nuclei of the lymphocytes are visible.

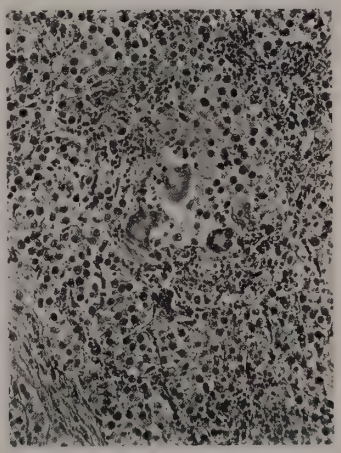

Fig. 4. SEMINOMA Another portion of the tumor shown in Fig. 3. Note several giant cells (center of field) surrounded by light epithelial cells whose cell membranes are distinct.

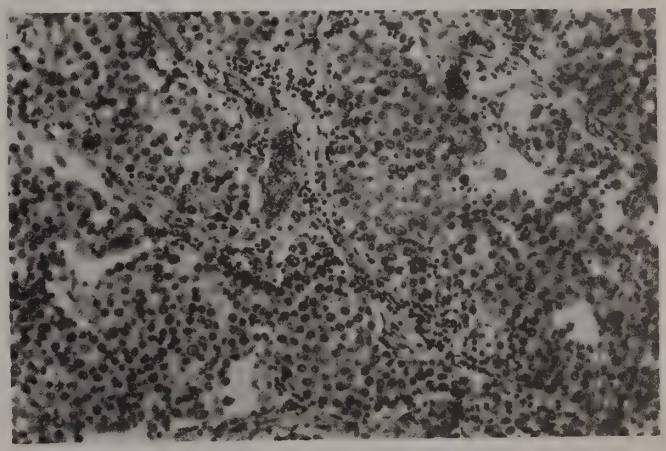

Fig. 5. SEMINOMA Higher magnification of a field of the tumor shown in Fig. 1. Note lymphocytic infiltration, especially in the connective tissue septa, between the epithelial cells.

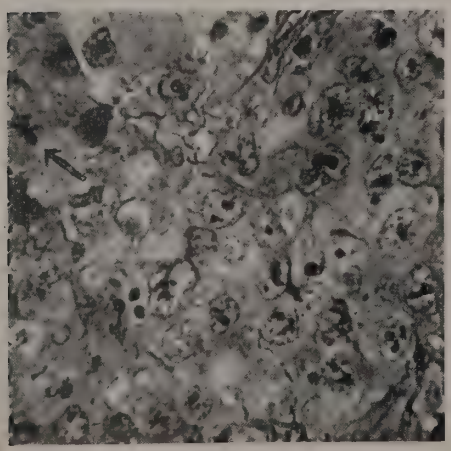

Fig. 6. SEMINOMA (courtesy of Dr. L. Berger). High magnification of a typical large cellular area. Note the prominent and often multiple nucleoli, well-developed and light cytoplasm, and a mitotic figure (marked by arrow).

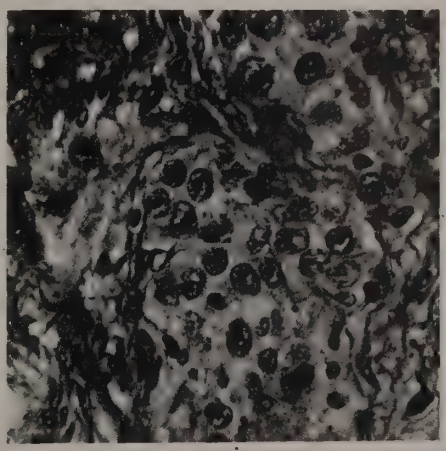

Fig. 7. SEMINOMA. Another region of the tumor shown in Fig. 6, illustrating the small type of epithelial cells. The nucleoli are again very prominent but the cytoplasm is comparatively poorly developed.

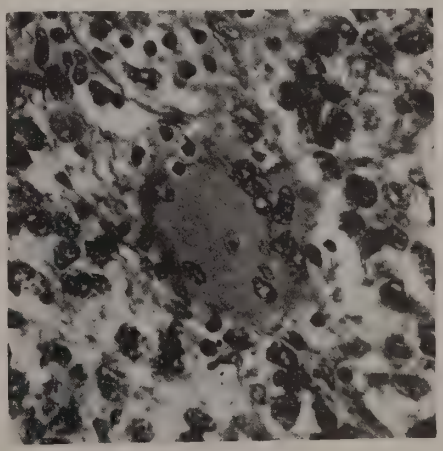

Fig. 8. SEMINOMA GIANT CELL. Yet another field of the tumor illustrated in Fig. 6 and 7. Note the structure of a typical large giant cell. There are several entirely independent nuclei. The outlines of the cytoplasm are indistinct and merge with the surroundings. A few lymphocytes appear to be engulfed by the giant cell.

If the patients are operated upon before the tumor has had time for extensive growth, surgical removal, especially if followed by X-ray treatment, may lead to permanent cures; many cases are known in which a more than 5-year survival was registered without any signs of *recurrence*.[1] It must be recalled, however, that in numerous other instances, recurrences take place even after apparently complete surgical removal, sometimes followed by X-ray treatment.[2]

In view of the fact that so many of the seminomas are bilateral and that the patients suffering from this tumor are frequently genetically stigmatized, pseudohermaphroditic or infantile individuals, conservative therapy hardly seems justified except in very rare cases.

THERAPY

In cases of ovarian seminoma the therapy of choice is complete *surgical* removal of the ovaries and adnexa, combined with panhysterectomy; the frequency of recurrence is too great to warrant conservative interventions. This is particularly true of large infiltrating seminomas, but should be the rule even in apparently circumscribed growths, especially if the patients are pseudohermaphrodites or if they suffer from malformations of the internal sex organs which are incompatible with normal sexual life. On the other hand, it is true that in a fairly large number of patients conservative removal of seminomas (leaving the contralateral ovary with the uterus and tube intact) corrected previously existing menstrual anomalies, hence unilateral ovariectomy may be considered in certain cases if the seminoma is very small and the accessory sex organs not severely deformed. As stated above, such conservative interventions have been tolerated without recurrences and have even been followed by normal pregnancy in a few cases. The risk entailed must be fully realized, however, and in each case weighed against the desirability of maintaining the function of the contralateral gonad. In many cases ablation of seminomas was followed by X-ray therapy as a prophylactic measure against incomplete removal of all malignant cells.[3]

The great *X-ray* sensitivity of the testicular seminomas is apparently shared by the corresponding ovarian tumors. Under the influence of deep X-ray treatment these tumors simply melt away and huge growths may almost disappear within a short time. In inoperable seminomas, especially if they have produced widespread metastases, roentgen therapy is therefore the treatment of choice. It also has its place, as stated above, following surgical removal of the neoplasms as a prophylactic measure against recurrences. If the tumor is still small when diagnosed, and if it can be removed completely, surgical therapy is preferable because it is safer. Perusal of the case reports describing the results of X-ray therapy for seminomas, shows that in spite of the usually impressive initial results, the neoplasms tend to become X-ray resistant and to recur after some time.[4]

Little is known as yet concerning the value of *radium* therapy in the treatment of ovarian seminomas, although at least in one case a 5-year cure was obtained in a women who developed a recurrence following surgical removal of a seminoma and was subsequently treated with radium.[5]

[1] *Kleine* A52120/34, *Meigs* 33256/35, *Dockerty and MacCarty* 77977/39.
[2] *Bonnet* A79440/28, *L'Esperance* A79456/28, *Dworzak* A27996/35.
[3] *Meigs* 33256/35, *Nyst* A32264/39, *Dockerty and MacCarty* 77977/39, *Lorber and Vesell* A33170/40, *Freedman* A71621/43, *Kirshbaum and Newman* A57477/43.
[4] *Béclère and Siredey* A79436/21, *Siredey* A79526/21, *Rouville and Madon* A79522/24, *Delbet* A79447/27, *Proust* A94675/27, *Keijser* A65161/30, *Moulonguet and Mallet* A64809/31, *Béclère* A79433/31, A79435/34, *Joly* A53044/34, *Gilliard* A79469/34, A79470/35, *Hückel* A95442/39.
[5] *Doubrère* A61924/33.

SEMINOMAS IN ANIMALS

Seminomas have repeatedly been observed in animals[1] and although they are much more common in the male, they also occur in the female gonad.

In the *fowl* an ovarian growth, presumed to have been a seminoma, occurred in association with definite masculinization following partial castration.[2] Another instance of a so-called "ovarian seminoma" or "clear celular carcinoma of the ovary" appears to have arisen spontaneuosly in a hen.[3] As has already been emphasized in connection with the tubular edenoma of the fowl ovary, the interpretation of these growths is rather difficult since the right gonad of the hen is, to some extent, normally ambisexual and can develop testicular tubules. Depending upon the degree of maturation, such proliferating testicular elements developing in the ovary may present themselves under the picture of tubular adenoma or seminoma respectively.

[1] *Innes et al.* A94672/38.
[2] *Pezard* 6317/22.
[3] *Ball and Pommier* B6521/29.

STRUMA OVARII

SYNONYMS: Struma ovarii, thyroid tumor of ovary, thyroid teratoma of ovary, ovarian thyreodermoid, teratoma strumosum of ovary, teratoma strumoides thyreodermoid ovarii, ectopic ovarian thyroid.

REVIEWS

Mönch A68107/29, Plaut 5543/33, Neumann A94509/37, Nicholson A94508/37, Wynne et al. 78538/40, Emge 79789/40, Geist B6672/42, Novak B109/44.

DEFINITION

The struma ovarii is an ovarian teratoid which consists exclusively, or at least predominantly, of thyroid tissue. The latter may resemble the normal thyroid or the various forms of goiter; in some instances it may undergo malignant transformation. Because of its potentially endocrine nature and histologic uniformity, this growth is discussed separately from other teratoids. It will be kept in mind, however, that small nodules of thyroid tissue may appear in any teratoid and that in general their size is approximately in proportion with that of the other organs of the embryoma. Data concerning these "organoid" thyroid nodules will be found in the chapter on teratoid tumors.

HISTORY

The struma ovarii was usually misinterpreted by pathologists who found it very difficult to understand that true thyroid tissue can occur within the ovary. Thus tumors, now known to belong to this group, have been diagnosed as a "folliculoma malignum",[1] as a type of "endothelioma"[2] or as ovarian metastases of primary thyroid growth.[3]

Thyroid tissue in the ovary had been described by several early investigators.[4] Pick[5] deserves credit for having recognized that these growths are actually teratoids in which the thyroid tissue predominates to such an extent that all other constituents are "crowded out" by it. This interpretation receives further support by the many examples of intermediate types between ordinary embryomas, having only small nodules of thyroid tissue, and tumors consisting exclusively of the latter.

PATHOLOGIC ANATOMY

Upon *macroscopic* inspection, the struma ovarii usually presents itself as a more or less irregularly shaped, nodular growth of brownish or bluish color. The cut surface is honey-combed by numerous small follicles and owing to disappearance of the partitions between these, large cystic cavities may be formed. The colloid which fills the cysts is brownish or honey-colored and usually of a sticky glue-like consistency. Thus, even macroscopically, the struma ovarii resembles ordinary goiter tissue (see case reports cited below).

Microscopically the growth consists of colloid containing follicles, or tubules and trabeculae which resemble the diffuse or nodular micro- or macrocystic cervical goiters of various types.[6] By the use of the modified Unna elastic tissue stain of E. J. Kraus, some follicles stain dark purple, others red or blue, as do the follicles of ordinary goiter tissue.[7] In some cases papillae covered by a high cylindrical epithelium, invade the follicles, thus imitating the thyroid structure characteristic of *toxic goiters* or *Graves' disease*.[8] In a case of clinically manifest Graves' disease,[9] characteristic lymph follicles were found in the ovarian struma and it may incidentally be mentioned that the Graves' disease symptoms disappeared after ablation of the ovarian growth. Colloid may also occur in the lymphatic spaces of an ovarian thyroid.[10]

It has been emphasized, however, that not all the colloid containing ovarian growths, which resemble goiter tissue, are actually derived from a thyroid primordium and that some so-called "thyroid tumors of the literature" greatly resemble ordinary cystadenomas. Hence it has even been claimed that all these tumors are merely *modified papillary or pseudomucinous* cystadenomas.[11] This interpretation is untenable especially because the struma ovarii may copy any type of the struma colli and does not give a positive mucicarmin reaction;[12] it contains iodine and thyroid hormone (see below) and in this respect also resembles thyroid tissue.

Unusual cases of struma ovarii may contain remnants of the ductus thyreoglossus[13] or the thyroid may completely fill out the marrow spaces of bone plates within a teratoid tumor which acts as its host.[14] One author[6] describes thyroid tissue in "cartilage plates", but it is evident from his microphotographs that he also dealt with struma tissue in the marrow spaces of bones.

[1] *Gottschalk* A64879/02.
[2] *Kretschmar* A76825/01.
[3] *Miller* A18279/37.
[4] *Bottini* A45513/889, *Böttlin* A45085/889, *Meinert* A76840/897, *de Voogt* A76701/899.
[5] A76860/02, A76862/20.
[6] *Neumann* A94509/37.
[7] *Kafka* A76819/21, *Thaler* A76887/23, *Morgen* A76849/24.
[8] *Körner* A76822/23, A76823/27, *Morgen* A76849/24, *Moench* A68108/29, *Emge* 79789/40.
[9] *Kovacs* A76824/24.
[10] *Aisenstadt* A76779/13, *Kermauner* A64800/32.
[11] *Bell* A80964/05, *Bauer* A76789/14, *Kaufmann* 39132/22, *Heinsen* 5545/32, A76818/33.
[12] *Plaut* 5543/33, *Neumann* A94509/37.
[13] *Fiebach* A20805/11.
[14] *Katsurada* A73865/01, *Plaut* A76866/30, 5543/33, *Kermauner* A64880/32.

Many additional data concerning the struma ovarii will be found in the relevant *case reports*.[1]

Malignant changes may also occur in ovarian thyroids and pertinent cases have been described under the names of "malignant ovarian struma", "teratoma ovarii malignum strumosum" or "struma ovarii carcinomatosa"[2] The malignant ovarian struma can lead to metastatic deposits of similar neoplastic masses in distant organs.[3] There are no exact figures concerning the incidence of malignant transformation, but it is estimated to occur in about 5-6% of the struma ovarii cases.[4] The carcinomatous ovarian struma tends to *metastasize* into the liver, mesentery and bones.

In one instance a *Brenner* tumor developed in combination with an ovarian struma.[5]

CHEMICAL COMPOSITION

The chemical composition of ovarian thyroid tissue is of interest especially with regard to the iodine and thyroid hormone content. Unfortunately, the *iodine* values, obtained by various authors with different methods, are not intercomparable; yet it may be said that in general they are higher than in other tissues, but somewhat lower than in the normal thyroid.[6]

The *thyroid hormone* content of ovarian thyroid tissue was determined[7] with the aid of the acetonitril and tadpole metamorphosis assays and was found to be comparatively high. Thus, both chemical and biologic tests support the view that ovarian struma tissue resembles true thyroid tissue.

INCIDENCE

The *general incidence* of struma ovarii is difficult to estimate, especially since the borderline between teratoids with thyroid inclusions and predominantly thyroid growths of the ovary, cannot be sharply drawn. Unless serial sections are made, the presence of thyroid nodules in a complex teratoid is detected only by coincidence; conversely, in predominantly thyroid growths, inclusions of other tissues are frequently present though not always detectable without a special search. Hence, various authors vary between 1.5 and 28.5% in their estimate of thyroid inclusions in ovarian teratoids. The average incidence being 11.6% according to a review article.[8] The incidence of struma ovarii among 297 ovarian teratomas of all types was 2.7%.[9]

The *age incidence* of the struma ovarii was as follows among the cases reviewed by one author:[10]

Years	No. of Cases
11-20	2
21-30	12
31-40	23
41-50	24
51-60	20
61-70	5
over 70	1

[1] *Bottini* A45513/889, *Meinert* A76840/897, *de Voogt* A76701/899, *Gottschalk* A64878/899, A76814/899, A64879/02, *Kretschmar* A64780/01, A76825/01, A76826/04, A76828/11, *Lecène* A73965/02, A73966/04, *Pick* A76860/02, A76861/02, A69435/03, A83441/20, A76862/20, *Anspach* A76783/02-3, A73207/02-3, A74665/03-4, *Meyer* A76841/03, A76842/03, A76843/12, *Glockner* A76811/03, *Walthard* A76896/03, A69440/04, *Tavel* A76886/04, *Vagedes* A76893/04, *Ulesko-Stroganowa* A76892/04, A76891/04, A69439/05, A76665/10, *Szulezewski* A76885/04, *Polano* A76869/04, A69436/04, *Pollosson and Violet* A76872/05, *Eversmann* A76799/05, *Bell* A76791/05, A80964/05, *Swanton* B13237/06, A76884/06-7, *Schipper* A76880/07, *Opitz* A76853/09, *Norris* A76852/09, *Frank* A76801/09, *van Aken* A76780/09, *Giannettasio* A83432/10, A21142/14, *Pröscher and Roddy* A76873/10, *Poli* A76871/10, *Maxwell* A76096/10-1, *Schauta* A76878/11, *Schickele* A76879/11, *Neu* A76851/11, *Boxer* A76792/11, *Fiebach* A20805/11, *Dingels* A76798/12, *Müglich* A76850/12, *Trapl* A76888/12, *Aisenstadt* A76779/13, *Sitzler* A76882/13, *Outerbridge* A76854/13, A80902/13, *Lindquist* A80901/13, *Barsieck* A76786/13, *Frankl* A76804/, A76805/14, A76806/31, A28153/34, *Bauer* A76789/14, *Ribbert* A76874/14, *Ries* A80908/14, *Moench* A76844/15, *Baldwin* A76785/15, *Platou* A23947/16, *Adolf* A76778/18, *Büll* A83415/19, *Persson* A80907/19, *Wood* A68583/19-20, *Bua* B8544/21, A76793/22, *Kafka* A76819/21, *Gerner* A76808/22, *Curtis* A76794/22, *Parodi* A76855/22, A76859/29, *Plauchu and Gaudon* A76864/22, A76865/23, *Bolt* A94817/23, *Albrecht* A73184/23, *Kovács* A76824/24, *Morgen* A76849/24, *Momigliano* A76848/24-5, *Körner* A80900/24-5, A76822/25, A26958/25, *Shaw* A94811/25-6, *Manasse* A94806/26, A76837/28, *Davidson* A76797/27, *Haggag* A76816/27, *Ginodman* B7220/27, *Werth* A76897/28, *Frankel and Lederer* A76802/28, *Althabe and Colillas* A76781/29, A76782/31, *Lazarescu and Pantzu-Lazarescu* A76830/29, *Daniel and Babes* A76795/29-30, A76796/30-1, *Stefancsik* A64444/30, A64443/30, *Plaut* A76866/30, *Trettenero* A76889/30, A65189/31, *Sampaio* A76877/31, *Macleod* A62939/31-2, *Heinsen* 5545/32, *Villate* A76895/32, *Witherspoon* A62959/32, *Mathias* A76839/32, *Lochrane* A62041/33, *Masson and Mueller* A61883/33, *Lyday* A52271/34, *Kleine* A52269/34, *Sanders* A28174/35, *Bazala* A76790/35, *Fahmy* A60006/36, *Bradenberg* A59922/36, *Aschkanasy* A59978/36, *Saidl* A95226/37, *Kleine* A95443/39, *Castano* A97261/39, A96599/40, *Jouregui et al.* B10135/42, *Moraes et al.* B10822/44.

[2] *Kretschmar* A76826/04, *Polano* A76869/04, *Proscher and Roddy* A76873/10, *Frankl* A76803/12, *Mohr* A76847/12, *Morgen* A76849/24, *Körner* A76823/27, *Werth* A76897/28, *Shapiro* A76881/30, *Eerland* A61747/32 A79275/32, *Plaut* 5543/33, *Wynn et al.* 78538/40, *Emge* 79789/40.

[3] *Eerland* A96017/36.

[4] *Emge* 79789/40.

[5] *Plaut* A61889/33.

[6] *Meyer* A76842/03, *Neu* A76851/11, *Schauta* A76878/11, *King and Norris* A65163/31, *Plaut* 10087/31, 5543/33, *Masson and Mueller* A61883/33, *Wynne et al.* 78538/40.

[7] *Plaut* 10087/31, 5543/33.

[8] *Wynne et al.* 78538/40.

[9] *Gusberg and Danforth* B6260/44.

[10] *Sitzler* A76882/13.

PATHOGENESIS

The pathogenesis of struma ovarii does not require special consideration here as this is merely one example of the teratoid group of ovarian tumors whose pathogenesis will be discussed later. Suffice it to say that the true thyroid nature of these growths appears to be well established on the basis of the previously mentioned evidence. Histologically, especially with regard to their staining reactions, and chemically, with regard to their iodine and thyroid hormone content, these growths resemble thyroid tissue; we shall see in the next part that they may even produce clinical manifestations of Graves' disease. It remains to be explained, however, why thyroid tissue develops, and even predominates in a considerable percentage of the ovarian teratoids.

Cases in which both the cervical and the ovarian struma became toxic (see below) indicate that the ectopic thyroid is sensitive to the same stimuli which influence normal thyroid tissue. In some cases[1] the cervical thyroid became enlarged and toxic after removal of a struma ovarii. These observations also support the view of close (hormonal?) correlations between the orthotopic and ectopic thyroids.

CLINICAL COURSE

Usually the symptomatology of struma ovarii does not differ from that of other ovarian teratoids unless the tumor induces manifestations of hyperthyroidism. The fact that these growths tend to produce *ascites* more frequently than other teratomas[2] is discussed in the chapter dealing with the latter. One case[3] was actually reminiscent of Meigs' syndrome.

Manifestations of *thyrotoxicosis,* such as an increased basal metabolic rate, tremor and tachycardia have been noted in several cases.[4] One author[5] estimates that thyrotoxicosis occurs in about 5-6% of all struma ovarii cases. It is noteworthy that in many pertinent instances the clinical symptoms were very severe and the B.M.R. rose up to 35%, or more, above normal. The final proof of the causal connection between the ovarian tumors and the clinical symptomatology is supplied by the fact that in the cases in which ovariectomy was performed the thyrotoxicosis subsided.

DIAGNOSIS

The clinical diagnosis of struma ovarii is usually impossible especially in those cases which do not lead to thyroid hormone overdosage symptoms. On the other hand, if an ovarian tumor (especially a dermoid) appears in a woman who suffers from Graves' disease and yet has a normal thyroid, the diagnosis of struma ovarii must be considered. It is well to remember, furthermore, that several of the ovarian strumas which caused Graves' disease, developed in patients whose cervical thyroid also became toxic. In these cases removal of the cervical thyroid produced but temporary improvement and final cure followed only after subsequent removal of the ovarian thyroid.[6]

THERAPY

The therapy of choice in all cases of struma ovarii is *removal of the growth* and this almost invariably necessitates complete ablation of the gonad itself.[7] In view of the ever present danger of malignant or toxic transformation in ovarian thyroid tissue, conservative measures or delay of the operative intervention are to be avoided.

The value of *X-rays* in the therapy of struma ovarii has only been studied in a single case.[8] In this patient the growth of the tumor appears to have been actually stimulated by the rays.

[1] *Trapl* A76888/12, *Bua* A76793/22.
[2] *Polano* A76869/04.
[3] *Brown and Shoor* A56057/42.
[4] *Körner* A76822/23, A76823/27, *Morgen* A76849/24, *Kovacs* A76824/24, *Moench* A68108/29, A68107/29, *Kleine* A52269/34, *Cantor and Kogut* A94523/36, *Aschkanasy* A59978/36, *Neumann* A94509/37, *Emge* 79789/40, *Hundley* A94507/40.
[5] *Emge* 79789/40.
[6] *Gusberg and Danforth* B6260/44.
[7] *Cohn and Kushner* A71805/44.
[8] *Thaler* A76887/23.

OVARIAN CHORIONEPITHELIOMAS

SYNONYMS: Chorion-epithelioma, Chorioepithelioma, chorionepithelioma malignum, chorion-carcinoma, "embryoma à évolution choriocarcinomateuse", syncytioma, chorioma, carcinoma syncytiale, deciduoma malignum.

The terms "epithelioma chorioectodermale" and "cystoepithelioma chorioectodermale" were used for certain giant-cell forming seminomas, incorrectly interpreted as chorionepitheliomas. It is also noteworthy that, especially in the old literature, relevant cases have repeatedly been described as giant cell carcinomas, alveolar sarcomas, ovarian pregnancies etc., but these terms are not synonymous with chorionepithelioma and were used only by investigators who failed to recognize the true nature of these growths.

REVIEWS

ENGLISH: Mathieu and Robertson A97627/39, *Sturley* A55953/42, *Geist* B6672/42, *Novak* B109/44.

FRENCH: De Walsche A80054/29-30, *Simard* A65177/31.

GERMAN: Hammerschlag A80065/04, *Krömer* A70091/08, *Assmuth* A80044/08, *Miller* A18279/37.

HUNGARIAN: v. Váró A80120/27.

ITALIAN: Colella A61375/33.

NORWEGIAN: Sunde A80117/20.

POLISH: Glinski A80063/05.

DEFINITION

The chorionepithelioma of the ovary is a malignant epithelial tumor characterized by its great morphologic and functional resemblance to placental tissue. According to one much quoted investigator[1] the following criteria must be estabilshed before a tumor can be diagnosed as a chorionepithelioma:

1) The tumor is composed of both syncytium and Langhans cells. These are arranged in masses or cords with Langhans cells inside and the syncytium around the periphery.

2) The tumor has no connective tissue stroma or vascular supply of its own, but its cells grow toward, surround and penetrate, maternal blood vessels.

3) There is coagulation of tissue, hemorrhage and necrosis.

These features indicate the great morphologic similarity between this type of neoplasm and normal placental tissue. Functionally, the excessive production and subsequent urinary elimination of gonadotropic hypophysoid hormones and the induction of clinical pregnancy changes, are characteristic of ovarian (as well as extra-ovarian) chorionepitheliomas. This further emphasizes their close relationship to placental tissue.

HISTORY

Chorionepitheliomas of the uterus were first described as malignant deciduomas, decidual sarcomas, giant cell sarcomas etc.[2] but later it was recognized that they represent carcinomas of the chorionic villi.[3]

The chorionepithelioma of the testis was first described in 1902 by Schlagenhaufer[4] and almost simultaneously several investigators[5] reported similar neoplasms in the ovary. A few years later Pick,[6] described his "epithelioma chorioectodermale" which, however, is now believed to have been a seminoma with giant cells. Several additional early reviews and case reports helped to clarify our views concerning this unusual ovarian tumor[7] which is now generally recognized to be a placental neoplasm.

CLASSIFICATION

Generally the chorionepitheliomas of the ovary are classified on the basis of their pathogenesis as follows:

1) *Ovarian chorionepitheliomas resulting from a pregnancy.*

a) From an ovarian pregnancy.[8]

b) From a chorionepithelioma of the uterus which developed following pregnancy. In such cases the original tumor may be eliminated by abortion before the ovarian neoplasm is noticed, thus rendering it difficult to recognize the ovarian growth as secondary.[9] Within this group one may further distinguish between hematogenous ovarian metastases and infiltration of the ovary by chorionepithelioma cells which invade the gonad directly or ascend to it through the oviduct. Secondary chorionepitheliomas may also arise from ectopic pregnancies developing in the oviduct or the pelvic peritoneum.[10]

[1] *Seitz* A80113/16.
[2] *Sänger* B96/889.
[3] *Kossmann* A70779/895, *Marchand* A80086/898.
[4] B94/02.
[5] *Kaufmann* A80070/00, *Albert* A80041/01, *Lubarsch* A80083/01, *Kleinhans* B227/02.
[6] A80099/04, A80100/05, A80101/05, B9110/05.
[7] *Krebs* A80076/03, *Risel* A80105/03, A80107/14, *Hansemann* A80066/04, *Schmaus* A78979/05, A80109/06, A80110/06, *Michel* A78704/05, *Niosi* A80094/05, A4979/07, *Forgue* A78292/06.
[8] *Sunde* A80117/20.
[9] *Risel* A80107/14.
[10] *Döderlein* A80055/08, *Iwase* A80069/08, *Fairbairn* A80058/09, *Barak* A80045/11, *Seitz* A80113/16.

2) *Ovarian chorionepitheliomas which are teratoid tumors* exhibiting a one-sided development of chorionic elements sometimes to the exclusion of other tissues.[1]

3) *Primary "common" ovarian carcinomas with trophoblast-like proliferations.*[2] It is somewhat doubtful whether this latter group should be listed as a subdivision of the true ovarian chorionepitheliomas although some prominent investigators[3] regard it as such.

PATHOLOGIC ANATOMY

Macroscopically the chorionepitheliomas of the ovary are round or ovoid, sometimes slightly nodular tumors of moderate size. In rare instances they tend to develop between the two laminae of the broad ligament. Their outstanding characteristics, namely their red color and brittle or spongy texture, are due to the hemorrhagic nature of these neoplasms. A connective tissue capsule may develop around the free portions of the tumor, although these highly malignant growths usually infiltrate the neighboring organs.[3]

Bilateral development is exceptional[4] and probably represents merely part of a generalized metastatic carcinomatosis, rather than multiple primary tumor formation.

Microscopically the characteristic features of the chorionepithelioma are those enumerated in connection with the definition of these neoplasms. Suffice it, therefore, to add a few words here concerning certain histologic details. *Mitotic figures* are generally plentiful[5] and the epithelial cells frequently contain considerable amounts of *glycogen.*[6] As stated above, the typical chorionepithelioma of the ovary possesses no *stroma*[7] and no *blood vessels*[8] of its own. On the other hand, its cells exhibit a great affinity towards the "maternal" blood vessels inasmuch as they penetrate under the vascular epithelium which is often pushed towards the lumen and eventually destroyed by them. Consequently, the neoplastic cells frequently invade the vessels and lead to hematogenous metastases. The tissues in the immediate vicinity of ovarian chorionepitheliomas are especially rich in blood vessels.[9]

In the ovarian tissue, which is in direct contact with the neoplastic cells, a *decidual reaction* is frequently demonstrable[10] and this may be at least partly, responsible for the error of early investigators who considered chorionepitheliomas to be decidual tumors.

In some cases, an ovarian pregnancy forms a neoplasm resembling a *hydatidiform mole* in which certain areas exhibit the characteristics of chorionepitheliomas.[11]

It is difficult to identify the various types of ovarian chorionepitheliomas with certainty; yet it may be said that, according to the numerous relevant *case reports,* some may have originated from an ovarian pregnancy (see also chapter on Ovarian Pregnancy in Sect. IV, Vol. VI). In other patients the tumor was probably secondary to a chorionepithelioma of the uterus or oviduct, while in the remaining instances it was presumably of teratoid origin.[12]

Secondary changes, especially widespread necrosis and fibrinoid degeneration, are very common in ovarian chorionepitheliomas.[13] This emphasizes their resemblance to the placenta.

Adhesions are almost invariably conspicuous and may connect chorionepitheliomas with the oviduct, the uterus or intestinal loops. Only in exceptional cases are the tumors free of adhesions and mobile.[14] Needless to say, these adhesions are of great surgical importance since they further increase the difficulties encountered in attempts to remove these brittle and easily bleeding neoplasms.

Although the chorionepithelioma tissue possesses great infiltrative and destructive tendencies. *remnants of ovarian tissue* frequently remain

[1] *Landau* A77019/04, *Voigt* A80121/25, *Momigliano* A80093/26, *v. Váró* A80120/27, *Simard* A65177/31, A65178/31, 69158/37, *Siegmund* 72594/32, *Tscherne and Schafer* A97418/39, *Sturley* A55953/42.

[2] *Niosi* A80094/05, A4979/07, *Schmaus* A80109/06, A80110/06, *Forgue and Massabuau* A80060/07, *Massabuau and Etienne* A78672/13, *Risel* A80107/14.

[3] *Miller* A18279/37.

[4] *Krömer* A80077/07, *Döderlein* A80055/08, *Kedrierski* A80071/12, *Klotz* A80074/13.

[5] *Risel* A80105/03, A80106/05, *Assmuth* A80044/08.

[6] *Marchand* B95/895, *Risel* A80105/03, A80106/05, *Seitz* A80113/16.

[7] *Assmuth* A80044/08, *Fairbairn* A80057/08-9, A80058/09, *Barak* A80045/11, *Seitz* A80113/16.

[8] *Marchand* B95/895, *Miller* A18279/37.

[9] *Boström* A80051/27, *Miller* A18279/37.

[10] *Simard* A65178/31, A65177/31, 69158/37.

[11] *Niosi* A80094/05, *Møller and Als-Nielsen* A80092/25, *Fraser and Statham* A80061/27.

[12] *Forgue* A78292/06, *Forgue and Massabuau* A80060/07, *Krömer* A80077/07, *Döderlein* A80055/08, *Iwase* A80069/08, *Fairbairn* A80057/08-9, A80058/09, *Bonney* A80050/09, *Davidsohn* A80053/10, *Barak* A80045/11, *Lebret* A80082/11, *Penkert* A80097/12, *Kedrierski* A80071/12, *Klotz* A80074/13, *Proust and Bender* A80102/13, *Miller* A80091/14, *Opitz* A80096/14, *Ries* A80104/15, *Bollag* A80048/16, *Seitz* A80113/16, *Frank* B92/16, *Kynoch* A80080/19, *Chisholm* A80052/20, *Phillips* A80098/20, *Krukenberg* A80079/20, *Bock* A80047/21, *Sunde* A80118/21, *Dougal* A80056/24, *Voigt* A80121/25, *Boström* A80051/27, *v. Váró* A80120/27, *Read* A80103/27-8, *Zalka* A80122/28, *De Walsche* A80054/29-30, *Maki and Takeda* A62248/31, *Preston and Gay* A95314/37, *Fikentscher* A96026/37, *Izuma* A97070/38, *Sbarcea* A32100/39, *Oda et al.* A96568/40, *Peters* A96618/40, *Backus and Griffin* A36168/41, *Heilmann and Wappler* A98124/41.

[13] *Fairbairn* A80058/09, *Barak* A80045/11, *Risel* A80107/14.

[14] *Read* A80103/27-8, *Zalka* A80122/28.

demonstrable.[1] This residual ovarian tissue may be atrophic[2] or contain corpus luteum cells.[3] As mentioned above, it may also undergo decidual transformation and is generally very well supplied with blood vessels.

The *contralateral ovary* may be transformed into a mass of cystic corpora lutea[4] probably as a result of excess gonadotropic hormone formation by the neoplastic chorionic cells. This change is the same as that seen in both ovaries of patients with extragonadal chorionepitheliomas (see Sect. IV, Vol. VI).

The combination of ovarian chorionepitheliomas with *other ovarian tumors* is uncommon. In one case, the contralateral ovary contained a "*cystadenoma simplex*".[5] Since chorionepitheliomas quite frequently develop from teratoid dysembryomas, it is not surprising to find *teratomatous* formations of various tissues in the vicinity of the neoplastic chorionic cells.[6] Such transitional types between common teratomas and chorionepitheliomas are discussed in the chapter dealing with the teratoid tumors of the ovary (see also part on classification in this chapter). It will be recalled that, according to the commonly accepted theory, the pure type of ovarian chorionepithelioma—not associated with pregnancy—is a unitissular teratoma in which the chorionic elements develop to the exclusion of other embryonic tissues; hence, it is debatable whether mixed neoplasms should be regarded as true chorionepitheliomas or merely as common teratomas in which chorionic cells predominate.

As previously stated, many relevant tumors are hematogenous *metastatic chorionepitheliomas,* the primary tumor usually being in the uterus[7] or Fallopian tube.[8] In other instances, a secondary ovarian chorionepithelioma develops due to direct infiltration of the ovarian tissue from an adjacent neoplasm or from a uterine tumor whose cells ascend to the gonad through the oviducts.[9]

Conversely, it is not surprising that if this very malignant neoplasm develops primarily in the ovary, it may produce *chorionepithelioma metastases* in other organs (e.g. the peritoneum, uterus, adrenals, liver, lungs, kidney, lymph nodes, skin, intestines, brain, etc.) and in many cases widespread generalized carcinomatosis results.[10]

INCIDENCE

The *general incidence* of the ovarian chorionepithelioma is very low, a fact clearly shown by the comparatively small number of case reports which could be assembled for this review. If secondary ovarian chorionepitheliomas are excluded, this may well be considered one of the rarest ovarian neoplasms.

The *age incidence* in a group of 29 cases was as follows:[11]

Years	No. of Cases
6-10	2
11-15	2
16-20	4
21-25	6
26-30	4
31-35	3
36-40	0
41-45	4
46-50	1
51-55	1
56-60	2

This series clearly indicates that no age appears to be especially predisposed to the formation of these tumors and that they may occur in children in whom the possibility of a previous pregnancy does not exist. One such tumor appears to have been congenital[12] and another developed in a congenitally pseudohermophroditic individual although the ovarian growth became manifest only after puberty.[13] Several additional instances may be quoted in which chorionepitheliomas developed in children less than 12 years of age[14] or 13-16 years of age.[15] In one 16-year-old patient the genitalia were so immature that fertilization was also highly unlikely[16] and in another case, a 13-year-old child, the hymen was unruptured. Additional cases in young intact virgins have re-

[1] *Kleinhans* A80073/02, *Assmuth* A80044/08, *Fairbairn* A80058/09, *Risel* A80107/14, *Seitz* A80113/16, *Dougal* A80056/24, *Read* A80103/27-8.
[2] *Simard* A65177/31.
[3] *Fraser and Statham* A80061/27.
[4] *Dougal* A80056/24.
[5] *Sunde* A80117/20.
[6] *Askanazy* A80043/04, *Hartmann and Karplus* A80067/29, *Oda* A96588/40.
[7] *Marchand* A80086/898, *Kaufmann* A80070/00, *Krebs* A80076/03, *Krasting* A77606/06, *Krömer* A70091/08, *Lutfi and Schükrü* 5563/33.
[8] *Risel* A80106/05, *Davidsohn* A80053/10.
[9] *Targett* A80119/898, *Solowij and Krzyszkowski* A80116/00, *Hammerschlag* A80065/04, *Davidsohn* A80053/10.
[10] *Kleinhans* A80073/02, *Risel* A80106/05, *Schmaus* A78979/05, A80109/06, A80110/06, *Barak* A80045/11, *Bollag* A80048/16, *Kynoch* A80080/19, *Dougal* A80056/24, *Zalka* A80122/28, *Schwarz* A80111/34, *Schwarz and Freund* A27229/34-5, *Fikentscher* A96026/37, *Backus and Griffin* A36168/41.
[11] *Miller* A18279/37.
[12] *Bonney* A80049/06-7.
[13] *Brauer* 5536/33.
[14] *Read* A80103/27-8, *Freund* A68177/29, *Fasold* A62927/31, *Bettinger* 43355/32, *Siegmund* 72594/32, *Witzberger and Agerty* A95127/37, *Tscherne and Schaffer* A97418/39, *Oda et al.* A96568/40.
[15] *Lubarsch* A80083/01, *Fikentscher* A96026/37.
[16] *Michel* A78703/05.

peatedly been described.[1]

The *pregnancy incidence* of chorionepitheliomas is comparatively high probably because so many of them are not true primary ovarian tumors but the direct result of neoplastic transformation in orthotopic or ectopic gestation sacs. There are no data, however, which would indicate a specially high pregnancy incidence of the true teratoid chorionepitheliomas.

PATHOGENESIS

The various pathogenic possibilities, which may lead to the formation of ovarian chorionepitheliomas, have been outlined in the part dealing with the classification of these tumors, since they are usually classified acording to the mechanism of their development. Suffice it to re-emphasize here that in all probability there is no single pathogenic mechanism which could explain the formation of all relevant cases. Some are evidently primary growths originating in the ovary, either from the chorionic villi of an ovarian pregnancy, or from the teratomatous transformation of a *parthenogenetic* ovum in which chorionic elements grow to the partial or complete exclusion of all other tissues. In support of this view, it has been emphasized that in the guinea pig chorionepithelioma-like structures appear to arise from parthenogenetically developing ova.[2] Instances of chorionepitheliomas in prepubertal children and intact virgins have been cited (see passage on age incidence) to show that this neoplasm may develop without a foregoing pregnancy.

In other instances the primary growth is outside the ovary (in the uterus, oviduct or peritoneum) and develops from a normal or ectopic *pregnancy*. This primary chorionepithelioma may metastasize in the ovary through three principal pathways: the blood stream, ascension through the oviduct, or direct invasion.

Whether common ovarian carcinomas with trophoblast-like portions should be considered a special type of chorionepithelioma is debatable, in spite of their morphologic resemblance to the latter. In the case of *giant cell-forming seminomas,* a fundamental relationship with the chorionepitheliomas has been denied. While any connection between chorionepitheliomas and other giant cell-forming ovarian neoplasms is admittedly highly problematic, it appears unwise to deny it without further evidence.

It is not inconceivable that various types of ovarian neoplasms may, under certain circumstances, assume teratoid potentialities which may find their explanation in the *organizer theory* of embryonic development. It is incompatible with the style of this Encyclopedia to go far afield into theoretic speculation, but it may perhaps be permissible to call attention to the great possibilities inherent in the application of the organizer theory to the multiform neoplasms which develop in the female gonad. In checking future borderline cases the determination of urinary gonadotropic hormone elimination should also be of great use in recognizing neoplasms with chorionic functional differentiation. The high urinary gonadotropic hormone titer in patients suffering from certain types of giant-cell containing tumors other than chorionepitheliomas (see gonadotropic hormone in urine in Sect. III), is of interest in this connection.

"*Klein's tumor*" with its "chorionähnlicher Funktion des Epithels" is in no way related to chorionepitheliomas. The relevant literature is discussed in the part on false, racemose, serous cysts.

For literature concerning data in support of the various pathogenic possibilities, the reader is referred to the parts on the definition and classification of the chorionepitheliomas.

CLINICAL COURSE AND COMPLICATIONS

Apart from the non-specific local manifestations of a rapidly growing malignant ovarian tumor, the clinical course of chorionepitheliomas is not very characteristic. In some cases irregular and prolonged *utrine hemorrhages* call attention to a possible endocrine disturbance,[3] but since so often chorionepitheliomas develop following normal or ectopic pregnancies, the vaginal bleeding is usually ascribed to placental remnants.

In children signs of *precocious puberty,* such as precocious menstruation and breast development, are often manifest.[4] These are due to the abnormal production of gonadotropic and folliculoid hormones by the neoplastic, chorionic tissue.

In adult women, *pregnancy changes* result from the endocrine activity of the tumor. Among these, the secretion of colostrum, discoloration of the vaginal mucosa and enlargement of the uterus are especially noteworthy.[5] In connection with the pathogenesis of these changes it should be kept in mind that it is not only the tumor itself which is a source of sex hormones; the ovaries also contribute to the endocrine disturbance as a result of the corpus luteum cysts formed under the influence of the excess gonadotropic hormones (see also Ovarian Changes due to Chorionepithelioma in Sect. IV, Vol. VI).

[1] *Albrecht* A80042/13, *Simard* 69158/37, A65177/31, A65178/31.
[2] *Loeb* A75862/11.
[3] *Sbarcea* A32100/39, *Sturley* A55953/42.
[4] *Fasold* A62927/31, *Siegmund* 72594/32, *Bettinger* 43355/32, *Tscherne and Schaffer* A97418/39.
[5] *Risel* A80107/14.

PLATE XVI

THYROID TUMORS AND CHORIONEPITHELIOMAS

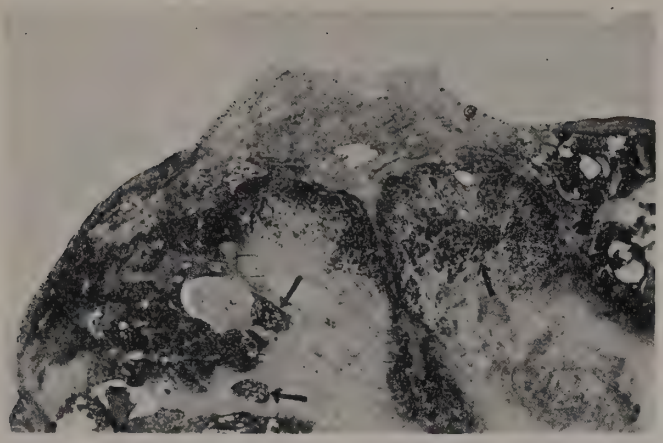

Fig. 1. STRUMA OVARII (courtesy of Dr. L. Berger). Very low magnification of a region consisting exclusively of thyroid tissue. Note irregular, dark epithelial regions containing thyroid follicles of varying diameter (some marked by arrows) and extensive white areas of partly edematous and partly hyalinized connective tissue. Such areas of degeneration are rather characteristic of struma ovarii. Other regions of this same tumor contained different organoid formations, characteristic of the cervical region (not represented in this field).

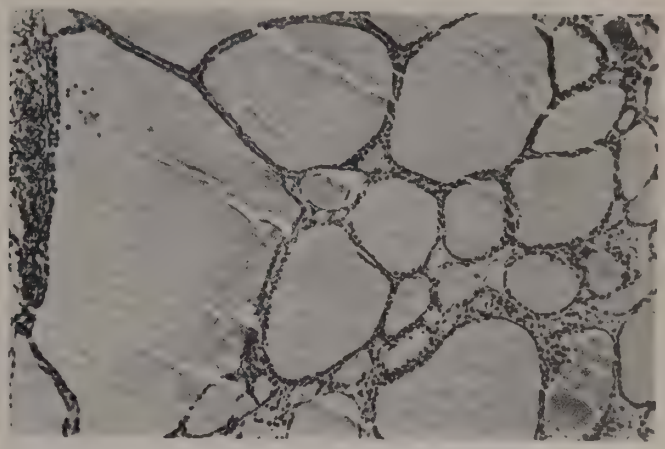

Fig. 2. STRUMA OVARII (courtesy of Dr. T. R. Waugh). Typical ovarian thyroid tumor containing no other tissue. This field illustrates a macrofollicular region.

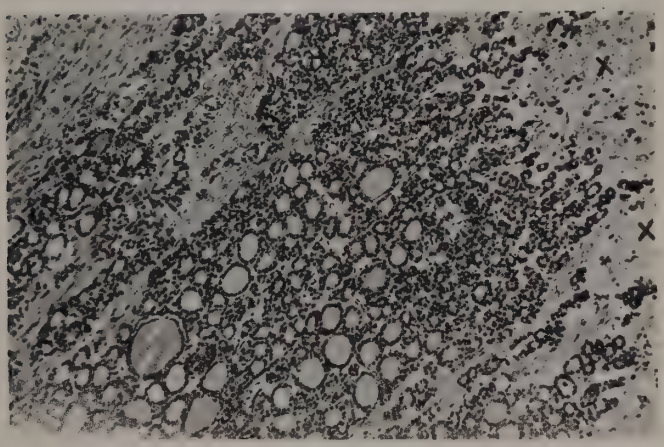

Fig. 3. STRUMA OVARII. Another region of the tumor represented in Fig. 2. Note medium sized thyroid follicles in the left lower corner of the picture; the follicular diameter becomes increasingly smaller towards the right upper corner. Interstitial colloid and edema are distinguishable between the smallest follicles in the right side of the field (X).

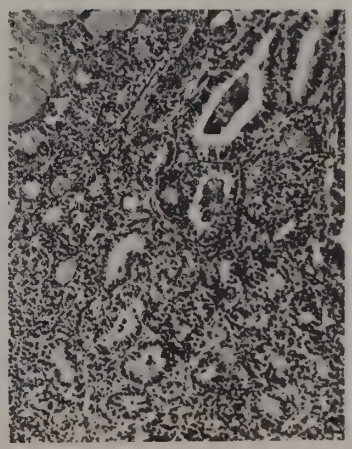

Fig. 4. STRUMA OVARII. Yet another field of the tumor represented in Fig. 2 and 3. Note three thyroid follicles partly within the field (upper left corner) while the rest of the picture consists almost exclusively of tubular formations. The latter have been variously interpreted as remnants of the ductus thyroglossus or "tubular adenomas".

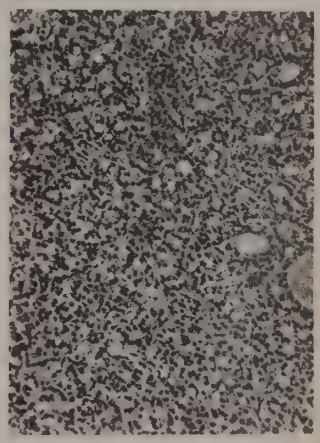

Fig. 5. STRUMA OVARII. Yet another region of the tumor illustrated in Figs. 2 and 4. An almost entirely solid region consisting of vacuolized epithelial cells. Only some of these have a slight tendency to form minute follicles. There are direct transitions between the typical thyroid-like appearance and this solid epithelial arrangement within the same tumor.

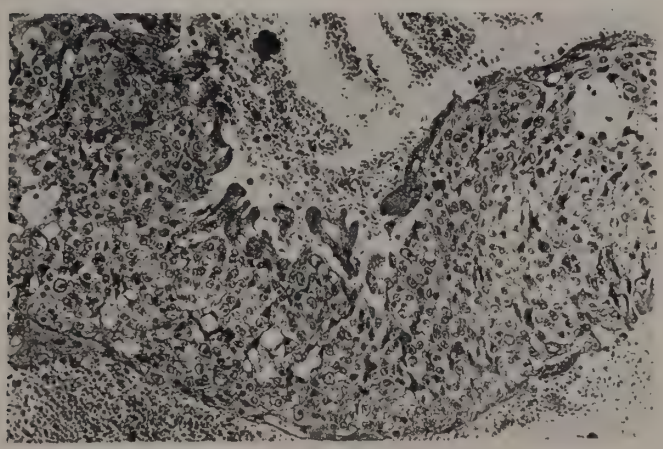

Fig. 6. CHORIONEPITHELIOMA (after L. C. Simard 69158/37). Part of a primary chorionepithelioma of the ovary. Note Langhans cells, bordered by large syncytial masses forming a villus.

Fig. 7. CHORIONEPITHELIOMA. Another region of the primary ovarian chorionepithelioma shown in Fig. 6. Note perivascular decidual cells in the ovary.

Signs of *pseudohermaphroditism* are not characteristic of chorionepitheliomas. In the few possibly relevant cases, the pseudohermaphroditic traits were congenital and the neoplasms developed secondarily in apparently predisposed individuals.[1] Seemingly pertinent cases were described as "epithelioma chorioektodermale", a designation erroneously used for giant-cell containing seminomas. The descriptions given are frequently such that a differential diagnosis between seminoma and chorionepithelioma is impossible and it is known that the former tumor has a definite tendency to develop in congenitally pseudohermaphroditic patients.

The *complications* which may occur in patients with chorionepitheliomas are essentially the same as those seen in women with other rapidly growing malignant neoplasms, hence they deserve no special consideration here (see chapters on Torsion and Hemorrhage in Sect. IV, Vol. VI).

DIAGNOSIS

The diagnosis of chorionepitheliomas is mainly based upon the local signs of an ovarian tumor in combination with evidence of excessive gonadotropic hormone production. The urine usually contains large amounts of gonadotropic hormone and sometimes also considerable quantities of folliculoid hormones (see relevant chapters on hypophysoid and folliculoid hormones in the urine in Sect. III and IV). Urinary bioassays do not, however, permit differentiation of the chorionepithelioma from normal or ectopic gestation. Unless pregnancy can be excluded with certainty, as in prepubertal children and virgins, ovarian chorionepitheliomas are clinically often indistinguishable from tubal or ovarian gestations. Since all these conditions require immediate surgical attention, such diagnostic errors are without serious consequences for the patient.

PROGNOSIS AND THERAPY

The *prognosis* of ovarian chorionepitheliomas is extremely grave, since this tumor is unusually malignant and rapidly progressive. Unless the neoplasm is surgically removed before it produces metastases, the outcome is invariably fatal within a short time. Even after radical surgical removal, fatal metastases and recurrences are very common. The urinary gonadotropic hormone excretion should always be checked following the operation since it is a good indicator of the continued presence of chorionepithelioma cells.[2]

The *therapy* of choice is early radical removal followed by deep X-ray treatment, but even cases so treated can rarely be saved.[3]

[1]*Polano* 12215/20, *Brauer* 5536/33.
[2]*Read* A80103/27-8, *Siegmund* 72594/32, *Fikentscher* A96026/37, *Tscherne and Schaffer* A97418/39, *Sbarcea* A32100/39, *Oda et al.* A96568/40.
[3]*Sturley* A55953/42.

PARA-OVARIAN CHORIONEPITHELIOMAS

The literature contains several reports concerning apparently primary chorionepitheliomas of the *broad ligament*[1] or the *vagina*.[2] It is difficult to furnish definite proof of the primary nature of such neoplasms, but in principle it is quite possible that chorionepitheliomas may form wherever other teratomas can originate.

As regards the pathogenesis, histology, clinical course, prognosis and therapy of these neoplasms, the reader is referred to the preceding chapter on Chorionepitheliomas of the Ovary where he will find information which is also applicable to the corresponding para-ovarian neoplasms.

[1]*Briquel* B6516/03, *Garkisch* B13307/07, *Moschcowitz* A91473/10-1, *Lecène* A91470/11, *Leriche* B6520/11, *Frank* B6518/16, *Bergeret and Moulonguet* B6517/23, A92948/23, *Engelhorn* A92950/24, *Davis* A92949/24, *Cleland and Wigg* B6519/24, *Murray* A91501/28.
[2]*Hicks* B13389/07, *Risel* B13315/07.

OVARIAN COMMON CYSTS

Synonyms: Ovarian dropsy, encysted ovarian dropsy, hydropisie hydatique, Sackwassersucht des Eierstockes, hydrovarium, cystoma ovarii, ovariocyesis, oothecocyesis, hydrops ovarii, hydrocele feminina.

The term "cyst" is used as a generic name for all cystic formations in the ovary including both the simple "retention cysts" which are not tumors in the oncologic sense of that word, and the "cystomas" which are true blastomas.

REVIEWS

DUTCH: Thomas A82051/858.

ENGLISH: Westmoreland A82107/856-7, *Nicholson* A81995/862, *Simpson* A82054/871, *Meadows* A81978/873, *Carter* A41238/883, *Burton* A40822/885, *Leidy* A81148/889-91, *Williams* A45780/891, *Robinson* A44182/892, *Bettman* A80940/895, *Walthen* A47125/895, *Phillips* A81125/898, *Davis* A50993/898, *Anonymous* B12841/04, *Findley* A80978/04, *MacCarty and Sistrunk* A70805/13, *Reder* A81102/19, *Chu* B8054/25-6, *Mahfouz Bey* A68103/29, *MacCarty* A61398/33, *Arnim* A53024/34, *Wellbrock* A51988/34, *Stabler* A95110/37, *Henshaw* A95215/37, *Geist B6672/42, Novak* B109/44, *Tilden* B11463/44.

FRENCH: Warin A82104/856-7, *Ollivier* A81997/861, *Nélaton* A81994/862, *Gallez* A82225/868-72, *Nolle* A81996/869, *Malassez and de Sinéty* A81970/876, A29383/879-81, *de Sinéty and Malassez* A82057/878, *Quénu* A29957/881, *Campistron* A80953/896, *Reynier* A81103/11.

GERMAN: v. Rokitansky A82042/855, *Kurrer* A70780/859, *Wild* A82109/861, *Säxinger* A82046/864, *Richter* A82035/864, *Waldeyer* A82098/868, A73013/870, *Hildebrandt* A81211/876, *Marchand* A70821/879, A70819/880, *Stöcklin* A96061/899, *Martin* A96833/899, *Kehrer* A74827/01, *Castorph* A80954/01, *Dobbert* A80974/02, *Falk* A70680/08, *Fabian* A70679/17, *Sternberg* A64845/26, *Mayer* A99597/26.

HUNGARIAN: Sztehlo A95116/36.

ITALIAN: Favalli A80977/850, *Acconci* A70557/889, *Pepere* A70883/899, *Cimoroni* B9123/05, B13214/07.

LATIN: Mueller A80935/857, *Nicolai* A80936/858, *Boetticher* A81008/864.

SPANISH: Quintanilla A82023/853, *de Vertiz* A82093/870, *Lizcano* A81154/04, *Laso and Meneses* A96701/28.

DEFINITION

Under the designation of "common ovarian cystomas" we shall discuss the various types of serous and pseudomucinous cysts, as well as the vast clinical literature concerning ovarian cystomas whose histologic structure was inadequately described.

Frequently ovarian cysts are reported in the literature merely because of their clinical interest. In many of these cases no microscopic studies were performed, while in others the histologic description is so inadequate that it is impossible to identify them with certainty. It was felt, however, that even these instances should be registered here if this Encyclopedia is to fulfill its purpose as a complete guide to the relevant literature, because even they may furnish valuable information. Thus some of the mammoth tumors described in old case reports are noteworthy simply because of their gigantic size, while cysts which heal as a result of spontaneous rupture are remarkable by virtue of their peculiar clinical course, irrespective of their histologic characteristics. For the purpose of classification it appeared important, therefore, to create a category into which such cases could be fitted. Since the serous and pseudomucinous cysts are by far the most frequent among all ovarian cystomas, it may be assumed, on the basis of mere statistical probability, that the great majority of the unidentified cysts belong to one of these two groups. It will be recalled, furthermore, that there are intermediate forms between the serous and pseudomucinous cysts[1] and that the clinical manifestations of these two types are essentially similar.

For these reasons the histologically unidentified, or incompletely identified cysts, and the serous and pseudomucinous cystomas will be discussed conjointly in this section, although the distinguishing features of the two latter groups will be given special consideration in the morphologic description.

HISTORY

In the ancient literature all types of cystic ovarian tumors were merely referred to as "hydrops ovarii" or "ovarian dropsy" and no distinction was made between the various subdivisions now recognized. Because of the conspicuous appearance of these growths and the many clinical complications to which they may give rise, the ovarian cystomas became known at a very early date and systematic scientific dissertations on this subject have been published ever since the 17th century. Although these early case reports are of little value to the student of histopathology, they are rich in data of historic interest.[2]

[1] *Fleischmann* A70694/16, *Meyer* A66176/32.

[2] *Salzmann* A81062/671, A81063/758, *Harderus* A81554/681, *Schoekopff* A81064/685, *Zwingerus* A82115/691, *Sloan* A82058/700, *Huth* A80933/701, A80932/768, A81036/774, *Imhoff* A81037/719, A81038/758, *Bassius* A81269/731, *Saviard* A80924/740, *Peyer* A82017/751, *Targioni Tozzetti* A82072/752, *Roederer* A81058/762, A81128/763, *Fehr* A81025/762, *van der Haar* A80944/762, *Etienvrin* A68457/765, *Durand* A68446/769, *Dubois* A68440/770, *Callisen* 68389/775, *Rogert* A82041/777, *Martin* A81973/778, *Johnson* A81598/783, *Mohrenheim* A81118/783, *Luzarche* A81966/783, *Martineau* A81974/784, *Tritschler* A82086/787, *French* A81535/787, *Ford* A81530/790, *Bistom* A80929/793, *Winship* A82111/794, *Le Roy* A81043/795, *Walker* A82099/799, *Denman* A68430/799, *Bosch* A68367/802, *Löffler*

Footnote cont'd.

It was soon noticed that ovarian cystomas may reach an enormous size[1] and gradually the early investigators learned to differentiate between the primarily cystic tumors and those in which cystic-like cavities develop secondarily in originally solid tumors as a result of liquefaction necrosis. They also became aware of the important distinction between benign cysts and the malignant cystic carcinomas and sarcomas. During the second half of the 19th century Fernbach[2] and Waldeyer[3] classified the ovarian cysts into the "glandular" and "papillary" growths, a distinction based not only on the obvious morphologic differences between these groups, but also upon their different biologic and clinical behavior. Not until the turn of the century, however, did pathologists learn to distinguish between serous, pseudomucinous and dermoid cysts, thanks to the classical investigations of Pfannenstiel.[4] He showed that, on the basis of the physico-chemical properties of their contents, the cysts can be classified into those with serous or ascites-like contents, mucinous or egg white-like contents and fatty or sebum-like contents. He also noted that the lining epithelium of the cyst cavities is characteristic for each type, consisting of cuboidal, usually ciliated cells in the first, high cylindric mucus-producing cells in the second and stratified squamous cells in the third variety. At an even earlier date Vegas[5] and Laskowski,[6] attempted a somewhat similar classification and Marchand[7] and Malassez and de Sinety,[8] pointed out that the type of fluid contained in ovarian cysts appears to be closely related to the type of lining epithelium. Yet it was only as a result of Pfannenstiel's[4] epoch-making investigations that the distinction between serous and pseudomucinous cystomas became clearly established as a natural basis for subdivision. It soon became evident, furthermore, that most of the typical papillomas belong to the serous, and most so-called "glandular cystomas" to the pseudomucinous group. This observation gave additional support to the concept that there is a deep, inherent difference between these cysts which justifies their segregation into distinct groups. The recognition of the dermoid cysts as teratomas (see chapter on Teratoids) revealed them as being of an entirely different nature.

The histogenesis of all these cysts is still unexplained and will be considered in the section on pathogenesis. It is of historic interest, however, to remember that from the vast group of the so-called serous cystomas, we gradually learned to distinguish certain specific entities, such as the follicle cysts, which are unilocular and hormone-producing, the "small cystic degeneration of the ovary" which essentially represents multiple small follicle cysts, and the mesonephroma which is likewise not hormone-producing and which may be of mesonephric origin. The remaining group of papillary or adenomatous serous cystomas, which is numerically the largest, is interpreted by some[9] as being composed of endosalpingiomas, that is, tumors derived from Müllerian epithelium similar to that seen in the Fallopian tube.

On the other hand, some of the cysts which would have been interpreted as pseudomucinous by the ancient pathologists, are now recognized to be examples of endometriosis or of so-called Brenner tumors. The bulk of these pseudomucin-producing cysts, however, including the "pseudomyxoma peritonei" which results from their rupture into the peritoneum, still forms a single large undifferentiated

[2]cont'd A81628/806, *Kelch* A81602/806-7, *Laignelet* A81618/807, *Cayol* A68399/808, *Engelmann* A81021/808-18, *Barker* 81262/810, *Hartog* A81562/810, *Petit* A82016/812, *Cunningham* A68423/813, *Henne* A81034/814, *Castellier* A68396/815, *Spalding* A82059/816, *Gaitskell* A81538/816, *Hellmann* A81570/816-8, *Croker* A68417/818, *Etienne* A81024/819, *Musnier* A81054/820, *Peipers* A82013/822, *Francis* A81533/823, *Wesener* A82106/823, *Rauch* A82026/823, *Habersham* A81550/823, *Adelmann* A81079/823-4, *Thomas* A69269/823-7, *de Grassi* A81032/825, *Strambio* A82067/826, *Forman* A81531/828, *Murray* A81992/828, *Darwall* A68426/828-9, *Cross* A68420/829, *Harivel* A81033/830, *Schneider* A82531/831, *Wood* A81074/831, *Dobson* A68433/831-2, *Fuchs* A81029/832, *Hawkins* A81563/833, *Teschemacher* A82078/833, *Stein* A81068/834, *Sanson* A82528/834, *Bartlett* 81266/834-5, *Dubrueil* A68442/835, *Staub* A81067/835, *Greetham* A81546/835, *Menzel* A81052/835, *Thibert* A82551/835-6, *Barlow* A81264/835-6, *Klaus* A81611/836, *MacCaldin* A81046/836, *Blasius* A68362/836-7, *Bluff* A68364/837, *Becker* A81005/838, *Toggenburg* A82085/838, *Douglas* A68439/839-40, *Gendrin* A81543/840, *Tavignot* A82075/840, A82074/840, A82073/840, *Harding* A81555/841, *Simpson* A82053/841, *Trowbridge* A82088/841-2, *Kissam* A81610/841-2, *Domeier* A80931/842, *Debrais* A81017/842, *Storrs* A82066/842, *Hey* A69313/842, A69312/842, *Roehr* A81059/842, *Ripault* A82036/842, *Jameson* A81593/842, A81592/856-7, *Bernard* A81278/843-4, A81006/849, *Judkins* A81600/843-4, *Cazeau* A81015/844, *Pluskal* A82263/844, *Van de Graaf* A81031/844, *Kennedy* A81604/844, *Lorbacher* A81045/844, *Wilkins* A82110/844, *Mombert* A82257/844, *Bissell* A81280/844, *Chomel* A68407/845, *Streicher* A81069/845, *Squibb* A82062/845, *Biermann* A80928/846, *Law* A81620/846, *Bennett* A81276/846, A81275/849, A81273/869, A81274/870, *Schreiber* A81129/846, *Eager* A68449/846, A68448/846, *Thompson* A82082/846, *Bainbrigge* A81257/846, A81258/851, *Lever* A81626/846-7, A81625/846-7, *Brown* A68379/847, A68377/847, A68960/852, A81010/862, A81011/868, *Kellock* A81603/847, *Velpeau* A82092/847, *Marsden* A81972/847-8, *Kennion* A81605/848, A81606/849, *Roosenburg* A81060/848, *M'Donnell* A81967/848, *Godart* A82464/848, *Wait* A82097/848-9, *Brindley* A68373/849, *Dewitz* A81019/849, *Cruveilhier* A68421/849, *Frost* A81536/849, *Tebbetts* A82076/849, *Timmermans* A81070/849, *Zander* A81075/849, *Gasca* A69592/849, *Mead* A81977/849-50, *Carnot* A81014/850, *Duclout* A81020/850. *Bennett* A82604/850.

[1]*Hünerwolffius* A81585/691, *Gandolphe* A81539/754, *Pulteney* A69754/794, *Hoditz* A81584/829, *Lever* A81627/848.

[2]A81026/863.

[3]A73013/870.

[4]A7554/898.

[5]A75985/864.

[6]A82578/867.

[7]A70821/880, A70819/880.

[8]A29383/881.

[9]*Barzilai* A71883/43.

group difficult to subdivide into any natural system of sub-groups.

CLASSIFICATION

The systematic classification of the ovarian cysts used in this Encyclopedia is based upon both their endocrine activity and their morphologic structure. It has been discussed in the passage dealing with the classification of ovarian tumors in general. Here I should only like to give a brief outline of the manner in which the material dealing with the "common ovarian cysts" (for definition see above) is listed in this chapter.

The gross morphologic characteristics of ovarian cysts (size, unilateral or bilateral distribution, adhesions, spread, etc.) as well as case reports, which are interesting only from a statistical or historic point of view, are listed in an introductory section on common cysts in general. This is followed by a detailed description of the features characteristic of the various specific types of serous and pseudomucinous cysts. The latter are subdivided as follows:

COMMON CYSTS

SEROUS	*PSEUDOMUCINOUS*
Macrocystic Unilocular (cystoma serosum simplex) Multilocular	*Macrocystic* Unilocular (cystoma pseudomunicosum simplex) Multilocular including "myxoma ovarii"
Microcystic (parvilocular including the "pseudostruma", "serous adenoma", fibroadenoma and serous cystadenoma [Tubular adenoma (serous) discussed in special chapter]	*Microcystic* (parvilocular) including "pseudomucinous adenoma", "parvilocular pseudomucinous cystoma", "epithelioma Wolffien" (usually malignant!), pseudomucinous cystadenoma and tubular adenoma (pseudomucinous)
Papilloma (internal and external) including "psammoma"	*Papilloma* (internal and external)
Racemose cystoma ("grape-like cystoma") True racemose cystoma False racemose cystoma	*Racemose cystoma* ("grape-like cystoma") False racemose cystoma
Peritoneal papillomatosis	*Pseudomyxoma peritonei*

The existence of *a priori* cystic primary ovarian carcinoma is extremely doubtful. All cystic carcinomas of the ovary are considered to result either from malignant transformation of originally benign cysts, or from metastases of extraovarian cancers. Both these types are discussed in the chapter on Common Carcinomas.

Because of the numerous forms of cystomas which represent intermediate types between the main groups of the above classification, the inclusion of individual cases under a specific heading is, of necessity, often arbitrary. For example, a specific instance of a pseudomucinous multilocular cystoma, which perforated and led to the formation of pseudomyxoma peritonei, may either be listed with the pseudomucinous cystomas or with pseudomyxoma peritonei, but is usually mentioned only once in order to save space. As far as possible such borderline cases are cited in connection with the sub-group which they illustrate best. The reader who is anxious to obtain a complete bibliography is urged to keep this in mind and to consult cross-references.

PATHOLOGIC ANATOMY

A. GENERAL MORPHOLOGIC CHARACTERISTICS.

Macroscopically ovarian tumors are exceedingly variable as regards size, color, shape, consistency, etc. The features typical of the various subgroups will be considered in the chapters specifically devoted to them; suffice it here to give an outline of those characteristics which are more or less common to the serous and pseudomucinous cystomas. This outline will serve as a general guide, especially to the old literature which placed comparatively little emphasis upon histologic detail.

An enormous number of papers contain case

reports of patients who suffered from common ovarian cysts and cystomas.[1]

[1]*Hoebeke* A81583/849-50, *Busch* A81013/851, *Buckmaster* A68385/851, *Winslow* A82112/851, *Wilson* A83590/851, *Suringar* A82068/851, *Mierendorff* A81053/851, *Legendre* A81623/851, *Coale* A68410/851, A68411/853, *Ware* A82101/851, A82102/857, A82103/859, *Le Bêle* A81042/852, *Burnett* A82142/852, *Berend* A88403/852, *Denham* A68429/852, *Chabert* A68400/852-3, *M'Dowel* A81114/852-8, *Tanner* A82070/852-3, A82071/853, *Swaving* A82069/853, *de Langenbeck* A81619/853, *Krause* A81041/853, *Irwin* A81591/853, *Hammond* A81552/853, *Danziger* A68425/853, *Hoffmann* A81035/853, A48352/896, *Salle-Estradère* A81061/854, *Richardson* A82034/854, *Banks* A81259/854, *Hayward* A81565/854, A81566/856, *Hafner* A81551/855, *Bartscher* A81267/855, *Seeger* A81066/856, *Mehlhose* A81050/856, *Hitchcock* A81578/856, *Denoix* A81018/856, *Buchannan* A68384/856, *Abeille* A81076/856, *Chassaignac* A68402/856-7, *Westmoreland* A82107/856-7, *Jobert* A81594/856, A81595/861, A81596/863, *Oppolzer* A81998/856, A81999/858, *Müller* A74934/857, *Eulenberg* A68458/857, *Cade* A82347/857, *Bulkley* A68386/857, *Alquié* A81249/857, *Curveilhier* A68422/857, A82362/867, *Disse* A68431/857, A68432/860, *Minchen* A81979/858, *Isak* A81039/858, *v. Franqué* A81534/858, *Fuller* A81537/858, *Finger* A81526/858, *Fifield* A81524/858-9, A81525/859, *Uytterhoeven* A82090/859, *Spiegelberg* A82060/859, *Spiltoir and Delteure* A82061/859, *Guérin-Roze* A82459/859, *Elliot* A68452/859, *Bauchet* A81270/859, *Tracy* A82556/860, *Schooley* A82049/860, *Chlebowski* A68406/860, *Ferris* A81522/860-1, *Brossard* A68376/860-2, *Womack* A82113/861, *Thiry* A82079/861, *Kaulich* A81601/862, *Greeve* A81547/862, *Pigeolet* A82018/863, *Hussey* A81588/863, *Hennig* A81571/863, *Helbich* A81569/863, *Fernbach* A81026/863, *Johnson* A81599/863, A42605/889-90, A50668/898, *Walter* A81072/864, *Ockel* A81055/864, *van Dommelen* A68435/864, *Boulton* A68368/864, *Armijo* A81250/864-5, *Favier* A81520/864-5, A81521/865, *Quinlan* A82022/865, *Klein* A81040/865, *Dodeuil* A82434/865, *Cantani* A68392/865, *Bueren* A81012/865, *Baart de la Faille* A81254/865, *Tufnell* A81298/865-8, *Klebs* A81612/865, A81613/866, *Leroy* A68731/866, *Fajole* A68460/866, *Day* A68428/866, *Bowen* A68370/866, *Babbington* A81255/866, *Hüter* A81586/866, A81587/867, *Legros* A81624/867, *Hybord* A88410/867, *Friederichs* A81027/867, *Ellsworth* A68454/867, *Cheever* A68404/867, *Palmer* A82502/867-8, *Schwab* A81065/868, *Mitchell* A81980/868, *Meyweg* A81049/868, *Born* A81009/868, *Campdoras* A68390/868-9, A68391/884, *Bellamy and Arnott* A81271/869-70, *M'Millan* A81968/870, *Kidd* A81609/870, *Hartmann* A81561/870, *Capozzi* A68393/870, *Clark* A68408/870, A83344/893, *Hand* A81553/870-1, *Ritchie* A82037/870, A82038/872, *Saboia* A82044/871, *Contreras* A68413/871, *Burns* A68387/871, *Hodge* A81579/871-2, A81582/874-5, *Salzer* A82047/872, *Shepard* A75132/872, *March* A81971/872, *Gaupp* A81542/872, *Cavazzani* A68397/872, *Lusk* A81965/872-3, *Thomas* A82081/872-3, *Porter* A69843/873, *Foster* A81532/873, *Dubois* A68441/873, *Curtis* A68424/873, *Cooper* A82831/873, *Wright* A82569/874, *Lefèvre* A81622/874, *Hawkins* A81564/874, *Ellis* A68453/874, *Atlee* A81253/874, *Easby* A69656/874-5, *Hewitt* A81574/874-5, *Mazzoni* A81976/874, A81975/874, *Epps* A81023/875, *Daury* A68427/875, *Chagnon* A68401/875, *Baschiere* A81268/875, *de Alarcon* A81248/875, *Kenny* A81143/875-7, A81607/876, *Wells* A81073/876, *Labbé* A81616/876, *Kerr* A81608/876, *Henry* A81572/876, *Hartigan* A81560/876, *Gareaudeaux* A81540/876, *Friedländer* A81028/876, *Dutrait* A68447/876-7, *Sinéty and Malassez* A82055/876, A82056/877, *Krönlein* A81614/877, *Rasumowsky* A82025/878, *Fochier* A81529/878, *Atthill* A74954/878, A40063/882, *Anonymous* A69573/878, A69574/884, A45725/890, A45726/890, A69566-898-01, *Goodell* A81545/878, A29273/880, A40596/881, A40076/882, *Stienon* A34830/878, A34831/878, *de Sousa* A29963/879, *Morisani* A29319/879, *Maygrier* A82480/879, *Lebedinski* A90082/879, *Colrat* A29270/879, *Conant* A29239/879, *Barlow* A81263/879, *Werth* A29389/880, *Laurenzi* A29569/880, *Beach* A29264/880, *Harris and Doran* A81559/880-1, *Bigelow* A81279/881, *Eder* A68451/882, *Lucio* A40397/882-3, *Wallace* A41279/883, *Haggard* A41261/883, *Dyson* A40240/883, *Coe* A41255/883, *Mundé* A41511/883, A41561/883, *Nunez de Sampelayo* A41317/884, *Barnes* A74965/884, *Baer* A40815/884-5, A40814/885, A40817/885, *Heurtaux* A40715/884-5, *Duncan* A40790/885, *Beates* A40463/885, *Tempini* A40986/885, *Wyman* A42012/886, *Terrillon* A82077/886, *Raingeard* A41819/886, *Rand* A82024/886, *Guillemet* A41848/886, *Janvrin* A42029/886, A47104/895, *Mohr* A80934/887, *Livon* A42234/887, *Cappi* A81332/887, *Dudon* A42258/887-8, A43395/889, *Martin* A42531/887-8, A47499/895, *Wettergren* A42361/888, *Kunert* A81459/888, *Bantock* A42246/888, A42247/888, *Griffith* A45122/889, *de Lostalot* A43472/889, *Frank* A43270/889, A48343b/896, A48270/896-7, *Smith* A43321/889-90, *Mendes de Leon* A43637/890, *Reckert* A45901/891, *Dixon* A45907/891, *Coley* A45723/891, *Ranka* A81493/892, *Kollock* A81144/892, *Bradford* A69551/892, *Slavjanski* A44706/893, *Croom* A46464/893, *Beatson* A47338/893-4, *Roberts* A74541/893-04, *Pozza* A69845/894, *Meyer* A44701/894, *Masson* A44664/894, *Lefour* A69622/894, *Closs* A44745/894, *Sato* A81500/895, *Hooper* A47456/895, *Adami* A80937/895, *Balls-Headley* A47295/895, *Murphy* A48365/895-6, *Hofmokl* A91970/896, *Condamin* A48332/896, *Baker* A48430/896, *Aquino* A48259/896, A48238/896, *Hellier* A49144/897, *Cartledge* A49139/897, A69560/899, *Hernandez* A80945/897-8, *Vidal and Barillot* A50685/898, *Steele* A50593/898, *Shoemaker* A49218/898, *Humiston* A49215/898, *Hamonic* A50483/898, *Dupuy* A50689/898, *Dudley* A50602/898, *Réal* A81494/899, *Nordberg* A69834/899, *Jacobson* A80948/899, *Fukui* A69657/899, *Emory* A69587/899, *Bailey* A69540/899, *Amano* A80938/899, *Kelly* A69616/00, *Duret* A69584/00, *Bidwell* A69545/00, *Burns* A74821/00-1, *Shtraukh* A74549/01, *Wolff* A81302/01, *Ries* A81495/01, *Rabajoli* A81127/01, *Magnarapa* A69823/01, *Gloninger* A69595/01, *Birschtein* A69546/01, *Mallett* A81156/01-2, *Hill* A80947/01, A80946/01, *Hyde* A69608/01, A69607/01, *Murata* A81470/02, *Gill* A69593/02, *Tate* A74560/02, A74559/05, *Mattei* A69827/03, *Monturiol* A81119/03, *Mandillou* A81157/03, *Clark* A80969/03, *Augier* A80962/03, *Jessett* B8987/03, *McGlinn* A69822/04, *Meisenbach* A81284/04, *Cornil* A80970/04, *Jordan* A69613/04-5, *Newton* A81123/04-5, *Vance* A74570/04-5, *Squire* A74553/05, *Legg* A69623/05, *Pollosson* A69842/05, A81286/05, *Beguerestain* B13167/06, *Oui* A69836/06, *Evans and Coombe* A81448/06, *Chastenet de Gery* A80941/06, *Brown* B13227/07, *Edington and Findlay* B9388/07, *Viannay* B9397/07, *Lenoir* B13252/07, *Wanless* B13277/07, *Michel* B13334/07, *Guerive and Molinier* B13289/07, *Jones* A81188/09, *Amann* B11296/10, *Kaufmann* B11309/10, *Ramon y Cajal* A81233/10, *Ross and Hendrick* A81236/11, *Vayssière* A81197/12, *Maccabruni* A81084/14, *Black* B16241/15, *Stratmann* B9587/16, *Teliega* B9570/16, *Barry* B11918/16, *Ritchie* B11909/16, *Forster* B11920/16, *Work* B11910/16, *Oastler* A81093/17, *Loop* B21310/17, *O'Reilly* B11813/18, *Holmes* B9348/20, *Maury* B21283/20, *Ashhurst* B21191/21, *Chun* B8677/21-2, *Stajano* B21077/22, *Kenney* A81190/23, *Arrigoni* A81163/23, *Morgue-Molines and Guibal* A81090/24, *Mornard* B16024/24, *Greeley* A81185/24, *Falcone* A81182/24, *Darnell* A81169/25, *Aljovin and Busch* A81083/25, *Crain* B7206/27, *Metivet* B7172/27, *Failla* B7989/28, *Sichel* B10796/28, *Chavannaz and Magnant* B6010/29, *Tootell* A64560/29, *Sergeant* A64557/29, *Ribeiro* A65507/29, *Menicucci* A62530/32, *Worth* A62591/32, *Kieser* A52266/34, *Zuccotti and Schapira* A62490/35, *Solhaug* A27758/35, *Bolloli* A59647/36, *Avancini* A559644/36, *Cabot case* B21530/37, *Nelson* A97012/38, *Green* A97613/39, *Farias* A97489/40, *Abdulla and Rohini* A97331/40, *Zuckermann* A98093/42, *Andras* B11401/43.

The common cystomas of the ovary tend to acquire a great size by the formation of more and more cystic cavities and by proliferation of papillomatous masses; in the case of simple cysts the fluid content merely increases. Numerous case reports describe such *large* and sometimes truly enormous ovarian cystomas.[1] In certain cases the entire tumor was weighed, with the result that accurate figures concerning its size are available. These data indicate that not infrequently ovarian cystomas weigh *25-50 lbs.*,[2] *50-100 lbs.*,[3] *100-150 lbs.*,[4] *150-200 lbs.*[5] or even *more than 200 lbs.*[6] Probably the largest ovarian tumors on record are the multilocular cystomas which weighed *225 lbs.*,[7] *245 lbs.*[8] and *328 lbs.*[9] respectively. Some investigators measured the fluid content of ovarian cysts and found it to amount to *42 liters*,[10] *94 liters*,[11] *over 70 pints*[12] and in one case *23 gallons*.[13]

Spohn[14] describes his amazing case as follows . . . "Mrs. G., age 43, the mother of seven children, had been suffering for several years with an ovarian tumor. During this time she had been tapped frequently. When I called to see her, imagine my surprise on entering her room to find on the bed an immense mass as large as a barrel. I could not see the woman, but in looking over the mass could just see her head attached to it like an appendix. The tumor came almost up to her chin, and extended to midway between her knees and feet. When she lay on her side on a three-quarter bed it had to be supported on two chairs. She could not reach her navel with her hands by one and one-half feet and was so emaciated that without her tumor companion would hardly make a shadow. She could only take nourishment by the spoonful, and seldom retained it. When they wished to move her they rolled the tumor, and she went with it" . . . "I decided to reduce this tumor for one week, and with a small trocar succeeded in removing thirty gallons of a gelatinous fluid. On opening the abdomen I found many adhesions at points where she had been tapped. The tumor was of the left ovary, multicystic. I opened one cyst of large size, removing over six gallons. The thickened sac, removed with difficulty on account of adhesions, weighed 40 pounds, giving the tumor, as near as I could estimate, a total weight of 328 pounds. In closing the incision I had great difficulty getting the abdominal walls in satisfactory shape. There was so much serum and blood escaping that I was compelled to open a part of the incision and insert large pieces of gauze for drainage, treating the abdomen partly open. I took two months to close the abdomen. The patient made a good recovery."

Common cysts have a definite tendency to develop simultaneously or successively in both ovaries of the patient and numerous case reports list *bilateral* cystomas.[15]

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[1]*Cooper* A68414/852, *Boscredon* A68366/854, *Aberle* A81077/869, *Brunker* A68381/872-3, A68382/873, *Laroyenne* A40428/882, *Soller* A40577/882, *Neal* A41591/883, *Stone* A41319/883-4, *Bozeman* A40787/884, *Inverardi* A41780/886, *Peckolt* A42564/887, *Estes* A42162/887, *Tassi* A43514/889-90, *Buffet* A43497/890, A43301/890, *Abbott* A43386/890, A49198/898, *Peters* A43375/890, *Johnson* A45632/891, *Lawrie* A44260/892, *Gutierrez* A91801/893, *Tansini* A47152/894, *Ward* A47124/895, A81199/09, *Reifsnyder* A47431/895, *Cave* A48433/896, *Jeanne* A91810/897, *Bustillo Lirola* A48966/897, *Lee* A49124/897, *Edwards* A49209/898, *Pascal and Pilliet* A50514/898, *Plasencia y Lizaso* A83473/898, *Chuffart* A69565/899, *Eastman* A91788/899, *Bullitt* A83452/899, A83453/00, *Gilliam* A91799/899, *Pearse* A83470/899, *Browning* A69557/899-00, *Fisher* A91791/00, *Hagen-Torn* A91802/01, *Marshall* A83458/01, *Fussell and Schell* A91797/01, *Fagan* A91790/01, *Aquino* A83446/01, *Glasson* A91800/02, *Cleveland* A91773/02, *Meyers* A83462/03, *Idaszewski* A83444/03, *McCartney* A83455/03, *McGirk* A83457/04, *Pfaehler* A83472/04, *Newton* A83467/04, A83468/04, *Kholodkovski* A91815/04, *Benjamin* A83448/04, *Heinricius* A91805/04, A81135/04, *Solovyoff* A91840/04, *Abel* A83445/04, *Skutsch* A69170/05, *Cordier* A91774/05, B13348/07, *Morimoto* A83466/05-6, *James* A69610/06, *Cherevkoff* B13127/06, *Caballero* B13159/06, *Segond* A69169/06, *Gottignies* B13229/07, *Kaiser* B11271/10, *Horsley* B11270/11, *Baur* A78035/15, *O'Day* A23600/16, *Chenhall* B11834/17, *Collins* A81168/19, *Pelliza* A81095/19, *Benda* B8707/20, *Downes* B8720/21, *Baumann* B11734/21, *Harley* A81187/21, *Stratton et al.* A81110/21-2, *McConaghy* B11755/22, *Emmert* B20929/24, *Tambe* B7356/26, *Darnall* B7326/26, *Weeks and Delprat* B7256/27, *Nedergaard* A96704/28, *Nath* B5965/29, *Heekes* A63517/29, *Kehrer* A65612/29, *Renaud* A68115/29, *Sparks* A63446/29, *Pareja and Orosco* A67252/30, *Mosse* A64008/31, *Fairbairn* A62297/32, *Travan* A66069/32, *Benso* A66104/32, *Ballati* A61543/33, *Gibson* A61557/33, *Goddard* A52113/34, *Vachharajani* A27893/35, *Bonafos and Laffont* A61443/36, *Moolten* A61286/36, *Mayo and Zellhoefer* A59468/36, *Ort and Dickmann* A95307/37, *Strickland* A95328/37, *Kidd* A95367/37, *Bohnen* A97040/38, *Canabraba* A97606/39, *Roman* A97636/39, *Heller* A96609/40, *Lajos* A97711/40, A97391/40, *Perovic and Undiano* A98172/42.

[2]*Atlee* A87183/850, *Hayward* A81567/854, *Reifsnyder* A44156/892, *Morel* A83465/03.

[3]*Stewart* A45078/889, *Lanphear* A46494/892-3, *Southard* A47368/895-6, *Mayfield* A83460/899-00, *de Paula and Neri* B9431/17, *Glenn* A81183/20, *Fobes* A61381/33, *Khoroshmanenko* A27875/35, *Hamlin* A60008/36.

[4]*Gibb* A82460/855-6, *Kelly* A40977/885, A42125/886, *Duret* A44654/894, *Lynds* A50669/898, A50641/898, *Yahoub* B13267/05, *Poncet* A83474/06, *Motley* A64643/24, *Hutcheson* B20797/26.

[5]*Harris* A47407/895, *Lewis* B10767/28, *Lloyd et al.* A52121/34.

[6]*McGillicuddy* A83456/895, *Ward* A64647/22.

[7]*Binkley* A48369b/897.

[8]*Bullitt* A83452/899, A83453/00.

[9]*Spohn* A91842/05-6.

[10]*Guinaudeau* A65470/30.

[11]*Tuffier* A91850/06.

[12]*Burford* A44189/892, A46323/892-3.

[13]*Hintze* A81577/834-5.

[14]A91842/05-6.

[15]*Easterling* A68450/855, *Varrentrapp* A82091/860, *Hickman* A81575/865-6, *Gibbons* A81544/867-8, *Rex* A82028/870-1, A82029/874, *v. Dumreicher* A68443/871, *Atlee* A81252/871-2. *v. Mengershausen* A81051/876, *Coveenton* A86338/876-7, *Weinlechner* A40927/883, *Carter* A41603/884, *Lober* A81044/886, *Böhm* A42221/887, *Lee* A42717/888, *Mendes de Leon* A42455/888, *Weeks* A45205/888-9, *Zinke* A44222/892, *Dibrell* A44246/892-3, *Largeau* A44751/893, *Patwardham* A47505/895, *Bérard* A48242/896, *Thompson* A50982/898-9, *Boursier and Monod* A81328/899, A83335/899, *Walker* A83511/02-3, *Vincent* A74573/06, *Marshall* A81087/12, *Brodhead* A81670/14, *Phillips* A81096/14.

Some ovarian cysts are *unilocular*, that is, they contain a single cavity filled with either serous or pseudomucinous fluid depending upon the nature of the lining epithelium.[1] Such cysts rarely reach very considerable proportions although *large* unilocular cysts, weighing more than 20 lbs. have repeatedly been seen[2] and one such cyst weighed as much as *95 lbs.*[3]

Unlike the multilocular cystomas, it is unusual to find *bilateral* unilocular cysts.[4]

Multilocular cysts represent the most common variety, as indicated by the numerous relevant case reports.[5] Multilocular cysts frequently reach a very *large* size[6] and from cases in which the tumor weight was accurately measured we know that it may reach *20-30 lbs.*,[7] *40-50 lbs.*,[8] *60-70 lbs.*[9] or even *75 lbs.*[10] and probably most of the gigantic cystomas listed in the general section on cysts belong to the multilocular variety of the serous or pseudomucinous cystic tumors. The multilocular growth described by Atlee,[11] which contained 64 pints of chocolate-colored fluid, should also be cited although it may have been an unusual type of endometriosis. Not infrequently, multilocular cystomas are *bilateral*.[12]

The term *cystadenoma* (*Synonyms:* cystoadenoma, cystic adenoma, adenoma kystique, Zystadenom) is generally applied to that particular variety of a multilocular cystoma in which at least a large portion of the growth consists of small alveoli or tubules which imitate a glandular structure.[13] It

[1] *Trousseau* A82087/866, *Wagstaffe* A82096/869, *Penassier* A82014/873, *Bantock* A81261/873-4, A81260/874, *Thomas* A34837/878, *Lee* A29278/880, *Bottini* A29537/880, *Bassini* A29710/880, *Thornton* A29501/880, *Alezais* A29533/880, *Mattei* A40636/883, *Valerani* A41208/883, *Serre* A41722/886, A42239/888, *Baer* A41647/886, A41648/886-7, *Bell* A41733/887, *Hurley* A41678/887, *Bartlett* A42414/888, *Bulius* A42515/888, *Rutherford* A45259/889, A42568/889, *Ludlam* A45797/891, *Duncan* A46362/891, *Noriega* A44867/894, *Bailey* A69539/896, *Lauenstein* A49070/897, *Phillips* A81124/897, *Hennig* A81136/898, A50484/898, *Martin* A69825/899, *Morrison* A69833/01, *Schachner* A74545/01-2, *Fairbairn* A81449/03, *Cesa-Bianchi* A80968/05, *Sellheim* B8029/26.

[2] *Parkes* A41623/884, *Wile* A41014/885, A41666/886-7, *Cartledge* A45624/891.

[3] *Ranney* A40746/884.

[4] *Dervaux* A48993/897.

[5] *Twining* A82089/835-42, *Doorenbos* A82616/842, *Corrigan* A82642/852-8, *Richard* A82030/854-5, *Garrod* A81541/857, *Allix* A88402/859, *Grosser* A88398/859, *Kidd* A82669/861-2, *Hutchinson* A81589/862-3, *Collis* A82641/862-5, *Chatin* A68403/864-5, *Carmona* A68394/864-5, *Barton* A82628/868-71, *Boyron* A68371/869-70, *Blatchly* A68363/870, *Boettcher* A68365/870, *Lehmann* A82943/870, *Storer* A82065/871, *Atlee* A81251/871-2, *Briddon* A68372/871-2, *Hodge* A81580/872-3, A81581/874, *Croly* A82643/873-5, A68418/875-6, A68419/876, *Bergeron* A81277/874, *Hayes* A82660/874, *Brush* A68383/875, *Duroziez* A82650/876, *Pi y Suner* A82020/877, *Osthoff* A82000/877, *Malloch* A29254/879, *Berthold* A74886/879, *Meredith* A29353/880, *Gallez* A29716/880, *Bassini* A29708/880, *Erich* A29563/880-1, *Barron* A82627/880-1, *Duffey* A82646/880-2, *Duncan* A40110/881, *Duffey and Atthill* A40070/882, *Derville* A40213/882, *Leriche* A41342/883, *Izard* A41555/883, *Desguin* A40936/884, *Ménétrier* A82222/885, *Heurtaux* A41482/885, *De Luca* A82645/885, *Tuholske* A41665/886, *Claypool* A82639/886, *Nancrede* A41686/886, *Plasencia* A42132/885-6, A45073/888, *Limont* A82677/886-7, *Richardson* A41787/887, *Murphy* A41964/887, *Duret and Voituriez* A42161/887, *Bratton* A42433/888, *Baer* A42510/888, A42704/888, *Menocal* A45071/888, *Boyd* A42549/888, *Weed* A42625/888-9, *Collins* A42679/888-9, *Emery* A42520/888-9, *Stewart* A45189/889, *Ballenghien* A42596/889, A82624/889, *Barrena* A82625/889, A82626/889, *Chunn* A45172/889, *Chénieux* A45171/889, *Casuso* A42585/889, *Dods* A43335/889, *Shah* A45108/889, A44812/894, *Pascale* A42695/889, *Ferguson* A43418/889-90, *Galbraith* A42524/889-90, *Gómez* A82654/889/90, *Hager* A43366/890, *Gillion* A43606/890, *Frykman* A43528/890, *Cantacuziono* A43499/890, *D'Antona* A43571/890, *Janvrin* A43308/890, *Rabagliati* A43616/890, *Smith* A43487/890-1, A82693/03, *Ludlam* A45760/891, A45920/891, A46496/893, A46534/893, A44861/894, *Duret* A45660/891, A82648/896, A82649/896, *Quinones* A44038/891, *Maglioni* A45761/891, *Stirling* A46351/892, *Cleveland* A82640/892, *Cale* A82637/892, A47296/895, *Dibrell* A44247/892-3, *Araujo and Cuervo Marguez* A44187/892-3, *Roberts* A44265/892-3, *Manrique* A44594/892-3, *Magruder* A46401/892-3, *Bishop* A82632/893, A82633/894, A82634/899, *Schachner* A46572/893, *McLaren* A46337/893, *Hanks* A44824/894, *Masson* A44780/894, *Cartledge* A44649/894-5, A46325/893, *van Eman* A47123/895, *Lechner* A82618/895, A81145/899, *Balm* A47370/895, *MacDonald* A82212/895, *Kreider* A47461/895-6, *Thompson* A47397/896, *Burckhard* A48330/896, *Dumont-Leloir* A47403/896, *Balls-Headley* A48324/896, *Brownfield* A48403/896, *Martín Gil* A48492b/897, *Guillois* A49101/897, *Westerfield* A48422b/897, *Binkley* A48369b/897, *Dervaux* A48408b/897, *Duer and Blackburn* A49229/897-8, *Blesh* A50960/898, *Duplesis* A82647/899, *Malapert* A51005/899, *Elischer* A82651/00, *Baldwin* A82622/00, *Hall* A82658/00, A82659/03, *Giles* A82653/01, *Somers* A82695/01, *Anderson* A82621/02, A82620/04-5, *Kramer* A82674/02, *Martin* A82217/02, *Slovcheff* A82692/02, *McMurtry* A82214/02-3, *Gross* A82657/02-3, *Le Broun* A82636/03, *Gordon* A82655/03, *Brown* B12953/03, *Pieri* A82685/03, *Strak* A82696/04, *Battle* A82629/04, *Berard* A82631/04, *Flaischlen* A82652/04, *MacEvitt* A82213/04, *Grant* A82656/04-5, A81369/17, *Vanderveer* A82705/05, *Vance* A82703/05, *Johnston* B13163/06, A82666/06, *Bell* A82630/06, *Martín Aguilar* A82219/06, *Barkley* A81360/07, *Simacourbe and Lambert* A81380/08, *Guilbert* A81370/10, *Flatau* B11213/10, *Sebastian and Palanea* A81379/10, *Sebastian* A81362/11, *Prigge* A81082/11, *Harry* A81371/11, *Truesdale* A81381/11, *Wallois* A81382/11, *Cowie* A81364/13, *Kermisson* A81660/13, *Macfie* A81374/13, *Pothérat* A81378/13, *Brodhead* A81361/14, *Williamson* A81383/22-3, *Hefferman* B21011/23, *Fahrig* A97340/39.

[6] *Peaslee* A82012/862, *Rodenstein* A82040/879, A82039/879, *Bassini* A29709/880, *Terrier* A75739/884, *Barton* A42289/887-8, *Gangolphe* A91798/00-1, *Robins* A83476/03, *Onur* A27754/35, *Yu* A95344/37.

[7] *Ricketts* A82690/02, *Purcell* A83475/03-4.

[8] *Ludlam* A40455/882, *Barton* A42290/888, *Briddon* A43327/890, *Davis* A91780/896.

[9] *Eve* A29240/879, *Boerstler* A41500/885.

[10] *Crofford* A44194/892-3.

[11] A82285/872-3, A82286/874.

[12] *Weinlechner* A40926/883, *Baer* A40993/885, *Boyd* A42513/888, *Ludlam* A45921/891, *Mallett* A82215/899, *Boucher* A82635/02, *Plummer* A82687/04, *Martin* B13026/04, *Ricketts* B13273/07, *Levant and Bornoka* A81373/21.

[13] *Josso* A41484/885, *Hodenpyl* A42380/888, *Iversen* A42381/888, *Zielewicz* A45114/888-9, *Ewin* A45833/891, *Angeli* A46420/892, *Pinkerton* A83481/893, *Tate* A47154/894, *Vasten* A83485/896, *Friend* A91963/899-01, *Coley* A91961/00, *Sutton* A83483/00, *Peiser* A83480/01, *Zvyagintseff* A83488/02, *Fehling* A77479/03, *Anderson* A83477/03,

Footnote cont'd.

must be realized that the term cystadenoma is insufficient as a description to identify the histologic structure of a blastoma. Such growths may be serous or pseudomucinous and may or may not contain papillary portions. Details concerning these additional characteristics should be included as part of a complete designation (e.g. serous cystic adenofibroma, pseudomucinous papillary cystadenoma etc.). Differentiation between the cystadenoma and the so-called *solid adenoma* likewise lacks precision in many of the relevant papers. This latter term should be reserved for macroscopically solid tumors which reveal an adenomatous structure upon histologic examination. The designation cystadenoma is properly applied to tumors containing at least some macroscopically visible cystic cavities in addition to more solid adenomatous parts. The histologic characteristics of the various cystadenomas and solid adenomas are discussed below in the passages dealing with the subgroups of the serous and pseudomucinous cystomas. Suffice it to say here that cystadenomas may reach very large proportions[1] and several relevant neoplasms weighing between 50 and 90 lbs. have been described.[2] Even solid adenomas may become unusually large[3] but this is comparatively rare.

The *tubo-ovarian cysts* are cystic formations which communicate directly with the lumen of the Fallopian tube. If the latter is permeable they discharge their contents through the oviduct into the uterus and vagina.[4] The vast majority of these cysts, probably of inflammatory origin and closely related to the so-called tubo-ovarian abscess, are discussed in the chapter on the inflammations of the ovary (see Sect. IV, Vol. VI); hence, strictly speaking, they should not be listed with the ovarian tumors. In some cases, however, follicle cysts may perforate into the oviduct after having been connected with the latter by adhesions; in other cases cylindric epithelium or mere connective tissue lines the cyst cavity and hence it is often impossible to determine the pathogenesis and true nature of the cyst.[5] It is because of these diagnostic difficulties that the tubo-ovarian cysts are briefly mentioned here.

The contents of tubo-ovarian cysts are usually more or less serous fluids, a fact which clearly differentiates them from the pus-containing tubo-ovarian abscesses. This does not necessarily imply a non-inflammatory origin, since originally purulent exudates may, in the course of time, be replaced by clear transudates. In some instances a greatly dilated tube, which forms a hydrosalpinx, is so closely adherent to an otherwise normal ovary that so-called *pseudo-tubo-ovarian cysts* result; these of course, are never of blastomatous origin.[6]

The blood supply of tubo-ovarian cysts has been discussed by de Francesco.[7]

B. THE SEROUS CYSTOMAS.

Macrocystic Serous Cystomas. (*Synonyms:* serous cyst, cystoma serosum simplex uni- or multilocularis, germinal inclusion cyst, surface epithelium cyst of the ovary, kyste germinatif, Flimmerepithelkystom).

In the majority of cases, simple (non-papillomatous) serous cystomas are unilateral and a review of various statistics on this subject indicates that *bilateral* formation of such blastomas occurs only in 2-18% of the cases in various series.[8] Our own literature survey leads us to believe that simple serous cystomas are bilateral in about 8% of all cases, but it should be kept in mind that the serous papillomas—which form a sub-group of the serous cystomas—are usually bilateral (as we shall see from the paragraphs specifically devoted to the papillomatous growths).

In most cases serous cystomas are *multilocular* as indicated by the case reports listed above. It is incorrect to state, however, as some investigators do, that this is always so. It is probable that the widely divergent statistics on this subject are the result of differences in the interpretation of the term. Follicle retention cysts, which are always unilocular, have often been taken for serous cystomas and even among the true cystomas, those having one large main cavity being listed as unilocular even if small "daughter cysts" developed in their wall. It is known that serous cysts tend to be unilocular, and if additional cavities develop they (secondarily) merge with the main cavity due to absorption of the

[13]cont'd *Withrow* A83487/04, *Glockner* A91967/05, *Curti* A91779/05, *Schachner* A83482/05-6, *Robinson* A68497/10-1, *Woolsey* A68503/11, *Briggs* B16219/16, *Mayer* A68475/21, *Erdmann* A81181/21, *Bertner* A68486/22-3.

[1]*Curti* A91779/05.

[2]*Tate* A47154/894, *Robinson* A68497/10-1, *Mayer* A68475/21.

[3]*Glockner* A91967/05.

[4]*Robertson* A82519/851, *Richard* A81289/851, A82031/856-7, A82032/857, A82033/857, *Bennett* A82332/854, A82333/858, *v. Rokitansky* A82521/863, *Burnier* A29538/880, *Reboul* A81057/885, *Runge and Thoma* A40486/885, *Doran* A42255/887, A42256/887, *Varnaly* A41976/887, *Griffith* A81548/888, *Johnston* A45126/889, *Kötschau* A43469/890, *Schramm and Neelsen* A45643/890-1, *Slavjanski* A45775/891, *Robinson* A45929/891, *v. Rosthorn* A44132/892, A46377/892, *Duret* A47486/895, *Lawrence* A47423/895, A48412/896, *Goldspohn* A48322b/896, *Cullingworth* A48334/897, *Duncan* A48996/897, *Zahn* A49250/898, *Legueu and Cabaniols* A81147/00, *Nassauer* A81120/00, *Bonney* A75310/03, *Shoofs* B8891/03, *Bels* B8924/03, *Bailey and Cameron* A81312/04, *Fitzgerald* B13051/04, *Garcia de Arias* B12824/04, *Taylor* B12621/04-5, *Gaignerot* B13129/06, *Handley* B13117/06, *Cesa-Bianchi* B13106/06, *Boursier* B12900/06, *Latornche* B13199/07, *Oliver* A81094/17, *de Francesco* A68512/24, *Ledoux-Lebard et al.* A27876/35, *Schwarts and Schil* A97020/38, *Mavrodin* A97506/39.

[5]*Niderehe* B7502/25, *Miller* A18279/37.

[6]*Miller* A18279/37.

[7]A68512/24.

[8]*Hanks* A70749/888, *Miller* A18279/37.

separating septa. Opinions differ concerning the classification of intermediate cases. These divergences in definition must be kept in mind in connection with serous cystomas described as *unilocular*.[1] It should also be remembered that both in unilocular and in multilocular serous cystomas, a few papillary excrescences are frequently found, but unless they show prominent development it is not customary to list such growths as papillomas. In general, the serous cystomas, whether uni-or multilocular, are described as smooth-walled or "simple" if they are free (or at least almost free) of papillomatous excrescences, while if the latter are prominent we speak of serous papillomas. As indicated by our classification of the ovarian cysts, the multilocular variety is further subdivided into the macrocystic, microcystic and tubular varieties. The macrocystic type of serous cystoma usually contains only few compartments, thus differing from the macrocystic pseudomucinous cystomas which most commonly consist of numerous cysts.

Numerous *case reports* describe cystomas which contain a serous fluid and are lined by serous, sometimes ciliated, epithelial cells.[2]

Histologically the most characteristic feature of the serous cystomas is their epithelial lining which consists of cells containing a comparatively large, often elongated, nucleus which almost completely fills the cell body. In contradistinction to the pseudomucinous cysts, the lining epithelia are poor in cytoplasm and contain no pseudomucin. Frequently, though not invariably, their surface is covered by cilia. In some instances, the latter are distinguishable only in the epithelial cells of certain areas of the cyst wall.

X. It has been emphasized[3] that the cells of serous cysts may also contain some mucicarmine-positive granules so that the difference between the serous and pseudomucinous cystoma is not as fundamental as may be thought.

Microcystic or Parvilocular Serous Cystomas. Among the microcystic serous cystomas the *adenofibroma* is the most common variety. (Synonyms: Fibroma ovarii adenocysticum; fibroadenoma serosum; adenoma fibrosum; if stroma is especially prominent: fibroma with adenomatous inclusions; if some cysts are rather large: adenofibroma ovarii partim cysticum, cystoadenofibroma; if fibroma within a cyst: intracystic fibroma; if partially subdivided: adenofibroma ovarii disjunctum; if fibromas small and within epithelial tubules: adenofibroma intracanaliculare ovarii; if smooth muscles in stroma: fibro-myo-cystoma; if similar to thyroid: pseudo-struma).

Merely a quantitative difference in the relative proportion of parenchyme and stroma hardly justifies the creation of several special tumor types, hence, all relevant *case reports* will be discussed conjointly here under the heading of adenofibromas.[4]

Macroscopically, adenofibromas are solid tumors, although on the cut surface the larger cystic cavities may be detectable by naked eye inspection, at least in the form of small pores which on thin sections endow the tumor with a sieve-like appearance. Occasionally, so-called intracystic fibromas develop[5] which represent more or less purely fibrous growths originating in the wall and protruding into the cavity of serous cysts. The term adenofibromas ovarii disjunctum or succenturiatum[6] has been applied to those adenofibromas which are partly subdivided due to pressure by dense cutting adhesions.

Microscopically, the prominent feature of the adenofibromas is their strongly developed tissue stroma which resembles that of pure fibromas. It encloses gland-like lumina and small cysts which tend to congregate in irregular clusters, the lining cells possessing a granular chromphil cytoplasm. In the so-called adenofibroma intracanaliculare ovarii[7] the glandular spaces are lined by a single or double layer of ciliated epithelial cells and the growth resembles the intracanalicular fibroadenoma of the breast. Where smooth muscle cells are present in the stroma the term fibro-myo-cystoma has been employed,[8] but at present probably most relevant cases would be interpreted as endometriomas. The designation "cystoma ovarii papilliforme pseudostrumosum" or "pseudostruma of the ovary" has been suggested for a partly psammomatous and papillomatous microfollicular growth of this group which resembles thyroid tissue.[9] This variety of designations illustrates the histologic multiformity of the adenofibromas, yet as stated above, it is strongly felt that minor differences in structure, such as the relative predominance of one or the other tissue constituent, do not justify the establishment of separate groups or the coining of new terms. The entire field of ovarian oncology suffered greatly from the tendency of many investigators to create new

[1] *Weinlechner* A40647/883, *Hall* A70747/891, *Stübler and Brandess* A70975/25, *Galloway* A70718/35.
[2] *Harper* A70750/864, *Wells* A73020/864-5, *Watson* A73018/865-6, *Brodowski* A70601/876, *Spiegelberg* A70964/879, *Harris* A70851/880, *Lauro* A40253/882, *Borgherini* A40441/882, *Purcell* A70909/890-1, A70910/894-5, *Kelly* A70767/894, *Gangolphe* A70719/01, *Olshausen* A70876/05, A70877/10, *v. Grot* A70740/06, *Cornil* A70634/07, *Bouchet* A70596/07, *v. Neugebauer* A70869/09, *Gottschalk* A70732/10, A70733/10, *Mayer* A70829/26, *Kimura* A70769/30.
[3] *Glasunow* A95259/37.
[4] *Rubio y Gali* A29600/880, *Smith* A64893/08-9, *Schottländer* A70947/15, *Spencer* A64894/25-6, A64842/26, *Neumann* A70870/28, *Ritcher* A70923/29, *Fuchs* A67298/30, *Dworzak* 6582/32, *Frankl and Klaften* A28154/34, *Grolitsch* A96687/41, *Scott* A55564/42.
[5] *Papin and Sabaréanu* A70879/04, *Frankl* A64756/27.
[6] *Fuchs* A70714/30, A67298/30.
[7] *Adler* 40333/07.
[8] *Pascal and Pilliet* A50514/898.
[9] *Strong* A79074/14.

tumor entities and to suggest descriptive, complicated names for certain variants of the common cystomas. It is hoped that the elimination of such unnecessary subdivisions will do much to clarify this complex field of pathology and it is for this reason that special emphasis is placed in this Encyclopedia upon the explanation of essentially synonymous designations.

The *tubular adenoma* of the ovary is discussed in the sub-section on potentially endocrine tumors, under the heading of arrhenoblastoma. We mention it here merely because its cavities are "parvilocular" tubules, its cells frequently resemble those of the serous cystomas and occasionally the stroma tends to proliferate in a fibroma-like manner. Hence, on purely morphologic grounds it could be classed with the serous parvilocular blastomas. It should also be remembered that only a certain percentage of the tubular adenomas are virilizing and there is no infallible morphologic criterion which would permit the recognition of hormonal activity. Hence it is no more justifiable to separate the hormonally "silent" tubular adenoma from the hormone-producing arrhenoblastoma, than it would be to assume that hormone-producing and silent granulosa cell tumors represent two entirely distinct blastoma entities. Special emphasis is laid on this point since even some of the most eminent authorities e.g. Miller[1] continue to discuss the "two" tumor types separately in distinct chapters.

The *mesonephroma* (Schiller) is usually free of mucicarmine tingible material and on the basis of its structure could be classed among the serous parvilocular blastomas, but because of its peculiar specific characteristics we shall discuss it separately from the common cysts.

The so-called "*medullary cord cysts*" and "*rete cysts*" of Robert Meyer[2] should also be mentioned in this connection although it is difficult to prove their origin (see also chapter on Para-Ovarian Tumors in General).

Serous Papillomas. By far the most important and common variety of the serous cystoma is that characterized by innumerable, cauliflower-like excrescences, the so-called *papilloma (synonyms:* serous papilloma, papillary adenoma or cystadenoma, papillo-cystoma, fungating papilloma, papillenführendes Kystom, Flimmer-Papillärkystom, tumeur végétante de l'ovaire, cystoma serosum papilliferum uni- or multilocularis, cystoma phillodes proliferum; if the papillae are external: cauliflower excrescence, surface papilloma, Oberflächenpapillom, papilloma superficiale, cystoma papillare evertens; if psammoma bodies prominent: psammoma, psammomatous papilloma, cystofibroma papillare ovarii psammomatoedes, papilläres Psammokystom).

Macroscopically, the prominent feature of ovarian papillomas is the development of numerous arborizing papillae which give the growth a berry-like, coral-like or cauliflower-like appearance. In the event of filiform papillae the surface is velvety, while coarse papillae are often describd as mushroom-like. They tend to spread into the peritoneum and the broad ligament and often contain many calcified concretions of a sand-like character. These "psammoma bodies" may, in exceptional cases, reach a diameter of several millimeters, but usually they do not exceed a fraction of one millimeter. As we shall see in more detail later, the papillomas are rather subject to carcinomatous transformation and tend to produce ascites. Their growth rate is rarely rapid and in many cases the existence of such tumors has been noted 10-15 years before operation.[3]

The *size and shape* of papillomatous cysts is variable; they may be either nodular or round. They rarely reach the colossal proportions of the pseudomucinous cystomas. although some become large as indicated in the special passage on large serous cystomas, many of which belong to this group since their inner surface is usually, at least in part, supplied with papillae. The smallest papillomas measure only a few millimeters.[4] The *color* of papillomatous cysts is blue, brownish or yellow and when sectioned they prove to be multilocular in most cases. The cyst fluid may be clear, yellowish or greenish and is poor in pseudomucin.[3]

It is customary to distinguish between *internal and external papillomas*, although the excrescences on the peritoneal surface of cysts are probably secondary to perforations (papilloma evertens), while papillomas which develop on the ovarian surface, apparently without cyst formation, are frequently (though not always) due to rupture of a pre-existent cyst with subsequent disappearance of its walls. Hence, there is no reason to assume an inherent basic difference between the serous cystoma with papillary excrescences on its inner wall and the so-called surface papilloma.[5] Yet it is noteworthy that in some of these cases the papillomas developed directly on the ovarian surface without any visible indications of previous cyst formation. The "velvet-like" surface papillomas of the ovary belong to this latter category.[3]

[1]A18279/37.

[2]A76843/12, A74962/13, A73154/14.

[3]*Miller* A18279/37.

[4]*Flatau* A70693/04, *Ferran* A65973/09.

[5]*Kerr* A42427/888, *Nanu* A45103/889, *Frommel* A43527/890, *Paton* A44130/892, *Zander* A69443/893, *Amann* A70563/897, A70565/01, *Müller* A70861/898, *Wathen* A83512/00, *Gemmell* A70721/01, *Siedentopf* A70957/03, *Gottschalk* A70731/06, *Wiedmann* A73023/06, *Zacharias* A73029/07, *Miller* A70837/09, *Hinselmann* A70842/11, *Hahn* A70746/15, *Hofstätter* A70049/18-9, *Heberer* A70853/21, A70854/22, *Ahumada and Rubinstein* B6032/28, *Dorland* A70659/29, *Miller* A18279/37.

The majority of the papillomas are *bilateral*. The percentual incidence of bilaterality among papillomas is difficult to estimate accurately because of the great divergence in the published figures, which vary between 12% and 80%.[1] Our own survey of relevant case reports indicates an average frequency of about 65%. Numerous publications deal specifically with the bilaterality of papillomas because it is of practical importance to obtain an approximate estimate of the likelihood of papilloma development in the contralateral ovary if one gonad is affected by such tumors.[2]

The characteristics of the serous ovarian papillomas have been described in many case reports.[3]

Microscopically, the papillomatous cystomas prove to possess a lining *epithelium* which on the smooth part of the cyst wall is identical with that previously described as characteristic of the simple serous cystomas. On the papillae it is essentially similar, although occasionally it tends to be somewhat higher, that is, cylindric rather than cuboidal. It is important to remember that even in the lining of serous papillomas, goblet cells are occasionally present among the serous cells.[4]

The papillae contain a *stroma* which arises directly from the connective tissue of the cyst wall. This connective tissue is dense in the main stems of the papillae, and loose—with comparatively few nuclei—in the fine ramifications. It may contain round cells and plasma cells.[5] Emphasis has been laid on the fact that even in the secondary ramifications, the albuginea and primary follicles of the ovary may remain recognizable, that is, ovarian tissue is carried

[1]*Kahr* A95265/37, *Miller* A18279/37.

[2]*Gusserow and Eberth* A70742/868, *Thornton* A70991/876-7, A41874/887, *Quénu* A70912/885, A70915/886, A70914/886, *Lee* A70790/886, *Flaischlen* A70690/888, A70691/890, *Barnouw* A70581/889, *Lomer* A43372/889, *Terrillon* A70988/890, A70987/890, *Bokelmann* A70589/890, *Cleveland* A70621/892, *Jacobi* A70848/892, *McLean* A44124/892, *Pye-Smith* A44668/892-3, *Doran* A70658/892-3, *Walther* A46582/893, *Veit* A73007/895, *Sinclair* A47507/895-6, *Smith* A47324/895-6, *Hofmokl* A49088/897, *Fränkel* A70700/897, *v. Tóth* A70995/897, *Sietkin* A50907/898, *Ssjetkin* A70966/898, *Williams* A51022/898-9, *Cathelin* A70611/00, *Wimmer* A73026/01, *Walla* A69463/01, *Ferguson* A70684/01, A70683/08, A70685/10-1, A81891/11, *Donald* A70654/02, *Bovée* A70599/03, *Croft* A70638/03, *Courant* A70637/04, *Henkel* A70859/04, *Atkins* A70574/04-5, *Henrotay* A74722/04-5, *v. zur-Mühlen* A73030/05, *Pichevin* A69451/06, *Maiss* A70814/06, A70813/06, *Amann* A70569/10, *Bouchard* A70593/11, *Rosenstein* A70930/12, A70929/12, *Phillips* A70894/13, *Young* A81897/13, *Rouffart* A70932/21, *Bancroft* A81887/23, *Cameron* A70608/23-4, *de Ramón* A81100/25, *Wagner* A73012/26, *Descomps* A70651/27, *Polano* A70896/27, *Haupt* A70852/29, *Labhardt* A70782/31, *McCarty* A64392/32.

[3]*Prochaska* A70907/812, *Declaux* A81180/823-4, *Wilks* A73024/855-6, *Hicks* A81576/864, *Marcy* A70820/874, *Slavjanski* A29499/880, *Emmet* A29370/880, A29481/880, A70671/03, *Lee* A29419/880, *Coblenz* A29714/880, *Thornton* A70992/881, *Flaischlen* A29901/881, *Bang* A74885/881, *Doran* A40255/881-2, *Martin* A70822/882, A70823/886, A48281/896, A70824/897, *Bozeman* A40384/882, *Goodell* A70730/885, *Schröder* A70950/885, *Baer* A40959/885, *Braun v. Fernwald* A40964/885, *Mundé* A70862/886, *Johnstone* A41852/886-7, *Dawson* A70648/887, *Gars* A41778/887, *Velitz* A42186/887, A43324/889, *Netzel* A41818/887, A69448/887, *v. Rokitansky* A69456/887, *Burt* A74716/887-8, A74715/887-8, *Czempin* A70644/888, A70645/895, *Chrétien* A70616/888, *Wettergren* A42363/888, *Veit* A73006/889, *Mikhnoff* A69447/889, *Bantock* A70579/889, A44164/892-3, *Gardner* A42590/889, *Wacquez* A43496/890, *Garbuzoff* A43574/890, *Sandberg* A70939/891, *Saxer* A70941/891, *Walker* A45808/891, *Schönfeld* A70945/891, *Tuttle* A73001/891, *Tait* A45644/891, *Fränkel* A70703/891, A70699/897, *Sutton* A70976/892, *Cleveland* A70620/892, A70622/892, *Duret* A70666/892, A70667/10, *Krautwig* A74608/892, *Cullingworth* A70643/892, *Chrobak* A70617/892, *Lowers* A70796/892, *Williams* A46352/892-3, A73025/894, *Yamata* A69465/893, *Mikhailoff* A69441/893, *Cullen* A47070/894, *Jeffcoat* A44657/894, *Ross* A44836/894, *Hall* A44749/894, *Robson* A70925/894-5, *Elder* A70670/894-5, *Pfannenstiel* A70890/895, *Freeborn* A74721/895, A47451/895, *Keiffer* A74726/895, *Kirchner* A70770/895, *Liebrich* A70797/895, *Bastianelli* A70582/896, *Dirner* A70653/896, *Thomas* A69460/896, *Semb* A70956/896, *Gessner* A48349/896, *Jezievski* A70753/896-7, *Schrader* A70948/897, *Witherow* A48409b/897, *Larin* A49240/897, *Krüger* A74609/897, *Amann* A70564/897, *Troschel* A50952/898, *Mauclaire and Pilliet* A70827/898, *Apostolakis* A70572/898, *Bovée* A70598/898, *Chirchoff* A70615/898, *Strübe* A70397/898, *Anderson* A50915/898, *Baldy* A70578/898, A74711/898, *Kidd* A70768/899, *Anonymous* A69450/899, *Jacobson* A70849/899, *Uffenheimer* A73002/899, *Gould* A70734/899, *Norris* A69449/899, A70873/00, *Cestan* A69561/00, A74822/06, *Cohn* A70630/00, *Dranizin* A70661/00, *Mackenrodt* A70807/00, A70808/10, *Bishop* A70586/00-1, A74712/03-4, *Strassmann* A69458/01, *Tédenat* A69459/01, *Reid* A69455/01, *Dégardin* A70811/01, *Pompe v. Meerevoort* A70897/01, *Konrad* A74727/01, *Fuda* A91965/02, A91964/04, *Goldenberg* A70728/03, *Rendu* A70921/03, *Smyly* A70961/03, *Theilhaber* A70990/03, *François-Dainville* A70698/03, *Bonney* A74713/04, *Pozzi* A69454/04, *Spanton* A69457/04, *Broun* A70602/04, *Levison* A70795/04, *Bouchet* A70594/04, A70595/06, *Holzapfel* A70845/05, *McNamara* A69445/05, *Estor* A80943/06, *Potenko* A70901/06, *Jung* A74725/06, *Le Dentu* A81146/06, *Lili* A70798/06, *Michel* A83104/06, *Resinelli* A70922/06, *Kelley* A70766/06, *Frank* B13169/06-7, *Robson and Odgers* A70926/07, *Mansfeld* A70818/07, *de Rouville and Stoltz* A70935/08, *Gayet* A68469/08, *Schottelius* A70946/08, *Emrys-Roberts* A70673/08, *Frank* A70704/08, *Asch* A70573/09, *Francini* A70697/09, *Boldt* A70590/09, A70591/10, *de Blasi* A70649/10, *Forssner* A70695/10, *Lehmann* A70792/10, *Betow* A81888/12, *Delmas and Aymes* A70650/12, *Gminder* A70725/12, *Keep* A70763/12-3, *Evler* A70678/13, *Le Filliatre* A70791/13, *Judd* A68491/14, *Thompson* A68500/15, *Fleischmann* A70694/16, A68488/16, *Schwartz* A70952/17, *Peskind* A70886/17, *Bogart* A81889/17, *Lower* B21311/17, *Corcia* A70631/18, A68487/18, *Henrotay* A70841/20, *Thomson* B21279/20, *Lehoczky-Semmelweis* A70793/20, *Erdmann and Spaulding* A70674/21, *Spaulding* A70962/21, *Delbet and Bellanger* A81170/21, *Rowe* A81895/22, *Gibbon* A81892/22-3, *Hooper* A68490/23, *Potvin* A70902/23, *Ménétrier and Peyron* A81227/23, *Stevens* A70968/23-4, *Duclaux* B20926/24, *Watson* A73017/24-5, *Emerson* B7470/25, *Darnall* A70646/25, *Gaifami* A70716/25, *Eberhart* A70669/26, *Gresset* A70739/27, *Mayfield* A70830/27, *Nicholson* A70871/27, *Hedley* A70855/27-8, *Bell* A70584/29, *Taylor* A70982/29, *van Ramshort* A70917/31, *Natale* A53102/33, *Cicconardi* A70619/33, *Joachimovits* A70755/34, A28156/35, *Ellyson* A28150/35, *Brakemann* A95236/37, *Bovier* A97042/38, *Santa Cruz Pacheco* A97182/38.

[4]*Amann* A70564/897.

[5]*Cassola* A70610/25.

into the stalk of the papillomas.[1]

Several investigators distinguish between the so-called *stationary and the proliferating forms* of papillomas; the former have coarse papillae with a broad base, while the latter tend to have highly arborized gracile papillae whose epithelium is high cylindric and often consists of many layers among which goblet cells are not uncommon. This proliferating type is sometimes very difficult to differentiate from papillary carcinomas.[2] The number of ciliated cells is extremely variable[3] and the youngest papillae frequently consist merely of polymorph wedge-shaped epithelial cells, the so-called "cellules métatypiques".[4] Kleine[5] described benign cornifying adenopapillomas.

The *psammoma bodies* so common in serous papillomas, consist of degenerated, often hyalinized, material which tends to become calcified; they are either roundish or mulberry shaped, frequently with a concentric stratification reminiscent of the growth rings in trees. These bodies may be situated in the stroma or among the epithelial cells, although it is generally assumed that they originate from the latter.[6] Tumors very rich in psammoma bodies have been termed psammomas, psammopapillomas or psammocystomas[7] although they do not represent a tumor entity fundamentally different from other serous papillomas.

Contrary to the opinion frequently expressed in the literature, the presence of psammoma bodies is in no way indictative, or even suggestive, of malignancy, nor can these concretions be interpreted as a sign of ageing or involution of the neoplasm since they may be detectable in the earliest stages of papilloma development.[8]

The *blood vessels* of serous ovarian papillomas are usually very prominent but many of them tend to become hyalinized.[9]

The development of *papillomatous cysts in accessory ovaries or in the parovarium* has repeatedly been reported; in all these cases, however, the possibility of peritoneal re-implantation of orthotopically developed papillomas, and the formation of similar growths from the oviduct or heterotopic endosalpinx islets is difficult to eliminate unless histologically normal ectopic ovarian tissue is also formed (see chapter on Accessory Ovaries in Sect. IV, Vol. VI and Para-Ovarian Common Cystomas in present Volume.)

Serous Racemose Cystoma (True and False). In many instances the end-buds of serous papillomas are greatly enlarged and roundish. They are attached to the main stems of the papilloma tree by comparatively thin (stalk-like) pedicles so that a grape-like structure results. These are the *serous racemose cystomas. (Synonyms:* Racemose papilloma, grape-like papilloma, hydatidiform tumor of the ovary, kystes racémeux ou en grappe de l'ovaire, polypöses Eierstockskystom, beerenförmiges or traubenförmiges Papillom, traubenartiges Kystom, ovario policistico molare).

Generally two varieties are distinguished. In the first, each grape-like body represents a separate daughter cyst with an epithelial lining both on the outside (the papilla surface) and on the inside (which would normally correspond to the papilla stroma). This is generally referred to as the *true serous racemose cystoma;* it represents a multilocular papillomatous serous cystoma in which the daughter cysts happened to form within the papillae rather than in the main cyst wall as is usually the case. Histologically, the epithelium lining the surface of the "grapes" consists of a single layer of cuboidal or flat cells and does not differ essentially from that of ordinary papillae. The inner surface often has a similar lining consisting of a single layer of flat, cuboidal or cylindrical, sometimes ciliated, cells among which occasional goblet cells are interspersed.[10]

The other variety is the so-called *false serous racemose cystoma (Synonyms:* Edematous serous papilloma, Klein's tumor). Macroscopically, these blastomas resemble the so-called true serous racemose cystomas, but histologically the two types are readily distinguished, since the "grapes" of the false racemose cystoma contain no epithelial lining, the swelling being due solely to excessive stroma edema. Sometimes the fluid within the stroma splits the latter into several compartments, while in other cases the edema is uniformly distributed so that no cavities are formed. In either case the absence of lining within the swollen papillae is quite characteristic of the "false" type even if it contains so much gelatinous fluid that upon rupturing the papillae the impression of small cysts is gained. Furthermore, in both the true and the false serous racemose cystoma, the "grapes" are subject to self-

[1] *Betschmann* A70585/02.
[2] *Amann* A70564/897, *Bell and Datnow* A66142/32, *Shaw* A61532/32.
[3] *Semb* A70956/896.
[4] *Malassez and de Sinéty* A29383/879-81, *Flaischlen* A40044/882.
[5] A70777/37.
[6] *Coblenz* A29714/880, *Bezchinski* A43566/890, *Pfannenstiel* A45890/891, A70890/895, *Williams* A73025/894, *Kirchner* A70770/895, *Uffenheimer* A73002/899, *Witkiewicz* A79218/01, *Tusini* A71000/05.
[7] *Bovée* B9385/07, *Ahlström* A70561/17, *Sachs* A52300/34.
[8] *Pfannenstiel* A80267/05.
[9] *Uffenheimer* A73002/899, *Wiedmann* A73023/06, *Fabian* A70679/17, *de Francesco* A68512/24.
[10] *Jayle and Bender* A73054/03, *Tata* B8805/03, *Grasmück* A73049/08, *Bender* A73035/09, *Bolaffio* A73038/10, *Polakowski* A73074/11, *Dahlgren* A64419/30, *Putzu Doneddu* A95375/37.

amputation by rupture of their pedicle so that free, hydatid-like vesicles may be found in the peritoneum. The surface cells are similar to those found in ordinary serous papillomas although owing to the stroma edema they are more frequently atypical. This induced Klein[1] to assume that they have a chorion-like absorbing function and that the stroma edema develops as a result of this activity. This interpretation led to the assumption that the false serous racemose papilloma is a distinct tumor entity, essentially different from other papillomas. Treber[2] gave it the name Klein's tumor which was widely used, especially in the old German literature. Subsequently, however, it was recognized[3] that this is not a fundamentally distinct tumor type; the fluid accumulation in the stroma is merely due to circulatory disturbances and not to a specific physiologic activity of the lining cells. It is now generally accepted that both benign and malignant papillomas are eminently subject to the development of stroma edema and in this event either type is occasionally designated as "Klein's tumor".

Thus it appears that both the true and the false serous racemose cystomas are merely special modifications of the common serous papilloma. They are discussed as a special subgroup only because of their characteristic morphologic appearance which distinguishes them from the other papillomas. Additional details concerning both types of the serous racemose cystoma will be found in the relevant case reports.[4]

Peritoneal Serous Papillomatosis. In certain instances, serous papillomas of the ovary are accompanied by widespread papillomatosis of the peritoneum. It has already been mentioned that both the ordinary and the racemose serous cystomas are subject to self-amputation of papillae which then float freely in the peritoneum. It is not surprising, therefore, that in certain instances they may implant themselves on the peritoneal surface, at a distance from the ovary and if this process is very extensive we speak of peritoneal papillomatosis[5] or pseudomalignant ovarian papillomas.[6] Probably this condition is always secondary to rupture of papillomatous cysts and occurs in about 13%[7] to 29%[8] of the relevant cases. Frequently these re-implantations are found in the immediate vicinity of the ovary, tube and uterus[9] but they may occur in any part of the peritoneum,[10] and even in the thoracic cavity, in which case the aorta may be involved.[11] These peritoneal and pleural papillomas were considered by some to be distinct tumors developing independently of the ovarian papillomas, although as a result of the same growth stimulus.[12] This interpretation has been more or less generally abandoned, however in favor of the above-mentioned view according to which they are essentially transplants.

It is noteworthy that occasionally cysts may transplant themselves in a similar manner probably as a result of inoculation from racemose ovarian papillomas.[13]

The outcome of peritoneal papillomatosis will be discussed in the part on prognosis.

C. THE PSEUDOMUCINOUS CYSTOMAS

Macrocystic Pseudomucinous Cystomas. (Synonyms: Gelatinous cystadenoma, pseudocolloid ovarian tumor, colloid ovarian tumor or cystoma, mucoid cyst, pseudomucinous cystadenoma, Zystoid (Förster), Myxoidkystom (Waldeyer), Eierstockskolloid, kyste Wolffian, kyste entéroid de l'ovaire, kyste mucoid de l'ovaire, cystoma ovarii pseudomucinosum, cystoadenoma cylindrocellulare colloides ovarii, pseudomyxoma ovarii).

It is of historic interest that in 1847 Frerichs[14] described under the name of "Gallert und Colloidges-

[1] A70773/10, A70772/10, A70774/13, A66925/13, A69432/13, A70775/14.
[2] A73081/18.
[3] *Rösch* A66930/24.
[4] *Olshausen* A73071/884, A41468/886, *Hofmeier* A73052/888, A73053/892, *Cohn* A73041/888, *Klomp* A73056/891, *Chalot* A44744/893, *Ruge* A70936/895, *Odebrecht* A70874/895, *Buschbeck* A70607/897, *Stone* A73079/00, *Amann* A73031/01, A73032/11, *Hellier and Smith* A73051/02, *Betschmann* A70585/02, *Jayle and Bender* A73054/03, *Frangenheim* A73045/03, *v. Klein* A73055/04, A66925/14, *Bender* A73034/04, A73035/09, *Cova* A80971/04, *Nebesky* A73069/05, *Fromme* A73046/05, *Cornil* A73042/06, *Richolet* A73075/06, *Gerstenberg* A73048/06, *Schmid* A73078/06, *Le Jemtel* A73060/08, A73061/08, *Rochard* A73076/08, *Grasmück* A73049/08, *Bertino* A73037/09, *Bolaffio* A73038/10, *Christidès* A68465/10, *Polakowski* A73074/11, *Leriche* A73062/12, *Mériel* A73064/12, A73065/13, *Albrecht* A80042/13, *Kusuda* A73057/19-20, A73058/25, *Marotta* A73063/22, *Amreich* A73033/22, *Stübler* A70974/24, *Dahlgren* A64419/30, A73044/30, *Lebhardt* A73059/31, *Gilardino* A62300/32.
[5] *Ahlström* A70561/17.
[6] *Baer* B7686/38.
[7] *Pfannenstiel* A70890/895.
[8] *Martin* A70823/886.
[9] *Bryant* A70605/872, *Thornton* A70992/881, *Freund* A42635/889, *Cohn* A70630/00, *Beaussenat and Bender* A70583/02, *Cornil* A70633/05, *Schmidlechner* A93176/06, A82394/08, *Culbertson* A70640/25.
[10] *Dawson* A41636/884, *Mundé* A41992/887, *Dubrueil* A45863/891, *Burt* A45859/891, *Dobson* A44249/892, *Theilhaber* A46438/893, *Veit* A73008/893, *Cazenave* A47330/895, *Zenoni* A50561/898, A50491/898, *Müller* A74610/898, *Heitz and Bender* A70857/00, *Michaux* A70834/00, *Langmann* A74728/01, *Hollinger* A74606/03, *Cardarelli* A74717/05, *Tusini* A71000/05, *Olshausen* A70876/05, *Bertino* A68533/09, A68534/10, *Johansson* A70757/12, *Thompson* B9350/20, *Broun* A70603/23, *Estor and Villa* A70675/24, *Baksht* A62829/32, *Charbonnel and Masse* A62063/35, *Posatti* A61860/35.
[11] *Marchand* A70821/879, *Friedrich* A70711/888, *Heller* A70858/02.
[12] *Tusini* A71000/05, *Shaw* A63285/32.
[13] *Friedrich* A70711/888, *v. Velits* A43324/889, A73010/06, *Pye-Smith* A44668/892-3, *Williams* A73025/894, *Pozzi* A70905/04, A70904/04, *Mansfeld* A70818/07.
[14] A76968/847.

chwülste" a group of tumors consisting mainly of cysts with gelatinous or mucous contents. Later Virchow[1] studied these growths but concluded that the cyst contents are not elaborated by the lining cells. Additional studies of a purely descriptive and morphologic nature were published around the middle of the last century,[2] but these added little to our knowledge concerning the pathologic physiology and pathogenesis of these tumors. Waldeyer[3] believed that the mucinous material is formed by the bodies of degenerating and decomposing lining cells through a process of holocrine secretion. Only much more recently has it been realized that the lining cells actually secrete the pseudomucin-containing cyst contents.[4] It is now generally accepted that there is no essential difference between the macrocystic and microcystic (adenomatous or parvilocular) pseudomucinous blastomas, except that in the former it is secretion, while in the latter it is cellular proliferation that predominates.

Macroscopically the pseudomucinous cystomas prove to be enclosed in a connective tissue wall whose thickness is variable and may measure from a few millimeters to several centimeters. On the cut surface the numerous, pseudomucin-filled cavities are so characteristic that recognition of these tumors usually does not require histologic study. The inner surface of the individual cyst cavities has often been compared to a mucous membrane, such as that of the stomach, intestine or gall bladder. The contents are usually denser in the small cavities than in the large cysts and their consistency varies between that of almost solid colloid-like material and thin mucus. Macroscopically, entirely massive so-called "solid pseudomucinous cystomas" are rare and belong to the microcystic variety.

Macrocystic pseudomucinous multiocular cystomas frequently reach a very large *size*.[5] Pseudomucinous cystadenomas of 20-30 lbs.,[6] 30-40 lbs.,[7] 40-50 lbs.[8] or even considerably more than 50 lbs.[9] have repeatedly been described and probably most of the mammoth tumors discussed in the general section on ovarian cysts belong to this category. On the other hand, minute pseudomucinous cystomas measuring only a few millimeters in diameter have also been reported.[10]

The incidence of *bilateral* development is difficult to estimate in the case of pseudomucinous cystomas since relevant statistical data vary between 1.08% and 24%.[11] A review of 15 statistical surveys led to the conclusion that among 2242 cases of pseudomucinous cystomas described in the literature 214 (or 9.6%) were bilateral.[12]

Most of the macrocystic pseudomucinous cystomas are *multilocular* although *unilocular* cysts of this type have also been described.[13] These probably arise owing to secondary confluence of cyst cavities in originally multilocular tumors. The partial septa and trabeculae found in many of these unilocular cysts appear to be remnants of originally complete separations.

Numerous *case reports* describe the characteristic features of the macrocystic pseudomucinous cystomas.[14]

Microscopically the outer wall is found to consist of two or three fairly distinct layers of different density. The inner layer, which serves as a stroma for the epithelial lining, is usually cellular and rich in blood vessels.[15] It has been claimed that elastic fibers are especially plentiful[16] and even smooth

[1]A77123/848, A77124/859.
[2]*Pagenstecher* A77060/849, *Peaslee* A77064/849, *v. Rokitansky* A77077/853.
[3]A73013/870.
[4]*Lücke and Klebs* A70130/867, *Klebs* 39061/876, *Olshausen* A70876/05, *Pfannenstiel* A64886/08.
[5]*Briskew* A82287/832, *Jackson* A76998/849, *Curling* A76939/861, *Aufriew* A76905/06, *Jones* A69611/06, *Macnaughton-Jones* A77030/06-7, *Jones* B13153/06-7, *Knoop* A77007/08, *Rosenstein* B11273/09, *Koenig* A77008/13-4, *Albrecht* A76900/14, *Maiss* A77032/26, A77034/27, *Pillai* A77069/27, *Velazco Suarez* A96709/28, *Hauptmann* A53166/33, *Hayare* A27743/35, *Gafencu and Gheorghiu* A61482/35, *Evans* A31511/39.
[6]*Dührssen* A76951/897, *Furber* A64642/27.
[7]*Bégouin and Papin* A76911/21.
[8]*Solis* A62177/35.
[9]*Kovats* A77012/33, *Crossen and Soule* A76938/34.
[10]*Schickele* A76879/11, *Spencer* A64842/26, A64894/25-6, *Masson and Hamrick* A65619/30.
[11]*Panas* A77062/871, *Sarazin* A77084/876, *Gross* A76982/13, *Mazet* A77037/14, *Turenne* A81195/15, *Dehelly* A77168/27, *Masson and Hamrick* A65619/30, *Fleming* A64219/31, *Kermauner* A73104/32, *Park* A31348/39.
[12]*Miller* A18279/37.
[13]*Fernbach* A81026/863, *Meyweg* A81049/868, *Waldeyer* A73013/870, *Olshausen* A41468/886, *Mayer* A69828/02, *v. Velits* A73010/06, *Smith* A77099/06, *Kusuda* A73058/25, *Kermauner* A73104/32, *Park* A31348/39.
[14]*Bailly* A81256/854, *Fox* A76965/864, *Förster* A76963/865, *Lücke and Klebs* A70130/867, *Wyman* A77131/868, *Böttcher* A76918/869, *Croly* A76936/876-7, *Rindfleisch* A77076/878, *Breisky* A76921/879, A76922/879, *Jasinskim* A29394/880, *Burgess* A29407/880, A29345/880-1, *Roberts* A29960/881, *Currier* A76940/882, *Cornil and Ranvier* A76935/882, *Heurtaux* A41483/885, *Poupinel* A82021/886, *Sutton* A45130/889, *van der Meij* A77116/889, *Poullet* A45638/890, A69844/891, *Bernhard* A76914/891, *Etheridge* A76955/891, *Cleveland* A45751/891, *Czempin* A76941/894, *Hooper* A47456/895, *Hodgson* A47383/895-6, *Panzer* A77063/899, *Jasinski* A76999/899, *Opitz* A77055/899, A77057/00, *Giltay* A91966/02, *Mauclaire* A81158/04, A81117/04, *Clermont* A81336/04-5, *Cimoroni* A76930/05, *Orlow* A77058/06, *Smith* A77099/06, *Driessen* A76950/08, *Gleiss* A76974/08, A76975/09, *Rosenstein* A77078/10, A77079/12, *Forssner* A76964/12, *Lahm* A77016/14, *Karhausen* A81189/20, *Kuge* A77014/23-6, *Cignozzi* A81209/25, *Tedenat* A77112/26, *Foote* A73601/27, *Murray* A77046/27, *Kimura* A77004/27, *Hertz* A71401/28, *Drennan* A76949/29, *Askanazy* A76907/29, *Masson and Hamrick* A65619/30, *Frank* A76966/33, *di Giacomo* A52112/34, *Fiolle* A61481/35.
[15]*Waldeyer* A73013/870, *Malassez and de Sinéty* A81970/876, *Olshausen* A40742/885.
[16]*Doran* A70475/884.

muscle fibers are often present[1] in the capsule. Unlike serous papillomas pseudomucinous growths rarely contain calcified concretions.[1] The epithelium tends to invaginate itself—in the form of gland-like tubules—into the wall of the large cystomas. These processes have often been compared to Lieberkühn's crypts.[2] Occasionally the epithelial cells form so-called pseudopapillae in the crypts. Unlike the true papillae these formations consist only of irregular epithelial buds without any connective tissue stroma. When thick mucus plugs the opening of small crypts, further secretion of the lining cells gradually enlarges the lumen until a secondary or daughter cyst is formed. Continuous repetition of this process results in the typical multicystic blastomas, that is, the adenomatous portions are transformed into a cystoma.[3] The periphery of the cyst walls is usually irregular, owing to the formation of pseudopapillae of a different type; these consist of a simple connective tissue stroma lined by the pseudomucinous epithelium and are actually partial crescent-like septa within the main cavity which on cross-section resemble papillae.[4] The epithelial cells appear to be situated directly upon the stroma and a membrana propria or limitans is at least not very evident. Such a membrane has been described by some[5] under the name of "sub-epithelial endothelium" but could not be demonstrated by others.[6] The epithelium consists of a single layer of high cylindric cells similar to those of the intestine, cervix uteri, stomach or gall bladder.[7] In certain regions, however, especially at the tips of pseudopapillae, the epithelium may be stratified and one author[8] claimed that circumscribed areas of stratification were detectable in 24% of his cases. The height of the epithelial cells varies between 10-40μ or even 50μ and that of the usually oval, elongated nucleus, between 5 and 12μ[9]. Under the influence of distention caused by rapidly accumulating secretion, the lining cells of the cyst cavity may be stretched and compressed so that they assume a cuboidal or even flat endothelium-like appearance. Such compression of the cells is often seen in the older large cysts but may also occur in small ones, and indeed different areas of the lining within the same cyst may consist of epithelial cells of extremely variably height. The cytoplasm is rather uniform and eosinophilic, although slight granulations are often seen in the vicinity of the nucleus. The number of goblet cells is variable, sometimes all the lining cells of a cavity are of this type, while at other times only a few of them are interspersed between the other columnar cells. Their nucleus is sickle shaped and closer to the lumen than that of the common cylindric cells.[10] Resting epithelial cells are low cylindric and contain no pseudomucin. During mucus formation the fine granular cell contents become homogeneous and increasingly more abundant so that the cell becomes larger and filled with a transparent mass of pseudomucin which is subsequently excreted into the lumen. After this the process is repeated and the cell goes through these same changes again.

It is of special interest that many pseudomucinous cystomas (especially the microcystic variety) contain *argentaffin cells* similar to those found in the intestine.[11] This has been interpreted as supporting the view that they are of entodermal origin. Pseudomucinous cysts containing large amounts of *melanin-like pigment material* ("Abnützungspigment") are rare; they may resemble melanosarcomas.[12]

Pseudomyxoma ovarii. (Synonyms: myxoma of the ovary, Geleetumor). This blastoma type represents a modification of the common pseudomucinous cystoma. It is characterized by the fact that the cyst contains the extremely thick, almost solid, pseudomucin β and the walls are exceedingly thin and brittle.[13] These tumors do not often reach a large size because of their great tendency to rupture. Most of the pseudomyxoma peritonei cases (see below) arise from ovarian tumors belonging to this group (see also mucoid degeneration of stroma in section on Secondary Changes in Ovarian Fibromas).

The pseudomyxoma ovarii is comparatively often *bilateral*.[14] Not infrequently, after the removal of one ovary for pseudomyxoma, the remaining gonad becomes similarly affected.[15] Occasionally, pseudomyxoma ovarii on the one side is associated with the development of a cystocarcinoma on the other side.[16]

Histologically the pseudomyxoma ovarii does not differ in any important respect from the ordinary

[1]*Kuge* A77014/23-6.
[2]*Fox* A76965/864, *Lücke and Klebs* A70130/867, *Waldeyer* A73013/870, *Malassez and de Sinéty* A81970/876, *Klebs* 39061/876, *Olshausen* A40742/885.
[3]*Böttcher* A76918/869, *Waldeyer* A73013/870.
[4]*Glockner* A70013/04, A70014/05.
[5]*Malassez and de Sinéty* A81970/876, A29383/879-81.
[6]*Böttcher* A76918/869, *Fox* A76965/864, *Waldeyer* A73013/870.
[7]*Lücke and Klebs* A70130/867, *Waldeyer* A73013/870, *Stoecklin* A96061/899, *Glockner* A70014/05, *Pfannenstiel* A64886/08.
[8]*Shaw* A61896/33.
[9]*Miller* A18279/37.
[10]*Böttcher* A76918/869, *Miller* A18279/37.
[11]*Masson* A95406/38.
[12]*Lahm* A77018/24, *Lippmann* A77027/24, *Liepelt* A96711/28.
[13]*Netzel* A42129/885. *Pfannenstiel and Krömer* A76283/890, A64886/08, *Lauwers* A74590/899-00, *Gebhard* A73657/899, *Pfannenstiel* A80267/05, *Hofmeier* A77212/05, *Ahlström* A77135/09, A77137/16-7, A77138/17, *Saeki* A65628/28.
[14]*Runge* A41821/887, *Reh* A77276/896, *Toth* A77308/896, *Kretschmar* A77226/897, *Westphalen* A77322/899, *Kapp* A77220/00, *Santlus* A77286/02, *Marchand* A77239/07, *Ahlström* A77135/09, *Goursolas* A77194/11, *Fränkel* A77185/12, *Jablonski* A77217/21, *Dehelly* A77168/27, *Sauvé* A77287/27, *v. Nagy* A77254/33.
[15]*Korn* A41505/885, *Martin* A78665/899, *Kapp* A77220/00, *Polano* A77270/01, *Hofmeier* A77212/05, *Ahlström* A77135/09, *Goursolas* A77194/11, *Schilling* A77288/11, *Westermark* A77320/11.
[16]*Masson and Hamrick* A65617/30, A65618/30.

pseudomucinous cystadenoma except that at certain points the "colloid" contents tend to erode the lining epithelium and to infiltrate between the connective tissue fibers of the cyst wall. This prepares the cystoma for rupture.[1]

On the basis of the available data it would appear more justifiable to consider the pseudomyxoma ovarii not as a distinct tumor type but rather as a variety of the common pseudomucinous cystadenomas.

Microcystic (or Parvilocular) Pseudomucinous Cystomas. (Synonyms: Pseudomucinous adenoma, parvilocular pseudomucinous tumor, solid adenoma of the ovary, pseudosolid adenoma of the ovary, pseudomucinous tubular adenoma, pseudomucinous adenofibroma, "épithelioma Wolffien"; if partly macrocystic: pseudomucinous cystoadenoma.)

It is of historic interest that Pfannenstiel[2] was probably the first to call attention to the rare macroscopically solid pseudomucinous adenoma of the ovary. Several subsequent investigators described similar tumors in which some cysts were of a macroscopically visible calibre while other portions were solid, as judged by the naked eye, but revealed themselves as adenomatous upon histologic study.[3]

Macroscopically the microcystic pseudomucinous cystoma exhibits no typical features other than its solid, sometimes porous structure. Microscopically it is characterized by small gland-like cystic cavities lined by a pseudomucinous epithelium (sometimes with argentaffin cells) and embedded in a rather dense fibrous stroma.[4] It may be the site of papillomatous proliferations and malignant transformation. This type is termed by Schiller[5] "parvilocular cystoma". From it he differentiates the "parvilocular adenofibroma" which presents duct-like or gland-like tubules, also embedded in a fibromatous stroma and probably originating from the rete ovarii. In spite of the morphologic similarity between this latter tumor and the arrhenoblastoma or testicular adenoma of the ovary, Schiller[5] believes that the non-virilizing type should be separated. Be this as it may, the adenofibroma contains few or no pseudomucin-producing cells and hence in this Encyclopedia we list it among the serous blastomas.

Schiller[5] also emphasized that some of the tumors described in the early literature as examples of the microcystic pseudomucinous cystoma were actually atypical Brenner tumors, metastatic ovarian carcinomas, adenofibromas, etc., a fact which should be borne in mind in connection with the evaluation of purportedly relevant case reports.

In this connection special attention is called to the so-called "épithélioma Wolffien" or *Wolffian epithelioma.* This tumor is frequently mentioned and plays a prominent role in the French literature, yet practically no reference is made to it in other than French publications. It is described as a pseudosolid blastoma which is greyish, reddish or marble white on the cut surface. Histologically it consist of solid epithelial nests, papillae and tubes lined with cuboidal or cylindric cells whose nucleus is basally located and whose cytoplasm gives a positive pseudomucin reaction. These tumors are frequently malignant; they contain no Leydig cells and do not lead to clinical manifestations of virilism.[6] One such tumor was associated with adenomyosis of the uterus and endometriosis of the Fallopian tube[7] and some of the so-called "mesonephric cystomas" are strikingly similar to adenomyosis.[8] The tumor described by Lallemant[9] as an ovairan *carcinoma originating from remnants of the mesonephros* bears a certain resemblance to the Wolffian epithelioma. The same is true of the *mesonephroma* although the latter contains little if any pseudomucin and tends to form renal glomerulus-like structures so that it is readily distinguishable from the microcystic pseudomucinous blastomas.

Unfortunately the many pathologists who expressed the view that certain ovarian blastomas may be of mesonephric origin, generally failed to consult each other's papers and to correlate their observations. Hence the relevant literature is hopelessly confusing and gives the erroneous impression of numerous distinct blastoma types when actually the tumors belong to one or the other recognized class listed in this Encyclopedia. A survey of the literature fails to reveal adequate reasons necessitating the separation of the "Wolffian epithelioma" from pseudomucinous adenomas and adenocarcinomas of the ovary; hence it is listed as belonging to this latter group. Some of the serous "mesonephric cysts", on the other hand, are common serous microcystic blastomas, while others are ovarian "endometriosis cysts", parvilocular adenofibromas or rete cysts. The mesonephroma of Schiller exhibits rather outstanding characteristics which indicate that it may be a special tumor entity, but efforts to distinguish

[1] *Ahlström* A77135/09, *Miller* A18279/37.
[2] A64886/08.
[3] *Glockner* A70013/04, A82184/04, A70014/05, *Koenig* A77008/13-4, *Kermauner* A73104/32, *Miller* A18279/37.
[4] *Popoff* A65626/30, *Masson* A95406/38, *Calkins and True* A97535/41.
[5] A57680/43.
[6] *Jacquot and Fairise* A78470/13, *Masson* A64790/23, *Rouville et al.* A78926/24, *D'Allaines and Bertrand* A77962/24, A77963/24, *Rouville and Carrera* A78925/24, *Madon and Guibal* A78648/24, *Leveuf and Heraux* A78604/26, *Delannoy and Breton* A78199/26, *Martin and Noël* A78666/27, *Corsy and Montpellier* A78174/27, *Müller* A78743/31, A64397/31, *Wallart and Scheidegg* A52194/34, *Portes and Isidor* A52276/34, *Varangot* 68667/37, *Delannoy et al.* A95056/37, *de Girac* A97198/38.
[7] *Hamant et al.* A78397/29.
[8] *Kossmann* A70779/895, *v. Babo* A83478/00, *Vassmer* A83484/01.
[9] A78570/19.

other mesonephric cysts are merely confusing.

It is important to emphasize in connection with these tumors, that the term "épithélioma" is almost never employed by French pathologists to denote benign tumors. Hence it may be assumed that cases described as "épithélioma Wolffien" were always interpreted as malignant even if this was not specified in the pertinent publications. It is only for didactic reasons that we discuss this blastoma type in conjunction with the similar benign neoplasms.

Pseudomucinous Papillomas. While serous papillomas are very common, pseudomucinous cysts rarely form papillary excrescences. Yet the cystoma pseudomucinosum papillare (or cystadenoma proliferum papillare colloides) has long been recognized as a special type of the pseudomucinous cystadenoma which *macroscopically* resembles the velvety surface of intestinal mucosa.[1] These cystomas frequently reach a very large *size*[2] and in about 50% of the cases they develop bilaterally.[3] Generally their surface is smooth or nodular and only rarely do the papillae penetrate to the surface.[4]

Microscopically the epithelium of the pseudomucinous papillomas is considerably different from that of the serous papillary cystomas. The cells are high cylindric with basally located nuclei and some of them exhibit the typical pseudomucinous goblet cell appearance.[5] The pertinent cases described in the literature clearly identify such papillomas as a modification of the common pseudomucinous cystadenoma.[6]

Re-implantation of individual detached papillae in various parts of the peritoneum has been noted in a few cases,[7] but this complication is much more rare than in the case of serous papillomas. The condition which in the series of the pseudomucinous cystomas usually corresponds to the peritoneal generalization of the serous papilloma, is the pseudomyxoma peritonei.

Pseudomucinous Racemose Cystomas. Racemose cystomas such as those described in the serous series are extremely rare among the pseudomucinous blastomas. Their occasional occurrence is clearly shown, however, by several relevant *case reports.*[8] The individual "grapes" may reach a diameter of several inches and they are usually attached to the branches of the main stalks by comparatively thin pedicles.

Microscopically the pseudomucinous cystomas of this group reveal themselves as "true" racemose blastomas inasmuch as each individual "grape" represents a daughter cyst with a separate fluid cavity and both internal and external epithelial linings. The epithelium is typical of the pseudomucinous cystomas in general and hence does not require detailed consideration.

Pseudomyxoma Peritonei. (Synonyms: Werth's tumor, gelatinous ascites or peritonitis, maladie gélatineuse du péritoine, kyste ovarique avec ascites gélatineuse, enfermedad gelatinosa del peritoneo, mixoma del peritoneo, peritonitis pseudomyxomatosa gelatinocölothelioma, Gallertbauch, myxomatöse Entartung des Bauchfells, peritonitis chronica productiva myxomatosa).

The *history* of pseudomyxoma peritonei goes back to the middle of the last century. At that time several pseudomucinous cystomas, which ruptured into the peritoneum causing a gelatinous type of "peritonitis" were described.[9] The condition received only sporadic attention, however, until Werth[10] described it under the name of "pseudomyxoma peritonei".

The characteristic feature of this condition is that following rupture of a pseudomucinous ovarian cystoma, the slippery, jelly-like contents are evacuated into the peritoneal cavity. Here they are widely distributed owing to the peristaltic movements of the intestine, and continued secretion of fluid soon leads to considerable distention of the abdomen. As has been mentioned above, the pseudomyxoma ovarii type of cystoma is most prone to undergo rupture and thus to produce pseudomyxoma peritonei. The thick semi-solid, jelly-like secretion is not readily absorbed by the peritoneal epithelium and tends to produce a foreign body peritonitis. The serosa epithelium proliferates and its cells tend to desquamate. Then on the hyperemic peritoneal surface small roe-like nodules are formed which histologically reveal themselves as foreign body tubercles. Subsequently, granulation tissue invades the gelatinous masses and organizes them through penetrating connective tissue and blood vessels. These partially organized masses, as well as unorganized (sometimes continuously newly-formed) secretion, more or less completely fill the peritoneal cavity. The pseudomucinous material is gradually absorbed and removed through the lymphatic channels which may become plugged by the gelatinous

[1] *Olshausen* A40742/885, *v. Velits* A73010/06.
[2] *Miller* A18279/37.
[3] *Fromme* A73046/05, *Broun* A76927/08, *Stübler and Brandess* A76588/24, *Miller* A18279/37.
[4] *Pfannenstiel* A70890/895, *Frank* A76966/33.
[5] *v. Velits* A43324/889.
[6] *Byford* A76928/887, *Gavrilko* A75301/895, *Semb* A70956/896, *Wojnicz* A77130/27, *Webber* A77127/31, *Brandberg* A66145//32, *Albertz* A97343/38.
[7] *Pfannenstiel* A70890/895, *Fromme* A73046/05, *v. Velits* A73010/06.
[8] *Rüder* A77283/896, *Herrmann* A76992/01, *Meyer* A73067/12, *Mulier* A73068/13, *Moench* A77333/18, *Kusuda* A73057/19-20, *Hirschenhauser* A77328/21, *Stübler and Brandess* A76588/24, *Kaufmann* 39132/31.
[9] *Blasius* A81007/834, *Kilian* A77003/849, *Ogle* A77261/857-8, *Jackson* A69319/859.
[10] A77319/884.

masses. Occasionally, the pseudomucinous epithelium itself invades the peritoneal organs and continues to produce its secretion within them even if the tumor is not manifestly malignant. Re-implantation of pseudomucinous epithelium in various parts of the peritoneum results in intermediate forms between the ordinary pseudomyxoma peritonei and the pseudomucinous peritoneal papillomatosis described in a previous section.[1]

The clinical manifestations of this condition will be considered in the section dealing with those complications of ovarian cystomas resulting from rupture. Suffice it here to say that in certain cases the entire peritoneum may be transformed into glassy, myxomatous masses of organized secretion, a process indicative of healing.[2]

Numerous *case reports* describe the various forms of pseudomyxoma peritonei.[3]

The Propagation of Benign Ovarian Cystomas. Peritoneal propagation of ovarian cystomas received special consideration in the passages entitled peritoneal serous papillomatosis and pseudomyxoma peritonei because the peritoneal generalization of the serous papilloma by re-implantation of detached particles and of the pseudomucinous cystomas by rupture form important and rather well defined pathologic entities. The clinical implications of the perforation of serous and pseudomucinous cysts, either into the peritoneal cavity or into neighboring hollow organs, will be given attention in the part dealing with the complications of ovarian cysts. Here we shall merely consider certain general problems raised by the spread of the cystomas.

Probably many of the cases reported in the literature as examples of *metastases of benign ovarian cystomas* actually occurred following malignant transformation. Yet the possibility of such metastases must be kept in mind even when dealing with cysts which show no manifest signs of malignancy.[4]

During their growth most common cystomas of the ovary expand merely into the peritoneal cavity and, even if their surface is not completely free, they are connected with neighboring organs only by adhesions. A considerable number of common cysts, however, show what has been termed "*intraligamentous development*".[5] According to Miller,[6] who surveyed the statistical data given by 11 independent observers, among 3629 ovarian tumors (mainly cystomas), 440 (or 12.1%) proved to exhibit this type of growth.

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[1]*Miller* A18279/37.

[2]*Schley* A77291/31.

[3]*Bristowe* A82343/860-1, *Simpson* A82052/861-2, *Hutchinson* A77215/862-3, A77216/865-6, *Cayley* A77164/867-8, *Spiegelberg* A77299/870, *Grove* A82472/870, A81549/871, *Menzel* A77245/873, *Beinlich* A82329/875, *Smith* A77297/878, *Péan* A77265/880, *Mennig* A77244/880, *Mayer* A77242/880, A40604/882, *Bozeman* A40211/882, *Netzel* A77256/883, *Baumgarten* A74968/884, *Werth* A77319/884, *Macdonald* A77238/884-5, *Olshausen* A40742/885, *Mundé* A40738/885, *Negri* A40981/885, A77255/885, A42723/888, *Parish* A40836/885, *Schlegtendal* A41033/885, A42071/886, *Korn* A41505/885 *v. Swiecicki* A77301/885, *Runge* A42005/885, A41821/887, *Donat* A77171/885, *Geyl* A77186/887, *Neubauer* A77258/888, *Rosoff* A77280/889, *Westermark and Annell* A45268/889, *Hammarsten* A45792/890-1, *Oliver* A45845/891, *Rosinski* A77279/891, *Strassmann* A44005/891, *Fränkel* A44025/891, A77184/01, A77185/12, *Lair* A77232/892, *Duffner* A44605/893, *Bettmann* A77150/893, *Ratschinsky* A77275/895, A77273/895, A77274/897, *Hertz* A77206/895, *Tait* A47396/895, *Mendes de Leon* A77243/896, *Reh* A77276/896, *Rüder* A77283/896, *Tóth* A77308/896, *Wendeler* A77318/896, A47413/896, *Boursier* A48297/896, A49043/897, A48986/897, *Kretschmar* A77226/897, *Jasinski* A77219/897, *Grisson* A77196/897, *Peters* A77266/898, A77267/899, *Herczel* A77205/898, *Westphalen* A77322/899, *Kapp* A77220/00, *Lauwers* A77234/00, A77233/00, *Eiger* A77177/00, *Villar* A81518/00, *Weber* A77317/01, A77316/01, *Smith* A77296/01, *Lewitzky* A77236/01, *Polano* A77270/01, *Leo* A77025/02, *Santlus* A77286/02, *Mond* A77246/02, A77247/02, *Götte* A77189/03, *Morton* A66990/04, *Chavannaz* A76929/05, *Brokesch* A77161/05, *Roche* A92121/05, *Bender* A77149/05, A80939/05, *Beckh* A77147/05, *Hörmann* A74615/05, A77211/06, *Constantinesco* A74719/05-6, *Lorrain and Chardon* A77237/06, *Brothers* A77162/06, *Hirst* A77209/06, *Amann* A77139/06, A77140/10, A76903/10, *Häberle* A77199/06, *Barbour* A77146/06-7, *Marchand* A77239/07, *Muret* A77251/07, *Chevillotte* A77165/07, *Hahn* A77200/07, *Schumann* A77293/08, *Brewitt* A77159/08, A77160/08, *Kummer* A77230/09, *Pollosson and Violet* A77070/09, *Ahlström* A77135/09, A77137/16-7, A77138/17, *Askanazy* A77142/09, *Schilling* A77288/11, *Westermark* A77320/11, *Goursolas* A77194/11, *Wilson* A77324/12-3, *Tedenat* A77302/13, *Christiani* A77166/13, *Abadie* A77133/13, *Ekler* A77178/13, *Fischer* A77182/13, *Boldt* A77154/13, *Jäger* A77218/14, *Goldschmid* A77190/14, *Fatscher* A77180/14, *Fleischer* A76961/16, *Bailey* A77144/16, *Küster* A77228/18, A77229/18, *King* A77221/19, *Bigga* A77151/20, *Jablonski* A77217/21, *Krivsky* A77227/21, *Holstee* B11676/22, *Novak* A77259/22, *Bell* A76913/23, *Albrecht* A76901/25, *Buzzi* A81206/25, *Körner* A77223/26, *Lehmann* A77235/26, *Gierke* A77187/26, *Bolaffio* A77153/26-7, *Hedley* A77202/27, *Sauvé* A77287/27, *Hamdi et al.* B8199/27, *Dougal* A77173/27-8, *Otto* A77263/28, *Gräfenberg* A77195/28, *Hornung* A96779/28, *Heijl* A77203/28, *Lahm* A77231/29, *Baniecki* A77145/29, *Condamin and Brunat* A65910/29, *Masson and Hamrick* A65618/30, A65617/30, *Dougal* A77174/31, *Tessi Teitun* A64021/31, *Padgett* A64011/31, *Dieker* A66153/31, *Moulonguet* A77249/32, *Behrend* A66103/32, *v. Öttingen* A77260/32, *Shaw* A61896/32-3, *Blanc Fortacin* A62284/32, *Lenormand* A61397/33, *Gubern Salisach* B12361/33, *Antoine* A28090/35, *Bracco* A61842/36, *Decoulx and Patoir* A96014/37, *Soupault* A77298/38, *Decoulx and Bastien* A97047/38, *Imbert and Guidoni* A95364/38, *Laignel-Lavastine and Duguet* A96620/40.

[4]*Virchow* A73011/857, *Coyne* A68416/874, *Winternitz* A73027/888, *Schnutgen* A68530/18, *Miller* A18279/37.

[5]*Raffa* A29337/880, *Faber* A75952/883, *Terrier* A40907/884, *McMurtry* A41834/887, *Byford* A41709/887, *Terrillon* A42281/888, *Reed* A86268/888, *Goodell* A42199/888, *Delbet* A80972/888, *Fani* A42664/889, *Hofmokl* A43273/889, *Concato* A43389/889, *Keene* A80950/889-90, *Skene* A43404/890, *Noble* A45600/890, *Kollock* A45867/890, A45795/890-1, A69618/891, *Frank* A44200/892, *Brigidi* A44582/893, A48262/896, *Tansini* A47151/894, *Naumann* A47411/896, *Gilliam* A50636/898, *Norris* A82681/899, *van Dyk* A66975/01, *McReynolds* A81115/02, A81116/02, *Jaboulay* A82665/04, *Bérard and Patel* A81320/05, *Martin* A81088/09, *Riotte* A81104/24, *Weiller* A62539/32.

[6]A18279/37.

In the individual series surveyed by this investigator the percentual incidence of intraligamentous development varied between 4.5 and 21.3%. These data indicate that it is by no means uncommon for an ovarian neoplasm—especially a cystoma—to grow through the mesovarium into the broad ligament. This type of development is of special interest to the surgeon and has been discussed in some detail in the section concerned with the para-ovarian cystomas. It appears logical to discuss the true ovarian cystomas with intraligamentous development and the independent, primarily intraligamentous neoplasms conjointly, since in many individual instances it is practically impossible, to differentiate between the two types.

The cause for this intraligamentous development is that the cystomas grow mainly on the hilus side of the ovary into the mesovarium and broad ligament. On their anterior surface such intraligmentous ovarian cysts are covered by the anterior, and on their posterior surface by the posterior lamina of the broad ligament. The posterior lamina of the broad ligament is gradually displaced, however, by the growing neoplasm so that it first comes to lie on the upper and later actually on the posterior surface of the tumor. The two layers of the mesentery or mesosigmoid between which the cystomas spread also add to its dorsal covering and eventually the dorsal surface of the cyst is enveloped by four layers, namely the posterior and anterior layer of the broad ligament, as well as the two layers of the mesosigmoid.[1]

Lateral expansion may bring the tumor into direct contact with the uterus on the one side and the bony pelvis on the other. In the case of very large intraligamentous tumors the entire pelvic peritoneum may be lifted upwards towards the abdominal cavity. Caudal and dorsal (posterior) expansion brings the growth into the mesorectum and between the rectum and vagina.[2] Frontal (anterior) expansion introduces the neoplasm into the para-vesical subserous space and when it reaches a considerable size in this location the tumor raises the bladder craniad.[3] Extensive growth of an intraligamentous tumor leads to considerable elongation of the oviduct and compression of the uterus, urinary bladder and rectum.[4]

Bilateral intraligamentous ovarian cystomas may reach a considerable size so that the fundus of the uterus cannot be palpated. In such instances the uterus is entirely immobilized in the pelvis, a condition similar to that seen in the event of extensive pelvic exudates.[5]

In the case of *atypical intraligamentous development* the ovarian neoplasm may grow into the ligaments on one pole and freely into the peritoneal cavity on the other, thus expanding in both directions simultaneously,[6] or it may cause atrophy of its coverings, due to stretching of the peritoneum, and grow into the peritoneal cavity without any distinct covering.[5]

In the case of serous papillomas, propagation under the peritoneum into the broad ligament[7] and into the retroperitoneal tissue towards the mesosigmoid[8] is not uncommon. Furthermore papillomas of one ovary may be transposed to the other side and develop in this abnormal location.[9]

Pseudomucinous cystomas may grow in Douglas' space and become impacted behind the uterus.[10] Intraligamentous development is perhaps somewhat less frequent than among the serous cystomas and occurs only in about 7% of the cases, as judged by a statistical analysis of 896 pseudomucinous cystomas.[4] In some instances, pseudomucinous cysts spread between the laminae of the peritoneum towards the mesosigmoid or mesorectum.[11]

The papillary pseudomucinous cystomas may elicit secondary cysts in the *spleen*.[12] In these cases it is very probable that propagation does not occur through the lymph or blood vessels but by direct re-implantation through the peritoneum.

The *appendix* is especially frequently the site of a pseudomucinous growth in pseudomyxoma peritonei.[13] If both the ovary and the appendix are similarly affected it may be impossible to ascertain the origin of the lesions, since the appendix may also form primary pseudomucinous cysts, the rupture of which can cause pseudomyxoma peritonei. This appendicular involvement will receive further consideration in the part dealing with the pathogenesis of pseudomyxoma peritonei. Infiltration of the *oviduct* and *uterus* is likewise common.[14]

[1] *Vanverts and Paucot* A81196/11, *Gaston* A97680/39.
[2] *Jean and Villechaize* A97225/39.
[3] *Forgue and Crousse* A91555/25.
[4] *Miller* A18279/37.
[5] *Olshausen* A41468/877-86.
[6] *Kaltenbach* A82925/875-6.
[7] *Walla* A69462/01, *Jordan* A70760/14.
[8] *Brook* A75291/04, *Redlich* A70919/09, A70920/09, *Pullmann* A81099/09, *Naegeli* A81091/17, *Chalier* A81207/22, *Astier* A59643/36.
[9] *Pi-Figueras* A61291/35.
[10] *Körver* A77009/04, *Shaw* A61896/33.
[11] *Frank* A76966/33.
[12] *Polano* A77270/01, *Myer* A77252/07, *Schultze-Heubach* A77091/21, *Brandberg* A66145/32.
[13] *Krug* A77013/891, A44029/891-2, *Albertin* A76899/09, *Eden* A77176/12, *Bondy* A77155/13, *Rathe* A77272/13, A77271/13, *Gorke* A77191/17, *Hartmann and Binet* A77201/18-9, *Donald* A77170/22, *Dougal* A77172/22, *Müller* A81229/23-4, *Richter* A77278/24-5, *Ferguson* A77181/24-5, *Körner* A77222/25, *Fairbairn and Sims* A77179/27-8, *Hornung* A77213/28, *Lieblein* B12291/29, *Schulze* A77292/29, *Hudacsek* B12282/29, *Dietl* A77169/30, *Loven* B1057/31, *Alberti* B1044/31, B21631/31, *Monod and Vuillième* B21656/31, *Nagy* A77254/33, *Bittmann* A97232/39.
[14] *Meyer* A77041/06, *Kitai* A77005/25, *Miller* A18279/37.

On the other hand, the exceptional involvement of *lymph nodes* in pseudomyxoma peritonei[1] is highly suggestive of malignancy.

SECONDARY CHANGES IN COMMON OVARIAN CYSTOMAS AND IN THE REMAINING OVARIAN TISSUE: The common ovarian cystomas are frequently connected by strong *adhesions* with adjacent organs such as the oviduct, uterus, mesentery and the intestines. This is of practical importance because of the possible resulting interference with the function of other peritoneal organs and the difficulties encountered in connection with the surgcial removal of the growths.[2]

In the surroundings of serous cystomas adhesions were observed in about 31-56% of the cases.[3] It must be kept in mind, however, that different observers may or may not include a certain case in this group if the adhesions are inconspicuous. Among the serous papillomas, more than 50% form adhesions, according to most statistics.[4] In some cases, bilateral papillomas tend to fuse.[5] The adhesions of papillomas may be so widespread and dense that the peritoneal cavity is almost completely obliterated; this leads to very severe complications in the event of attempted operative removal of the growths.[6]

Among the pseudomucinous cystomas, adhesions are particularly frequent. In certain series they have been found in as many as 69% of the cases[7] and a review of more than one thousand relevant instances showed that the average incidence is 41.6%.[4] The cystoma may adhere to the liver,[8] the appendix,[9] the bladder[10] or the intestines[11] and in the event of bilateral cystomas the two tumors may fuse.[12]

Among the *secondary changes* which may occur in ovarian cystomas, necrosis and gangrene are the most important.[13] These are usually due to circulatory disturbances which interfere with the nutrition of the growths. Torsion of the pedicle is one of the most common causes of massive necrosis involving the entire cystoma and may also lead to its hemorrhagic infarction (see chapters on Torsion and Hemorrhage in Sect. IV, Vol. VI).

Among the *serous papillomas* fatty degeneration of the cyst wall (reminiscent of that seen in arteries) has been noted[14] and pseudoxanthoma cells are frequently visible under the epithelium.[15] It is important to distinguish these from corpus luteum cells with which they have often been confused. Hyalinization of the cystoma wall[16] or the stroma of the papillae[17] may also occur. The so-called "myxomatous" degeneration of the stroma, to which many investigators refer, is actually a stroma edema and has been discussed in the passage on serous racemose cysts as the "false racemose cystoma". Calcification of degenerated cells leads to the formation of the psammoma bodies described above. (Massive calcification is treated in the chapter on Calcification in Sect. IV, Vol. VI).

In *pseudomucinous cystomas* liquefaction necrosis results in the formation of cavities which contain pus-like necrotic material instead of the usual gelatinous contents.[18]

Fatty degeneration tends to affect the epithelia of the pseudomucinous cystomas more than their connective tissue stroma[19] and fatty droplets, cholesterol crystals, as well as degenerating epithelial cells are almost constantly found within the cyst contents.[4] Severe progressive degeneration with complete loss of the typical tumor structure in some areas has been observed in 15% of the cases in certain series.[15] Fatty degeneration of the cystoma wall frequently leads to subsequent calcification and causes histologic changes similar to those seen in atheromatous arteries.[14]

In *pseudomyxoma ovarii* extensive degeneration and necrosis of septa and the external wall of the cystoma are common precursors to subsequent rupture which is so frequent in this type of pseudomucinous cystoma.[20]

In *pseudomucinous papillomas* partial necrosis may also occur.[21] As stated above in connection with the serous papilloma, the so-called myxomatous degeneration of the papillae is actually a simple stroma edema.[22]

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[1] *Ahlström* A77136/10.
[2] *Krvszk* A69323/852, *Barratt* A81265/865-6, *Pouillet* A82510/869, *Auerbach* A82309/874, *Weinlechner* A75227/874, *Noegerath* A29727/881, *Polk* A68867/882, *Terrillon* A41515/883, A45153/889, *De Rombaix* A69579/888, *Hofmokl* A43277/889, *Jentzer* A45125/889, *Braun* A43408/890, *Coutourier* A47332/895, *Wathen* A48257/895-6, *Pillet* B9420/07.
[3] *Lippert* A76008/05, A64789/05, *Miller* A18279/37.
[4] *Miller* A18279/37.
[5] *Martin* A70825/852 *Marchand* A70819/880, *Stewart* A46510/893, *Mansfeld* A70818/07, *Labhardt* A70782/31.
[6] *McLean* A70809/892, *v. Velits* A73010/06, *Malcolm and Gibb* A70816/21.
[7] *Lippert* A76008/05, A64789/05.
[8] *Bernhard* A76914/891, *Gibson* A61557/33.
[9] *Martin* A77033/870.
[10] *Thomas* A77115/881.
[11] *Terrier* A77113/875, *Lapeyre and Mendez-Liamozas* A53049/34.
[12] *Amann* A70566/01.
[13] *Harvey* A45090/888, *Laroche* A47107/894, A44636/894, *André and Michel* A47990/898, *André* A50492/898, *Benton* A69544/02, *Chambers* A81208/14, *Nürnberger* A61888/32.
[14] *Fox* A76965/864, *Malassez and de Sinéty* A29383/879-81.
[15] *Shaw* A61896/33.
[16] *Kirchner* A70770/895, *Spencer* A70963/23.
[17] *Kirchner* A70770/895, *Müller* A70861/898, *Shaw* A61896/33.
[18] *Pfannenstiel* A76283/890, *Glockner* A70013/04, A70014/05.
[19] *Waldeyer* A73013/870, *Wells* A81301/02.
[20] *Ahlström* A77136/10, A77137/16-7, A77138/17, *Nagy* A77254/33.
[21] *Gosopath* A76980/24.
[22] *Pfannenstiel* A70890/895, *Shaw* A61896/33.

Sarcomatous degeneration of the stroma may also occur in various common cystomas.[1]

The *ovarian remnant* may remain approximately normal in spite of the development of large cystomas and this accounts for the fact that even voluminous bilateral cystomas do not necessarily result in menstrual disturbances or sterility. In most cases, however, the ovarian parenchyme is compressed or stretched by the tumor and merely represents a nodule in the cystoma wall. Secondary changes due to torsion of the cyst pedicle, infection, hemorrhagic infarction, etc. are discussed in the chapters specificially concerned with torsion, inflammation, hemorrhage etc. in Sect. IV, Vol. VI.

Serous cysts usually replace the entire ovarian parenchyme after they reach a certain size.[2] *Serous papillomas* frequently affect the ovary inasmuch as part of its tissue is actually transformed into the blastoma and the remainder merely forms the base of the papilloma; it may only be recognizable upon histologic examination, although occasionally it is fairly well preserved.[3]

Pseudomucinous cysts tend to be sharply demarcated from the ovarian remnant which appears in the wall of the cyst in the form of a funnel-shaped or disk-like body.[4] In such cases the ovarian stroma usually contains normal primary follicles as well as mature follicles and even corpora lutea.[5] The ovary may be found in the vicinity of the cyst pedicle or at some distance from it, sometimes even on the opposite pole.[6] The "*pseudomyxoma ovarii*" type of tumor usually destroys most of the ovarian tissue although occasionally remnants of it are detectable.[7] *Racemose pseudomucinous cystomas* affect the ovarian remnant in approximately the same manner.[8]

The *pedicle* is extremely variable in all types of cystomas. It may be unusually long and hence highly predisposed to torsion, or it may be thick and short; indeed, in many cases there is no definite pedicle. It must also be emphasized that since in most cases the ovary forms part of the tumor, the macroscopically visible pedicle is usually not merely the stalk of the tumor itself, but that of the affected ovary as well.[3]

COMMON CYSTOMAS IN COMBINATION WITH OTHER OVARIAN TUMORS: In patients with common ovarian cystomas other ovarian tumors develop with unusual frequency. Thus simultaneous development of *dermoids and common ovarian cysts* is often seen.[9] The most common combination is that of *dermoids and pseudomucinous cysts* which is sometimes referred to as a "muco-dermoid cyst".[10] In these instances it has been assumed by some investigators that the pseudomucinous part of the blastoma is the result of cystic degeneration of gastrointestinal tract segments in the embryoma. However, combination of *dermoids with serous cysts*[11] and especially *dermoids with serous papillomas*[12] is likewise not rare. Furthermore, there may be a *dermoid in one and a common (serous or pseudomucinous) cyst in the other ovary.*[13] In some of these cases, bilateral common cysts are combined with a dermoid on one side, or bilateral dermoids with a common cyst on one side. The great frequency of dermoids in combination with other tumors as well as that of bilateral common cysts and bilateral dermoids (see also section on dermoids) is strongly indicative of some inherent predisposition for tumor formation in patients bearing such growths.

[1] *Elder* A41606/883, *Friedländer* A77501/891, *Eden* A77465/893, *Vineberg* A44760/894, *Cullen* A48387/896, *Fairbairn* A74743/898, A73551/899, *Freund* A65991/899, *Cohn* A70630/00, *Limnell* A70119/01, *Alcock* A77343/03, *Krebser* A77607/03, *Potocki and Bender* A82172/04, A77752/04, *Taylor* A77843/05, B13103/06, *Abadie and Bender* A77338/05, *Gardner and McLeary* A79969/08, *Krömer* A70091/08, *Pucher* A77757/09, *Wermuth* A77897/10, *Andres* A76904/19, *Kusuda* A73058/25, *Naeslund* A79988/30, *Mahfouz Bey* A64189/31.

[2] *Shaw* A61896/33.

[3] *Miller* A18279/37.

[4] *Stratz* A70395/894.

[5] *Sänger* A77083/879.

[6] *Kermauner* A73104/32.

[7] *Gottschalk* A77192/01, A81132/01-2, *Ahlström* A77137/16-7, A77138/17.

[8] *Kusuda* A73058/25, *Miller* A18279/37.

[9] *Flesch* A73595/872, *de Lara* A83071/873, *Hölscher* A73794/878, *Valat* A76670/887, *Stumpf* A43622/890, *Mackenrodt* A44091/891, *Klein* A73894/893, *Hanks* A44822/894, *Coe* A73433/894, *Niemer* A76217/895, *Tournay* A47511/895, *Dartigues and Claisse* A73466/899, *Savage* A76462/00, *Reed and Paine* A82689/03, *Gaudemet and Bouchot* A73655/05, *Norris* A68675/06, A76227/06, *Smith* A68121/29, *Gellé* A61927/33.

[10] *Williams* A41226/883, *Doran* A70475/884, *Terrier* A42000/887, *Reboul* A76367/888, *Poupinel* A43482/889, *Pfannenstiel* A76283/890, *Boursier and Monod* A73349/897, A50525/898, *de Argenta* A50657/898, A50941/898, *Herczel* A50505/898, A77205/898, *Gottschalk* A73696/899, *Hermann* A76992/01, *Reed and Paine* A76372/03, *Hue* A68751/04, *Swain* A70978/04, *Begouin* A73277/05, A68613/05, *v. Velits* A73010/06, *Macnaughton-Jones* A76047/06-7, *Woltring* A76768/09, *Nyström* A76231/11, *Mériel* A76115/11, *Tixier* A81112/14, *Santy and Perrenot* A76457/14, *Dransfeld* A73513/18, *van der Elst* A76672/20, *Martzloff* A76081/22, *Stübler and Brandess* A76588/24, *Koucky* A73916/25, *Kusuda* A73058/25, *Foote* A73601/27, *Smith* A68121/29, *Mandelstamm* A68104/29, *Wilson and Sims* A65120/31, *Tedenat* A66216/31, *Flemming* A64219/31, *Rankin and Donald* A62946/32, *Shaw* A61896/33, *Bowles* A97352/40.

[11] *Rydygier* A44703/894, *Krömer* A50971/899, *Selhorst* A70955/00, *Winston* A68958/01, *Tridondani* A76657/03, *Perriol* A68629/03, *Bernot* A73289/10, *Tallei* A82756/24.

[12] *v. Velits* A42186/887, *Sutton* A70976/892, *Stratz* A70395/894, *Stöcklin* A96061/899, *Schmidlechner* A68632/05, *Amann* A70568/06, *Carmichael* A70609/12-3, *Bloch* A70588/14, *Kermauner* A64880/32.

[13] *Braun* A40962/885, *Braun von Fernwald* A83045/888, *Bode* A73317/896, *Goelet* A48998/897, A48439b/897, *Günzburger* A73716/899, *Dienst* A73493/899, *Jessett* A68926/03-4, *Paine* A68942/04, *v. Velits* A73010/06, *Hellier* A73762/11, A73761/11, *Menne* A76111/11, *Charbonnel and Pierre-Nadal* A73423/12, *Potherat* A81377/13, *Fabian* A70679/17, *Rouffart* A70932/21, A70933/24, *Stübler and Brandess* A76588/24, *Smith* A68121/29, *Mandelstamm* A68104/29, *Hoffmann* A79587/30, *Kermauner* A64880/32.

The development of *fibromas (usually mural fibromas) in common cysts*[1] is especially often seen in the case of serous cystomas and cystopapillomas. In this connection, the excessive development of fibroma-like stroma in common serous adenofibromas comes to mind. It probably indicates a predilection for the proliferative growth of connective tissue in tumors of this variety. The occurrence of a *fibroma in the contralateral ovary* of a woman bearing common cystomas on the other side is not rare.[2] In some instances a *fibroma in one and a pseudomucinous cyst in the other ovary* have been noted,[3] while in other instances a *fibroadenoma or papilloma in one and a pseudomucinous cyst in the other ovary* occurred simultaneously.[4] *A fibroma in one ovary with a papilloma in the other*[5] is a rare combination.

Leiomyomas are rarely found in ovaries bearing common cystomas.[6]

It is unusual to find a *serous cyst and a pseudomucinous cyst* in the same ovary.[7]

The close similarities in structure and the possible pathogenic correlations between Brenner tumors and pseudomucinous cysts are discussed in the chapter dealing with the former. In this connection it is of interest to mention here, however, that *Brenner tumors* often develop in the walls of large *pseudomucinous cystomas*.[8] Furthermore, a *Brenner tumor* in one ovary may be accompanied in the other ovary by a *pseudomucinous cystoma*[9] or a *cystoma lined by ciliated cells*.[10] Carcinomatous and sarcomatous transformation of common ovarian cysts is discussed in the sections on cystocarcinoma and cystosarcoma respectively, but it should be emphasized here that there may be a *cystic carcinoma in one ovary and a benign cystoma in the other*.[11]

A *sarcoma and a pseudomucinous cystoma* may develop in the same ovary,[12] but most of these cases are actually due to sarcomatous degeneration of the cystoma wall and will be discussed with the malignant cysts. Occasionally a sarcoma metastasis may lodge itself in a common ovarian cyst.[13]

Endometriomas and *common cysts* may develop in the same ovary[14] but it must be kept in mind that not every "chocolate cyst" is a true endometrioma. *Endometriosis* in one ovary and a *serous papilloma* in the contralateral gonad have also been observed in the same patient.[12]

Para-ovarian cysts[15] and *common ovarian cystomas* likewise tend to occur in the same patient.

Even *three different ovarian tumors may develop concurrently*. Thus a carcinoma, a fibroma and a common cyst,[16] a dermoid, a carcinoma and a common cyst,[17] a teratoma, a sarcoma and a papilloma[18] may be found simultaneously. In these cases it is often very difficult to distinguish between the independent coincidental development of three blastomas and secondary malignant transformation or one-sided stroma proliferation in a single originally uniform blastoma.

COMMON CYSTOMAS IN COMBINATION WITH EXTRAOVARIAN TUMORS: In bearers of common ovarian cystomas extragenital tumors may simultaneously develop,[19] but this is rare and probably coincidental.

The Histology of the Cyst Contents. During the last century a great deal of attention was focused upon the histologic features of the cyst contents. The practice of tapping ovarian cysts, so popular as a therapeutic measure at that time, furnished the clinician with specimens of cyst contents which were then carefully examined for diagnostic purposes. Certain cell types were described as characteristic of the serous and pseudomucinous cystomas respectively, while other cells were regarded as in-

[1] *Doran* A42021/884-5, *Williams* A69762/888, *Pilliet* A82686/893, *Nijhoff* A70186/899, *Tate* A70405/04, *Torggler* A70421/04, *Nyström* A76231/11, *Brohl* A65854/12, *Sutton* A65825/22, *Stübler and Brandess* A76588/24, *Kusuda* A73058/25, *Smith* A68121/29, *Kermauner* A64880/32, *Dougal* A65955/33, *Ramirez* B10141/43.

[2] *Lücke and Klebs* A70130/867, *Bourgoin* A47126/894, *Routier* A70251/01, *Leopold* A70110/06, *Briggs and Emrys-Roberts* A65852/07, *Kusuda* A73058/25, *Fleming* A64219/31.

[3] *Lücke and Klebs* A70130/867, *Wüstenberg* A88873/03, *Stübler and Brandess* A76588/24, *Smith* A68121/29, *Shaw* A61896/33.

[4] *Thienhaus* A83507/05, *v. Grot* A70740/06, *Fabian* A70679/17, *Kusuda* A73058/25, *Smith* A68121/29, *Kermauner* A64880/32, *Shaw* A61896/33, *McIntyre* A55678/42.

[5] *Westermark* A70442/10, *Smith* A68121/24.

[6] *Odintsoff* A74642/01, *Doran* A70478/02, *Münchmeyer* A70497/02, *Basso* A65810/05.

[7] *Semb* A70956/896, *Kusuda* A73058/25.

[8] *Glockner* A70014/05, *Lahm* A64784/14, *v. Werdt* A64866/14, *Fleischmann* A70694/16, A68488/16, *de Lemos* A64787/19, *Spencer* A64894/25-6, *Frankl* A64756/27, *Schiffmann* A62948/32, *Freund* A53159/33, *Abraham* A73085/33, *Bettinger* A73087/33, *v. Szathmary* A73138/33, *Frankl and Klaften* A28154/34, *Reist* A64890/34, *Kleine* A64882/39, *Novak and Jones* A33609/39.

[9] *Macnaughton-Jones* A64884/898, *Spencer* A64894/25-6, *Bettinger* 5539/33, A73087/33, *Plaut* A61889/33, A64887/33.

[10] *Neumann* 42642/27.

[11] *Mears* A87037/872-3, *Amann* A77966/899, A77967/899, *Bell* A81165/08.

[12] *Smith* A68121/29.

[13] *Barnes and Konzelmann* A28142/35.

[14] *Payne* A32556/40, *Dannreuther* A36032/41.

[15] *D'Antona* A41650/886, *Wettergren* A42360/888, *Potter* A45669/890-1, *Ferrari* A44085/891, *Cristovitch* A83346/893, A83347/893, A83348/893, *Walton* A74575/893, *Ludlam* A47356/895, *Thorén* A47474/895, *Semb* A70956/896, *McLean* A48446/897, *Cleveland* A50527/898, *Stokes* A69135/00, *Polak* A69452/01, *Doran* A69582/02, *Delétrez* A69577/02, *Abadie and Moitessier* A88732/03, *Barton* A81316/04, *Kusuda* A73058/25.

[16] *Samuels* A50683/898.

[17] *Wehowski* A76724/06.

[18] *Stewart and Eglington* A70969/11.

[19] *Graefe* B8876/02, *Scharlieb* A70943/10-1, *Neef* B11908/16, *Dougal* A76947/30, *Miller* A18279/37.

dictative of carcinomatous transformation.[1] Most of the cells which float freely in the cyst fluid are severely altered by secondary degenerative changes and their histologic appraisal is extremely difficult; yet at a time when any major operation was fraught with considerable danger, it was important to use even these doubtful diagnostic aids to formulate the indication of surgical intervention.

Special attention was given at that time to small bodies found in the cyst fluid which were referred to as *Drysdale's corpuscles*.[2] These were probably the nuclei of epithelial cells which underwent fatty degeneration.

It is claimed that if a drop of filtered or centrifuged ovarian cyst fluid is allowed to dry on a glass slide, histologic examination of the residue reveals characteristic *crystallization patterns* in the case of serous, pseudomucinous, parovarian and follicle retention cysts (dermoid contents give no such patterns) and these may be of diagnostic value.[3]

Several reviews deal with the histologic characteristics of cyst contents.[4]

CHEMICAL COMPOSITION

The chemical characteristics of the fluids found in ovarian cysts have been the subject of many investigations.[5] For comparative data the reader is also referred to the chapter dealing with the chemical composition of normal ovarian tissue (see Sect. IV, Vol. I).

Some investigators attempted to determine the presence of *toxic substances* in ovarian cystomas. This work showed that the cyst contents are comparatively innocuous, since large quantities must be administered to experimental animals before toxic manifestations result. If considerable amounts are injected, degenerative lesions may occur in the kidney or liver and a pronounced local reaction is elicited at the site of injection,[6] but all these phenomena are not very specific.

An analysis of the contents of serous cystomas revealed that their specific gravity varies between 1007-1040 and their reaction is usually alkaline and they have a high *protein* content.[7] Bell and Datnow[8] determined the content (in both serous and pseudomucinous cysts) of total solids, water, inorganic matter, organic matter, calcium, mucin, pseudomucin, fats, soaps, free fatty acids, cholesterol, total nitrogen, protein from nitrogen, sugar and urea. The serous cysts analyzed contained exceedingly variable quantities of *dry substance* (1.42-22.37%). The percentual concentration of organic (0.63-15.43%) and *inorganic material* (0.79-4.0%) are subject to enormous variations. Even mucin and pseudomucin may be found in serous cystomas, sometimes in considerable quantities; indeed, in three out of four cysts analyzed, pseudomucin was found. Calcium is not always present in serous cystomas, while all the pseudomucinous cystomas analyzed contained calcium. The percentual concentration of organic material in these cysts varied between 0.467-9.34%, and the inorganic material from 0.22-1.24%.[9]

More recent studies led to the conclusion that fluids from actively secreting common cysts usually have a *high nitrogen, protein and potassium* but a low *chloride* content, while the reverse is true of cysts with a less actively secreting epithelium and those in which the cyst wall is denuded.[10]

Both serous and pseudomucinous cysts contain varying quantities of *albumin*[11] and a variety of *glycoproteins*. It will be recalled that the latter are conjugated proteins containing protein plus a prosthetic group which is a carbohydrate. The sugar part of the molecule may be separated from the protein by hydrolysis. Early workers isolated "*paralbumin*" and "*metalbumin*" from the fluid of ovarian cysts.[12] Paralbumin was later shown to be merely a combination of metalbumin with varying quantities of serum albumin and serum globulin, and since metalbumin itself was considered to be more closely related to mucin than to albumin, it was called *pseudomucin*.[13] Pseudomucin was said to be a product of the goblet cells lining the cyst, just as *mucin* is a product of the goblet cells of the gastric mucosa. As glycoproteins, both mucin and pseudomucin are similar in many respects, but they differ in several properties. Mucin is soluble in dilute alkali, but insoluble in water and dilute acids, including acetic acid. Pseudomucin is soluble in dilute alkali and also in water and acetic and other

[1] *Wells* A82308/864, *Joly* A82298/870, *Danforth* A82290/878, *Goodell* A29985/881, A40539/882, *Baer* A40005/881-2, A40006/882.
[2] *Drysdale* A82291/873, A82292/882, A40624/883, *Edwards* A40071/882, *Mann* A40635/883, A41265/883.
[3] *Hochloff* B11641/35, B11642/35, *Kárpáti* A97618/39.
[4] *Garrigues* A40440/882, A40591/882, *Herter* A96830/899.
[5] *de Fontenelle* A82299/824, *Leo* A82301/826, *Schrader* A82306/854, *Folwarczny* A82293/858, *Boedeker* A82339/859, *Méhu* A77038/869, A40053/881, *Maly* A82302/871-2, *Hodge* A82296/872-3, *Buckham* A82288/879, *Tait* A29324/880, *Robin* A29989/881, *Garrigues* A40440/882, A40591/882, *ørum* A77053/884, *Gönner* A40939/884, *Kondratowicz* A82300/884, *Schmitt* A41869/887, *Herter* A96830/899, *Ferroni* A76957/00, *Rouslacroix* A81290/01, *Hochloff* B11641/35, B11642/35, *Stolfi* A97416/39, *Kárpáti* A97618/39.
[6] *Auche and Chavannaz* A49200/898, A80959/899, A80960/899, A80958/899, A80961/00, *Leary et al.* B13454/17.
[7] *Miller* A18279/37.
[8] A66142/32.
[9] *Bell and Datnow* A66142/32.
[10] *Watts and Adair* B6248/44.
[11] *Galabin* A29482/880.
[12] *Scherer* A77086/852, A77085/852, *Haerlin* A76983/862, *Obolensky* A77052/871, *Huppert* A76997/876.
[13] *Hammarsten* A40112/881, A76985/882, *Landwehr* A77020/883-4, *Lepierre* A77026/898, *Zängerle* A77132/00.

weak acids. Both are precipitated by alcohol.[1] The carbohydrate group of mucin is *mucoitin sulfuric acid,* whose constituent parts are *surfuric acid, acetic acid, glucuronic acid,* and *glucosamine.*[2] The carbohydrate of pseudomucin has not been as clearly defined, due largely to the fact that autolytic and other enzymatic changes take place in the fluid content of ovarian cysts, especially those of long standing, with the result that the constituent sugars and acids may be partially split. It was shown that acetic acid and variable amounts of glucosamine are present, together with other dextro-rotary sugars which are not glucose, mannose or galactose.[3] The protein part of pseudomucin was found on hydrolysis to contain arginine, but no other substance with a *guanidine* nucleus.[4]

Pfannenstiel made a further division of pseudomucin into the more commonly occurring *pseudomucin* α, and the less frequently encountered *pseudomucin* β and *pseudomucin* γ.[5] This division was also made largely on the basis of solubilities. Later, *paramucin* insoluble in water and precipitated by acetic acid[6] and *paramucin* β[7] were described. *Paramucosin*[8] isolated from paramucin is probably analogous to *mucosin* which is the product obtained on partial hydrolysis of mucoitin sulfuric acid to the disaccharide of glucosamine and glucuronic acid.[9]

More recently, the mucous substance isolated from gastric mucosa has been termed a *mucopolysaccharide* rather than a glycoprotein and the term mucin is avoided entirely. A mucopolysaccharide is not a true protein, but rather a nitrogen containing carbohydrate, the acid groups of which form salts with the basic amino groups of various proteins.[10] This throws some doubt on the nature of pseudomucin as well. Indeed, on the basis of the literature cited, it would seem that the use of the term pseudomucin to describe the substance found in ovarian cysts is not entirely justified. There is no histologic evidence that the goblet cells which produce "mucin" in the gastrointestinal tract are in any way essentially different from those producing "pseudomucin" in ovarian tumors. As we have seen above, the chemical distinction between "mucin" and "pseudomucin" is likewise far from clear-cut. It is based mainly on differences in the physical characteristics of the two substances such as solubility, density, tinctorial properties etc. Such physical properties may be expected to vary due to condensation of fluids or chemical break-down changes resulting from prolonged storage within the cyst cavity. It would hardly be justified to base a classification of goblet cells and their secretion products on the basis of such vague minor differences.

It so happens that at about the middle of the 19th century, the pathologists who first paid attention to the mucinous cysts as distinct from the serous varieties, coined the term "pseudomucinous cystoma" in the belief that the lining cells and their secretions are essentially different from ordinary mucous cells and their mucinous product; all subsequent investigators followed this terminology without reviewing the data upon which the distinction was based. It should be especially emphasized, therefore, that up to the present time chemical investigations furnished *no definite evidence indicating that the ovarian mucinous substances are essentially similar to or different from those produced by other mucous cells.* Until the mucinous substances produced by various types of goblet cells have been adequately characterized by modern chemical methods, there appears to be no reason to refer to ovarian cysts as "pseudomucinous" cystomas. The term mucinous cystomas appears preferable since it is shorter and does not imply a distinct chemical or morphologic entity. The older designation is retained in this Encyclopedia only in order to avoid the confusion which may arise from a new terminology in this already rather complex field of pathology.

Special attention is drawn to the fact that the morphologic and chemical similarity between the cells of the pseudomucinous cysts and the mucinous cells of the gastrointestinal tract rates as an important argument in favor of the entodermal derivation of these ovarian tumors (see part on Pathogenesis). This argument would hardly be valid if we assumed that pseudomucinous and mucinous cells are fundamentally different from each other. Yet mucinous cystomas may originate in the appendix and these are in every respect similar to the "pseudomucinous" cystomas of the ovary.

In view of the possible derivation of pseudomucinous cystomas from fetal entoderm, it is interesting that they contain *ferments* such as are normally found in the gastro-intestinal tract, namely trypsin,[11] amylase,[12] pepsin[13] and saccharase.[14] In some instances, apparently even peroxydases,[15] glycine and asparagine-decomposing ferments have been demonstrated[13] in them. Serous cystomas, on the other hand, are free of saccharase.[14]

Bile acids[17] and *lipids*[18] may also be encountered in ovarian cystomas.

[1]*Hammarsten* A97465/884, *Pfannenstiel* A76283/890, *Zängerle* A77132/00, *Hawk and Bergeim* A97466/37.
[2]*Levene* A97464/22.
[3]*Neuberg and Schenker* A97463/12, *Fürth et al.* A97461/34.
[4]*Fuchs* A97462/35.
[5]*Pfannenstiel* A76283/890.
[6]*Mitjukoff* A77043/895.
[7]*Ferroni* A76957/00.
[8]*Leathes* A77023/899-00.
[9]*Levene* A97464/22.
[10]*Meyer* A95460/38.
[11]*Tachibana* 2465/29.
[12]*Tachibana* A77105/27.
[13]*Tachibana and Abe* A77110/29.
[14]*Lecène and Bierry* 16970/23.
[15]*Loele* 18358/34.
[17]*Bennett* A80966/868-71.
[18]*Momigliano* A81089/25-6.

Data concerning the *hormone content* of ovarian cysts are discussed conjointly with the ovarian and hypophysoid hormone content of various other tissues in the corresponding passages of Sect. III, Vol. V and Sect. IV, Vol. V.

Serologic studies revealed the occurrence of A, B and O blood group substances in the contents of pseudomucinous ovarian cysts.[1]

INCIDENCE

General Incidence: A statistical survey of 3141 ovarian tumors published by different investigators revealed that 21% of them were *serous cystomas*.[2] Data concerning the comparative frequency of simple and papillary ovarian cystomas are somewhat confusing and difficult to evaluate because the various investigators use different standards in the identification of a tumor as a papilloma. Some list all cases with papillary excrescences under that heading, while others require that extensive papillary formations be present if the growth is to be classified as a papillary cystoma.[3] Thus one author[4] estimates that about 15% of the ovarian tumors are papillomas, while others estimate this figure to be 8.67%,[5] 8.1%,[6] or 8.5%.[7] Among 200 cystic ovarian tumors of one series,[8] 18% were papillomas but some of these manifestly belonged to the pseudomucinous variety. In many other statistical surveys, follicle cysts and para-ovarian cysts are included among the common ovarian cystomas and consequently the relative incidence of papillomas becomes much lower, about 2-5%.[9]

Macrocystic pseudomucinous cystomas are probably more frequent than any other cystic ovarian blastoma and various investigators estimate that 33-66% of all ovarian tumors belong to this category.[10] Our own survey of the literature indicates that the lower figure is probably closer to the general average. This is in good agreement with the calculations of Miller[11] who surveyed 2409 cases of ovarian tumors reported in the literature and found the incidence of pseudomucinous cystomas to be 33.6%.

There are enormous variations in the figures given by various authors concerning the *comparative frequency of serous and pseudomucinous cystomas.* Thus, one worker[12] estimates that the proportion of serous to pseudomucinous is about 1:8, while another investigator[13] believes that the pseudomucinous variety is only half as common as the serous. The latter conclusion is not in agreement with the majority of the statistical reports and although the exact incidence is difficult to estimate, the pseudomucinous tumors appear to be more common than the serous.

Pseudomucinous papillary cystomas are estimated to represent 3.5%,[13] 11.5%,[14] 24.1%[15] or 27.3%[16] of all pseudomucinous tumors. The lowest among these figures are almost certainly erroneous since in a series of 1101 ovarian tumors, in which even follicle and corpus luteum cysts were included, the incidence of pseudomucinous papillary cystomas was 6%.[17] The so-called "*pseudomyxoma ovarii*" is comparatively rare, a fact which is partly due, however, to the failure of many investigators to distinguish between ordinary macrocystic pseudomucinous tumors and this variety. It is estimated that 4.8%[12] or perhaps even 14.7%[13] of the pseudomucinous cystomas have thick jelly-like contents and exhibit the general characteristics of pseudomyxoma ovarii.

Several investigators published statistics concerning the *comparative incidence of ovarian cysts in married and unmarried women.* It has been estimated that among the pseudomucinous cysts about one-fourth, to be specific, 25.4%,[18] 24.3%,[15] or 26%[19] occur in unmarried, the rest in married women. Among 127 married women with pseudomucinous cystomas only 6.3% were *sterile* in one series of observations.[18] Other statistical surveys give a much higher incidence of sterility, namely 16%,[15] 18%[19] and 30%[20] respectively.

The *microcystic pseudomucinous cystomas* of the parvilocular or adenomatous variety are much rarer than the macrocystic type. They represent hardly more than 2-5% of the pseudomucinous growths as judged by a survey of the relevant case reports although exact statistical studies are not available.

Age Incidence: Both serous and pseudomucinous ovarian cysts may occur at any *age*. Many cases—some with very large cystomas—have been observed

[1] *Morgan and van Heyningen* B11441/44.
[2] *Miller* A18279/37.
[3] *Ross and Pearse* A97016/38.
[4] *Pfannenstiel* A70890/895, A64886/08.
[5] *Shaw* A61896/32-3.
[6] *Kelly* A70489/894, A83038/898-00.
[7] *Stübler and Brandess* A70975/25, A76588/24.
[8] *Erdmann and Spaulding* A70674/21.
[9] *Bernstein* 81758/36, *Miller* A18279/37.
[10] *Lippert* A76008/05, A64789/05, *Lockyer* A70121/18, *Tietze* A64203/31, *Shaw* A61896/32-3.
[11] A18279/37.
[12] *Martin* A78665/899.
[13] *Kusuda* A73058/25.
[14] *v. Velits* A73010/06.
[15] *Smith* A68121/29.
[16] *Masson and Hamrick* A65619/30.
[17] *Bernstein* 81758/36.
[18] *Stübler and Brandess* A76588/24.
[19] *Fleming* A64219/31.
[20] *Kermauner* A64880/32.

in children.[1] These cysts may even occur in the fetus[2] or in infants during the first few months of life.[3]

Conversely ovarian cysts are also quite common among elderly women[4] and many cases have been reported in patients of 60 years or more.[5]

A survey of several statistical compilations by different authors indicates that *simple serous cystomas* occur most frequently during the reproductive period of life, but may be observed at almost any age.[6] In one extensive statistical survey[7] the distribution was as follows:

Years	%
11-20	5
21-30	25
31-40	27
41-50	24
51-60	13
61-70	5
71-80	1

Thus, more than 18% of the simple serous cystomas observed by these investigators occurred after the menopause.

Serous papillomas have an approximately similar age distribution as judged by a review of eight statistical surveys dealing with a total of 552 cases among which the incidence was as follows:[6]

Years	No. of Cases
11-20	8
21-30	97
31-40	159
41-50	140
51-60	97
61-70	43
71-80	4
81-90	1

Simple pseudomucinous cystomas had the following age distribution in a statistical survey of 1670 cases:[6]

Years	No. of Cases
0-10	2
11-20	80
21-30	399
31-40	403
41-50	341
51-60	281
61-70	140
71-80	24

The *racemose type of pseudomucinous cystoma* appears to occur most frequently in older women.[8]

For *pseudomyxoma peritonei* the age distribution among 178 cases was as follows:[7]

Years	No. of Cases
15-19	1
20-29	9
30-39	11
40-49	52
50-59	51
60-69	40
70-80	14

[1]*Berchelmann* A69765/846, A69766/874, *Pana* A69792/856, *Battye* A69764/860, *Jackson* A69780/860-1, A69781/862, *Noble* A69789/864, *Wegscheider* A69797/870-2, *Goodrich* A69778/871-2, A69777/872, *Pooley* A69793/872, A29328/880, *Sharp* A69795/874, *Cupples* A74875/874, *Leared* A69782/878, *Chenoweth* A40585/882, *Polotebnoff* A41866/887, *Dor* A41911/887, *Byford* A44015/891-2, *Keen* A46472/893, A46471/893, A46529/893, *Walter* A64646/895-6, *Baldy* A50987/899, *Puyol* B13390/07, *Cheney* A81650/09, *Zellweger* A81437/13, *Potvin* A81439/14, *Findley* A64641/21, *Crowell* A81653/21, *Nalle* B21061/23, *Wilson* B21083/23, *Secor* A64645/26, *Leveuf and Heraux* A78604/26, *Rosival* A67263/30, *Minne and Gernez* A64007/31, A77042/31, *Wakeley* A66099/32, *del Campo* A61372/32, *Hipsley* A61561/33, *Kafka* A27873/35, *King and Hawes* A59694/36.
[2]*Doran* A40069/881, *Lafond* A81193/10.
[3]*Lorrain* A69786/852, *Boullard* A69768/854, *Schultze* A69794/859, *Carr* A69771/872, *Cullingworth* A69773/874, *Leduc* A69784/878, A69785/878, *Thomas* A29358/880, *Osler* A40900/883-4, *Solis* A74551/896, *Power* A51013/897-8, A49245/898, *Lönnberg* A50611/898, *Cima* A50565/898, *Beckett* A50626/898, *Durante* A50603/898, *Dubé* A80975/899, *Takesaki* A81295/00, *MacGillivray* A81375/07, *Gaifami* A81658/19, *Downes* B8720/21, B8545/21, A81655/21, *Consoli* A81652/24, *Holzman* B15666/27, *Dodek* A61554/33, *Atakam* A62053/36, *Witzberger and Agerty* A95127/37, *Moraes Rego* A97008/38, *Minne and Gernez* A97230/38, *Newmann* A96523/38, *Miller* A97296/39, *Bulfamonte* A37502/42, *Rankin and Eger* A98174/43.
[4]*Cartledge* A44140/892, *Kelly* A46372/893, *Delaunay* A47302/895, *Hammond* A81186/17, *Köhler* A77010/28.
[5]*Lapré* A69903/845, *Bird* A69899/847, *Dufour* A82149/849, *Lorain* A69904/854, *Rogers* A69905/857, *Wells* A69909/858-9, *Vignes* A82094/861, *Villard* A82095/870, *Waldenström* A69908/874, *Storrs* A69907/875, *McNutt* A29352/879, A29401/880, *Smythe* A40297/883, *Heurtaux* A40892/883-4, *Guillemet* A41202/883-4, *Giddings* A69900/884, *Moreau* A41507/885, *Hervouét* A69901/885, A69902/885, *Shepherd* A69906/886, *Wettergren* A42360/888, *Vance* A42737/888, *Johnson* A42529/888-9, *Farr* A43631/890, *Da Costa* A45752/890-1, *Haynes* A45729/891, *Verstraete* A49159/897, *Siedentopf* A70957/03, *Robinson* A74542/04, *Driessen* A70662/08, *Goldschmied* A70729/22, *Spencer* A70963/23, *Everett* A68006/29.
[6]*Miller* A18279/37.
[7]*Stübler and Brandess* A76588/24, A70975/25.
[8]*Rüder* A77283/896, *Kusuda* A73057/19-20.

Papillary pseudomucinous cystomas generally affect older women and are frequently seen after the menopause.[1]

Pregnancy Incidence: An unusually large number of ovarian cysts has been reported in pregnant women. This is perhaps partly due to an increased growth rate and the tendency of ovarian cysts to undergo torsion and rupture which calls attention to them during pregnancy, but partly also to the fact that many such cysts are "silent" and therefore first noted at a routine antenatal pelvic examination. Many relevant *case reports* describe the complications in gestation and parturition which may be elicited by ovarian cystomas.[2] It is remarkable that, in many of these cases pregnancy continued to its physiologic termination in spite of the fact that both ovaries were almost completely destroyed by the cystomas, in fact, in some relevant instances no trace of normal ovarian tissue could be found. The reader is also referred to the parts on the therapy of ovarian cysts and other tumors where additional data are listed, indicating that at least during the second half of gestation even complete ovariectomy does not terminate pregnancy. Hence it is clear that the internal secretions of the gonads are not essential after the embryo and the placenta have reached a certain degree of maturity.

A statistical survey of the material published by 4 reviewers indicates that approximately 6% of the patients presenting themselves because of *serous cystomas* are pregnant.[1] *Pseudomucinous cystomas* in pregnant women[3] are considerably less frequent

[1]*Miller* A18279/37.

[2]*Wittke* A69897/826, *Kesson* A69863/826-7, *Fereday* A69818/831-2, *Hewlett* A69858/832, *Robbs* A69878/838, *Maier* A69868/839, *Vanotti* A69890/844, *Melion* A69869/844, *Somerville* A69884/844, A69885/846-7, *Thibaut* A82550/847, *Dourlen* A69817/847, *Litzmann* A69866/852, *Tufnell* A69889/852, *Gibson* A69851/854, *Schnyder* A69883/854, *Hirsch* A69803/854, *Barth* A69808/856, *Hecker* A69854/856, A69855/857, *Lémoin* A69865/859, *Pendleton* A69877/860, *Clay* A69814/860, *Casati* A69812/861, *Jetter* A69804/861, *Hunter* A69862/861, *Otis* A69875/861, A69876/862, *Pollock* A87062/862, *Goldschmidt* A69802/862, *Hemken* A69311/863, *Donovan* A69815/863, *Steinhaus* A69887/864, *de Moura* A69871/867, *Doumairon* A69799/868, *Chantreuil* A69813/869, *Hicks* A69860/870, A69861/888, *Wells* A69892/870, A69893/872, *Hein* A69856/870-2, *Nicholson* A69872/871, *Zagiel* A69898/871, *Guéniot* A69853/872, *Treille* A69807/873, *Dougall* A69816/874-5, *Wasson* A69891/875, *Battey* A69809/875-6, *Ruge* A69880/875-6, *Kidd* A87060/875-6, A69864/876, *Veit* A70428/876, *McMahon* A69867/879-80, *Pippingsköld* A29327/880, *Noeggerath* A69873/881, *Zagiell* A40062/881, *Schauta* A40372/882, A82427/14, *Moller* A41216/882, *Fischel* A69820/882, *Bruntzel* A40358/882, *Butler-Smythe* A41579/883, *Fetscherin* A69801/884, *Nolting* A69805/884, *Heydenreich* A69859/884-5, *Remy* A69806/886, *Herrgott* A69857/886, A41883/887, *Bailey* A41706/887, *Bouteillier* A41983/887, *Doléris* A41880/887, *Truzzi* A41795/887, *Heilbrun* A41850/887, *Schetkin* A69882/887, *Prewitt* A42538/888, *Terrillon and Valat* A42357/888, *Blume* A69810/888, *Angelini* A45212/889, *Ashton* A42595/889, *Decamps* A43333/889, *Naumann* A45183/889, *Noriega* A45230/889, *Terrillon* A45155/889, *Häusler* A93477/890, *Hirst* A43539/890, A50579/898, *Köhler* A44064/891, *Baudron* A93507/891, *Dodge* A93537/891, *Prokopjeff* A44155/891, *Potherat* A91723/892, A91721/892, *Rosenstein* A69184/892, *v. Weiss* A46384/892, *Meredith* A70831/892, *McKee* A46432/893, *Krimer* A93479/893, *Napier* A46540/893, *Meyer* A44781/894, *Jacobs* A91662/894, *Condamin* A93529/894, A93530/00-1, A93531/02, *Duncan* A93541/895, *Avtandiloff* A47337/895-6, *Breed* A93518/895-6, *Custodio Cabeca* A93534/896, *Cocard* A69630/896, *Burrows* A93505/896, *Phillips* A91712/897, *Jones* A91666/897, A91665/02-3, *Anderson* A93493/898, *Pozza* A91724/898, A91725/898, *Pinzani* A91716/898, *Bonté* A93513/899, *Gutiérrez* A91653/899, *Divaris* A69631/899, *Wagner* A69179/899, *Hurel* A69634/899, *Nowak* A91706/899, *Ghedini* A91648/899-00, *Pinard and Segond* A91715/00, *Stone* A69407/00, *Fehling* A69645/01, *Fothergill* A69646/01, *Fisher and Martinoff* A91638/01, *Lafont* A93482/01, *Thyne* A91756/01, *Bue* A69638/02, *Guerin-Valmale* A69648/02, *Knoll* A69635/02, *Kingsbury* A91670/02, *Platon and Troin* A91717/02, A69182/02, *Troin* A69178/02, *Cocq* A69640/02, A69641/03, *Perdue* A91710/03, *Cumston* A93533/04, *Dührssen* A69644/04, *Lapeyre* A91678/04, *Vasiliu and Negruzzi* A91761/04, *Puech* A91731/04, A82423/13, *Aguilar* A93492/05, *Yartseff* A93491/05, *Brothers* A93519/05, *Polak* A69183/05, *Porter* A91720/05, *Piana* A91713/05, *Tarantino* A91752/05, *Martin Aguilar* A91692/05, A91693/06, *Bergesio* A93509/06, *Bleynie* A69636/06, *Gerstenberg* A73048/06, *Shtraikher* A69404/06, *Jaubert and Nimot* B13195/06, *Tardif* B13251/06, *Pfannenstiel* A82422/07, *Martin* B13499/07, *Guinard* A81682/08, *Ramon y Cajal* A81696/08, *Guillemet et al.* B11316/09, *Jeannin and Brac* A70751/09, *Brouha* A81671/01-1, *Brindeau* A81669/11, *d'Hotman de Villiers* A81683/11, *Bott* A81668/12, *Bonnet-Laborderie* A81667/12, *Buzzoni* A81672/12, *Bender* A81631/12, *Couvelaire* A82414/12, *Lepage and Tissier* A81689/12, *Vincent and Ferrari* A81734/12, *Thomas* A81664/12, *Barrett* A82411/13, *Chueco* A81674/13, *de Framond* A81662/13, *Schmücker* A82409/13, *Kemp* A81684/13, *Orlandi* A81694/13, *Puech and Vanverts* A82408/13, A82407/13, A82424/14, *Aziz-Fikret* A82410/14, *Betow* A81665/14, *Ward* A81738/14, *Lepage* A81688/14, *Beach* A82412/16, *Patton* A69181/16, *Rossier* A81698/16, *Kleinschmidt* A82406/18, *Alvres-Pinto* A82405/19, *Grosse* A21324/19, *Bernard* A81661/20, *Stiassnie* B21277/20, *Spencer* A82428/20, A82429/25, *Fränkel* A26972/20, *Fleming* A81679/20, *Dambrin* A81675/20, *Gilles and Gay* A81681/20, *Tourneux* A81730/20. *Vignes* A81732/21, A81733/21, *Rotter* B21218/21, *Paucot* B8652/21, *Remy* B8658/21, *Voron and Bouget* A81737/21, *Tomaselli* A81729/21, *Carboni* B11764/22, *Bello* B8554/22, *Cantalamessa-Carboni* B8556/22, *Szymanowicz* A81700/22, *Vey* A82430/22, *Vanverts and Guenez* A81731/22, *Abbott* B8528/22, *Sieber* B21076/23, *Bartholomew* B20984/23, *Davis* A81677/23, *Sachs* A82425/23, *Sternberg and Watson* 81699/23, *Brandess* A82413/24, *Kickham* A81685/24, *Knebel* A81686/24, *Sage* A82426/24, *Pérez and Guiroy* A81695/25, *Rizzacasa* A81697/25, *Porritt* B7508/25, *Wetterwald* A81739/25, *Ayars* B7322/26, *Ricevuto* B8028/26, *Keller* B7991/26, B7232/27, *Litzenberg* B7168/27, *Picard* B7086/27, *Nutt* B7081/27, *McDonald* B7169/27, *Péry and Boursier* A77067/27, *Pastiels* B10777/27, *Derankova* B8191/27, *Devraigne* B5922/28, *Lutaud* B5933/28, *Manzi* B5936/28, *Sappey* B10792/28, *Blacklee* A66278/29, *McCullough* B5934/29, *Caverly* A65060/31, *Brault* A61367/32, *Colle and Montagne* A61376/32, *Rosensohn* A61436/32, *Fruhinsholz and Hamant* A61384/33, *Riche et al.* A61647/33, *Vayssière* A61539/33, *Dougal* A76948/34, *Stacy* A51985/34, *Voron and Brochier* A27762/34, *Keller* A27874/35, *Tiber and Turkel* A59481/36, *Kovats* A95223/37, *Cambon and Plasse* A97045/38, *Courtois* A97050/38, *Martella* A97229/38, *Hofweber* A97615/39, *Holtermann* A97617/39, *Leynen* A97622/39, *Helwig* A97382/40, *Valle* A97724/40, *Hoh* A97482/41, *Argonz and Schaffer* A97777/42, *Nucci* A97815/42, *Capone* A66751/43, *Watts and Adair* B7320/44.

[3]*Kermauner* A64880/32.

and among 887 cases of ovariectomy for such growths only 2.81% was performed during gestation.[1] Papillary pseudomucinous cystomas are especially rare in pregnant women[2] and the same is true of the pseudomyxoma ovarii which usually destroys most of the ovary.[3]

Ectopic pregnancy is comparatively rare in women with common ovarian cysts (see part on Complications, below).

Puerperal Incidence: During the puerperium ovarian cysts are likewise commonly found, although less frequently than during gestation. This comparatively high incidence may be due partly to increased growth during the preceding gestation period. Such complications as rupture, prolapse and torsion during delivery and secondary infection after child-birth undoubtedly also play an important role as factors inducing the patient to seek medical advice at this time. Cysts which appeared under the clinical picture of an ovarian abscess, resulting from a septic puerperium, are discussed in the chapter on Inflammations of the Ovaries (see Sect. IV, Vol. VI). Here we consider only those cases in which the ovarian tumor appears to have been a typical serous or pseudomucinous cyst or papilloma.[4]

Racial Incidence: In negro women common ovarian cysts are frequently found[5] but perhaps not as frequently as in white women.[6] Ovarian cystomas have also been noted in *Annamites*,[7] *Hindus*,[8] *Australians ("gin")*,[9] *Chinese*[10] and *Javanese*.[11]

PATHOGENESIS

The histogenesis of the *serous cystomas* has given rise to a great deal of speculation and numerous theories have been proposed to explain their origin.[12] It would not be profitable to discuss all of these in detail, since many of them are founded on such flimsy evidence that they do not deserve serious attention. Suffice it to say that their possible derivation from the *parovarium*[13] or *Wolffian body*[14] and from remnants of *medullary cords* in the hilum region[15] have been considered. The fact that cyst or adenoma-like enlargement of the *rete tubules* may be produced in animals chronically treated with testoids or folliculoids,[16] suggests that perhaps the rete may also give rise to cystomas and cystadenomas.

The morphologic similarity between serous papillomas and the mucosa of the Fallopian tube is striking, and primary papillomas of the oviduct strongly resemble those of the ovary. This speaks in favor of the theory that the serous papillomas may result from regurgitated *oviduct epithelium* which re-implants itself upon the ovarian surface.[17] A similar theory concerning the derivation of endometriosis cysts from ectopically located or transplanted endometrial cell groups has much in its favor and supplies a parallel to the above-mentioned theory concerning the origin of the serous papillomas. Papillomas of the tube are very rare, however, in comparison with the common serous papillomas of the ovary and hence many investigators do not subscribe to the concept that the latter are of Fallopian origin. Sampson[18] pointed out that endosalpingiosis of the ovary may occur following salpingectomy and this observation gives further support to the concept that the serous cystomas are actually "endosalpingiomas".

A particularly popular concept is that the serous papillomas originate from follicular *granulosa cells*.[19] This view appears to be supported by the observation that ciliated cells, and sometimes even definite papillomatous excrescences, may appear

[1]*Miller* A18279/37.
[2]*Fuchs* A68847/13, *Spencer* A61809/33.
[3]*Jablonski* A77217/21.
[4]*Douglas* A68438/731, *Spiegelberg* A69886/867, A69888/868, *Weinlechner* A40513/881, *Limont* A66986/886, *Doléris* A42438/888, *Baldy* A43450/889-90, *Hofmokl* A44256/892, *Löhlein* A48276/896, *Dujardin* A69633/896, *Gottschalk* A49023/897, A49234/898, A69647/898, *Hirst* A91658/890-00, *Azaïs* A69629/04, *Chiarabba* A69639/06, *Ronsheim* A81235/17, *Ferrand* A81629/20, *Bernard* A81661/20, *Vignes* A81733/21, A81732/21, *Spencer* A82429/25, *de Micheli* A65493/30, A65492/30, *Madan y Diago* A97625/39, *Jeannin* A97384/40, *Agostinelli* A97332/40, *Gavioli* A98118/41.
[5]*Brown* A50990/899, *Royster* A69172/899-00, A69171/00, A69173/02, A69174/02, *Williams* A69177/00, A69176/01, *Leigh* A69628/02.
[6]*Stone* A69175/899.
[7]*Dubruel* A69583/03, *Gaide* A69589/06.
[8]*Curran* A86465/875, *Augino* A48259/896, A48238/896, *Das Gupta* B7463/25.
[9]*Thom* A88116/03.
[10]*Heine* A77546/894, *Stratz* A70395/894, *Lewis* B10767/28.
[11]*Stratz* A70395/894.
[12]*Chereau* A68405/848, *Eve* A70676/885-6, *Gibbes* A43341/890, *Jones* A81138/00, *Clark* B9109/05, *Anitschkow* A70571/09-10, *Menetrier et al.* A68522/22, *Rohdenburg and Hellman* A81105/25, *Lepper* A28006/35.
[13]*Olshausen* A41468/877-86, A87489/877, *Doran* A68436/882, A70475/884, A70657/887-8, *Popow* A70899/02.
[14]*Pepere* A70883/899, *Tusini* A71000/05, *Guillemin* A73050/22, *Turmann* A70999/25.
[15]*Coblenz* A70624/881, A40334/881, *Olshausen* A70877/10.
[16]*Champy* A95241/37, A95242/37.
[17]*Kossmann* A70779/895, *Glasunow* A95259/37, *Barzilai* A71883/43.
[18]B5709/30, B5684/30.
[19]*Frerichs* A76968/847, *Meyweg* A81049/868, *Köeberlé* A70087/878, *Galabin* A29245/879, A82294/879-80, *Fischel* A70687/880, *Coblenz* A70624/881, A40334/881, *Williams* A41226/883, A69464/891, *Doran* A70475/884, *Ziegler* A69397/884-02, *Neumann* A76203/886, *v. Velits* A43324/889, *Steffeck* A43591/890, A44642/894, *Bulius* A69687/891, *Stratz* A70395/894, *Pozzi and Beaussenat* A49007/897, *v. Franqué* A50571/898, *Pfannenstiel* A7554/898, *Schröder* A64835/01, *Brewis* A70600/05-6, *Massabuau* A70826/06, *Recasens* A81101/08, *Schochet* A90872/15-6, *Robinson* A67262/30, *MacLeod* A52125/34, *Gardner* A92816/38.

within otherwise normal follicles. It has, therefore, been assumed that the normal granulosa cell may, under certain circumstances, transform itself into a ciliated serous cell and thus give rise to papilloma formation.

Perhaps the most generally accepted theory, however, is that serous papillomas are derived from the *germinal epithelium* of the ovarian surface.[1] The earliest stages in the development of surface papillomas are characterized by a "velvet-like" transformation of the ovarian surface. In these cases the covering of the papillae appears to be normal germinal epithelium.[2] According to one author[3] most cystic papillomas develop from "germinal inclusion cysts" which are demonstrable in 64% of all normal ovaries and in 100% of the apparently normal ovaries of women in whom the contralateral gonad bears a serous papilloma. These inclusion cysts probably arise from invaginations of the surface covering which subsequently lose their connection with the ovarian lining and are thus transformed into cysts. It has been claimed[4] that the ovarian surface covering always contains some ciliated cells and that tubular invaginations of it—also lined by ciliated cells—invade the ovarian stroma. From such tubules, side-branches may develop and subsequently their cavity may become more and more subdivided until a papilloma-like structure results. In any case it is perhaps unnecessary to establish a special category for the "germinal inclusion cysts"[5] or surface epithelium cysts[6] of the ovary since the structures described by these designations are indistinguishable from early stages of serous cystomas.

Some investigators believe that the ciliated epithelium of oviduct fimbria may spread over part of the ovarian surface either as a result of a congenital abnormality[7] or due to a postnatal growth process.[8] In this case cyst formation by ingrowth from the surface could subsequently follow. This concept is in a sense intermediary between the endosalpingeal and the germinal or surface epithelium theory. Limnell[9] was of the opinion that primary follicles may develop into serous cystomas soon after their formation from the germinal epithelium, which is another modification of the surface lining theory. Another compromise view holds that serous cysts may arise either from the surface epithelium or from the follicular granulosa and that it is not necessary to derive all of them from the same source.[10]

There is also a great deal of controversy concerning the pathogenesis of *pseudomucinous cystomas*.[11] Some investigators attempted to derive them from "*Pflüger's tubes*"[12] but it was pointed out[6] that this theory is hardly worth discussing, since Pflüger's tubes are not formed in the human ovary. Similarly, the view that these cysts are due to "colloid degeneration" of the ovarian *stroma*[13] can hardly be considered by contemporary pathologists. The possible derivation of these cysts from the *follicular epithelium* has been suggested[14] mainly because occasionally certain areas of the follicular granulosa appear to be transformed into pseudomucinous cells.[15] This view was strongly contradicted, however.[16] Some investigators believed the pseudomucinous cysts to originate from the *parovarium*[17] or the *germinal epithelium*,[18] but there is little evidence to support such assumptions.

The possibility that the pseudomucinous cystomas may be derived from *Müllerian epithelium* has also been considered.[19] It was emphasized that the same "Ur-Keimepithel" which gives origin to the ovarian surface lining, also forms the Müllerian ducts and that the epithelium in the uterine cervix strikingly resembles that of some pseudomucinous cystomas. It is well to remember, however, that in normal ovaries, the surface epithelium never contains pseudomucinous cells although ciliated serous cells are often found in it.

At present the most commonly accepted view is that first suggested by Hanau[20] and Kappeler[21] who regarded the pseudomucinous cystomas as derived from *fetal entodermal inclusions*. This would mean that these tumors are teratoid growths and indeed Sutton[22] classified them as a special type of dermoid in which intestinal epithelium predominates. The striking resemblance between the pseudomucinous cystomas and the gastrointestinal epithelium (especially its tumors), their frequent association with dermoids in the form of "muco-dermoid cysts"

[1]*de Sinéty and Malassez* A82057/878, *Flaischlen* A40044/882, *Nagel* A88239/888, *Pozzi* A43584/890, *Frommel* A43527/890, *Pfannenstiel* A45890/891, *Semb* A70956/896, *Wendeler* A11814/897, *v. Franqué* A50571/898, *Amann* A11478/899, *Gebhard* A73657/899, *Limnell* A70119/01, *Pick* A7097/01, *Walthard* A64863/03, *Betschmann* A70585/02, *Wiedmann* A73023/06. *Gottschalk* A70732/10, *Meyer* A64795/16, *Miller* A18279/37, *Scott* A55564/42.
[2]*Frankl* A70706/03.
[3]*McCarty* A64392/32, A67243/30.
[4]*Flaischlen* A40044/882.
[5]*Novak* A63534/41.
[6]*Miller* A18279/37.
[7]*Marchand* A70821/879.
[8]*Williams* A69464/891.
[9]A70119/01.
[10]*Steffeck* A43591/890.
[11]*Noeggerath* A29354/880, A77049/880, *Gottschalk* A81132/01-2, *Lahm* A64784/14, *Dörfler* A76945/28.
[12]*Fernbach* A81026/863, *Böttcher* A76918/869, *Olshausen* A70877/10.
[13]*Förster* A76963/865, *Meyweg* A81049/868, *Rindfleisch* A77076/878.
[14]*Gottschalk* A81132/01-2.
[15]*Gardner* A92816/38.
[16]*Frankl* A76805/14, *Goodall* A73686/19-20, *Miller* A18279/37.
[17]*Coblenz* A70624/881, A40334/881, *Kossmann* A70779/895.
[18]*Fischel* A70687/880, *Goodall* A73686/19-20.
[19]*Kossmann* A70779/895, *Wendeler* A47413/896.
[20]B22473/885.
[21]A73862/896.
[22]A45130/889, B7195/27.

and the presence of argentaffin cells[1] and intestinal ferments (see part on Chemical Composition of Common Ovarian Cysts) in these cystomas convinced many subsequent workers that these neoplasms are essentially monodermal teratoids.[2]

It is now almost unanimously agreed that *pseudomyxoma peritonei* results from the rupture of pseudomucinous cystomas and their consequent generalization in the peritoneal cavity. It is true that both in women and in men the appendix may form pseudomucinous tumors and that their rupture may also lead to pseudomyxoma peritonei. Nevertheless the theory according to which all cases of peritoneal pseudomyxoma result from primary appendicular tumors[3] is certainly incorrect, especially since in most cases the appendix is entirely normal.[4] The frequent coincidence of pseudomyxomatous tumors in the appendix and ovary is certainly noteworthy, however, (for literature see passage on propagation of pseudomucinous cysts, above). Probably both organs are capable of primary pseudomyxoma formation and subsequent rupture of these tumors may lead to peritoneal pseudomyxoma with a predilection for ovarian metastases in the case of primary appendicular tumors and vice versa.

The histogenesis of pseudomucinous cysts and peritoneal pseudomyxoma has been reviewed repeatedly.[5]

A great deal of attention has also been given to the role of *heredity* in the development of common cysts. In this connection it has been pointed out that ovarian cysts frequently develop in sisters[6] and twins,[7] as well as in the daughters of women who bear similar growths.[8] The occurrence of ovarian cysts in women with malformations of the urogenital system[9] likewise tends to emphasize the importance of hereditary predisposition (see also passages on Racial Incidence and Clinical Course of Common Cysts).

Whether it is justified to assume that *trauma* may lead to ovarian cyst formation[10] is rather doubtful. Following hysterectomy the ovaries may undergo cystic degeneration (see passage on Effect of Uterus Extirpation upon Ovaries in Sect. IV, Vol. IV) but usually only in the form of small follicle cyst formation; true cystomas rarely develop under these conditions.[11]

The *experimental production* of ovarian cysts[12] yielded no convincing data concerning their functional pathogenesis. but it is noteworthy that the tissue of pseudomucinous cystomas taken from women has been successfully transplanted into mice and rats. Such grafts showed definite growth after the lapse of 3 months provided the implantation was carried out intraperitoneally in the vicinity of the kidney. In the second mouse passage the transplants grew less vigorously and in the third passage no growth occurred.[13]

CLINICAL COURSE

REVIEWS: Manrique A81047/873, A81048/875, *Gallez* A81030/873, *Tipjakoff* A43003/887, *Maury* A81283/889, *Montgomery* A47500/895, *Kreiss* A81192/23, *Aza* A71384/28, *Curtis* A63170/30-42, *Baksht* A62828/32, *Pickell* A61646/33, *Mueller* A59472/36.

In contrast to the hormone-producing cysts, the symptomatology of the common serous and pseudomucinous cysts is not very characteristic. Generally, the presenting symptom is a *mass* in the lower abdomen which is usually situated on one side of the midline or in Douglas' space. In view of the great variability in the size, shape and consistency of the ovarian cystomas little can be said concerning typical features which would facilitate their identification by pelvic examination. It is also noteworthy that, especially in very adipose women, the tumor may attain a remarkable size before the patient notices it; even then her only complaint may be an increase in the volume and hardness of her abdomen. Unless inflammatory changes or nutritional disturbances affect the cyst, it is usually neither painful nor tender to touch.

The *menstrual cycle* is frequently unaffectd by the common ovarian cysts; but if much ovarian tissue is destroyed there may be *amenorrhea*[14] while in other cases *menorrhagias* or *metrorrhagias* develop[15] and the menstrual cycle becomes irregular.[16] *Postmenopausal hemorrhages* may also occur[17] and in one unusual case apparently *normal cyclic bleeding* recurred long after the menopause in a woman

[1]*Masson* A95406/38.
[2]*Landau* A77019/04, *Schickele* A76879/11, A75850/22, *Frankl* A76805/14, *Ribbert* A76874/14, *Meyer* A64795/16, *Ley* A78607/19-20, *Lecène and Bierry* 16970/23, *Shaw* A61896/32, *Williams* A62958/32, *Masson* A95406/38.
[3]*Bondy* A77157/13, *Gorke* A77191/17, *Körner* A77223/26, *Gräfenberg* A77195/28.
[4]*Biggs* A77151/20, *Otto* A77263/28, *Baniecki* A77145/29, *v. Nagy* A77254/33, *Antoine* A28090/35.
[5]*Gottschalk* A77192/01, *Gangl* B12359/33.
[6]*Löhlein* A47409/896, *Hauptmann* A53166/33.
[7]*Leared* A69782/878.
[8]*Simpson* A81293/05, *Cottalorda et al.* A70635/35.
[9]*Lee* A81621/879, *Voff* A49136/897.
[10]*Wilson* A41901/887.
[11]*Frankenstein* A70705/08.
[12]*Vignes* A95435/37.
[13]*Zondek et al.* A98187/43.
[14]*Rendu* A83109/894, A83108/895, *Kosmak* A81372/20, *Miller* A18279/37.
[15]*Masse* A77248/876, *M'Mordie* A42201/888, *Reamy* A44001/891, *Oliver* A45848/891, *Rendu* A44157/892, A69849/893, *Reid* A48370/896, *Lewers* A48387b/897, *Camelot* A81323/04, *Eudes* A81081/07, *v. Fekete* A79279/27, *Nakayama* A65624/30, *Miller* A18279/37.
[16]*Lepper et al.* A96607/38.
[17]*Lepper et al.* A99467/38, *Rickford and Whapham* A98177/42.

whose ovaries contained multiple cysts (no histology.).[1] The pathogenesis of these uterine hemorrhages is not very well understood. Fränkel[2] expressed the view that ovarian cystomas may cause widespread endocrine disturbances by influencing the hormone production of the pituitary but, except for the hormone-producing cysts, no adequate evidence for this assumption is as yet available. While some of the serous microcystic cystomas or fibroadenomas of the ovary are associated with menstrual irregularities[3] others are not, and there is no definite proof of their ability to elicit endocrine disturbances.[4]

In some instances of common cysts, especially in those in which the metrorrhagias occur after the menopause, the possibility of uterine cancer must be considered and several instances have been described in which common ovarian cystomas, especially serous papillomas, and *carcinoma uteri* developed simultaneously.[5] It is debatable whether these two conditions were merely coincidental or whether there is some etiologic connection between them. More frequently *uterine fibroids* occur in bearers of common ovarian cystomas especially serous papillomas[6] and *endometrial polyps* may develop either in conjunction with fibroids or without the latter.[7] The combination of common ovarian cystomas with irregular bleeding, uterine fibroids and polyps is not sufficiently constant to make an etiologic correlation obvious without statistical analysis; yet in view of the fact that these changes are so frequent in women with tumors (follicle cysts, small cystic degeneration, folliculomas) which are known to induce hyperfolliculoidism, the possibility of a hormonal etiology should be considered. Without extensive histologic study of the cystic growth on serial sections, it would be impossible to exclude the presence of small islets of granulosa or theca growths which could produce excessive amounts of folliculoid hormones. Suffice it to call attention to the possibility that certain elements in common cystomas may be the source of folliculoid hormones and influence the uterus through the intermediary of the latter.

Sometimes common cysts are associated with *adenomyosis and endometriosis* (external adenomyosis) of the uterus.[8] This again may be due, at least partly, to hyperfolliculoidism.

The mere mechanical pressure caused by the growing cystomas sometimes led to serious *displacement of the uterus*[9] and causes its *retroversion* or *retroflexion*[10] and even *prolapse* (the latter is discussed below under Complications). In rare instances a one-sided cystoma may cause *rotation of the uterus* around its axis and consequent disturbances due to torsion.[11] Secondary *atrophy of the uterus*[12] or *hypertrophy*, especially of the cervix[13] may also occur. In a few cases ovarian cysts developed in women whose internal sex organs were congenitally malformed and exhibited *aplasia or atresia of the uterus and vagina*,[14] *uterus duplex*,[15] *uterus unicornis*,[16] uterus *bicornis unicollis*,[17] or *uterus trifidus*.[18] In these cases the possibility must be kept in mind that a common hereditary etiologic factor could have been responsible for the uterine malformation and the ovarian cyst.

Signs of *pseudohermaphroditism* are rarely noted in women bearing common cystomas.[19] In pertinent cases it should be kept in mind that certain areas of an apparently common type of cystoma may have developed into tissue (Leydig cells, hypernephroma or arrhenoblastoma tissue) capable of producing testoid hormones and that the pseudohermaphroditic differentiation of the sex organs is not necessarily the result of the ovarian tumor formation but the two, if related at all, may merely be concurrent manifestations of an error in development.

The *oviduct* is also frequently affected in patients with ovarian cystomas. The cases in which the cyst cavity communicates with the Fallopian tube have been discussed in the morphologic section under the heading of "tubo-ovarian cysts". Ovarian papillomas

[1] *Maling* B13330/07.
[2] A68511/23-4.
[3] *Dworzak* 6582/32.
[4] *Scott* A55564/42.
[5] *Forssner* A70696/, *Driver* A82437/858, *Hayes* A69308/879, *Ludlam* A40454/882, *Jessett* A70752/896-7, *Atkins* A70574/04-5, *Fuchs* A70715/08, *Bouchard* A70593/11, B11302/11, *Werner* A73021/13, *Delannoy and Breton* A78199/26, *Fernandes* A96024/36, *Yun* A59484/36, *Nicoletti* A95079/37, *Miller* A18279/37, *Freire* A97368/40.
[6] *Hare* A81556/864-5, *Panas* A77061/871, *Lawrence* A69328/878, *Edis* A82445/879, *Seeley* A29731/880, *Quénu* A70912/885, A70915/886, A70914/886, *Mallet* A81465/887, *Mann* A41815/887, *Iversen* A42394/888, *Negri* A42725/888, *Czempin* A70644/888, *Sztembarth* A45233/889, *Crawford* A81340/892, *Monod* A46308/892, *Mann* A46448/893, *Scheffer* A70944/896, *Lovrich* A70802/897, *Dirner* A48409b/897, *Everke* A70677/899, *Heger* A881455/02, *Senn* A81502/02, *Piet* A81484/04, *Kaufmann* A70762/10, *Rosenstein* A70928/10, A70927/10, *Mériel* A73065/13, *Strassmann* A70972/15, *Barrett* B21192/21, *Aubert* A81886/22, *Rouffart* A70933/24, *Fontoynont* A68008/29, *Miller* A18279/37.
[7] *Hemken* A69311/863, *Coe* A40278/883, *Crawford* A81340/892, *Piet* A81484/04, *Pugliatti* A70908/35, *Miller* A18279/37.
[8] *Miller* A18279/37.
[9] *Voisin* A81519/803, *Miller* A18279/37.
[10] *Martinetti* A82479/884, *Fraipont* A45693/891.
[11] *Winter* A82157/899.
[12] *Packard* A82499/863, A82500/867.
[13] *Bristowe* A68374/853-4, *Mo* A82491/876, *Dumreicher and Heschl* A82439/876-7, A82440/877, *Didier* A45245/889, *Farr* A43631/890, *Desbonnet* A44803/894, *Pépin* A81473/05.
[14] *Gould* A82468/864-5, *Gomez Pamo* A40566/882, *Lee* A83223/05.
[15] *Cestan* A81333/01.
[16] *Yamada* A82158/896.
[17] *Rossi* A97434/40.
[18] *Depage* A44818/894.
[19] *Olshausen* A41468/877-886, *Roten* B13/895, *Davis* A7006/00, *Alberti* 37893/05, *Grawitz* B14-05, *Hofbauer* A80132/09, *Fruchaud and Vialle* B20712/26, *Miller* A18279/37.

frequently occur in combination with papillomas of the oviduct.[1] In other instances a cystoma may cause considerable elongation of the oviduct,[2] hydrosalpinx,[3] hematosalpinx,[4] or amputation of the contralateral tube[5] all of which are generally due to the mechanical disturbances resulting from the formation of adhesions. Amputation of the homolateral oviduct is especially frequent in the case of torsion (see chapter on Self-Amputation in Sect. IV, Vol. VI). Simultaneous occurrence of salpingitis with ovarian cystomas is likewise common.[6]

Enlargement of the *mammary glands* is rare but may occur with common ovarian cystomas perhaps owing to folliculoid hormone production by some of the cells in the tumor. This change usually disappears after ablation of the growth.[7]

Among the metabolic effects of ovarian cysts, *emaciation* is seen, especially if the tumor reaches a considerable size.[8]

Very large tumors may also seriously interfere with respiration thus causing *asphyxia*.[9]

A comparatively common accompaniment, especially of the papillomatous ovarian cysts, is the development of *ascites* which may reach considerable proportions.[10] The relevant statistical data are difficult to interpret because of differences in the criteria used to identify the cysts, but our own review indicates that serous cysts, and especially serous papillomas produce definite ascitic accumulations in about 30-60% of the cases while among pseudomucinous cystomas the incidence of ascites is hardly more than 10%. It is important to realize that although ascites is more common in malignant ovarian growths, it is no pathognomonic criterion of the latter as it occurs quite frequently with benign cystomas. Conversely, it must be remembered that probably many of the supposedly relevant cases, especially those described in the old literature as benign cystomas or papillomas with ascites, were actually unrecognized ovarian cancers.

Pleural fluid accumulations are less common than ascites, but may occur with or without the latter in women suffering from ovarian cystomas and papillomas.[11] These cases are reminiscent of the so-called "Meigs' syndrone" seen in ovarian fibromas, but the casual connection between the ovarian growths and the hydrothorax is still unclarified.

Glycosuria[12] or *albuminuria*[13] are rare accompaniments of ovarian cysts but at least the glycosuria appears to be casually connected with the ovarian blastomas since in many relevant cases sugar elimination ceased after removal of the cysts.

The *cardiovascular system* is frequently affected, especially by the large cystomas which impose a considerable additional strain upon the heart sometimes causing hypertrophy (occasionally with marked hypertension). It may lead to displacement of the heart due to mechanical factors and to severe cardiac failure.[14] Dilation of veins[15] and the formation of hemorrhoids[16] are other examples of mechanically induced vascular disturbances.

Changes in the *blood count*, especially a more or less pronounced degree of anemia, may also occur with ovarian cystomas[17] and in one patient a pseudomucinous cyst and papillary adenoma of the ovary was accompanied by a leukemoid blood picture.[18] The latter may have been casually connected with the ovarian lesion since the blood count returned to normal after removal of the growth.

Among the *gastrointestinal symptoms*, persistent vomiting due to peritoneal irritation by the cyst

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[1]*Doran* A70657/887-8, *Green* A44058/892, *Smith* A47324/895-6, *Sinclair* A47507/895-6, *Clark* A50566/898, *Ramsay and Giles* A70916/00-1.

[2]*Fuller* A82457/857-8.

[3]*Panas* A82504/876, *Iversen* A42391/888, *Winslow* A42546/888-9, *Goelet* A46469/893, A50575/898, *Sitzenfrey* A77295/08.

[4]*Thornton* A40844/884-5, *Walla* A69462/01.

[5]*Salgado* A59475/36.

[6]*Iversen* A42384/888, A42387/888, *Fedorenko* A81450/890, *Jacobi* A70848/892, *Jacobs* A74723/892, *Lemichez* A47408/896, *Pfannenstiel* A70891/896, *Cornil and Peraire* A76934/06, *Culbertson* A81216/19.

[7]*Lepper et al.* A99467/38.

[8]*Helmuth* A75515/884-5.

[9]*Battye* A69764/860, *Gelineau* A69996/876.

[10]*Berger* A82118/722, A82119/758, *Jördens* A81597/796, *Heidrich* A81568/824, *Cloquet and Larrey* A68409/840, *Larrey* A69326/840-1, *Ward* A82100/840-1, *Palmer* A82503/851, *Bolton* A82341/851, *Busi* A68388/851, *Bruzelius* A69742/866, *Boinet* A86146/869, *Panas* A77061/871, *Marsden* A82477/872, *Caubet* A82820/874, *Bellamy* A81272/874, *Fravel* A29374/879-80, *Terrillon* A42080/885, A43515/890, *Dudon* A70664/886, A69942/886-7, *de Larabrie* A81460/885-6, *Terrier* A41971/887, *Montgomery* A42318/888, *Ballenghien* A82623/889, A43297/899, *Pascale* A42694/889, *Lomer* A43372/889, *Cabot* A43498/890, *Sutugin* A45611/890, *Frascani* A82617/890, *Doran* A70658/893, A46526/893, *Touvenaint* A47475/895, A70996/895, *Arene* A48239/896, *Williams* A51022/898-9, *Kinkead* A82672/898-9, *Pujebert* A81126/00, *Prodanoff* A82197/01, *Papanicol* A81472/01, *Perrilliat* A81482/03, *Henkel* A70859/04, *Péraire and Cornil* A77066/06, *Jones* A81221/11, *Maier* A70812/14-5, *Preble* A70906/15-6, *Reynès* A81234/20, *Gosopath* A76980/24, *Warren* A65191/31, *Hsu* A66123/32, *Gernez and Gasne* A70722/34.

[11]*Marsden* A82477/872, *Terrier* A41321/884, A41926/887, *Demons* A82432/887, *Freund* A42635/889, *Wrzyszozynski* A46419/892, *Ott* A70878/890, *Williams* A73025/894, *Resinelli* A49192/897, *Preble* A70906/15-6, *Bell* A70584/29, *Natale* A53102/33, *Bianchi* B21413/38.

[12]*Imlach* A40976/885, *v. Lennep* A43625/890, *Croom* A48265/895-6, *Beyea* A76916/00, A76915/00, *Cohn* A74718/01, *Evelt* B153/07, *Henkel* A21625/09, *Solovjeff* B154/10, *Stolper* 48291/13, *Saidl* A62256/32.

[13]*Cloquet* A82357/841, *Södermark* A43589/890.

[14]*v. Russdorf* A82524/867, *Hardy* A69306/886, *Abbott* A43386/890, A49198/898, *Rübsamen* A77082/11, *Marais and Kermorgant* A75864/21, *Kimura* A65162/30.

[15]*Flaischlen* A76960/09.

[16]*Seeley* A29731/880, *Skene* A81509/00.

[17]*Helmuth* A75515/884-5, *Cleveland* A43523/890, *Bender* A80965/03.

[18]*Winans* A65195/31.

is probably the most important.[1] The exceptional occurrence of gastric ulcers in cyst-bearing patients[2] is probably coincidental.

Among the nervous symptoms ano-rectal or lumbar *pain* is a very common complaint[3] and in some cases ovarian cysts cause severe dysmenorrhea.[4] Less frequently cardiac neuroses[5] and *mental disturbances*[6] have been observed.

COMPLICATIONS

REVIEWS: Douglas A43265/889, A81445/890, *Martin* A96824/899, *Potherat* A81491/893, A81490/893, *Ciuti* A47441/895, *Seitz* A70954/03, *Clarkson* B13203/07, *Clivio* B13187/07.

Among the most frequent and important complications are *hemorrhage* into the cyst cavity or, after rupture, into the peritoneum; *torsion* of the pedicle and *abscess formation* due to secondary infection. All these have been discussed in the chapters specifically devoted to the above mentioned lesions (see Sect. IV, Vol. VI) and hence will not be treated here. *Malignant transformation* results in carcinoma or, more rarely in sarcoma formation within the cysts and is given special attention in the chapters on ovarian carcinoma and sarcoma respectively (see below).

By far the most common incident likely to complicate the course of ovarian cysts is their *rupture*, with subsequent evacuation of the cyst contents into neighboring organs, most frequently the peritoneum.[7] The flooding of the peritoneal cavity with the cyst contents may lead to marked peritoneal irritation and in the case of infected cysts to actual peritonitis. The "peritoneal papillomatosis" subsequent to rupture of serous papillomatous cysts and the "pseudomyxoma peritonei", which usually results from intraperitoneal evacuation of pseudomucinous cysts, have been discussed in the passage on Pathologic Anatomy (see above).

Although rupture of ovarian cysts frequently occurs without any detectable immediate cause, this complication is usually elicited by some trauma such as a blow to the abdomen, vomiting, labor, a pelvic examination, etc. In rare instances it may result in a permanent cure and not infrequently the same cyst *ruptures repeatedly*, a phenomenon which has been termed "hydrops ovarii periodicus" and leads to the intermittent disappearance of

[1] *Böhm* A82136/880, A40627/883, *Deale* A47345/896.
[2] *Labit* A69324/878.
[3] *Lorey* A82255/867, *Reamy* A44001/891, *Bolen* 84398/43.
[4] *Duncan* A41844/887, *Dorsett* A69676/07-8.
[5] *Boldt* A82340/886.
[6] *Edwards* A82446/818, *Roussel* A82523/841, *Mäurer* A40315/881, *Terrillon* A41973/887.
[7] *Lhéritier* A87538/835, *Blaquiere* A82338/836-7, *Domville* A82436/842-3, *Schlesier* A82530/843, *Camus* A82350/844, *White* A82566/845-6, *Bainbrigge* A82596/847, *Trautwein* A69796/847, *Dugas* A82438/852, *Tuffnell* A69889/852, *Simpson* A82535/852, A82536/853, A82537/871, *Lee* A69331/857, A69330/884, *Wells* A82564/858, A82565/860, *Fuller* A82458/858, *Farrar* A82451/858, *de Castella* A82351/858, *Rigler* A82518/859, *Pitman* A82509/859, *Barry* A82323/859, A82324/861, *Fifield* A82452/860, A82453/862, *Cockle* A82358/861, *Soltan* A82543/862, *Oppolzer* A82498/863, *Holmes* A86209/863-4, *Zotti* A82570/868, *Palm* A82314/868, *Kidd* A82671/868-71, *Kroker* A82311/869, *Chrobak* A82354/869, *Jessop* A69320/871, *Duncan* A82441/872, A82442/878, A29369/879, *Taillaux* A82546/873, *Menzel* A82485/873, A82486/876, *Gosselin* A82466/874, *Nepveu* A82495/875, *Martinet* A82478/875, *Kryzan* A82312/875, *Calkins* A82348/875, *Hagan* A69303/876, *Raborg* A82514/877, *Keith* A69322/877, *Vanzetti* A82559/877, *Schüller* A82532/878, *Chadwick* A82352/878, *Mundé* A82492/878, A40368/882, A40431/882, A74903/884, A68607/885, A68606/885, *Cleeman* A82356/879, A82355/879, *Buechner* A29478/880-1, *Wiltshire* A40350/881, *Hunter* A29986/881, A29838/881, *Schauta* A40372/882, *Laroyenne* A40569/882, *Lenepveu* A40223/882, *Boerner* A66967/883, *Waite* A41233/883, *Burton* A86153/884, *Thiriar* A74913/884, *Zwicke* A82571/884, *Emmet* A82448/884, A41638/884, A82449/885, *Willits* A82567/885, *Doran* A40829/885, *Newman* A42064/886, A42101/886-7, *Limont* A66986/886, *Desguin* A82433/886, *Cordier* A68415/886, *Ball* A41670/886, *Aubert* A74957/886-7, *Baer* A41645/886-7, *Schmid* A42238/887, *Barton* A42292/887-8, A42293/888, A42415/888, *Prewitt* A42538/888, *Dolard* A42371/888, *Wallace* A42478/888, *Morison* A42401/888-9, *Hofmokl* A43275/889, *Heitzmann* A45091/889, *Pantzer* A45231/889, *Polaillon* A45195/889, *Casini* A66968/890, *Schwarz* A43588/890, *Beale* A43985/891, *Gross* A46589/891-2, *Zigura* A83513/892, *Moore* A44665/892-3, *Stobbaerts* A83504/893, *Duffner* A44605/893, *Peterson* A46453/893, *Sheldon* A44673/894, *Dunning* A47485/894-5, *Hall* A47117/895, *Kitagawa* A66983/895, *Farrell* A47489/895, A48435b/897, *Storer* A69032/896, *Demons* A48302/896, A66974/00, B13321/07, *Mitchell* A66988/896, *Bogdanik* A48401/896, *O'Conor* A48984/897, *Scharfenberg* A66961/897, *Solé* A49016/897, *Moulonguet* A49072/897, A49050/897, *Gage* A48380b/897, *Tóth* A50518/898, *Blanc* A50563/898, *Arnal* A50956/898, *Lamugue* A82714/898, *Köppen* A66984/899, *Martin* A96824/899, *Grodecki* A66979/899, *Sutton* A83483/00, *Haultain* A66980/00-1, A66981/01, *Das* A66971/01, A66972/01, *Fossard* A82712/01, A82713/01, *Jacobs* A74724/01-2, A66982/04, *Termier* A69033/02, A69034/02, *Smith* A67000/02, A66999/02, *Spencer* A69031/02, *Oliver* A66991/03, *Clark* A66969/03, *Potherat* A66995/03, *Goffe* A81451/03, *McCann* A66987/03, *Young* A69037/04, *Potherat and Lutaud* A66997/04, A66996/04, *Brokesch* B12775/04, *Alcock* A66962/04, *Elder* A66976/04-5, *Polak* A66994/05, *Daniel* A66970/05, *Monprofit* A81469/06, *Severeano* B13245/06-7, *Boldt* A81386/07, *Leroy and Dubar* B13328/07, *Bogdanovics* B13210/07, B13318/07, *Dewailly* B9410/07, *Schickele* B11290/09, *Gessen* B11278/09, *Briggs* A81388/09, *Ott* A81403/09, *Harvey* A81396/10, *Cumston* A81391/10, *Cuzzi* A81392/11, *Schaeffer* A81411/12, *Massonnaud* A81385/12, *Messa* A81399/12, *Patel* A81404/12, A81405/13, A81406/25, *Tédenat* A70984/13, *Summers* B11870/18, *Fergusson* A81393/19, *Kalyanvala* B5549/19, *Mondor and Bouchard* A81400/23, *Frers* B8278/23, *Bell* A76913/23, *Melchior* A81398/24, *Pérez and Guiroy* A81695/25, *Albrecht* A76901/25, *Phaneuf* B20816/26, *Herrmann* A65548/29, *Condamin and Brunat* A65910/29, *Dougal* A76948/30, *Domenico* B21162/30, *Gilardino* A62299/32, *Heiman* A62303/32, *Florence and Graeff* A66118/32, *Carpentier* A61373/33, *Brown* A61369/33, *Masson and Philips* A61636/33, *Orrù* A61643/33, *Sachs* A52300/34, *Sövényhásy* A62175/35, *Wanderly Filho* A61775/35, *Lębovitz* A95225/37, *Decoulx and Patoir* A95201/37, *Lenozowski* A97001/38, *Massabuau et al.* A97004/38, *Bowen* A97604/39, *Deschamps* A97706/40, A97705/40, *Spring* A97415/40, A97828/42.

ovarian cysts.[1] In a rather unusual case of this type an ovarian cyst ruptured 17 times, always re-establishing its cavity.[2] Apparently under certain conditions a patient can become sensitized to her own ovarian cyst fluid, and develop a "serum rash" after rupture.[3]

Perforation into the *oviduct*[4] results in a "tubo-ovarian cyst" and is discussed in the corresponding passage (see above).

In the case of adhesions with adjacent organs, the cyst contents may be discharged directly into the latter. Thus many cases are known in which perforation occurred into various parts of the *intestinal tract* causing discharge of the cyst fluid through the intestine and the establishment of a fistula between the bowel and the cyst.[5] This leads to secondary infection of the cyst cavity. Perforation may also occur into the *urinary bladder*,[6] *gall bladder*,[7] *oviduct* (see "tubo-ovarian cysts"), *uterus*,[8] *vagina*,[9] or directly to the *body surface* through the skin or navel.[10] Occasionally *complicated fistulae* are established owing to repeated perforations in different directions. Thus the same cyst may rupture into both the rectum and the Fallopian tube[11] or the skin and the vagina,[12] thus connecting these organs with each other.

As a result of mechanical interference with the intestinal tube, *ileus* can be produced by ovarian cysts or their adhesions.[13]

Pressure upon the ureters can cause hydronephrosis and even anuria due to *ureteric obstruction*.[14] In one series of observations more or less pronounced changes in the upper urinary tract (hydronephrosis, pyelitis, etc.) were noted in 82% of the women with ovarian cystomas.[15]

Incarceration of large ovarian cyst in the pelvic cavity may also elicit manifold serious disturbances.[16]

The increased intraabdominal pressure occasioned by the growing cyst, frequently causes *utero-vaginal prolapse*,[17] and various types of herniae. Probably because of the direction of the pressure, *umbilical herniae* are especially frequent in women with large cystomas,[18] but *femoral*,[19] *inguinal*[20] or *diaphragmatic*[21] herniae may also occur.

Interference with the blood supply to the lower extremities tends to produce *edema of the legs*, sometimes under the clinical picture of the "phlegmasia alba dolens".[22] In many of these cases complete occlusion of the iliac or femoral veins by *thrombi* was demonstrable and this in turn occasionally led to pulmonary *embolism*.[23]

Appendicitis is comparatively common in women with ovarian cysts, so much so that an etiologic relationship between the two is considered probable

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[1] *Pätsch* A82501/835, *Waters* A82105/842, *Huss* A69316/856, *Ballard* A82320/870, *Thomas* A75186/879, *Meredith* A40318/880, *Hunter* A40019/881, A75537/885, *Ruge* A43587/890, *Robinson* A46312/892-3, A46348/893, *Wilson* A82205/897, *Malcolm* A50546/898, *Ascari* A82711/03, *Bevan* A82371/19.

[2] *Reuss* A29773/881.

[3] *Kennedy* B7490/25.

[4] *Bennett* A82332/854.

[5] *Fraser* A82455/844, *Grabacher* A82469/846, *Smith* A82541/852, *Nonat* A82496/853, *Lumpe* A82474/858, *Payne* A82987/861, *Salter* A82527/862, *Lacrousille* A69325/864, *Murchison* A82493/866-7, *Quinby* A82513/875, *Terrier* A82547/877, *Le Double* A82253/878, A82252/878, *Cuvier* A82364/878, *Tournay* A40002/881, *Smart* A40510/882, *Hernandez* A40660/883, *Broomall* A82345/884, *Radcliffe* A40877/885, *Alexander* A41977/887-8, *Formad* A42681/91, *Dean* A45692/890, *Lediard* A43636/890, *Cripps* A47133/894, A44627/894, A48374b/897, *Smythe* A40976/897, *Thomas* A69035/00, *Harries* A27871/35.

[6] *Bennett* A82330/848-9 A82331/858, *de Lamallerée* A41620/884, *Courrent* A42339/888, *Martin* A77035/05, *Sorel and Marquer* A81238/08, *Bonamy* A81387/09, *Pillet* A70895/13.

[7] *Lucy* A69821/00.

[8] *Vassallo* A82316/862, *Bell* B7451/24.

[9] *Weitenkampff* A82563/836, *Hounsell* A69315/864, *Kemp* A81684/13, *Grad* A70736/18, B9448/18, B9442/18.

[10] *Beattey* A74829/852-8, *Quass* A82512/871-2.

[11] *Decori* A82367/852.

[12] *Grognot* A82310/877.

[13] *Bennett* A86143/858, *Lejeal* A69332/868, *Hayem* A69307/868, *Ryan* A82525/876, *Henry* A29413/880, *Mathes* A40343/881, *Satterthwaite* A82529/881, A29990/881, *Ayer* A41732/887, *Peters* A70887/895, *Curgenven* A47342/896, *Shalita* A49133/897, *Mordret* A50488/898, *Savory and Nash* A70940/01, *Gottschalk* A81132/01-2, *Meriel* A77040/08, *Ronsheim* A81235/17, *Speese and Skillern* B21382/17, *Woodman* B11777/22, *Leveuf* A81225/25, *Cabot* B10775/28, *Wodarz* B5949/28, *Serafini* A65109/31, *Nestor* A65102/31, *Beall* A66102/32, *Machado* A61568/33.

[14] *Rayer* A82516/853, *Fullar* A82457/857-8, *Mears* A82483/874, *Terrillon* A41543/884, A74562/898, *Tillman* A43560/890, *Vanverts* A49041/896, *Matheson* A27751/35, *Morris and Juracsek* A95299/37.

[15] *Kretschmer and Kanter* A95270/37.

[16] *Christovitch* A43567/890, *Rendu* A45670/890, A45639/890, *Briele* A76926/03, *Vanverts* A95433/38.

[17] *Boinet* A86146/869, *Heath* A69309/871, *Seeley* A29731/880, *Ashe* A40932/883, *v. Rokitansky* A40264/883, *Roesger* A82691/891, *Moreau* A82224/892, *Boursier* A44740/893, A46461/893, *Jouve* A81307/893, *Thiriar* A81514/893, A81513/893, A81512/893-4, *Swain* A49077/897, *Jasinski* A77219/897, *Wettergren* A82156/897, *Pépin* A81473/05.

[18] *Soriano* A82544/869, *Boinet* A86146/869, *Velasco* A29530/880, *Cazin* A29969/881, A86158/881, A29983/881, *Polaillon* A40484/885, *Galton* A86193/887, *Solovjeff* A44620/893, *Montgomery* A50511/898, *Jones* A81221/11, *Loicq* A70800/22.

[19] *Page* A66992/882-3, A40292/883, *Pike* A47466/895, *Wettergren* A82156/897.

[20] *Battle* A66963/05.

[21] *McArdle* A51962/34.

[22] *Gignoux* A75492/867, *Verneuil and Terrier* A77120/877, *v. Rokitansky* A87326/878, *Baer* A40991/885, A40992/885, A41041/885, A41016/885, *Ballenghien* A82623/889, A43297/899, *Savage* A74633/01-2, A74623/02, *Evans* A31511/39.

[23] *Gouguenheim* A82467/865, *Duguet* A34826/878, *Hofmokl* A45663/889-90, *Cleveland* A43523/890, *Box* A48329/896, *Engel* A62296/32.

by many clinicans.[1] The frequent simultaneous occurrence of pseudomyxoma peritonei and appendicular pseudomyxoma has been discussed in the passage on the propagation of pseudomucinous cysts.

Generalized peritonitis complicates ovarian cysts, especially if they become infected and subsequently rupture into the peritoneum[2] (see also chapter on Inflammations of the Ovary in Sect. IV, Vol. VI and paragraph on ruptured ovarian cysts in this chapter).

Among the unusual complications of ovarian cysts we may mention the simultaneous development of *gall stones*,[3] *omental cysts*,[4] *kidney cysts*,[5] *ectopic kidney*,[6] *urachus cysts*,[7] *tubal pregnancy*,[8] *pyosalpinx*[9] and *tuberculous salpingitis*.[10]

DIAGNOSIS

REVIEWS: DUTCH (*Jessurun* A82187/02).

ENGLISH: Brown A82141/850, A82140/850, A82139/850, *Hewitt* A82237/859, A82236/860, *Atlee* A77143/873, *Gillette* A82229/879, *Byford* A29433/880, *Dickson* A29833/880-1, *McGraw* A41588/883, *Emmet* A40914/885, *Rudall* A46599/893, *Barton* A82178/895, *Rishmiller* A49109/897, *Routh* A82198/01, *Palmer* A82195/01, *Wilson* A69036/01-2, *Sampson* A81357/07, *Gowlland* A81351/11, *Macfarlane* A70806/12, *Gardner* A81350/18, *Peple* A81355/20-1, *Troutt* B5943/29, *Chalfant* A65061/31, *Wilson* A97028/38.

FRENCH: Boinet A82137/840, *Chomel* A82143/843, *Naghi* A82128/861, *Clavé* A81016/862, *Billot* A82121/872, *Koeberlé* A82247/876, A82248/877, A82249/878, *Bernadac* A82120/877, *Terrillon* A45154/889, *Tillaux* A46414/893, A82200/898-9, A82201/899, *Folet* A50929/898, *Monod* A82191/00, *Brault* A61367/32.

GERMAN: Wild A82130/859, *Raichle* A82264/868, *Spiegelberg* A82272/873, *Rheinstaedter* A82267/875, *Schultze* A82270/879, *Werth* A82284/879, *Althan* A29894/881, *Seligsohn* A42580/888, *Pichevin* B12786/04, *Fraenkel* A82183/05.

ITALIAN: De-Cristoforis A82145/865, *Baccelli* A82117/876, *Landi* A29398/878, A82251/878, *Pestalozza* A42424/888, A42425/888, *Poso* A74631/899, *Vanasia-Scimone* A81359/07, *Marinelli* A81354/13, *Vaccari* B7186/27.

JAPANESE: Yokoda A46439/892.

LATIN: Ferrari A82175/861.

RUSSIAN: Dobrinin A82123/869, *Novitski* A82192/895-6.

SPANISH: Rubio A40058/882, *Horcajo Hernandez* A82176/00, *Becerro de Bengoa* A81343/19, *de Aragon* A81341/22.

The diagnosis of ovarian cysts does not tend to present great difficulties. It is based primarily on the history of the disease and on the findings at bimanual *palpation*. The smaller growths remain in the pelvis and are usually freely movable roundish bodies in the ovarian region.[11] In the case of larger growths the diagnosis must be based upon abdominal palpation and percussion.[11] It should be kept in mind that cystic ovaries may be transposed into the contralateral side of the pelvis and consequently elicit abnormal signs.[12] In some cases *X-ray* examination proves of great help.[13]

Diagnostic puncture of the cysts through the vaginal route was a popular procedure during the last century, as was therapeutic drainage. Microscopic and chemical examination of the cyst contents helped in the correct recognition of cystomas and frequently even mere inspection of the escaping fluid was sufficient to differentiate between abscesses, echinococcus and the serous, pseudomucinous or dermoid cysts.[14] At present this procedure is but rarely indicated[15] because the dangers connected with it generally outweigh its value. It may be mentioned, incidentally, that intestinal cysts (enterocystomas) may become impacted in Douglas' space and simulate ovarian cystomas. In this case diagnostic puncture only adds to the confusion, since the contents of such enteric cysts (and even the histologic structure of their lining) may be indistinguishable from that of pseudomucinous ovarian cystomas.[16]

Küster's sign, which occasionally permits distinction between dermoid cysts and other cystomas, is discussed in the section devoted to the former.

Peptonuria sometimes occurs following rupture of large cysts with subsequent absorption of their contents from the peritoneum. This has been claimed to be of diagnostic significance[17] but its value is somewhat doubtful.

In tubo-ovarian cysts *escape of fluid through the vagina* may be the presenting symptom,[18] while in other cases acute abdominal *pain*[19] or urinary *incontinence*[20] are the first manifestations of ovarian

[1] *Switalski* A70979/897, *Werder* A49195/898, *Cox* A69571/01, *Collins* A74611/01, *Shoemaker* A81508/04, *Eitel* B13022/04, *Ransford* B13008/04, *Berard* B12861/05, *Bell* A81319/06, *Ferbert* B12887/06, *Corner* A81338/06, *Koch* A70778/09, *Franzius* A80201/11, *Berry* A68485/23, *Mayne* A64927/29, *Jeanneney and Rosset-Bressand* A70850/30.

[2] *Wood* A82568/868, *Baldwin* A82319/876-7, *Wiltshire* A40206/881-2, *Hue* A41251/883, *Barth* A45622/890, *Matlakowski* A43548/890, *Pfaff* A46501/893-4, *Tarrell* A81510/895.

[3] *Baldwin* A81313/01, *Smithies* A81237/18, *Thomas* A81241/24.

[4] *Oliver* A81230/14.

[5] *Kay* A86217/888, *Segale* B8768/03.

[6] *Hegner* B13325/07.

[7] *Helmuth* A29350/879.

[8] *Martin* A46284/892, *Norris* A70873/00, *Rubin* A81356/17, *Johnston* B11846/18, *Materzanini* B7171/27, *Joachimovits* A70754/34, *Mair* A97404/39.

[9] *Bovée* B8908/03, *Schiller* B13055/04, *Jacobs* B13052/04-5.

[10] *Grad* B11307/10.

[11] *Schultze* A82269/864, *Novak* A63534/41, A94367/44.

[12] *Pi-Figueras* A61291/35.

[13] *Brown* A61369/33, *Astier* A59643/36, *Loud* A95283/36, *Niseggi and Moreau* A97600/41, *Novak* A94367/44.

[14] *Spiegelberg* A82271/869, A82199/879, *Walker* A82278/870-1, *Westphalen* A69298/875, *Weinlechner* A82279/876, *v. Rokitansky* A69216/878, *Tait* A29324/880, *Garrigues* A82226/882, A41281/883, *Piazza* A42274/887, *Martin* A96836/899.

[15] *Marinozzi* A96513/37, *Gomez Camejo* A97612/39.

[16] *Podleschka* B21723/32.

[17] *v. Jaksch* A69431/883, *Küstner* A40720/884.

[18] *Robertson* A82519/851, *Terrillon* A42572/888.

[19] *Ramond* A67258/30, A97014/38.

[20] *Picard* A47981/898.

cysts. These cases are rare, however, and in general the diagnosis rests upon the past history and the result of bimanual palpation.

From a differential diagnostic point of view it is especially important to distinguish ovarian cysts from *ascites*. Since both these conditions may cause considerable enlargement of the abdomen they have frequently been confused. A history of liver cirrhosis, cardiac decompensation, renal disease, peritoneal carcinomatosis and other conditions which usually produce ascites, speak in favor of the latter. In the case of ascites the abdomen shows tympany ventrad and dullness in the flanks in the recumbent patient; the dullness tends to sink whenever the position is changed. In ovarian cysts, on the other hand, tympany is in the flanks and craniad from the tumor while the dullness inventral, there being no change in these findings when the patient's posture is altered. Furthemore, if the abdominal wall is not too thick, palpation of the abdomen usually permits a sharp delineation of the tumor outlines in the case of ovarian cysts[1]

Uterine fibroids and ovarian cysts are often confused especially in the case of soft edematous or cystic, pedunculated fibroids. This error is sometimes difficult to avoid although large fibroids are usually hard and nodular thus manifestly differing from cysts. However, since the therapy of choice is surgical in either case, a faulty diagnosis will rarely have serious consequences.[2]

Pregnancy has frequently led to confusion with ovarian cysts although the fetal heart sounds and active movements of the child usually help diagnosis in advanced stages of gestation. In the early stages, the gonadotropic hormone content of the urine permits an accurate diagnosis in most cases. This problem of differential diagnosis is, therefore, no longer a frequent source of error as it was in previous years.[3] The occurrence of a *hydramnion* may add to the diagnostic difficulties.[4] In many cases ovarian cysts simulate *ectopic pregnancies* and vice versa, especially if they rupture under dramatic symptoms of peritoneal hemorrhage.[5] In such cases even the gonadotropic hormone excretion is no certain criterion since it is frequently not significantly augmented in ectopic gestation.

Tuberculous peritonitis may easily be mistaken for an ovarian cyst.[6] Since it frequently causes an encapsulated ascites between loops of intestine and omentum palpation and percussion fail to differentiate it from ovarian cysts. A history of pulmonary tuberculosis and tuberculin tests are sometimes of value. It should also be kept in mind that tuberculous peritonitis is likely to cause slight fever in the evenings. If the pelvic organs are normal, as judged by palpation, and the encysted mass is situated higher up in the abdomen, tuberculous peritonitis should be suspected, although some cysts with long pedicles may cause errors even in these cases.[7] The occasional type of *tuberculous salpingitis*[7] or *common pyosalpinx*[8] may also present itself under the symptomatology of an ovarian cyst.

Adiposity may lead to enormous enlargement of the abdomen such as is caused by large ovarian cystomas and in some cases pelvic examination under anesthesia may become necessary in order to arrive at the correct diagnosis.[7]

Among other conditions which have been confused with cystic ovaries we may mention *echinococcus* of the liver or the retroperitoneal tissue,[9] *appendicitis*,[10] *gastric myoma*,[11] *hydronephrosis*,[12] *pyonephrosis*,[13] *kidney cyst*,[14] *floating kidney*,[15] *ptotic*

[1] *Rostan* A82268/837, *Hutchinson* A81590/864, *Wells* A82282/864, *Desgranges* A82146/867-8, *Irnelath and Gosselin* A82243/869, *Peruzzi* A82262/869, *Kaufmann* A82246/876, *Weinlechner* A82281/876, *Hinze* A82238/879, A82239/880, *Gibier de Savigny* A40309/881, A82227/881, *Kommerell* A82250/883, *Gulliver* A42714/888, *Monod* A44209/892, *Barton* A82177/05, *de Vivo* A81347/07, *Dienst* A81348/12, *Chauffard* A81344/13, *Hare* B5542/19, *Gay* A62877/32, *Remmelts* A51979/33, *Brakemann* A61920/33, *Bais* A53025/34, *Sancho Castellano* A59710/34-5, *Novak* A94367/44.

[2] *Lee* A82254/871, *Williamson* A82280/876, *Emmet* A34827/878, *Baker and Cutler* A82132/879, *Drysdale* A29480/880, *Weinlechner* A40251/882, *Ladijensky* A82127/886, *Joubert* A43504/890, *Alexander* A45680/891, *Monestie* A82223/893, *Duret* A44655/894, *Philippart* A82684/895, *Collins* A82181/895-6, *Pichevin* A82196/897, *Indelli* B16244/15, *Brocq* B7198/27, *Aza* A66270/29, *Greenhill* A61386/33, *Clivio* A97607/39, *Novak* A94367/44.

[3] *Obertenuffer* A69874/816-8, *Gilbert* A82228/853-4, *Corrigan* A82144/855, *Brennan* A82138/859, *Fifield* A82150/859-60, A82151/862, *Bidron* A82134/872, *Martel* A82256/875, *Boldt* A43362/890, *Ludlam* A44661/894, A44698/894, *Varnier* A82204/01, *Oliver* A82194/03, *Wood* A82206/06, B13125/06, *v. Thun* A81358/09, *Fabre and Rhentier* A81349/11, *Pankow* A65625/30, *Zuckermann* A97410/41,

[4] *Herzberg* A81247/13, *Wetterwald* A81739/25, *Maister* A96702/28.

[5] *Rendu* A82266/874, *Johnston* A45126/889, *Bernardy* A45722/890-1, *Baldy* A45719/890-1, *Rosenstein* A69184/892, *Armstrong* A44188/892, *de Vlaccos* A74574/00, *Alfieri* B11294/09, *de Aragon* A81346/15, *Cornell* B21257/20, *Sigwart* B11767/22, *Petridis* B7177/27.

[6] *Gardner* A40468/884-5, *Davy and Roper* A76942/01, *Mangiagalli* A70817/12, *Azara* A81342/14, *Decio* A76943/31.

[7] *Novak* A94367/44.

[8] *Moiroud and Casalta* A61285/35.

[9] *Maigné* A50486/898, *Gutiérrez* A82185/00, *Delbet and Nazim* B9409/07, *Marchini* B10771/27, *Macciotta* A52124/34, *Merlino* A53101/34.

[10] *Hammond* A81352/13, *Allende* B11731/22, *Florence and Graeff* A66118/32, *Carpentier* A61373/33, *Bernstein* 81760/38.

[11] *Zwolinski* A97250/39.

[12] *Rosenberger* A29468/880, *Lefour* A82189/03, *Marshall* A82190/05, *Brändle* A81246/06, *Clemm* A81345/25, *Fruchaud* A61383/32, *Tagliaferro* A97640/39.

[13] *Delannoy and Driessens* A66111/32.

[14] *Krusen* B12891/06.

[15] *Mundé* A82259/888, *Fruchaud* A61383/32.

spleen,[1] *pelvic varicocele,*[2] *cyst of the urachus,*[3] *cyst of Meckel's diverticulum,*[4] *umbilical hernia,*[5] *intestinal tumor,*[6] lumbar *lymph nodes* enlarged by a malignant neoplasm,[7] *hepar cysticum congenitum,*[8] *a cyst of the omentum or mesentery,*[9] *a tumor of the abdominal wall,*[10] *a distended or abnormal urinary bladder,*[11] or even a large *gall bladder.*[12]

PROGNOSIS

REVIEW: Pozzi A69453/04.

The *growth rate* of common ovarian cystomas is extremely variable. Some grow very rapidly,[13] others slowly, and cases are on record in which such cysts were known to have existed for 20 years,[14] 35 years[15] and even 50 years.[16]

A comparatively small proportion of ovarian cystomas *heals spontaneously,* usually following rupture and subsequent absorption of the growth.[17] Pseudomyxoma peritonei may heal by transformation into glassy organized myxomatous masses.[18]

The *peritoneal "metastases"* tend to disappear after removal of the primary growth in cases of peritoneal papillomatosis and pseudomyxoma peritonei; in fact even mere laparotomy may have a curative effect as stated in the part on Therapy.

If cystic tumors are merely excised from the ovary they often *recur* in the gonadal remnant and if the whole ovary is removed, the contralateral gonad frequently becomes the site of cyst formation. These recurrences are particularly common in papillomas[19] and may occur many years after supposedly complete bilateral ovariectomy.[20] Pseudomucinous cystomas may also recur after apparently complete removal, but this is rare.[21]

As stated in the morphologic section, serous papillomas are very frequently bilateral. Hence, it is not surprising that after unilateral ovariectomy for a serous papilloma, the *contralateral gonad is often the site of similar tumor formation.*[22] Except during the child-bearing age it is, therefore, advisable to remove both ovaries in cases of papillomas even if only one gonad is manifestly affected.[23] Pseudomucinous cystomas are less prone to recur in the contralateral gonad although relevant cases have been described[24] and hence following ovariectomy for cystic tumors periodic check-ups are always indicated.

Not infrequently, secondary *recurrences develop in the abdominal scar* following surgical removal of serous papillomas[25] or pseudomucinous cystomas.[26] And it is noteworthy that the transplant may be malignant even if the removed ovarian cystoma was proven to be benign.[27]

The most serious consideration in connection with the prognosis of the common cysts is the possibility of *secondary malignant transformation* which is also particularly frequent among the papillomas. It may occur in untreated cases or in ovarian remnants left behind in the event of conservative surgical therapy.[28]

In general, however, it may well be said that the post-operative prognosis of common ovarian cystomas is excellent. In the event of unilateral ovariectomy the patient usually remains fertile and *normal pregnancies may ensue.*[29]

THERAPY

The cystic ovary usually undergoes such marked changes that complete ovariectomy is necessary. Removal of the ovaries for cyst formation was probably the earliest abdominal operation ever performed. Many of the pertinent old publications

[1] *Escobar Pires* A97611/39.
[2] *Casanovas* A65058/30.
[3] *Doran* A51128/898.
[4] *Spirito* A97218/38.
[5] *Hopkins* A44771/894.
[6] *Hornowski* A82186/06, *Vital* B8659/22, *Kramann* A95224/37.
[7] *Smith* A74634/893.
[8] *Atakam* A62053/36.
[9] *Lemarigny* B7166/27, *Elkin* A71393/28, *Luker* A97154/38, *Motta* A97212/38, *Dondi* A96617/41.
[10] *Guenther* A82124/868, *Cattaneo* B6007/28.
[11] *Oliver* A82193/899, *Bombi* A94800/37.
[12] *Kynoch* A82188/05.
[13] *Petit* A82015/876, *Canniot and Drain* B11268/09, *Murphy* A81376/16, *van de Poll* B13468/17-8, *Guyot et al.* B8027/26.
[14] *Gosopath* A76980/24.
[15] *Willard and Wilson* A82708/899.
[16] *Harris* A81557/871-2, A81558/872.
[17] *Rogers* A82520/858, *Boscher* A82342/867, *Avrard* A82318/868, *Brown* A68380/869, *Snow* A82542/869, *Sacré* A82526/869, *Philippart* A82508/871, *Cummins* A82363/875, *Santopadre* A69226/875, *Wright* A82114/876, *Lenoël* A69333/878, *Bernays* A82334/880, *Black* A40105/881, *McConnell* A40342/881-2, *Torrero* A40923/883, *Turretta* A41628/884, *Rosner* A69218/886, *Callanan* A82349/886, *Spadaro* A42658/889, *Viana* B9563/15, *Delannoy and Demarez* A95202/37.
[18] *Schley* A77291/31.
[19] *Terrier* A40808/884, *Jung* A74607/896, *Donald* A70654/02, *Malcolm* A81155/03, *Godart* A83652/05, A70726/05, *Bishop* A70587/05, *Odebrecht* A70875/05, *Meyer* A70832/10, *Flaischlen* A70692/10, *Hadden* A70743/23, *Vanverts* B5946/29.
[20] *Malcolm* A44830/894.
[21] *Terrillon* A42079/885, *Opitz* A77056/00, *Heinsius* A76991/08.
[22] *Henrotay* A74722/04-5, *Le Jemtel* A70794/06.
[23] *McCarty* A64392/32.
[24] *Wiener* A77129/14.
[25] *Laidley* A42308/888, *Weingärtner* A73019/01, *Roberts* A70924/03, *Tauber* A70980/27.
[26] *Audry* A43595/890, *Violet and Santy* A77122/12, A77121/12, *Laroyenne and Bouget* A77022/12, *Mohr* A77044/12, *Mourgue-Molines and Guibal* A77045/24, *Bride* A76924/30, A76925/31.
[27] *Heimann* A64454/30, *Skájaa* B6937/32.
[28] *Greenhow* A82471/877, *Bouilly* A47968/897, A49115/897, *Anderson* A50914/898, *Terrillon* A74563/898, *Roche* A83655/05, *Landau* A70783/15.
[29] *Vanverts* B7114/27, *de Girac* A97198/38.

are of considerable *historic* interest.[1]

The many *case reports* concerning ovariectomy for ovarian cysts illustrate the gradual development of surgical technic during the last 100 years. In addition to the publications dealing with serous and pseudomucinous cystomas, which are cited here, the reader is referred to the parts of Ovariectomy in the chapters on Ovarian Tumors In General (above) and Ovarian Diseases in General (Sect. IV, Vol. VI) where the technic is described as applied to various solid tumors, cysts, inflammatory lesions etc.[2]

[1]*Möller* A82965/798, *Maunder* A68706/805, *Mace* A82952/813, *Hedenus* A82908/814, *Newham* A82972/815, *Lathrop* A82936/817, *M'Dowell* A68684/817, *Neumann* A82971/821, *Smith* A75149/822, A75148/822-9, A75145/826, A75147/862, A75157/862, A75716//863, A86840/863, A75717/864, A81130/876, A75146/879, A42324/887-8, *Gallup* A69987/825, *v. Galanzowsky* A69985/828, *Rogers* A68895/829-30, A68896/829-30, A68897/829-30, A40321/881, *Sacchi* A75980/832, *Böhm* A82612/832, *Truckmüller* A69278/834, *Quittenbaum* A83624/835, *Jefferson* A83320/836-7, *King and Jeaffreson* A75080/836-7, *Jeaffreson* A74806/836-7, A74807/839-40, *Gay* A69989/836-7, A75489/859, A69990/877, *Hauff* A74694/837, *West* A75256/837-8, A75255/858, A75778/875, *Hévin* A86486/838, *Gorham* A83299/839, *Récamier* A69206/839, A69207/839, *Phillips* A74449/840-1, *Stilling* A75167/841, A75168/849-50, A75725/863, A75169/865, A75726/867-9, A75729/868, A75730/873, A75731/877, *Clay* A68996/842-3, A68997/843-6, A75441/863, A86167/876, *Walne* A75215/842-4, *Moos* A68713/843, *Key* A83323/843, *Emilian* A69962/843, *Désormeaux* A82574/843, *Bird* A74980/843, A74981/843-4, *Southam* A75158/843-4, A75159/845, *Cooper* A74457/844, *Atlee* A75365/844, A75369/868, A75368/871, A75366/871, A75367/872, A75370/872, A75371/873-4, *Hayny* A83307/845, *Kiwisch* A82928/846, A75083/850, A75084/851, *Solly* A75156/846, *Hawkins* A74695/846, A41310/884, *Arnott* A86548/846-8, A74949/884, A45621/887-9, *Page* A74440/846, A75673/859, A75672/867, A40370/882, A82682/889-90, *v. Scanzoni* A74531/846, A74911/853-4, A74532/869, *Hunt* A82917/846, A82919/847, A82918/847, *Bainbrigge* A82597/847, A82598/847, *Vaullegeard* A86536/847-8, *Tilt* A69275/848, *Bühring* A82573/848, *Buckner* A83097/848, A68971/848, A68972/850-1, A68970/870, *Heyfolder* A74839/848, A74840/849, *Houstoun* A86489/849, *Knorre* A75089/849, *Branson* A75066/849, *Crouch* A75453/849, A74465/849, *March* A87245/849, A68696/850, *v. Haartman* A75507/849-50, *Grimshaw* A74673/850, *Cornish* A74459/850, A75446/850, *Duffin and Lee* A75473/850-1, *Deane* A69924/850, A87279/851, *Michel* A82963/850-5, A82962/852, *Smith and Blount* A75715/876.

[2]*Belchier* A76912/734, *Duffin* A76952/851, *Elkington* A69960/851, *Dunlap* A69949/851, *Langenbeck* A75109/851-3, *Peaslee* A86375/851, A86259/874-5, *Rawitz* A68878/852, *Parkman* A86256/852, *Martin* A70825/852, A48281/896, *Herrich* A74833/852, *Howard* A74862/852-3, *Bennett* A75378/852, A74975/856, A75379/857, A75380/857, *Gabb* A87284/852, A69982/852-3, *Tanner* A75177/852, A75178/853, A75179/858, *Corrigan* A82642/852-8, *Bayless* A74971/853, *Howie* A74864/853-4, *Childs* A75435/853, A75436/858, A87271/861, *Gross* A74677/853, A75502/873-4, A40285/883, *Granville* A74670/854, *Erichsen* A69967/854, A69968/858, A69969/859, A75480/859, A86345/861, *Craig* A75448/854-5, A75449/855, A74461/873, *Teale* A75737/854, A75183/862, *Brown* A68961/854, A75411/859, A75412/860, A68962/861, A68963/861, A68964/862, A75413/863, A75414/863, A68965/864, A75415/866, A86150/870, A68966/871, A40670/884, A68967/886, A43453/890, A69556/01, *Holston* A74855/855, *Garrard* A69988/855, *Barth* A82600/855-7, *Schuh* A74536/856, *Sawyer* A74530/856-7, *Winton* A75784/856-7, A75783/857, *Long* A75591/857, *Ackley* A74941/857, *Wells* A75765/857-62, A75234/858, A75235/858-9, A74926/858-9, A75236/858-9, A68610/859, A75766/859, A74928/859, A75237/859, A87000/859-60, A75767/859-66, A75239/860, A87001/860, A75240/860-1, A75241/860-3, A75245/861, A69297/861, A75242/861, A75243/861, A75244/861-3, A75771/862, A75770/862, A75249/863, A75250/863, A77128/863, A75251/864, A75776/865, A75252/865, A75253/865, A75254/871, A87176/876, A75233/880, *Hutchinson* A75538/857-8, A77214/857-8, A75057/861, A75059/861, A75539/862, *Ramskill and Hutchinson* A75688/858, *Pope* A68868/858, *Nelson* A75661/858, *McRuer* A68691/858, *King and Hutchinson* A75557/858, *Joseph* A74810/858, *Humphrey* A74870/858, *Hewett* A75521/858, *Warren* A75222/858-9, *Hamilton* A74685/858-9, A74686/859-60, A75508/861, A74687/879-80, A75509/884, A81644/14, *Mussey* A74416/858, A87309/872, *Utterhoeven* A69187/858, A69190/865-6, *Townsend* A75195/859, *Holt* A75530/859, *Ferry* A75483/859, *Buckingham* A68969/859-60, *Bell* A74973/859-60, A87252/871, A75377/879, *Millar* A68712/859, A82964/868-9, *Nunn and Brown* A75664/859, *Workman* A75267/860, *Worms* A86123/860, *Wratislaw* A75786/860, *Roemer* A68893/860, *James* A74805/860, *Byford* A75424/860, A68974/863, *Curling* A75454/860, A87276/861, A75455/867, *Crosby* A74463/860, A74464/870-1, *Gibb* A86348/860-1, A87288/861-2, *Henwood* A74832/860, A75518/875-6, *Harper* A75510/860, A74690/879, *Nunn* A87310/861, A74431/861, *Warner* A75221/861, *Forster* A87283/861, *Davies and Curling* A87278/861, *Bradford* A75404/861, *Barnes and Hutchinson* A87250/861, *Cooper* A74458/861, *Hicks and Bryant* A75523/861, A74841/861, A75524/861, *Nélaton* A75660/861-2, A74418/862, *Roberts* A74909/861, A29495/880, A74910/881, A29961/881, A46598/893-4, *Wood* A75266/862, *Anonymous* A75427/862, A75428/878, A69575/889, A75429/880, *Stutter* A75172/862, *Bickersteth* A75383/862, *Parise* A75675/862, *Litchfield* A75588/862, *Koepl* A75568/862, *Greenhalgh and Skey* A75500/862, *Ellsworth* A69961/862, *Dewes* A75469/862, *Breck* A75406/862, *Huguier* A86212/862-3, *Campbell* A68978/862, A29900/881, A46463/893, *Demarquay* A75461/862, A75463/869, *Desgranges* A75466/862, A75467/862, A69931/867, A69932/867, *Fergusson* A86347/862, A86346/862, A87282/863, A69981/863, A69977/865, *Kidd* A75075/862, A87295/873, A75556/879, *Keith* A75550/862-6, A86922/863-4, A47308/895, A69615/00-1, *Koeberlé* A75563/862, A83101/862, A83102/863, A87296/863, A75090/864, A75091/866, A75565/867, A75564/867, A75566/867, A75092/867, A75093/869, *Oldham and Bryant* A87311/862, A74434/863, A86372/863, A87312/863, *Priestly and De Morgan* A75685/862, *Priestly and Hulke* A75687/862, *Priestly and Henry* A75686/862, *Williams* A75261/863, *Valette* A86401/863, *Spanton* A87334/863, *Regnault* A75689/863, *De Morgan* A75462/863, *Lyon* A87303/863, *Hulme* A74869/863, *Grafton* A87289/863, *Gaulegac* A75488/863, *Gairdner* A82152/863, *Bryant* A75417/863, *Crockatt* A75452/863-4, *Black* A74985/863, A46322/892, *Boinet* A74991/863, A75392/868, A75393/868, A75394/868, A75395/868, A74992/869, A75396/870, *Breslau* A75407/863, A68604/865, *Buchanan* A75418/863-71, A68968/864-5, A78418/865-6, A87268/867-8, A78418/869-71, A75422/876, *Emmet* A69963/863, A87281/867-8, A69964/868, *Holmes* A68605/863, A74896/863, A75529/864-5, A74854/864-5, A41263/883, A75528/884, *Krassowski* A75099/863, A74900/863, *Kimball* A75076/863, A75077/865-9, *Lacroix* A87298/863, A87297/864, A87299/867, *MacGillivray* A68685/863, A68686/864, A29252/879, *Ollier* A75666/863-4, A75667/864, A75668/865-6, A74437/867, *Simon* A75713/863, A75135/872, *Walsh* A75220/863, A75761/873, *Vegas* A75985/864, *Terry* A75743/864, *Nussbaum* A75665/864, *Marshall* A75603/864, *Liddon* A75122/864, *Krackowizer* A75098/864, *Herrgott* A75519/864, *Hannover* A74688/864, *Groethuysen* A74676/864, *Brett* A75408/864, *Miner* A74402/864-5, *Clark* A75438/864, A75439/867, A68995/879-80, A81636/23, *Collis* A75444/864,

Footnote cont'd.

[2]cont'd A74454/864, *v. Dusch* A69951/864, A75476/865, *Grimsdale* A75501/864, A74675/865, *Howitz* A74865/864, A75534/864, A74866/867, *Jordan* A74809/864, A69612/03, *King* A75079/864, A75082/879-80, A75081/884, *Murray* A75658/864, A75657/870, *Richardson* A68884/864, A75691/877, *Serre* A75128/864, *Williams* A86580/864, *Serre and Courty* A75130/864, *Peaslee* A77065/864, *Scott* A75708/864, A87333/868-9, A75709/874, A74537/874, *Henning* A74831/865, *Zenker* A82207/865, *Sharpin* A75131/865, *Richet* A68885/865, *Polano* A69841/865, *Pick* A74450/865, *de Montet* A74404/865, *Mandruzzato* A86037/865, *Hicks and Durham* A75525/865, *Ikawitz* A75060/865, *Grube* A75504/865, *Greenhalgh and Paget* A74671/865, *Elliot* A75479/865, *Dard* A69919/865, *Boucher* A75400/865, *Beale and Wood* A87251/865, *Feliciani* A69975/865-8, *Cheever* A68988/865-74, A68989/873, A68991/877, *v. 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Footnote cont'd.

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*d'Oliveira Feijao* A40055/881, A74435/881, *de Paoli* A40530/882, *Novaro* A40404/882, *Marcacci* A68695/882, *Lebredo* A40078/882, *Lauro* A41293/882, *Klotz* A40194/882, *Cuzzi* A40444/882, *Brosseau* A40212/882, *Pulido* A40354/882, *Bonet y Amigo* A41304/882-3, A41523/882-3, *Cosentino* A41256/882, A41476/885, *Del Castillo de Pineyro* A40564/882, A40584/882, A40583/882, *Doyen and Barral* A41349/882, A41258/883, A41531/883, *Helmuth* A40597/882, A74893/884-5, A74699/884-5, A74894/884-5, *Polk* A40437/882, A40371/882, *Ripoll* A68888/883, *Rice* A68883/883, *Prochownick* A41514/883, *Potter* A41249/883, *Mascarel* A41540/883, *Little* A75124/883, *Leriche* A40259/883, *Lucas-Championnière* A68680/883, *Kispert* A75559/883, *Ferrari* A40630/883, *Chauvenet* A40887/883, *Caponotto* A41285/883, *Carter* A41252/883, *Briddon* A41524/883, *Creus* A41240/883, *Bolling* A41522/883, *Beauregard* A82602/883, *Zwicke* A74931/883-4, *Spediacci* A40644/883, *Berry* A41577/883, A47439/895, *Ceci* A40628/883, A42083/885, A42046/885, *Ponte* A41513/883-4, A45850/891, *Sacré* A41217/883, A45187/889, A45673/890, *Terrier* A41567/883, A41516/883, A41568/883, A40646/883, A41297/883-7, A41320/884, A75740/884, A75741/884, A75739/884, A41542/884-5, A40760/884-5, A80300/885, A42135/886, A41297/887, A41999/887, A42209/887, A42241/888, A42326/888, A42409/888, *Terrillon* A41570/883, A41569/883, A41207/884, A40910/884, A45079/888, A45159/889, A42660/889, A42659/889, A43646/890, A43645/890, A44160/892, A44134/892, A74561/898, A74564/898, *Will* A41301/883-4, A75260/886-7, *Wallace* A41629/884, *Wasseige* A41325/884, *Vocht* A75208/884, *Tuholske* A75200/884, *Takaki* A75176/884, *Pizzamiglio* A68865/884, *Périer* A40902/884, *Oven* A40901/884, *Nuñez Sampelayo* A74430/884, *Nasi* A40739/884, *McClellan* A40896/884, *Martinetti* A40870/884, *Lussana* A40729/884, *Hagen-Torn* A40920/884, *Galton* A75486/884, *Fetherston* A75484/884, *Deces* A40888/884, *Corcoran* A75445/884, *Hendee* A74700/884-5, *Margossoff* A68698/884-5, *Sharp* A40748/884-5, *Winslow* A75264/884-5, *Eastman* A40912/884,

Footnote cont'd.

Quite frequently *enormous cysts* have been removed because of cystic transformation.[1] Many instances

[2]cont'd. A40859/884-5, A40499/884-5, *Hill* A40716/884, A43367/889, *Kollock* A75094/884, A75096/886, A75095/886, *Macdonald* A68683/884, A75593/884-5, *Plasencia* A40483/884-5, A40838/885, *Wile* A40957/884-5, A41013/885, *Volkov* A40885/885, *Lloyd* A40477/885, A42718/888, *Porro* A41057/885, *Mulchand* A42034/885, *v. Mansfelde* A68694/885, *Lenger* A40798/885, *Jerzykowski* A40867/885, *Hofmann* A42054/885, *Duncan* A41045/885, *Burton* A40822/885, *Billroth* A40961/885, *Buffet* A86151/885-6, *Cupp* A42019/885-6, *Gardner* A75487/885-6, *Closs* A69000/885-6, *Nancrede* A82679/885-7, *Baer* A41042/885, A40461/885, *Braun von Fernwald* A68601/885, A68602/885, A40966/885, A74714/886, A88034/886, A45215/889, A42672/889, A42671/889, A42668/889, *Leighton* A75119/885, A41467/885, *Montfort* A74405/885-6, A74407/886, A74406/886, *Zweigbaum* A41667/886, *Velits* A75207/886, *Vrable* A41763/886, *Villette* A41700/886, *Tillaux* A75748/886, *Serre* A75712/886, *Roth* A74470/886, *Pinnock* A68863/886, *Lawson* A75115/886, *Gars* A69591/886, *Cauchois* A41802/886, *Cullingworth* A42048/886, *Anderson* A74945/886-7, *Trombetta* A41794/886-7, *Le Bec* A75578/886, A41813/887, *Nowlin* A42102/886, *Peck and Hill* A41690/886-7, *Peck* A42321/888, A43352/889, *Uspenski* A42184/887, *Raymondaud* A68877/887, *Penfold* A42236/887, *Paquet* A41995/887, *Nilsen* A42172/887, *Mattei* A41816/887, *Koehler* A41963/887, *Hyer* A82664/887, *Gervis and Jones* A86196/887, *Gilis* A42198/887, *Fraenkel* A41736/887, *Dudley* A41940/887, *Carson* A41841/887, *Cameron* A41936/887, *Carfrae* A45219/887-8, *Schokman* A42495/887-8, *Arango and Arango* A45240/887-9, *Chalot* A86161/887, A86162/887, *Chrobak* A69564/887, A68994/888, *Lutz* A41914/887, A41915/887, *Smyth* A82694/887-8, A42468/888, *Bogaevski* A45168/888, *Heinricius* A42379/888, *Torrance* A42498/888, *Anonymous* A42735/888, A69540/899, *Rochet* A42323/888, *Roche* A42540/888, *Raymond* A42539/888, *Quicke* A42404/888, *Parkes* A42431b/888, *Neve and Neve* A42727/888, *Netchaeff* A42272/888, *Meyers* A42316/888, *Merz* A69829/888, *Keil* A42530/888, *Galton* A42439/888, *Delassus* A42711/888, *Cushing* A42518/888, *Negri* A42723/888, A42722/888, A42724/888, *Castagné* A42436/888, *Byers* A42481/888, *André* A42288/888, *Fasola* A42343/888, A42342/888, *Iversen* A42385/888, A75544/888, A42395/888, *Matlakowski* A42532/888, A43283/889, A43549/890, *Menocal* A45071/888, A45699/891, *Gwynn* A43272/888-9, *Amaral* A42594/888-9, *Morison* A42402/888-9, A47079/894-5, *Utley* A45081/889, *Serrano* A45145/889, *Zielewicz* A45114/888-9, *Stevens* A45077/889, *Stone* A45260/889, *Mugnai* A42650/889, *McMordie* A42560/889, *Malthe* A45182/889, *Kuskoff* A69621/889, *Kumar* A69620/889, *Grammatikati* A42636/889, *Faucon* A45173/889, *Bratton* A42630/889, *Bleynie* A45242/889, *Menger* A45228/889-90, *Michael* A42644/889-90, *Morris* A43611/889-90, *Platt* A43403/889-90, *Pelton* A42618/889-90, *Noble* A83496/889-90, A83497/890-1, *Pascale* A42700/889, A45191/889, A42692/889, A42693/889, A42698/889, *Sztembarth* A45198/889, A45199/889, *Stewart* A82698/889, A45147/889, *Urso Ortega* A43383/889, A45827/890, *Rabagliati* A43617/890, *Van Lennep* A43624/890, *Tsander* A45675/890, *Schwartz* A43556/890, *Södermark* A43557/890, *Storchi* A74556/890, *Terrillon* A70987/890, A43382/890, A70988/890, A43559/890, *Ricketts* A45606/890, *Peugniez* A45602/890, *Mariani* A82216/890, *Rinehart* A45821/890-1, *Cotton* A43330/890, *Cox* A88960/890, *Abernathy* A43410/890, *Russell* A45607/890, A47393/896, A81426/17, *Poupinel* A43377/890, *Thorén* A44135/891, *Schramm* A77088/891, *Solovjeff* A44102/891, *Bettencourt* A45905/891, *Ryder* A45770/891, *Waitz* A77315/891, *Naidu* A45735/891, *Millard* A45667/891, *Maglioni* A44150/891, *Desbrosiers* A44018/891, *Chiarleoni* A44109/891, *Tait* A45644/891, *Heeley* A46302/891-2, *Krug* A44029/891-2, *Mann* A43997/891, A69824/00, *Kelly* A44205/892, *Emmet* A76954/892, *Schaldemose* A44220/892, *Snyder* A44184/892, *Kingman* A44062/892, *Jameson* A44118/892, *Hofmeier* A73053/892, *Gramm* A69596/892, *Psalidas* A44131/892-3, *Ludlam* A44207/892, A44066/892, *Angeli* A46420/892, *Colzi* A69568/892, A83345/892, *Casuso* A46280/892, A46422/892-3, *Waldo* A46513/893, *Söderbaum* A46412/893, *De Renzi* A46525/893, *Pinkerton* A83481/893, A69840/893, *Price* A46569/893, *Pearson* A46499/893, *Owen* A46433/893, *Mackle and Parkinson* A46565/893, *McDonnell* A46446/893, *Freudenberg* A46391/893, *Dayot* A46561/893, *Desbonnets* A46562/893, *Christovitch* A46585/893, *Bishop* A46515/893, *Curryer* A44628/893, *Stewart* A46510/893, A69572/00, *Monnier* A46537/893, A46536/893, *Tansini* A44643/894, *Rendu* A44834/894, A44728/894, *Tate* A47157/894, *Marks* A44832/894, *Lopez Cilla* A44829/894, *Licéaga* A44752/894, *Fortin* A44748/894, *Bergh* A44764/894, *Doran* A44820/894, A48340/896, *McMurtry* A44699/894-5, A50642/898, *Patwardhan* A47392/895, A48416/896, *D'Urso* A47380/895, *Herzfeld* A77207/895, *Phelps* A47144/895, *Touvenaint* A70996/895, *Thorén* A47474/895, *Martinez* A47463/895, *Farrell* A47450/895, *Boursier* A69549/895, A48986/897, *Duret* A47486/895, *Hundley* A47459/895-6, *Pratt* A48369/896, *Naumann* A47410/896, *Nacciarone* A48414/896, *Fink* A48305/896, *Flinn* A48345/896, *Vasten* A83485/896, *Finlayson* A48341b/896-7, *Yamano* A75824/897, *Sierra* A74550/897, *Schotte* A48416b/897, *Stouffs* A49158/897, *Elwert* A74605/897, *Dickson* A70652/897, *Juvara* A69614/897-8, *Stinson* A74555/897, A49157/897, A49060/897, *Horsley* A50607/898, *Carstens* A50662/898, *Rosendo Gutiérrez de Velasso* A74544/898-9, *Ferguson* A50928/898-9, *Shah* A50516/898, A74548/00, A74547/00, *Okada* A69835/899, *Chuffart* A50963/899, *Buda* A69558/899, *Kime* A91817/899, A91816/899, *Schopf* A83502/00, *Mikhailovski* A69830/00, *Croom* A91776/00, *Lea* A74729/00-1, *Stehman* A74554/01, *Ritchie* A74539/01, *Reinprecht* A69847/01, *Martinoff* A69826/01, *Ranson* A70918/01, *Hubbard* A69604/01, *Gillam* A69594/01, *Kittrell* A82673/01-2, *Walla* A73014/02, *Morestin* A69831/02, *Donald* A69581/02, *Coelho* A69567/02, *Bousquet* A69550/02-3, *Ramón Secchi* A82688/02-3, *Vasilio and Negruzzi* A74572/03, *Spadaro* A74552/03, *Küstner* A69619/03, *England* A93047/03, *Ciechomski* A91772/03, *Conwell* A69569/03, *Kerr* A82668/03, A82670/05, *Taylor* B12770/04, *Swain* A70978/04, *Spanton* A69457/04, *Pozzi* A70904/04, A70905/04, *Körver* A77009/04, *Villarreal* A82707/05, *Schäfer* A70942/05, *Tarantino* A74558/05, *Pepin* A82683/05, *Hofmeier* A77212/05, *Higuchi* A69600/05, A69599/05, *Glockner* A70724/05, *Hopgood* A69603/05, *Duret* A83354/05, *Dehaye* A69576/05, *Borochowitsch* A88138/05, *Denucé* A69578/06, *Cohn* B13188/06, *Pichevin* B13090/06, *Rouffart* B13240/06, *v. Velits* A73010/06, *Goullioud* A70735/08, *Lancial* A81648/11, *Braschke* A76920/12, *Bland* A81633/13, *Vanverts* A81435/13, A81436/14, *Kennedy* A81659/14, *Kaarsberg* A81646/16, *Peterson* B13701/16-7, *Stretton* B21278/20, *Schäfer* A81427/21, *Revnès and Salen* A81422/22, *Reeder* B8681/22, *Bermudez* B8287/22-3, *Dieulafé* A81640/23, *Beuttner* A81632/25, *Svendsen* A68124/29, *Chueco et al.* A70618/30, *Erdmann* A66115/32, *Melchior* A52283/34, *Dhruv* A52100/34, *Reeb* A27755/35, *Russum* A95424/38.

[1]*Echevarria* A91789/896, *Dumont-Leloir* A91786/896, *Fortun* A91792/898, *Wörner* A91855/899, A91854/899, *Nott* A83469/899, *Sengensse* A91835/00, *Franchini* A91796/01, *Hirst* A91808/01, *Lagoutte* A91819/01-2, *Donald* A91785/03, *Schaepelynck* A91834/03, *Legg* A91830/04, *Zacharias* A93229/04, *Tucker* A91849/06, *Smith* A91839/06, *Knight* A81647/09, *Smythe* A81430/14, *Vance* A81434/15, *Buendia* A81634/23-4, *Stone* A81431/24, *Reynès* A81421/24, *Heimburger and Ewers* A81645/21, *Loveland* A81416/25, *Cotte* A70636/27, *Harttung* A95400/38, *Boeminghaus* A97233/39.

are known in which the extirpated ovarian cysts weighed 20-30 lbs.,[1] 30-40 lbs.,[2] 40-50 lbs.,[3] 50-60 lbs.,[4] 60-70 lbs.,[5] 70-80 lbs.,[6] or even over 80 lbs.[7]

Cysts with *intraligamentous development* may cause technical difficulties[8] but these can generally be overcome.

The removal of ovarian cysts through the *vaginal route* which obviates the necessity for wide opening of the peritoneal cavity, was preferred by many surgeons during the period before aspectic methods became well-established[9] and even now the vaginal approach is preferred by some, at least in certain selected cases.[10] It has been used successfully in women with tubo-ovarian cysts.[11] The procedure is greatly facilitated by preparatory puncture and evacuation of the cyst. Some surgeons like to combine this with the establishment of pneumoperitoneum.[12] In general, however, the vaginal approach is not to be recommended, for reasons enumerated in the chapter on Ovarian Tumors in General (see part on Therapy).

Removal of cysts by *conservative surgical interventions* is possible only if there is no question about the benign nature of the growth. This technic is advisable especially in women who have not, as yet, reached the menopause. The usual interventions (wedge excision, enucleation etc.) are essentially the same as those practiced for the conservative surgical treatment of other ovarian tumors. They have been described in detail, together with their prognosis, by the surgeons who developed them.[13] In the case of unilateral papillomatous cysts it had been customary to remove both ovaries with the view of preventing recurrences and possible secondary cancerous transformation of the growth; yet involvement of the healthy contralateral ovary is not sufficiently frequent to warrant such a drastic procedure, especially in young women.[14]

Among the *complications of complete or partial ovariectomy* intestinal obstruction due to the formation of adhesions,[15] accidental incision of the bladder or ureter,[16] thrombosis of regional veins with subsequent pulmonary embolism[17] and phlegmasia alba dolens[18] are of importance. Suppuration, which may lead to peritonitis, was a common complication during the last century[19] but is almost always avoidable with modern surgical conditions.

The singular ocurrence of postoperative insanity following balation of a papillary cystadenoma of the ovary[20] is reminiscent of the psychic disturbances occasionally noted after ovariectomies for other reasons (see Sect. IV, Vol. III) and probably has no specific connection with the particular blastoma removed.

During *pregnancy* the surgical removal of ovarian cysts creates special problems. During the second half of gestation the presence of the greatly enlarged uterus, as well as the hyperemia of the pelvic organs leads to technical difficulties, while during the first half of pregnancy deprivation of ovarian hormones may result in abortion. As stated in the passage concerning the pregnancy incidence of ovarian cysts, the latter are common in gestation and frequently lead to complications (torsion, hemorrhage, impaction in the pelvic cavity etc.) which necessitate an immediate surgical intervention. The results obtained by various surgeons who removed ovarian cystomas during gestation[21] as well as study of the case reports concerning ovariectomy performed in

[1] *Bird* A87185/843, A87186/843-4, *Beales* A87184/851, *Rohrer* A87323/869, *Smith* A40881/885.
[2] *Byford* A87194/863, *Shepard* A87234/872, *Cluness* A87196/874-5, *Le Conte* A91826/00.
[3] *Elkington* A87204/849, *Wells* A87240/859, *Gentilhomme* A87208/861-2, A87209/863, *Stilling* A87236/865, *Péan* A87229/866, *Hubert* A74868/878, A74867/878, *Herczel* A91807/899, *Martin Aguilar* B13332/07, *Cole* A81637/15.
[4] *Saboia* A87233/873-4, *Wooton* A87242/874, *McNutt* A29352/879, A29401/880, *Tate* A47154/894, *Smith* A91838/00.
[5] *Johnson* A42529/888-9, *Foster* A91793/03.
[6] *Alsten* A87182/871-2, *Da Costa* A45752/890-1, *Juvara* A91812/897-8, *Miller* A83463/01, *Allen* B7445/25.
[7] *Monestie* A83464/893, *Cullingworth* A91777/895, *Lee* A91828/895, *Rouffart* A91833/899-00, *Lewis* B10767/28, *Thoms* A95431/38.
[8] *Raffa* A29337/880, *McMurtry* A41834/887, *Hofmokl* A43273/889, *Noble* A45600/890, *Frank* A44200/892, *Tansini* A47151/894, *Gilliam* A50636/898, *Beuttner* B8542/21, B8555/22, *Ten Teachers* B6383/38, *Novak* A63534/41.
[9] *Byford* A42296/888, A44079/892-3, A44226/892, *Lvoff* A46305/892, A44232/892, A44148/892, *Böhme* A69534/895, *Segond* A70953/897, *Goelet* A48439/897, *Schramm* A70949/899, *Kynoch* A70781/899.
[10] *Chueco* B7205/27.
[11] *Taylor* B12621/04-5.
[12] *Sfameni* A81428/11, *Chueco* A67286/30, A65063/31.
[13] *Currie* A82841/837, *Bottini* A86554/867, *Nicolaysen* A82973/870, A86575/871, *Terrier* A40120/881, *Polaillon* A40084/881, *Schröder* A41006/885, *Delaunoy* A46556/893, *Goldspohn* A81131/03-4, *Ward* A82399/10, *Nagel* B11256/10, *Silhol* A81429/13, *Bonnet-Laborderie et al.* A90660/14, *Hyde* A82385/15, A81893/17, *Peterson* A81419/17, *Sippel* A82397/17, *Fitz-Gerald* A81642/19, *Roeder* A81423/22, *Lapeyre* B7235/27, *Houdard* B7226/27, *Moulonguet* A52164/34, *Fernandes* A97055/37, A97056/38, *Bonney* A95351/38, *Miller and Willson* A97813/42, *Dionisi and Sammartino* B10816/44.
[14] *Nagel* A81894/10.
[15] *Minor* 29596/880, *Eyster* B13192/06, *de Rouville and de Carrera* A81425/23-4, A81424/24.
[16] *Schopf* A74535/886, *Ward* A73016/10, *Green* A81643/14, *Sebestyen* A52306b/34.
[17] *LeConte* A91827/05, A82675/05.
[18] *Fochier* A41845/887.
[19] *Lever* A86567/855, *King and Hutchinson* A86565/858, *Luizy* A86568/881, A86569/882.
[20] *Secor* B11914/16.
[21] *Bouteillier* A41983/887, *Doleris* A41880/887, *Naumann* A45183/889, *Decamps* A43333/889, *Angelini* A45212/889, *Meredith* A70831/892, *Guinard* A81682/08, *Jeannin and Brac* A70751/09, *Brouha* A81671/10-1, *d'Hotman de Villiers* A81683/11, *Lepage and Tissier* A81689/12, *Vincent and Ferrari* A81734/12, *Thomas* A81664/12, *Couvelaire* A82414/12,

Footnote cont'd.

pregnant women for diverse reasons (see chapter on Effect of Ovariectomy on Pregnancy in Sect. IV, Vol. III) justify the following conclusions: The usual complications of ovarian cysts are more apt to occur in pregnant than in non-pregnant women; ovariectomy is indicated at any time during gestation if ovarian cysts produce complications which endanger life; during the first three months of pregnancy removal of the ovary bearing the corpus luteum is likely to produce abortion unless adequate doses of progesterone are administered; during the last month of pregnancy, if ovariectomy has to be performed before delivery, simultaneous cesarean section is indicated in order to avoid possible rupture of the recent scar during labor.

In earlier days some surgeons recommended the autotransplantation of the corpus luteum of gestation in order to avoid abortion in women whose cystic ovaries had to be removed during the first few weeks of pregnancy. Although some success has been claimed by those who used this procedure[1] it has no place in modern surgery, because the likelihood of a functional take is remote and much better results may be expected from treatment with active luteoid preparations (e.g. progesterone or pregneninolone).

During the *puerperium* ovariectomy does not tend to pose any special problems.[2]

The *age* of the patient is not a very important factor in considering the advisability of ovariectomy for cystic tumors. Ovarian cysts have been successfully removed in children only a few months old[3] as well as in older children;[4] conversely, aged women usually tolerate ovariectomy about as well as any other peritoneal operation of similar severity.[5]

In cases of generalized *peritoneal serous papillomatosis*[6] and *pseudomyxoma peritonei*[7] removal of the ovarian tumor is frequently followed by disappearance of the peritoneal "metastases". In some of these instances the tumor was considered to be malignant, but scrutiny of the relevant descriptions and microphotographs suggests that they were probably benign neoplasms on the verge of malignant transformation. It is doubtful whether the beneficial action of ovariectomy upon the secondary growths should be regarded as due to deficiency in ovarian hormones. In several of these cases the peritoneal lesions vanished even if removal of the primary growth had to be abandoned during laparotomy because of widespread adhesions. The effect of laparotomy in these cases is rather reminiscent of that seen in peritoneal tuberculosis which likewise tends to regress following exploratory laparotomies.

The *statistical* analysis of ovariectomy as a therapeutic measure in the treatment of cystomas has been the subject of several reviews.[8]

Puncture or *tapping* of cysts is still occasionally practiced as a conservative measure, assuring temporary relief to patients who cannot be submitted to a major operation, yet this procedure is mainly of historic interest now. In the days before aseptic technic insured against the constant danger of infection, the safest and most popular surgical therapy of ovarian cysts was to puncture them. In many cases this was done whenever sufficient fluid was formed to make the patient feel uncomfortable. In order to aid the withdrawal of fluid, aspiration by suction was frequently employed and various types of drains and aspirators were devised for this purpose. Some surgeons preferred to leave a permanent drain in the puncture hole thus assuring continuous drainage of fluid. Depending upon the anatomic position of the growth and the personal preferences of the surgeons, cysts were punctured and drained either through the abdominal wall or through the vagina. In the latter case, there is comparatively little danger of causing generalized peritonitis since the cysts are usually firmly adherent to the fornix of the vagina. One great danger of tapping lies in the fact that sudden relief of the internal pressure may lead to fatal hemorrhage into the cyst cavity. Hence evacuation of the cyst contents must proceed slowly. Another danger is the possibility of abscess formation due to secondary infection of the cyst cavity from the outside. It is noteworthy, however, that many of the early surgeons rather encouraged the development of a mild chronic infection since the

[21]cont'd *Chueco* A81674/13, *Betow* A81665/14, *Orlandi* A81694/13, *Grosse* A21324/19, *Dambrin* A81675/20, *Vanverts and Guenez* A81731/22, *Szymanowicz* A81700/22, *Manzi* B5936/28, *Devraigne* B5922/28, *Fruhinsholz and Hamant* A61384/33, *Voron and Brochier* A27762/34, *Nicora* A97130/38, *Capone* A66751/43.

[1]*De Lee* B11898/16.

[2]*Weinlechner* A40513/881, *Doleris* A42438/888, *Capone* A66751/43.

[3]*Power* A51013/897-8.

[4]*Cupples* A74875/874, *Chenoweth* A40585/882, *Polotebnoff* A41866/887.

[5]*McNutt* A29352/879, A29401/880, *Smythe* A40297/883, *Guillemet* A41202/883-4, *Moreau* A41507/885, *Shepherd* A69906/886, *Johnson* A42529/888-9, *DaCosta* A45752/890-1, *Haynes* A45729/891, *Cartledge* A44140/892, *Kelly* A46372/893, *Verstraete* A49159/897, *Heekes* B7482/25.

[6]*Thornton* A70991/877, A70992/881, A41874/887, A40844/895, *Leopold* A41749/887, *Freund* A42635/889, *Lomer* A43372/889, *Sutugin* A70977/890, *Burt* A45859/891, *Theilhaber* A46438/893, *Cazenave* A47330/895, *Liebrich* A70797/895, *Traschel* A50952/898, *Werder* A50687/898, *Pozzi* A70904/04, A70905/05, *Fränkel* A70702/05, *Maiss* A70813/06, *Routh* A70934/07, *Flaischlen* A70692/09-10, *Corcia* A70631/18, *Codman* A70626/18, A70627/18, *Erdmann and Spaulding* A70674/21, *Hooper* A68490/23, *Gucci* A70741/27, *Gardner and Traut* A70720/28, *Wintz* B12407/30, *Maury* B12403/31, *Taylor and Alsap* A62952/32.

[7]*Boursier* A49043/897, *Günzburger* B12401/899, *De Beule* B13176/06, *Pfannenstiel and Krömer* A64886/08, *Ries* B12404/24, *Labhardt* B12402/28, *Masson and Hamrick* A65617/30, *Schley* A77291/31.

[8]*Josephson* A70761/01, *van der Hoeven* A70843/05, *Pompe van Meerdervoort* A70898/05.

consequent inflammatory lesions tended to help obliteration of the cyst cavity thus inducing a permanent cure.

Mere puncture or tapping cysts, without subsequent removal of their walls, is no longer common in surgical practice; hence at the present time the many interesting aspects of this intervention can only be studied by perusal of relevant *case reports* described in the literature.[1]

Tapping of ovarian cysts was sometimes carried to extremes, difficult for contemporary physicians to understand. Thus in certain instances the procedure was repeated on the same patient 32,[2] 77,[3] 78,[4] 119,[5] 161,[6] 174,[7] and even 400 times.[8] As a result of repeated tappings a single cyst can yield as much as 683 liters,[9] 100 gallons[10] or 576 lbs.[11] in certain instances. In two cases approximately 500 gallons, that is well over 2 tons of fluid, were removed over periods of 6 to 7 years by 130 and 368 tappings, respectively.[12] In a similar extreme case repeated tapping of a single cyst yielded 16,000 lbs. of fluid.[13]

Tapping through the vagina proved especially useful in *pregnant* patients in whom ovarian cysts mechanically interfered with delivery.[14]

Puncture of ovarian cysts may be performed at any *age* and Solis[15] describes the case of a child in whom a single puncture of a congenital cyst affected a permanent cure.

The ancient practice of tapping ovarian cysts enriched the medical literature with many curious case reports of this sort. Not the least amusing among these is an inscription on a tombstone discovered in Bunhill cemetery, City Road E.C. (England) which reads as follows: "Here lies Dame Mary Page, relict of Sir George Page, Bart. She departed this

[1]*Delaporte* A82848/753, *Le Dran* A82941/753, *Pye* A69204/762, *Barnard* A82605/802, *Chevalier* A82825/812, *Vermandois* A69287/813, *Key* A82927/828, *Dittmer* A82853/831, *Pigne* A82019/836-7, *Dohlhoff* A82854/838, *Thomson* A69272/838-9, *Ingleby* A69317/839, *Gigon* A82894/840, *Schwabe* A69237/841, *Mauris* A82579/842, *Ollenroth* A82583/843, A82976/844, *Cazeaux* A82822/844, *Hampeis* A82902/844, *Melion* A82959/844, *Brown* A82791/844, A68378/852, *Richolet* A69211/845, *Heidenreich* A82909/847, *Bellinger* A86553/847, *Tebay* A69266/847, *Crull* A69150/848, *Mailly* A81969/849, *Uhde* A69185/850, *Budd* A82810/851, *Davies* A82846/852, *Simpson* A69246/852, A69247/871, *Tanner* A69262/852, *Wicke* A82589/852, *Betschler* A82608/852, *Notta* A82975/853, *Velpeau* A69284/853, *Moynier* A81991/853, *Rees* A69208/854, *Menninger* A82960/854, *Schnetter* A69231/855, *Lever* A82946/855, *Buckingham* A82808/855, *Landrat* A82577/856, *Picard* A82996/856, *Barbrau* A82322/856, *Cavasse* A82821/856, *Cruveilhier* A82840/856, *Herpin* A82911/856, *Chassaignac* A82823/856, *Pidoux* A82997/856, *Peaslee* A82988/856, *Saurel* A69227/857, *Vengoechea* A82588/857, *Pernod* A82585/857, *Barnes* A82599/857, *McDaniel* A82951/858, *Coulon* A82289/858, *Sloane* A82538/858, *Brower* A82788/858, *Valette* A69281/858, *Preuss* A69203/858, *Pallen* A82981/859, *Steinthal* A69253/859, *Baldy* A82572/859, *Uytterhoeven* A69188/859, *Gueneau de Mussy* A82900/859, *Pitman* A83000/859, *Evans* A82871/859, *Childs* A82826/859, *Legrand* A82942/860, *v. Franqué* A82887/860, A82888/864, *Launay* A69327/861, *Bertrand* A82606/861, *Anderson* A74946/861, *Cooke* A82830/862, *Dodeuil* A68434/862, *Steuermark* A69254/862, *Storer and Warren* A69258/862-3, *Müller* A82968/862-3, *Dumreicher* A82859/863, *Brisbane* A82785/863-4, *Packard* A82979/863, A82980/867, *Deprés* A82850/864, A82851/873, *Musset* A82582/864, *Bourneville* A68369/864, *Buys* A82812/864, A82813/865, *Goering* A69151/865, *Rohden* A69215/866, *Araus* A82594/866, *Sanne* A69225/866, *Mazzoni* A82955/866, A82954/866, A82956/878, A82957/881, A82958/884, *Courty* A82833/866, A82835/67, A82834/867, *Marti* A82805/866-7, A82806/868-9, *Crawford* A82839/867, *Folet* A82883/867, *Warren* A69288/867, *Laskowski* A82578/867, *Lelong* A82944/867, *Thoman* A69268/868, *Teillais* A69267/869, *Bryant* A86556/869, *Southam* A75823/869, A69252/869, *Boye* A86555/869, *Sullivan* A69260/869, *Corliss* A82832/869, *Noeggerath* A82974/868-70, *Weinlechner* A86311/870, A69290/871, A69291/875, A69292/876, A69295/879, A40517/881, *Joüon* A86563/870, A82923/871, *Calderon* A82814/870, *Landi* A82935/871, *Vance* A69282/871-2, *Clay* A68999/872, *Johansen* A75962/872, *Chrobak* A82827/872, *Battey* A86551/872, *Marzolo* A75606/872, A75607/874, A68705/876, *Lambert* A82934/872, *Millot* A82581/873, *Keller* A82926/873, *Foot* A82885/873, *Teale* A86290/873, *Tillaux* A69274/873, *Tirifahy* A69276/873, *Martin-Aguilar* A82953/874, A82218/05, A82220/06, *Boissiers* A82775/874, *Poetschki* A82586/874, *Panas* A82984/874, *Day* A82847/875, *Sell* A69239/875, *Svensson* A69261/875-6, *Wright* A69302/876, *Edes* A82866/876, *Delore* A82849/876, *v. Ehrenstein* A82868/876, *Eder* A82862/876, A82863/877, A82864/878, A82865/878, *Hume* A69606/877-8, *Saint-Vel* A69223/877, *Palmer* A82982/878, A82983/878, *Dolan* A82855/878, *Schröder* A69233/878, *v. Winiwarter* A34841/878, *Mignon* A82580/878, *Bryant* A82807/878, *Lusk* A82948/878, A82949/879, *Stimson* A69256/879, A69255/879, *Berthold* A74888/879, *Maar* A82950/879, *Farge* A82872/879, *De Renzi* A29458/880, *Streng* A69259/880, *Duplouy* A40042/881, *Thomas* A29966/881, A40031/882, *Stevens* A40373/882, *Pean* A40245/882, A42615/888, A42616/888, *Bacon* A40621/883, *Brochin* A40651/883, *Zweifel* A40270/883, *French* A40283/883, *Weddington* A41631/883-4, *Goodell* A41201/884, *Singer* A40749/884, *Polk* A40903/884, *Berthod* A41302/884, *Zacharevich* A40489/885, *Bantock* A41474/885, *Potocki* A69202/886, *Benedict* A69543/886, *Morsly* A82967/886, *Terrillon* A41972/887, *Parrish* A41895/887, A41864/887, *van Heuverswyn* A42474/887, A41951/887, *D'Antona* A42422/888, *Neëloff* A45184/888, *Pascale* A45192/889, *Hofmokl* A43274/889, *Ferguson* A45909/891-2, *Yoshida* A46353/892, *Barber* A46279/892, *Kelly* A46397/893, *Vanderveer* A46604/893, A44621/893, A46580/893-4, A74571/895, *Morison* A47081/894-5, *Sgambati* A74546/895, *Rendu* A47320/895, A74538/896, *Boursier* A81327/895, *Sirkar* A47395/896, *Allaben* A69536/00, A69537/00, *Peterson* A69837/02, *Uthmöller* A88060/05, *Littauer* A81649/11, B11265/11, *Pillai and Lam* A63463/29, *Tottenham et al.* A64561/29, *Ajello* A62281/32, *Fortier and Gately* A52261/34.

[2]*Schrägle* A69232/852.

[3]*Goodson* A41553/883.

[4]*Atkinson* A82595/844.

[5]*Vast* A69283/875.

[6]*Vance* A42737/888.

[7]*Campbell* A82815/877.

[8]*Hughes* A82916/878.

[9]*Souligoux* A77101/08.

[10]*Bennett* A82603/854.

[11]*Gregg and Talbot* A82898/863.

[12]*Shands* A91836/04, *Malcolm and Gibb* A70816/21, B8678/22, B8679/22.

[13]*Ashby* A83447/06.

[14]*Bender* A81631/12.

[15]A74551/896.

life March 11th, 1728 in the 56th year of her age. In 67 months she was tapped 66 times; Had taken away 240 gallons of water without ever repining at her case or ever fearing the operation."

Another frequently used practice in early ovarian surgery was the *injection of various irritating fluids* into the cyst cavity. This was done in order to cause a local reaction with adhesions, eventually leading to complete permanent obliteration of the cyst. A variety of technics were evolved during the last century for this intervention.[1] Some surgeons used rather odd methods. Thus one early gynecologist[2] inserted a tube into the cyst through the rectum and then injected various astringents.

The most common procedure for obliterating the cyst cavity was the injection of various *iodine solutions* into the lumen after evacuating the cyst contents. This was often successful but many severe complications occurred owing to the absorption of excessive amounts of iodine or to erosion and subsequent internal rupture of the cyst wall.[3]

Among other irritating fluids injected into the cyst cavity for therapeutic reasons we may mention *acetic acid,*[4] *zinc chloride,*[5] *potassium chlorate,*[6] *gold oxide,*[7] *"ioduret of iron"*[8] as well as *lithium, ammonium* and *lead salts.*[9] Some surgeons used plain *water,* especially hot water, for rinsing the cyst cavity.[10] Indeed the imagination of physicians dealing with ovarian cysts during the last century, appears to have known no limits. In the wine-raising provinces of Italy some ingenious physicians[11] discovered a novel and original use for *wine,* enthusiastically advocating its virtues as a fluid with which such cysts should be lubricated, while during the same period in France one of their colleagues[12] was busy stuffing *onion juice* into the ovarian cysts of his patients.

Cauterization has also been used for puncturing ovarian cysts.[13]

Other physicians were in favor of *electric treatments* in the form of electro-puncture or "electrolysis" or by merely applying various types of electric current to the cyst region.[14]

During the pre-aseptic period the process of *marsupialization* was recommended by many surgeons. It consists of the establishment of a permanent communication between the cyst cavity and the outside through incision of the cyst, whose walls are then sutured to the skin of the wound or kept patent by drains. Generally granulation tissue fills out the cyst cavity which eventually disappears.[15] Even in modern surgery marsupialization with subsequent excision of the lining membrane may have its place in the case of some very large cysts.[16]

The treatment of ovarian cysts by *pressure* was first advocated by Brown.[17] A truly impressive case of a permanent cure following mechanically induced rupture of the cyst was reported by Bezencenet.[18]

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[1] *Rigollot* A69212/831, *Holscher* A82913/837, *Dutard* A82861/851, *Peaslee* A86257/856, A86258/856, *Thoulouse* A69273/858-9, *Bribosia* A82781/870, *Boinet* A82773/870.

[2] *Homans* A82914/872.

[3] *Allison* A82591/846-7, A29425/880, *Leslie* A82945/847-8, *Thomas* A82587/850, A69271/851, A69270/863, *Boinet* A82614/852, A82615/855, A82771/856, A82730/856, A82772/863, A82774/869, A40210/882, A40382/882, *Bouche de Vitray and Desmartis* A82778/853, *Tartivel* A69263/853, *Dumont* A82858/853, *Duplay* A82860/853, *Sandras* A69224/853, *Fincinus* A82874/854, *Ameuille* A82593/854, *Simpson* A69248/854, A69249/871, *Shattuck* A69245/855, *Brown* A82802/855, A82801/855-7, *Rouyer* A69220/856, *Velpeau* A69285/856, *Rayer* A69205/856, *Edwards* A82867/856, *Paupert* A82986/856. *Fock* A82882/856, A82881/857, *Dolbeau* A82856/856, *Garreau* A82891/856, *Boulbene* A82779/857, *Roemer* A69214/857, *Pignant* A82999/857, *Philippart* A82994/857, *Hardwick* A82904/857, *Foucart* A82886/857, *Lawrence* A82939/857, *Garrod* A82892/857, *Abeille* A82590/857, *Gilbert* A82895/858-9, *Besnier* A82607/859-63, *Black* A82611/859, *Savage and Wells* A69228/859, *Gérin-Roze* A82893/859-63, *Uytterhoeven* A69189/859, *Wells* A69296/860, *Löwenhardt* A82947/860, *Orth* A82978/860, *Smith* A69250/860-1, *Krüger* A82576/861, *v. Scanzoni* A69230/863, A69229/863, *Bonnafont* A82776/864, *Dougherty* A82857/865, *Biswas* A82610/866, *Rose* A69217/868, *Peruzzi* A86064/868, *Fürst* A82890/869, *Bouchard* A82777/870, *Petersen* A82991/871, A82992/873, A82993/876, *Lebert* A82940/873, *Hanks* A82903/873-4, *Wirsen* A69300/874, *Paillard* A82584/875, *Casson* A82818/877, A82819/877, A86156/877, *Weinlechner* A86636/877, A69293/877, *Harrison* A82905/878, A82906/879, *Casati* A82817/879, *Billroth* A82609/879, *Després* A40386/882, *Cianciosi* A82828/883, *de Silva Jones* A41295/883, *Cantieri* A40934/883, A82816/883, *Terrillon* A42280/888, *Ortiz* A43316/889, *Rhett* A43554/890, A43553/890.

[4] *Broadbent* A82786/866, *Junker* A82924/866.

[5] *Terrillon* A42137/886, *Anger* A42114/886.

[6] *Craig* A82838/866, A82837/865-6, *Turchi* A69279/870, *Hopkins* A82915/876, *Davidson* A82845/879.

[7] *Guionnet* A82901/874.

[8] *Tuton* A69280/843-4.

[9] *Hunter* A82920/877, *de Silva Jones* A44791/894, A44732/894.

[10] *de Montmeja* A82966/870, *Sainte-Ange* A69222/876, A69221/876.

[11] *Mezzini* A82961/862, *Pedrini* A41269/883.

[12] *Venot* A69286/860.

[13] *Rouge* A69219/870, *Mossop* A74412/876-7, *Fontan* A82884/886-7.

[14] *Rodolfi* A69213/858, *Namias* A82970/860, *Scoutetten* A69238/865, *v. Grünewaldt* A82899/868, *Flies* A82880/869, *Fieber* A82875/871, A82876/876, A82877/876, A82878/876, A82879/876, *Hayes* A82907/874, *v. Ehrenstein* A82870/876, A82869/876, *Clemens* A82829/876, *Semeleder* A69241/876, A69242/877, A69243/877, A69244/878, A40608/882, A40420/882, A41756/886, *Hesse* A82912/877, A29275/880, *Mundé* A82969/877, *Cutter* A82842/877, A82843/878, A82844/878, *Ultzmann* A69186/878, *Pierce* A82998/878, *King* A42716/888, *Hall* A45176/889, *Cserey* A43569/890, *Noeggerath* A45601/890.

[15] *Houstoun* A76996/734, *Buckingham* A82809/868, *Kappeler* A86564/874, *Tripier* A69277/878, *Hubert* A29939/881, *Lawrie* A44121/891-2, *Alloway* A69538/894-5, *Kinghorn* A47105/894-5, *Bertholdt* A47329/895, *Monod* A50510/898-9, *Hansson* A69598/03.

[16] *McGrath and Eiss* A27878/35.

[17] A82789/844, A82790/844, A82792/846, A82793/846-7, A82794/848, A82795/849, A82796/850, A82797/852, A82798/852.

[18] A82335/869.

His patient was radically cured by her sympathetic husband who ruptured the cyst by means of a vigorous kick in the belly. Others favored more conservative technics such as bimanual compression, puncture with subsequent application of pressure, etc.[1]

Ligature of the ovarian vessels with the view of obtaining atrophy of cystic ovaries has been recommended for large adherent cysts which were difficult to remove otherwise.[2] This procedure is rarely feasible and extremely dangerous because of the subsequent necrosis.

X-ray therapy has occasionally been recommended.[3] It is of questionable value in simple serous or mucous cysts, but is highly to be recommended as a post-operative prophylactic measure in cases in which malignancy is suspected[4] and in patients in whom only part of an ovarian papilloma could be removed.[5]

Radium therapy has been advocated as a post-operative measure following partial ablation of pseudomucinous cystomas combined with pseudomyxoma peritonei.[6]

Other *non-surgical* technics for the therapy of ovarian cysts were popular only before the introduction of modern surgical methods[7] and will hardly ever be indicated to-day. Among the internal therapeutic measures used in the past, mercurial diuretics,[8] ergot preparations,[9] viburnum prunifolium,[10] opium,[11] balneological therapy,[12] massage[13] and the application of leeches to the uterine cervix[14] may be mentioned. The use of the electric current[15] also had its proponents and some relevant data have previously been discussed in connection with the so-called "electrolysis" of ovarian cysts.

[1]*Bourjeaurd* A82780/857, *Richardson* A69210/865, *Hensot* A82910/876, *Rheinstaedter* A69209/879.
[2]*v. Antal* A40379/882.
[3]*Moscariello* B10803/27.
[4]*Belot* A81630/23, *Aubourg* A70575/23, *de Martel and Sourdel* A81417/23, *Lape* A70786/24, *Faure* A81641/25, A70682/30, *Dorland* B6045/29, *Douay* A61923/33, *Moulonguet* A52164/34, *Counseller and Desjardins* A95245/37.
[5]*Lapeyre and Estor* A52270/34.
[6]*Hadden* A70744/24.
[7]*Lauwers* A82937/855, *Lachaze* A82931/857, *Peaslee* A82989/866, *Tassi* A69264/870, *Küthe* A82929/871, *Word* A69301/873.
[8]*Brown* A82792/846, *Juarrero* A49068/897.
[9]*Gray* A82897/876-7.
[10]*Chavett* A82824/870.
[11]*Perotton* A82990/833.
[12]*Laennec* A82932/828, *Lalesque* A82933/857, *Lavigerie* A82938/871.
[13]*Ivanoff* A82922/879, *v. Winiwarter* A82400/08-9.
[14]*Goupil* A82896/857-8.
[15]*San Juan* A41752/886.

PARA-OVARIAN COMMON CYSTS

Synonyms: Broad ligament cyst.—The terms "parovarian cyst" or "cyst of the Wolffian body" etc. are often used as synonyms for para-ovarian cyst, but this is inadmissible for reasons explained in the chapter on para-ovarian tumors in general.

REVIEWS

ENGLISH: *Doran* A70475/884, *Wright* A91445/897, *Kerr* A91403/897-8, A91404/898, *Anonymous* A69654/898, *Robinson* A91429/00, *Keith and Doran* B6387/10, *Ten Teachers* B6383/38, *Gilbert and Sheorey 82747/41, Geist B6672/42.*

FRENCH: *Vautrin* A41472/885, *Terrillon* A42008/885, A45156/889, A42113/886, *Koeberle* A90175/886, A41504/886, *Raimondi* A91372/897, *Muller* A64810/34.

GERMAN: *Alsberg* A40273/882-3, *Killian* A90174/885, A41466/885, *Wykowska-Dunin* A88686/889, A88687/889, *Rossa* A91206/899, *Gibelli* A91391/04, *Miller* A18279/37.

ITALIAN: *Ferroni* A91385/03, *Bucco* A88691/04.

RUSSIAN: *Phenomanoff* A90186/887, *Lvoff* A91224/02.

SPANISH: *Serret* A90189/886.

DEFINITION

The definition of para-ovarian cysts, in the sense in which this term is used in the present Encyclopedia, is evident from what has been said in the corresponding part of the chapter on para-ovarian tumors in general. It is obvious that if a para-ovarian tumor is cystic, or at least prevailingly cystic, it will be referred to as a para-ovarian cyst.

CLASSIFICATION

The classification of para-ovarian cysts forms part of the general classification of para-ovarian tumors, which has been discussed under Classification and Pathogenesis in the chapter on Para-Ovarian Tumors in General. Perhaps it should be re-emphasized, however, that classification on a purely pathogenic basis—which appears to be theoretically the most logical—is impractical since in many cases the origin of the cyst cannot be determined with certainty. It is also important to remember that the present chapter deals merely with

the so-called "common cysts" of the para-ovarian region, that is to say, the serous and pseudomucinous varieties, as well as those cystic tumors which have no characteristic distinguishing histologic attributes. Morphologically well defined varieties of specifically para-ovarian cysts (e.g. cysts of the Wolffian body, Gartner's duct, Müllerian derivatives) have been discussed in the part on Pathogenesis in the chapter on Para-Ovarian Tumors in general, while cystic varieties of well defined tumor types, which have their counterpart among the ovarian tumors (fibromas, sarcomas etc.) are treated in separate chapters following each of the corresponding ovarian neoplasms.

PATHOLOGIC ANATOMY

MACROSCOPIC CHARACTERISTICS: The *size* of para-ovarian cysts is very variable. Most of them are comparatively small, pedunculated vesicles, but in certain cases such cysts may reach an unusually large size[1] and contain 20-30 liters[2] or even 30-40 liters[3] of fluid and indeed in one case a broad ligament cyst—successfully removed—weighed 130 lbs.[4]

Most of the para-ovarian cysts are simple, unilateral neoplasms, but in a certain number of cases a *multilocular* structure[5] or *bilateral* development has been observed.[6]

The *position* and spread of para-ovarian cysts has been discussed in the chapter dealing with para-ovarian tumors in general while their *shape, consistency* and *color* are so variable that it does not appear profitable to discuss them in detail.

The interested reader is also referred to the numerous *case reports* which describe the various characteristics of the so-called para-ovarian cysts.[7]

MICROSCOPIC CHARACTERISTICS: Histologically the para-ovarian cysts almost invariably prove to be lined by a serous—sometimes ciliated—epithelium. The occasional occurrence of pseudomucinous cysts in the para-ovarian region has been mentioned in the part on Pathogenesis in the chapter on Para-Ovarian Tumors in General. As stated there, it is highly probable that many, if not all, of them do not originate in para-ovarian embryonic vestiges, but are secondary neoplasms resulting from the re-implantation of self-amputated ovarian pseudomucinous cysts or parts of such.

PARA-OVARIAN CYSTS IN COMBINATION WITH OTHER PARA-OVARIAN TUMORS: Para-ovarian cysts are very rarely seen in combination with other para-ovarian tumors. Occasionally, intraligamentous *sarcomas* have been observed in women with intraligamentous cystomas.[8]

CHEMICAL COMPOSITION

Very few data are available concerning the chemical composition of para-ovarian cysts and the fluid which they contain. In general it may be said that the fluid in para-ovarian cysts is essentially similar to that of ovarian cysts and of extremely variable composition. The actively secreting cysts usually contain a fluid with a high nitrogen, protein and potassium content, while their chloride content is low. Less actively secreting cystomas, on the other hand, are rich in chlorides, but low in nitrogen, protein and potassium.[9]

INCIDENCE

It is diffcult to estimate the *general incidence* of para-ovarian common cysts on the basis of available data. Their frequency is usually expressed in comparison with that of ovarian cysts, the evidence being gathered from the reports of surgeons who register para-ovarian cysts at the occasion of ovariectomy

[1] *Reverdin* A41820/887, *Tansini* A45852/891, *Rodgers* A46505/893, A50949/898, *Targett* A88784/898, *Jessett* A91327/02, *Cestan* A91295/03, *Morestin* A88719/03, *Neuvialle* A88685/04, *Hammond* A88707/05, *Serfaty* A91358/18, *Tédenat* A91514/22.

[2] *Forgue* A88704/899, *Jeanbrau and Moitessier* A88714/00, A88713/00, *Withrow* A88748/05.

[3] *Wylie* A44735/894, *Itzkowitsch* A88684/04, *Nagel* A88721/04.

[4] *Pratt* A91426/08.

[5] *Deaver* B20997/23.

[6] *Goodell* A42526/888, A42553/889, *Dubar* A49171/897, *Secord* A91433/08-9, *Dambrin and Bernardbeig* A81638/20.

[7] *Iszenard* A90173/875, *de Sinéty* A88245/876, *Gillette* A76973/877, *Duncan* A90163/878, A90164/879, *Mazzotti* A88718/879, *Lesavre* A90150/879, *Fischel* A70687/880, *Gibier* A90167/881, *Doran* A40937/882-3, A41771/887, *Goodell* A40631/883, A90169/883, A90170/885, *Lesi* A88717/883, *Christen* A90147/883, *Rubeska* A88726/884, *Hume* A88736/884-5, *Oliver* A40741/885, *Polaillon* A88723/885, *Strüh* A90151/886, *Steele* A42006/886, *Terrillon* A43001/887, *Gerster* A90166/887, *Burt* A74715/887-8, A88693/887-8, *Lanelongue* A42486/888, *Decressac* A88700/888, *Mangin* A42452/888, A49129/897, *Baer* A42509/888, *Stewart* A45149/889, A45148/889, *Richelot* A43354/889, *Tansini* A43513/890, *Doléris* A43573/890, A43393/890, A45861/891, *Ameschot* A46316/892, *Beatson* A47339/893-5, *Tédenat* A44793/894, A88743/00, *Sacchi* A74640/895, A91353/07, *Vautrin* A91439/895-6, *Toffoletto* A48397b/896, *Pichevin* A83240/896, *Brigidi* A48371b/896, *Héresco* A88709/896, *Laroche* A91370/896, *Bovée* A48383/896, *Adams* A91374/897, *Cocquelet* A91369/897, *Vineberg* A48398b/897, *Shimonek* A88728/897, *Kiriac* A48444/897, *Fraikin* A88705/897, *Wathen* A50652/898, *Parmalee* A91420/898, *Briggs* A50893/898, *Arima* A88834/899, *Chuffart* A88698/899, *Davis* A91379/899, *Kleinwächter* A88716/899, *Malartic and Loin* A91411/00, *Jabouly* A88711/00, *Crofford* A91378/00, *Carrez* A88694/00, *Bennecke* A88682/02, *Peterson* A91423/03, *Foerster* A91388/03, *Chavannaz* A88696/03, *Morel-Lavallée and Eschbach* A91416/04, *Grimoud* A88706/04, *Ward* A88731/05, *Evans* A88702/05, *Marcy* A91413/05, *McArthur* A91333/06, *Froget* A91389/07, *Purslow* B13271/07, *Souligoux* A91436/08, *Vance* A91438/11, *Vanverts and Paucot* A81196/11, *Toulson* B9564/15-6, *Smith* A91362/15, *Gibson* A91317/15, *Beuttner* B21253/20, *Sherrill* B21222/21, *Bégouin and Lafargue* A91504/22, *Iyer* A70847/27, *Das Gupta* A91509/30, *Maciulis* A91512/33.

[8] *Wathen* A49094/897, *Goldschmidt* A77522/27.

[9] *Heil* A88708/897, *Watts and Adair* B6248/44.

for cystic tumors in the ovarian region. In most of the published series, the incidence is estimated to be about 10% of that of ovarian cysts.[1]

Still less is known about the *age incidence* of para-ovarian common cysts, although case reports indicate that they may occur in children[2] as well as in aged women long after the menopause.[3]

The *pregnancy incidence* is not particularly high although the likelihood of a para-ovarian cyst accidentally being detected during gestation is comparatively great since such cysts, if they reach a certain size, may interfere with the development of the uterus and later, with the actual process of delivery.[4]

PATHOGENESIS

The pathogenesis of para-ovarian common cysts has been discussed in the chapter on Para-Ovarian Tumors in General.

CLINICAL COURSE

The clinical course of para-ovarian common cystomas is so similar to that of the corresponding ovarian cystomas that it hardly deserves any detailed consideration here. These cysts do not produce any endocrine disturbances; they cause signs and symptoms merely by virtue of their physical presence and expansion. Their tendency to grow into the ligaments is greater than that of ovarian cystomas.[5]

Combination of para-ovarian cystomas with *uterine fibroids* is quite common.[6] This, however, is probably coincidental and in some cases the cysts which were supposed to be para-ovarian were in reality adenomyosis cysts which are known to be frequently associated with uterine fibroids. *Uterine malformations*, such as uterus subseptus,[7] may also occur in bearers of para-ovarian common cysts. *Metrorrhagias* are occasionally noted if the para-ovarian tumor becomes sufficiently large to interfere with uterine blood supply[8] but in exceptional instances they may be seen even in patients bearing very small "parovarian" cysts.[9]

The *Fallopian tube* is often elongated in the case of large para-ovarian cysts, due to the traction and pressure exerted by the latter.[10]

Ascites[11] or *pleural fluid accumulations*[12] are rarely seen in connection with para-ovarian cysts.

COMPLICATIONS

Para-ovarian common cystomas tend to elicit the same complications which arise from ovarian common cystomas. Thus they may lead to intraperitoneal *hemorrhage, torsion* of the pedicle, secondary *inflammation* of the cyst cavity etc., all of which are discussed in Sect. IV, Vol. VI in connection with similar complications of ovarian tumors.

Rupture of the cyst into the peritoneal cavity is likewise common, especially in the case of large para-ovarian cystomas.[13] In a very exceptional instance, a para-ovarian multilocular cyst resulted in *eventration*.[14]

Among the rare complicating factors which have to be considered in connection with para-ovarian cysts, we may also mention *compression of the ureter* which, of course, will only occur in the case of large cystomas,[15] the formation of a *tubo-ovarian abscess*,[16] or an *ovarian abscess*.[17] It is not surprising that occasionally *tubercular salpingitis*,[18] or *tubercular peritonitis*,[19] as well as *non-specific salpingitis*[17] or *non-specific, acute peritonitis*[20] may also occur in patients with para-ovarian cystomas. The connection of these conditions with the para-ovarian neoplasms is usually coincidental.

DIAGNOSIS

The clinical diagnosis of para-ovarian tumors is always difficult and usually impossible. The following criteria are often mentioned as permitting differentiation of the *para-ovarian cystomas* from corresponding ovarian neoplasms; the para-ovarian cysts are more flaccid, grow more slowly and tend to displace the body of the uterus, as well as the

[1] *Batchelor* A44581/893, *Kossmann* A96841/899, *Bufe* A96007/37.
[2] *Cortiguera* B6459/896, *Eastman* A88829/00, *Dandois* A88828/01, *Deane* A81654/13.
[3] *Hamonic* A88765/07, *Loubat* B6454/23.
[4] *Tait* A40668/883, *Schulz* A93486/888, *Baron* A50957/898, *Lund* A88816/00, *Strassmann* A91364/04, *Brothers* A83337/06, *Oui* B6467/11, *Vanverts* B6448/12, *Pottet and Levy* B6449/12, *Begouin* B6450/22, B6451/23, *Pery and Mangé* B6452/23, *Lantuéjoul and Réglade* B6453/24, *Pastorini* A65104/30, *Davidson* A91510/35.
[5] *Ten Teachers* B6383/38.
[6] *Polk* A41206/884, *Byford* A41710/887, *Wylie* A44735/894, *Fraikin* A88735/897, *Jacobs* A88737/00, *Brown* A88734/02, *Opitz* A88739/06, *Patel* A91421/08, *Pelcot* A91502/24.
[7] *Peterson* A69839/03.
[8] *Pelcot* A91502/24.
[9] *Pery et al.* B6468/24.
[10] *Lepmann* A81152/01, *Brown* B12952/03, *Ten Teachers* B6383/38.
[11] *Jones* A91401/06.
[12] *Giglio* A50667/898.
[13] *Wins* A48367b/896, *Delagénière* A91381/897, *Eynard* A91384/899, *Bossuet* A88733/04, *Matti* B11288/09.
[14] *Barrena* A88749/891.
[15] *Keller* A68541/21.
[16] *Mériel and Baudet* A91415/10.
[17] *Price* A41656/886-7.
[18] *Walter* A88746/01.
[19] *Martin* A47359/895-6.
[20] *McMurtry* A41783/887, *Derera* B13139/06-7.

cervix, towards the opposite side, sometimes upwards; they are situated at a lower level in the pelvis and may obliterate the fornix of the vagina. During their growth the para-ovarian cysts tend to expand the broad ligament and may cause considerable lengthening of the uterine body and stretching of the Fallopian tubes; the latter are usually situated above (craniad) from the tumor. Only in exceptional instances is it possible, however, to palpate the normal ovaries and the uterus as separate from the cyst. The various differential diagnostic criteria of the para-ovarian cystomas have been discussed in several relevant reviews.[1]

From a differential diagnostic point of view confusion with *uterine fibroids*,[2] *ectopic gestation*,[3] *omental cysts*[4] and *normal gestation*,[5] *hydrosalpinx*,[6] *salpingitis*,[7] *appendicitis*[8] and in rare instances, free *ascites*[9] may also have to be considered. It is hardly necessary to discuss all these differential diagnostic points in detail as they have already been dealt with in the part on the Diagnosis in the chapter on Common Ovarian Cystomas.

PROGNOSIS

In general it may be said that para-ovarian cystomas are slowly-growing tumors with a good prognosis, although, occasionally rapid growth may also be seen.[10] In spite of this, surgical removal of para-ovarian cysts is indicated, if they are large enough to produce any symptoms, since complications due to torsion, rupture, malignant transformation are ever present dangers for the patient. It will also be rememberd that if the tumors reach a considerable size, they may lead to severe disturbances owing to compression of other pelvic organs; furthermore, the development of adhesions may make surgical removal much more difficult, if the intervention is postponed.

Recurrence of para-ovarian cystomas has been observed[11] but is a comparatively rare phenomenon.

THERAPY

With regard to the therapy of para-ovarian cysts, the only justifiable procedure is the removal of the growth as soon as it is recognized. As we have already mentioned in the part on Prognosis, para-ovarian common cystomas do not tend to regress spontaneously and since they represent a constant source of danger (complications due to torsion, hemorrhage, rupture, compression of other pelvic organs, malignant transformation, etc.), it is very advisable to remove the cysts at the earliest possible date.

The intervention of choice is *extirpation of the cyst by laparotomy* through a suprapubic incision. As with ovarian cysts, this route gives the surgeon the best view of the operative field and greatly facilitates the separation of adhesions, if such are present. It may be necessary to remove the ovary and even the Fallopian tube, together with the para-ovarian cyst, if these adjacent organs are involved in solid adhesions; otherwise, simple enucleation of the cystoma may suffice. If there are many adhesions, or if the cyst is very large and spreads deep into the broad ligament or mesentery, the operation may be quite difficult but, in the majority of the cases, enucleation is a simple procedure, especially if the cyst has a definite pedicle.[12] Even very *large* para-ovarian cystomas have often been removed in this manner.[13]

Adhesions may be responsible for such surgical complications as accidental *incision into the bladder*.[14] Similarly adhesions may be the cause of accidental *transection of a ureter* and in such instances an anastomosis between the ureter and the bladder should immediately be performed.[15] Among other factors which are likely to complicate the course of the operation, the simultaneous existence of *preg-*

[1]*Carson* A40385/882, *Selhorst* A48254/896, *Picqué* A91425/897, *Kossmann* A96841/899, *Pichevin* A91424/05, *Mento* B13405/16, *Bégouin* A91503/22, *Deniker* A91551/25.
[2]*Chenhall* A91506/21, A91507/22.
[3]*Doege* A88756/895, *Toogood* A88745/896, A88744/896.
[4]*Albina* B11831/18.
[5]*Cushier* A41328/884, *Chueco and Fellner* A52091/34.
[6]*Péraire* B9355/19.
[7]*Celos* A88695/01, *Saint* B9489/19.
[8]*Matti* B11288/09.
[9]*Bergeret et al.* A30646/39.
[10]*Terrillon* A42282/888, *Handfield-Jones* A48348b/896.
[11]*Goodell* A45120/889, *Hadden* B5541/19, B9474/19.
[12]*Koéberlé* A75889/872-3, *Browne* A90159/879, *Goodell* A90168/882, A44145/892, *Antal* A90153/884, *Montgomery* A40676/884, A40675/884-5, A40801/885, *Storchi* A40752/884, *Almström* A40783/885, *Bogaevski* A42044/885, *Lebedeff* A90149/885, *Negri* A90183/885, *Braun von Fernwald* A90157/885, A88752/887, A90158/888, A45217/889, *Polaillon* A41493/885, A90187/885, *da Costa* A41649/886, *Poggi* A41786/886, *Menocal* A41817/886-7, *Phenomenoff* A90186/887, *Terrier* A41899/887, *Mangin* A42400/888, *Terrillon* A88785/888, A45163/889, A45156/889, A88786/898, A88789/898, A88790/898, *Sacré* A45186/889, *Potter* A45702/890, *Khelminski* A88767/891, *Neyra* A88775/891, *Fenton* A45834/891-2, *Cook* A46326/892, *Fournel* A44170/892, A88759/892, A88760/892, *Hall* A44114/892, A91395/898, A91394/08, *Rose* A88780/892, *Parvin* A44212/892-3, *Mann* A44593/893, *Villeneuve* A46607/893, *Gangitano* A91390/894, *Jacobs* A48353/895-6, *Goelet* A48438b/897, *Kelly* A48980/897, *Hawkins* A91399/897-8, *Beyea* A88750/898, *Flemming* A91387/898, A91386/898, *Giglio* A88761/898, *Clarke* A91216/898, A91214/899, *Monod* A88773/899, *Naylor* A91417/899, *Petroff* A91227/899, *Kossmann* A96841/899, *Newman* A91226/02, *O'Callaghan* A91418/02, *Taylor* B13018/04, *Sysnozhonski* A91373/04, *Martin Aguilar* A91414/05, *Purcell* A91427/05, *Giles* A88762/06, *Riche* A91428/06, *Keyes* A91223/07, *Ross* A91430/10, *Grosse* A91393/13, *Chamorro-Benard* A91272/19, *Beuttner* A65454/20, *Markley* B21212/21, *Schrup* A91513/35.
[13]*Stewart* A45149/889, *Rogers* A46505/893, A88777/893, A50949/898, *Wathen* A88793/00, *Trotter* A88791/03.
[14]*Noeggerath* A90184/881.
[15]*Delagénière* A91380/897.

nancy[1] or of extensive *uterine fibroids*[2] may be mentioned, but these complicating factors are no contra-indication to the removal of the tumor, since pregnancy usually proceeds normally after the operation and fibroids may be removed simultaneously with the para-ovarian cyst.

Removal of para-ovarian cysts through the *vaginal route* is but rarely possible.[3] This procedure is not recommended except in the case of occasional small para-ovarian cysts, especially those developing during pregnancy,[4] and those arising from Gartner's duct which tend to be situated in the immediate vicinity of the vagina.[5]

Among the antiquated therapeutic procedures, simple *puncture* of the cyst[6] may be mentioned but since this intervention rarely, if ever, effects a permanent cure, it is recommended only in selected cases as a palliative measure. *Drainage* of the cyst cavity through an extensive incision,[7] *marsupialization*[8] as well as *injection of irritating solutions*, for instance, iodides,[9] have all been tried in patients with para-ovarian cysts during the last century, that is, at a time when similar interventions were in vogue for the treatment of ovarian cystomas. At the present time, the employment of such procedures is entirely unjustified, in view of the much greater safety afforded by the contemporary surgical technics for intraperitoneal operations.

Radium treatment should be reserved for inoperable cases.[10]

[1]*Tait* A40668/883, *Baron* A50957/898, *Lund* A88816/00, *Strassmann* A91364/04, *Grosse* A91392/13.
[2]*Villarreal* A91441/03.
[3]*Yastrebeff* A88794/888, *Syanozhenski* B13017/04, *Taylor* A91437/04-5, *De Palma* A91382/07-8.
[4]*Strassmann* A91364/04.
[5]*Kossmann* A96841/899.
[6]*Greliot de Giromagny* A90172/883, *Terrillon* A90192/885, A41972/889, *Reverdin* A41820/887.
[7]*Hofmokl* A44255/891-2, *Salmon* A88781/894, *Watkins* A91443/899.
[8]*Lucas-Championnière* A91409/03.
[9]*Bouilly* A90155/884.
[10]*Markley* B21212/21.

COMMON CYSTOMAS IN ANIMALS

Cyst formation in the ovaries of animals has not been extensively studied, although the available literature indicates that it is of some practical importance in veterinary medicine. One of the greatest deficiencies of the pertinent literature is the failure to distinguish clearly between follicle cysts (which tend to produce hyperfolliculoidism) and other types of cystic tumors.[1]

It may be said, however, that in *fish* ovarian cysts are not uncommon.[2] They also occur in the *ass*,[3] *cat*,[4] *cattle*,[5] *dog*,[6] *guinea pig*,[7] *horse*,[8] *mouse*,[9] and *pig*.[10] Most of the instances reported in cows and mares were associated with nymphomania. This makes it very probable that the cysts were derived from follicles and led to excessive production of folliculoid hormones (see also chapter on Follicle Cyst in Animals).

[1]*Marchal* B6523/884, *Taskin* B6524/25, *van der Kaaij* A96146/32.
[2]*Freund* B21371/23, *Plehm* B21372/24, *Schweizer* B21573/27, *Klemm and Freund* 6523/30.
[3]*Marton* B6555/26.
[4]*Robinson* A42277/888, *Coquot and Nenkoff* A65605/30.
[5]*Küchenmeister* A81615/852, *Flamichaud* B6562/886, *Courrier* 24723/25, *Frei* A67568/31.
[6]*Petit and Bissauge* B12650/05, B6606/07, *Zibordi* B6616/27, *Coquot and Nenkoff* A65605/30.
[7]*Courrier* 24723/25.
[8]*Harms* B6549/, *Galtier* B6534/877, *Schneidenmühl* A82048/883, *Pollock* A43481/889, *Colin* A69626/899, *Albrecht* A69625/04, *Hobday* A69627/06, *Peyron* B20947/24, *Montmitonnent* B6535/30.
[9]*Slye et al.* B9358/20.
[10]*Festal* A81523/857, *Rayner* A82027/864, *Pichi* B12787/04.

PLATE XVII

COMMON CYSTS

Fig. 1. SIMPLE UNILOCULAR CYST ARISING FROM SURFACE OF THE OVARY. In this, as well as in all subsequent illustrations on this plate, the ovary is indicated by a dotted area, the germinal epithelium as well as the surface lining of cysts is represented by a heavy line, the inner lining of cysts and the surface of papillomas by a thin line.

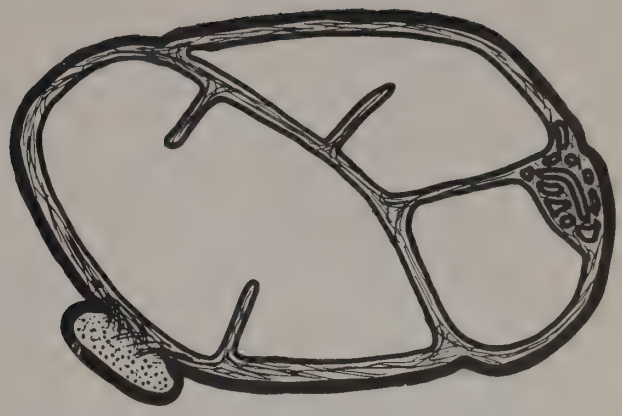

Fig. 2. MULTILOCULAR, MAINLY MACROCYSTIC, COMMON CYSTOMA WITH A SMALL MICROCYSTIC AREA IN THE RIGHT PART OF THE PICTURE. Note that on this level there are three distinct large cystic cavities, some partially subdivided by cristae which are remnants of originally complete septa. The large cysts are formed due to rupture of smaller cavities into each other and subsequent disappearance of the septa. The small microcystic area contains gland-like acini and tubules, sometimes referred to as parvilocular or adenomatous formations. New macrocysts are formed owing to increasing fluid secretion and distension within the microcysts.

Fig. 3. UNILOCULAR CYSTS WITH AN INTERNAL PAPILLOMA. Note that the connective tissue of the papilloma tree arises from the stroma of the cyst wall. The point of origin of such papillomas is subject to great variations and not necessarily located near the ovary proper.

Fig. 4. UNILOCULAR CYST WITH TWO EXTERNAL PAPILLOMAS. Usually external and internal papillomas develop simultaneously within the same tumor and it is believed that most —if not all— external papillomas arise from the inner lining of the cyst, subsequent to perforation. In some cases, however, as in that illustrated here, external papillomas arise without any sign of internal papillomatous proliferation.

Fig. 5. TWO PAPILLOMAS ARISING DIRECTLY FROM THE OVARIAN SURFACE. Note also minute individual papillae to the left of the small papilloma. Such excresences give a characteristic "velvet-like" aspect to the ovarian surface and represent the earliest stages in surface papilloma formation.

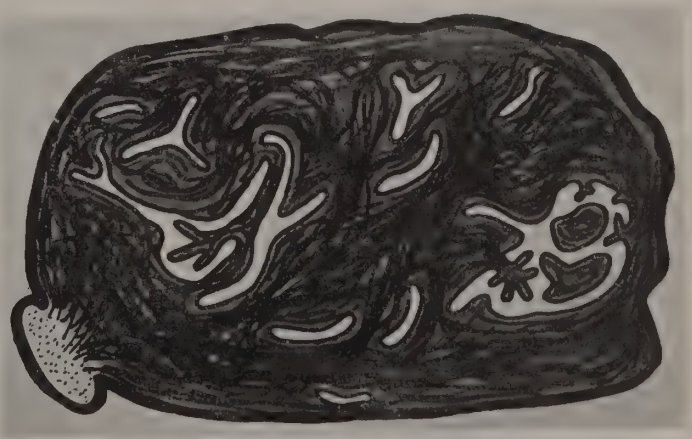

Fig. 6. LARGE ADENOFIBROMA. Note great prevalence of dense, thick connective tissue fibers. The epithelium lined spaces are parvilocular tubules which frequently branch and sometimes contain "intracanalicular" papillomatous proliferations. This tumor type is always serous.

PLATE XVIII

COMMON CYSTS

SCHEMATIC DRAWINGS ILLUSTRATING MICROSCOPIC STRUCTURE OF THE MOST IMPORTANT CYSTOMAS

Fig. 1. COMMON SEROUS, PARTLY MACROCYSTIC (lower left), PARTLY MICROCYSTIC OR ADENOMATOUS (upper right) CYSTOMA.

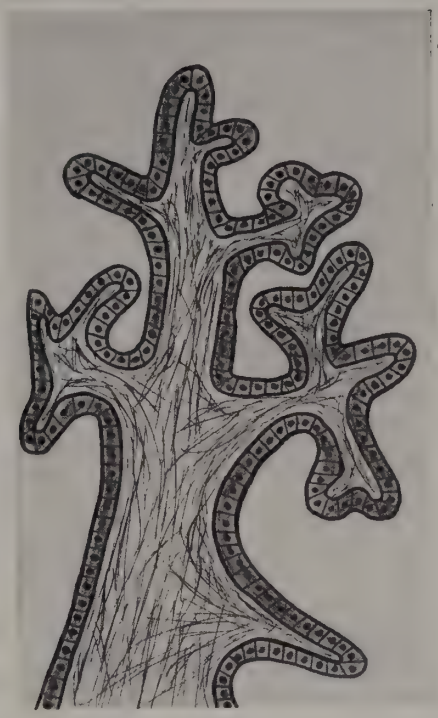

Fig. 2. COMMON SEROUS PAPILLOMA. This type is found on inner or outer surface of serous ovarian cysts; sometimes it arises directly from the surface of the ovary.

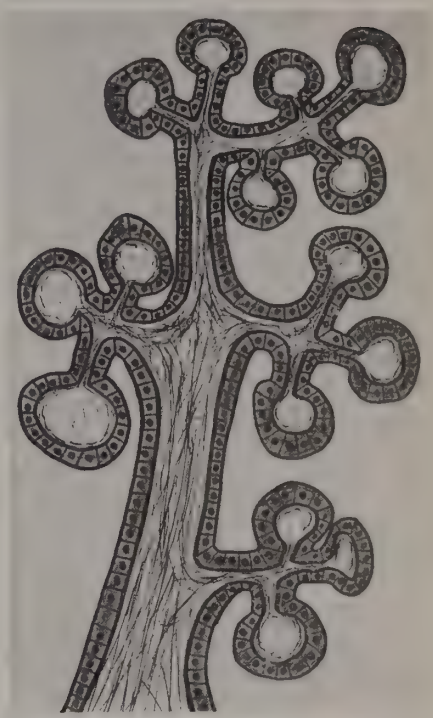

Fig. 3. FALSE RACEMOUS SEROUS CYSTOMA. Note grape-like arrangement of small "cystlets". The formation of these false cysts is merely due to localized stroma edema at the tip of the papillae. There is no actual cyst cavity but merely free fluid accumulation in the individual "grapes".

Fig. 4. COMMON PSEUDOMUCINOUS, PARTLY MACROCYSTIC (lower left), PARTLY MICROCYSTIC OR ADENOMATOUS (upper right) CYSTOMA.

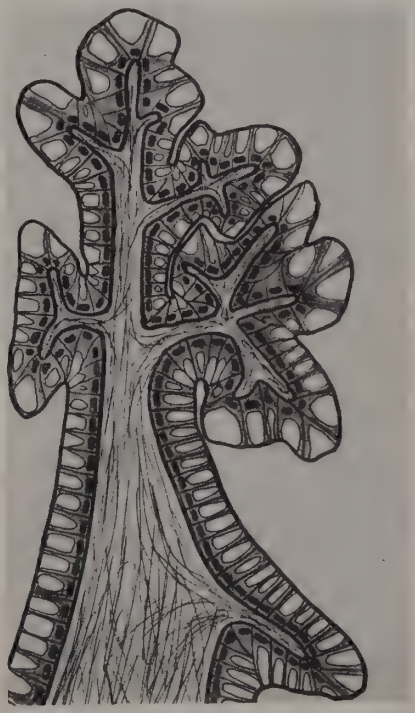

Fig. 5. COMMON PSEUDOMUCINOUS PAPILLOMA. This type differs from the corresponding serous papilloma merely by virtue of the pseudomucinous lining epithelium.

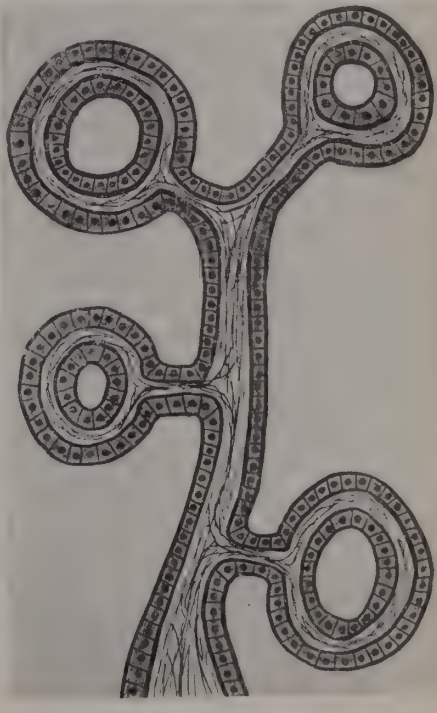

Fig. 6. TRUE RACEMOUS CYSTOMA. This type differs from the corresponding false racemous cystoma by virtue of the fact that each "grape" actually contains a separate cyst cavity lined by the same type of serous epithelium which also covers the surface of the papillae.

PLATE XIX
COMMON CYSTS

Fig. 1. LARGE OVARIAN CYST CAUSING CACHEXIA (after Winter B228/897). Note enormous enlargement of the abdomen, dilatation of veins in abdominal wall, marked cachexia and characteristic "facies ovariana".

Fig. 2. LARGE OVARIAN CYST CAUSING EDEMA OF LOWER EXTREMITIES (after Binkley A48369b/897). This patient bore one of the largest ovarian cysts on record. The entire cyst weighed 225 lbs., of this 175 lbs. was intracystic fluid. The weight of the patient before operation was 396 lbs. Note edema of legs and dilated abdominal veins.

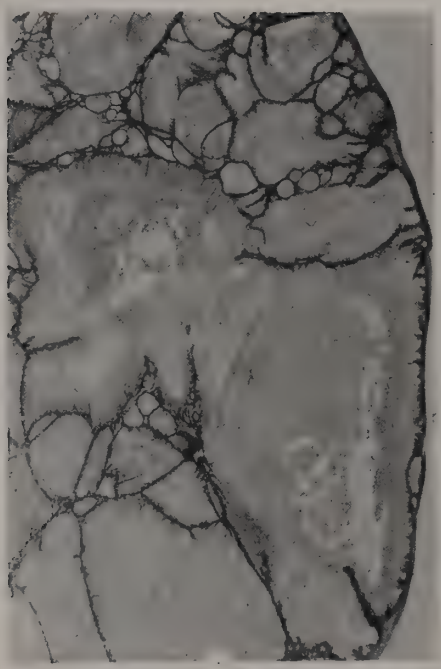

Fig. 3. MULTILOCULAR PSEUDOMUCINOUS CYSTOMA (courtesy of Dr. L. Berger). General appearance of a pseudomucinous, multilocular cystoma at low magnification. Note numerous independent cyst cavities filled by pseudomucinous fluid. The partitions between some of the cysts are incomplete (presumably, due to pressure atrophy and rupture of one cyst cavity into another). Papillomatous excrescences are noticeable on the surface of some such incomplete septa.

Fig. 4. PSEUDOMUCINOUS PAPILLIFEROUS CYSTOMA. The connective tissue of the main papilloma stem invades the smaller excrescences and furnishes them with stroma. The lining is typically pseudomucinous. Pseudomucin strands and cast-off cell debris are visible between the excrescences in the cyst cavities.

Fig. 5. PARVILOCULAR PORTION IN A PSEUDOMUCINOUS CYSTADENOMA (courtesy of Dr. L. Berger). Small pseudomucinous cyst cavities (resembling alveoli or ducts of glands) within a scirrhous connective tissue stroma. This field represents a microcystic or parvilocular portion in an otherwise typical macrocystic cystoma.

PLATE XX
COMMON CYSTS

Fig. 1. PSEUDOMUCINOUS CYSTOMA (courtesy of Dr. P. Masson). Septum between two cavities in a pseudomucinous cystoma, illustrating marked differences which may occur in the epithelium of two adjacent cavities. The cavity on the left is lined by a cylindric epithelium containing practically no pseudomucin, while that on the right posesses a high cylindric, typically pseudomucinous covering.

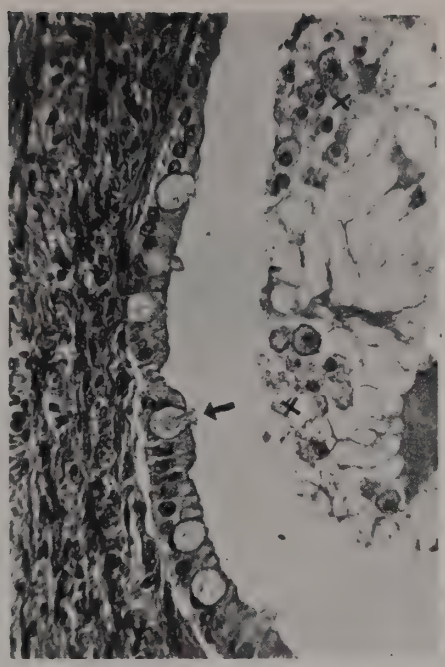

Fig. 2. PSEUDOMUCINOUS CYSTOMA. Note that in this field, the cyst cavity is lined by a cuboidal or low, cylindric, pseudomucinous epithelium. Most epithelial cells contain little or no pseudomucin but some are filled with secretion to such an extent that they assume a signet ring-like appearance. One cell (marked by arrow) is in the process of discharging the pseudomucin, while several other cells (X) have been cast off into the lumen, indicating a partially holocrine type of secretion.

Fig. 3. PSEUDOMUCINOUS CYSTOMA. Note the unusual height which may be reached by the pseudomucinous epithelial cells in some cyst cavities. One nucleus is out of line and apparently belongs to a cell which is in the process of holocrine discharge.

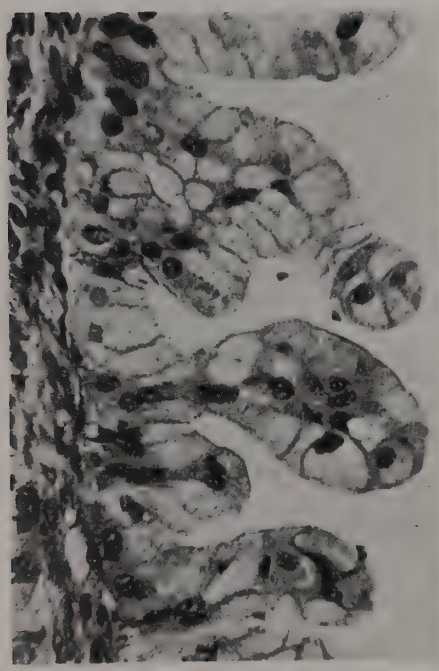

Fig. 4. PSEUDOMUCINOUS CYSTOMA. Note the characteristic, "pseudopapillary" formations which consist almost exclusively of epithelial proliferations without stroma.

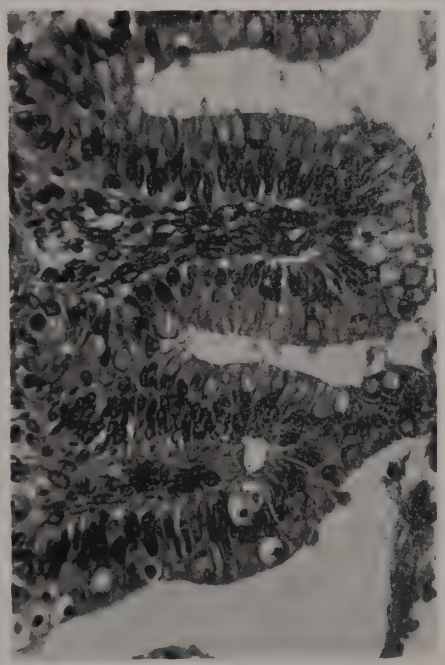

Fig. 5. PSEUDOMUCINOUS CYSTOMA. Note simple, tubular invaginations of surface lining, very reminiscent of those seen in the normal, large intestine.

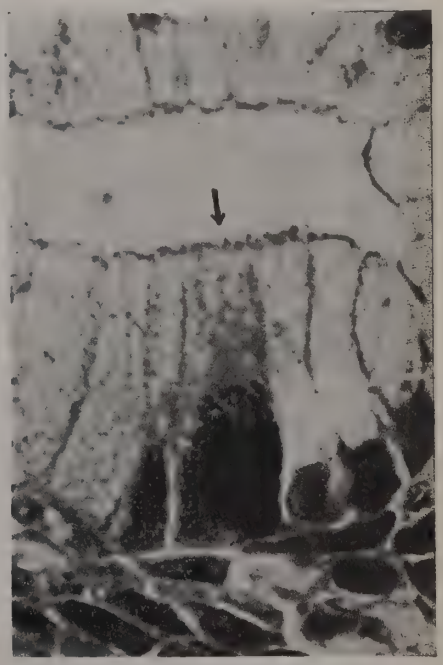

Fig. 6. ARGENTAFFIN CELLS IN A PSEUDOMUCINOUS CYSTOMA (courtesy of Dr. P. Masson). Note the numerous argentaffin granules around and below the nucleus of one pseudomucinous cell, (marked by arrow); the adjacent epithelium is entirely free of such granules. The argentaffin cells in pseudomucinous cystomas are similar to those found in the intestinal epithelium.

PLATE XXI

COMMON CYSTS

Fig. 1. GROSS APPEARANCE OF A MULTILOCULAR PSEUDOMUCINOUS CYSTOMA OF THE OVARY ON CROSS-SECTION (after Novak B109/44).

Fig. 2. GROSS APPEARANCE OF A PSEUDOMUCINOUS CYST WHICH RUPTURED AND PRODUCED PSEUDOMYXOMA PERITONEI (after Novak B109/44).

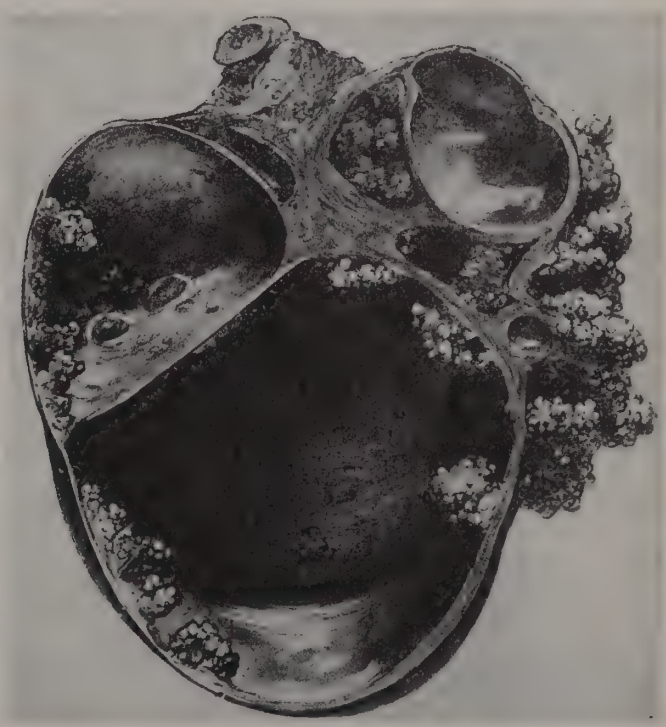

Fig. 3. GROSS APPEARANCE OF A PAPILLARY SEROUS CYSTADENOMA OF THE OVARY ON CROSS-SECTION (after Novak B109/44). Note the presence of papillomas both on the internal and external surface of the cyst walls.

PLATE XXII

COMMON CYSTS

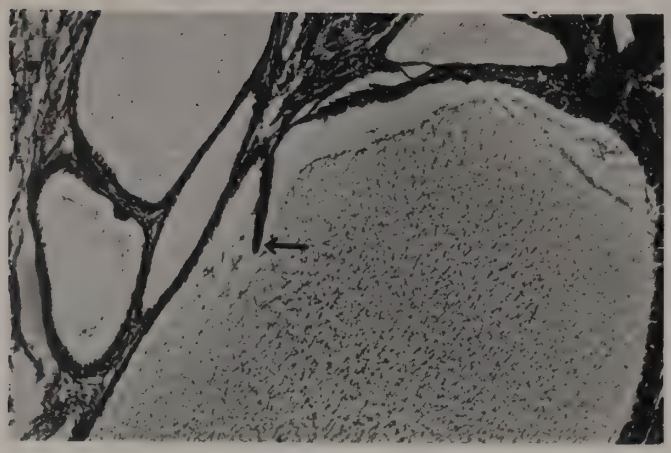

Fig. 1. SEROUS CYSTOMA. Multilocular, common, serous cystoma as seen under comparativley low magnification. Note cyst cavities of varying sizes and one crista, (marked by arrow) representing the remnant of a septum between two cyst cavities which perforated into each other.

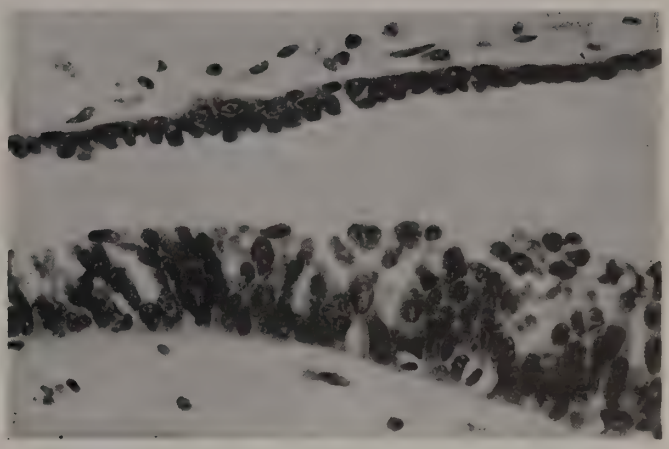

Fig. 2. SEROUS CYSTOMA (courtesy of Dr. P. Masson). High magnification of epithelial lining, showing cell details. Note that on the upper border the cavity is lined by a simple cuboidal, serous epithelium, while on the lower border, the epithelium is partly stratified and tends to form "pseudopapillae", devoid of connective tissue stroma. Compare the small nucleoli and the regular appearance of these cells with the highly atypical proliferations in serous carcinomas.

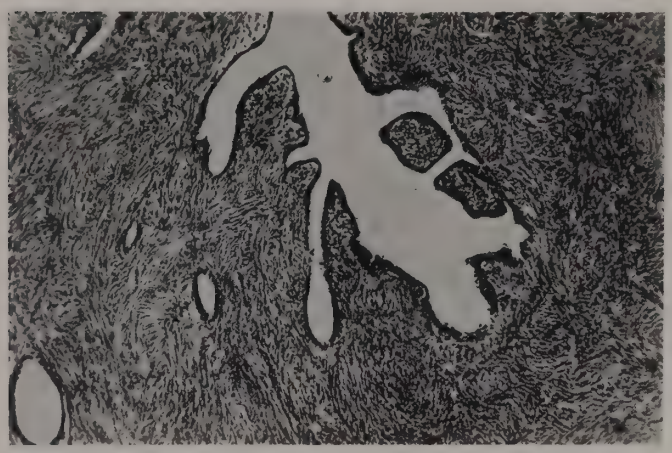

Fig. 3. SEROUS FIBROADENOMA. Note dense, connective tissue and irregular duct-like cavities, lined by simple, serous epithelium. Note intracanalicular proliferations.

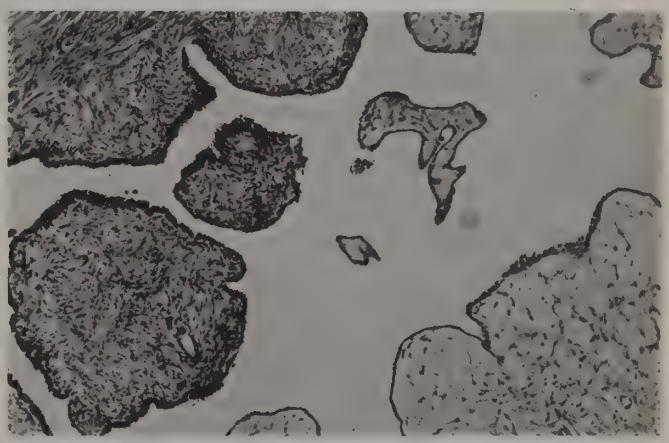

Fig. 4. SEROUS FIBROADENOMA. Higher magnification of intracanalicular proliferations in a serous fibroadenoma. Note that the stroma in the vegetations is partly solid and dense (left side) partly edematous (right side of field).

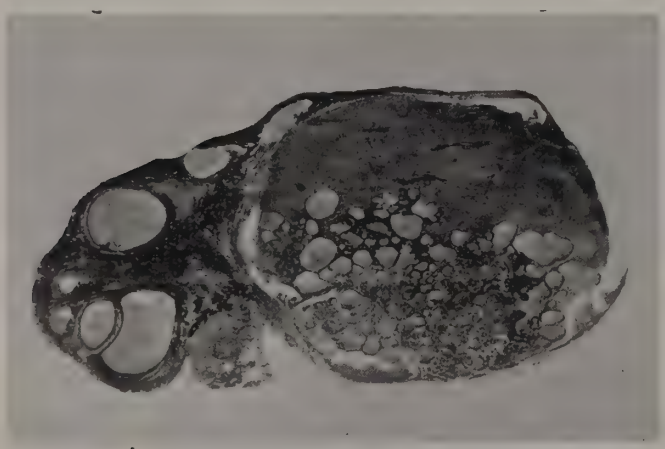

Fig. 5. INTERNAL, RACEMOSE, SEROUS PAPILLOMA (courtesy of Dr. L. Berger). Left side of field is occupied by normal ovarian tissue with follicles. On the right side there is a large serous unilocular cystoma from whose inner surface a racemose small papilloma arises near the ovarian attachment. Note that each papillary excrescence is transformed into a grape-like structure.

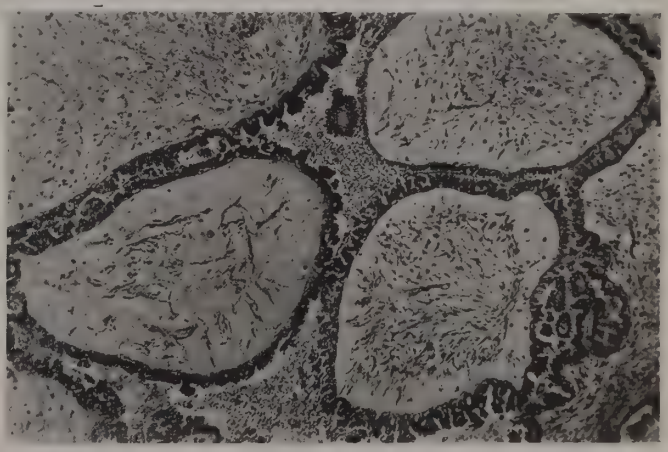

Fig. 6. INTERNAL, RACEMOSE, SEROUS CYSTOMA. Higher magnification of a small field in the tumor illustrated in Fig. 5. Note marked stroma edema in each of the "grape-like" papillary excrescences. The serous surface epithelium is somewhat stratified and suspicious of premalignant transformation.

OVARIAN COMMON CARCINOMAS

SYNONYMS: Cancer of ovary, malignant adenoma of ovary, malignant epithelioma of ovary.

REVIEWS

ENGLISH: *Jordan* A78486/00-1, *Norris* A74620/05-6, A74619/06, *Holmes* A78444/08, *Porter* A24009/16, *Peple* A78820/16, *Eden and Ley* A78236/21, *Pearl and Bacon* A78813/28, *Robinson* A67262/30, *Curtis* A63170/30-42, *Cameron* A64097/31, *Emge* A64099/31, *Stacy* A65181/31, *Fleming* A64219/31, *Estabrook* A78260/32, *Norris and Murphy* A62253/32, *Shaw* A61532/32, *Moench* A61571/33, *D'Arcy and Keatinge* A52098/34, *Pahlas* A51976/34, *Pyle and Clark* A28086/35, *Lynch* A59465/36, *Meigs* A95292/37, A97209/39, A34255/40, *Morton* A95070/37, *McMillan* A97424/39, *Sardi and Ahumada* A96623/40, *Pemberton* 80890/40, *Novak* A35848/41, B109/44, *Goodall* A37767/42, *Geist* B6672/42.

FRENCH: *Péan* A78812/879, *Poupinel* A42104/886, *Prat* A78856/893, *Michel* A69412/897, *Pozzi* A78855/07, *Dreyfus* A78223/07, *Huguenin* A78456/10, *Massabuau and Etienne* A78672/13, *Roux et Vinon* A78927/20, *Schickelé* A75850/22, *Leroux et al.* A27877/35, A61600/35, *Weinroth* A64865/35, *Mathieu* A97206/39.

GERMAN: *Kiwisch* A70081/852, *Eppinger* A78252/872, A78253/872, *Cohnheim* A78168/877, *Dybowski* A78232/880, *Debold* A88255/884, *Leopold* A41747/887, *Pietrusky* A78833/887, *Frank* A43269/889, A92146/889, *Lerch* A45139/889, *Neubaur* A78757/894, *Vogl* A79156/896, *Bellinger* A78043/897, *Heinrichs* A78426/899, *Martin* A78665/899, A96833/899, *Wendeler* A96825/899, *Feilchenfeld* A78273/01, *Arana* A78004/04, *Ribbert* A78883/06, A78884/11, *Schauta* A77789/07, *Jung* A78487/08, *Schottländer* A78998/13, A78999/15, *Horney* A78451/13, *Moench* A78716/18, *Frankl* A83392/19, A78304/19, *Holler* A78443/22, *Mayer* A78681/24-9, *A99597/26*, *Sternberg* *A64845/26*, *Borrmann* A78081/26, *Dietrich* A78211/26, *Döderlein* A78213/27, *Körner* A78532/27, *Fleiss* A78286/31, *Liepmann* A64102/31, *Weysser* A79201/32.

ITALIAN: *Alfieri* A63499/29.

SPANISH: *Votta* A97025/38.

DEFINITION

All (primary or secondary) malignant epithelial growths of the ovary are listed in this Encyclopedia as ovarian carcinomas. It should be kept in mind that in addition to the primary ovarian carcinomas, this definition includes ovarian cysts which have undergone malignant transformation, ovarian metastases of extragonadal cancers and even cases in which a carcinoma of an adjacent organ invades the ovary.

The malignant varieties of well defined specific epithelial tumor types such as for instance, the folliculoma, "luteoma" or dermoid cyst will be discussed in separate sections, although by definition they are also ovarian carcinomas. The present chapter will deal only with the "common carcinomas", a term under which we include solid primary ovarian cancers, serous and pseudomucinous cysts with carcinomatous transformation and all types of secondary ovarian cancers.

HISTORY

The historic development of our knowledge regarding ovarian cancers has been surveyed by Wolff[1] and Ewing.[2] Numerous interesting reports describing the pathology and clinical course of this disease will be found in the early literature.[3] It is evident from these descriptions that the various forms of cystic and solid carcinomas have been known to physicians for many centuries, but a clear-cut distinction between cancers and other tumors of the ovary was not made until about the middle of the nineteenth century when the histologic criteria began to receive due attention in the formulation of the diagnosis.

CLASSIFICATION

Various investigators have attempted to devise systems for the classification of ovarian carcinomas[4] (see also chapter on Ovarian Tumors in general).

Miller[5] has suggested the following:

1. *Primary,* macroscopically solid carcinomas which may, however, contain a variable number of more or less extensive secondary liquefaction cysts.

2. *Secondary* carcinomas arising from the malignant transformation of originally benign a) serous, b) pseudomucinous, c) dermoid and d) endometriosis cysts. (The possibility of a malignant transformation of endometriosis cysts is still in doubt according to some pathologists.) It will be noted that the term "secondary" in the sense in which it is used here, is not synonymous with "metastatic".

3. *Metastatic* carcinomas (including Krukenberg's tumors).

4. *Carcinomatous invasion from adjacent organs,* the so-called "fortgeleitete Karzinome" of the German investigators.

The classification used in this chapter concerns only "common ovarian carcinomas" as defined above.

It includes the following categories:

1. *Primary solid carcinomas* which may become,

[1]A79221/11.
[2]A64873/42.
[3]*Fontaine* A88256/753, *Malaval* A88349/753-9, *Fisher* A88307/785, *Marret* A88258/808, *Baldwin* A88268/809, *Holbrook* A88327/809-13, *Normand* A88354/809-16, *Blackstone* A88276/827-8, *Dobson* A88302/831-2, *Macfarlane* A88345/832, *Bush* A88290/839, *Lambert* A88338/846, *Renaud* A88368/847, *Reinsdorff* A88261/849.
[4]*Massabuau* A78670/18-9, *Massabuau and Etienne* A78671/20, *Ewing* A64873/42, *Merritt and Caulk* B15739/43.
[5]A18279/37.

at least partly, cystic due to liquefaction necrosis.

2. *Cystic carcinomas* arising through carcinomatous degeneration of originally benign common cysts.

3. *Metastatic carcinomas,* including Krukenberg's tumors as well as other multiple epitheliomas involving both the ovary and extragonadal tissues. Many of these are metastases of ovarian carcinomas but are discussed conjointly with the ovarian metastases of extragonadal cancers from which in some instances, it is difficult to separate them with certainty.

PATHOLOGIC ANATOMY

A. General Morphologic Characteristics. The structural appearance of the common ovarian cancers is extremely variable, which is hardly surprising since a great many heterogeneous growths are listed under this title. The macroscopic and microscopic features of the well characterized subgroups will be discussed conjointly in the chapters specifically devoted to them. The following outline is merely designed to sketch the characteristics common to ovarian cancers in general and to furnish an opportunity for the registration of those case reports of the ancient or purely clinical literature which were not accurately characterized as regards histologic structure. At first sight it may appear rather wasteful to assign space to the discussion of carcinomas which have not been histologically identified, or only incompletely so, but it must be borne in mind that important facts concerning the course, possible complications, prognosis, etc., can be learned even from ovarian cancers characterized merely on the basis of their clinical symptomatology.

In general, the malignant tumors of the ovary do not become as voluminous as do the benign growths, since death owing to the invasive and toxic properties of these blastomas occurs before they reach a very great size. Several cases of unusually *large* ovarian carcinomas can be found in the literature, however.[1]

Not infrequently ovarian cancers are *bilateral.*[2] A survey covering a large number of the published cases of ovarian carcinomas leads us to believe that if these are considered irrespective of structure and origin, approximately half of them are bilateral. This conclusion is in agreement with the findings of Miller[3] who scrutinized 1791 case reports—described by different authors—and found that in 50.5% both ovaries were involved. It will be seen from the subsequent paragraphs that the incidence of bilateral development is greater in some types of ovarian carcinomas than in others.

Numerous reviews deal with the *statistics* of ovarian cancers.[4] These statistical surveys furnish data concerning the incidence, frequency of bilateral development, formation of metastases, prognosis, etc. of ovarian cancers, all of which will be discussed in more detail in the corresponding chapters of this Encyclopedia.

The enormous number of *case reports* describing patients who suffered from ovarian cancers furnishes a rich material for statistical considerations.[5]

---

[1] *Jackson* A78464/850, *Brown* A88286/872-3, *Boursier* A78085/898, *Koenig* A78531/31.

[2] *Johnson* A78483/848-9, *Nunn* A88356/850, A88357/850, *Charteris* A88294/875, *Johannovsky* A78482/877, *Boussi* A78086/877, *Worship* A88395/878, *Schustler* A40267/883, *Carson* A41635/884, *Vanheuverswyn* A42473/887, *Löhlein* A78626/889, *Hanot* A92044/890, *Fleischmann* A78284/896, *Pilliet and Delaunay* A49189/897, *Meyer* A78701/897, *Schulze* A79005/01, *Jaboulay* A75288/02, *Gemmell* A78331/02, *Lecornu* A78585/02, *Clement* A78160/03, *Lockyer* A78621/04, *Garcia Arias* A75286/04, *Osterloh* A78799/04, *Hammond* A92043/05-6, A83391/07, *Brünings* A78114/06, *Mond* A78721/06, *Jellett* A92156/06, A92155/06, A78475/06-7, *Nebel* A78754/07, *Kerrawalla* A78513/07, *Lacouture and Rousseau* B13293/07, *Wiener* A79204/07, *Leroy* B13294/07, *Fergusen* A78274/08-9, *de Snoo* A79042/09, A75860/21, *Augier and Lucas* A83386/11, *Peterson* A75857/12, *Bongartz* A70592/13, *Bertino* A66921/13, *Meriel,* A78694/16, *Roux and Vinon* A75859/19-20, *Chenall* A83390/22, *Viannay* A66933/23, *Vanverts* A75861/23, *Cashman* A83389/24-5, *Reinhart* A78878/26, *Rosenstein* A78914/28, *Labhardt* A78564/31, *Culbertson* A78177/33, *MacGregor and Small* A96586/40.

[3] A18279/37.

[4] *Cohn* A42018/886, *Danielsen* A78183/887, *Peetz* A78815/889, *Anonymous* A79137/894, *Hänisch* A78392/898, *Heimann* A78422/898, A78423/899, *Tiemann* A79115/00, *Nencki* A78756/00-1, *Riechelmann* A78889/02, A78888/02, *Rieck* A78891/04, *Lippert* A64789/05, *Redlich* A78874/07, A78873/07, *Buday* A78125/08, *Schuster* A79007/08, *Steinhaus* A79055/10, *Nobiling* A78759/11, A78760/11, *v. Mielecki* A78708/13, *Bejach* A78041/19, *Nörr* A78761/19, *Ley* A78607/19-20, *Rau* A78869/22, *Mattmüller* A78675/23, *Bilz* A78056/23, *Berencsy and v. Wolff* A78047/24, *Norris and Vogt* A78764/25, *Müller* A78736/26, *Byron and Berkoff* A78136/26, *Janusz* A78472/26, *Matzen* A78676/27, *Kutscherenko and Solowiev* A78563/28, *Cornet* A78171/28, *Junghanns* A78488/29, *McWhorter and Cloud* A78646/30, *Wilinski* A79210/30, *Harms* A78403/30, A78404/31, *Welte* A79193/30, A79194/31, *Gunsett* B12166/30, *Wackerbauer* A79163/32, *Bilello* B21696/32, *Stoel* A79062/33, *Kaplan* A78494/33, *Supino* A79080/33, A79081/34, *Haug* A78409/33-4, *Scharla* A78958/34, *v. Numers* A52174/34, *v. Kenessay and v. Zalka* A78511/35, *di Francesco* A96027/36, *Pemberton* 80890/40, *Meigs* A34255/40, *Taylor and Greeley* A55414/42.

[5] *Smith* A88377/851, A46350/892-3, *Bucqoy* A88288/853, *King* A88332/853, A65475/29, *Price* A88366/853, *Skegg* A88376/853, *Paschall* A88360/855, *Storer* A88378/856-7, A88379/859, *Zimerman* A79234/857, *Gellé* A78330/858, *M'Ghie* A88346/859-60, *Lange* A88339/860, *Mosler* A78732/860, *Cleland* A87515/860-1, *Wells* A79192/863-4, A88391/874, *Kimball* A88331/864, *Hamilton* A88320/865, *Fischer* A88306/866, *Waldeyer* A79168/867, A79170/871, *Sköldberg* A87044/869, *Mears* A78684/871, A88350/874, *Drysdale and Sheffield* A88303/871, *Beebe* A78037/871, *Wernich* A79196/871, *Wright* A79225/871, *Thomas* A88381/871-2, *Duncan* A88304/872, *Parry* A78809/872, *Hayden* A88321/873, A92045/874, *Weber* A79180/873, *Hayes* A88322/873, A75287/874, *Cheever* A86557/874, *Foulis* A78295/875, *Poncet* A78849/876, *Chambard* A78146/877, *Philipson* A92019/877-8, *Sisteray* A88375/878, *Emmet* A77469/879, *Potain* A88364/879, *Wittrock* A88265/879, *Kirkley* A29443/

Footnote cont'd.

B. Primary Solid Carcinomas. The primary carcinoma of the ovary is always solid at first[1] although its *size, shape, color and consistency* are subject to great variations. Owing to nutritional disturbances within the tumor, certain areas may become soft and eventually liquefied so that the growth secondarily assumes a cystic appearance.

The data given by various investigators concerning the frequency of *bilateral* solid ovarian carcinomas are extremely variable.[2] In general, it may be stated, however, that statistical surveys which include all types of solid ovarian cancers reveal bilateral development in about half of the cases. Thus in a series of 151 solid ovarian carcinomas[3] 46.4% were bilateral and one author[1] who collected 373 cases from the reports of nine statistical series, calculated the average incidence of bilateral development to be 52.8%.

It is highly probable that the vast majority of bilateral solid carcinomas are metastatic and secondary to cancers of other organs. In some instances a primary ovarian carcinoma of one gonad may have caused metastases on the contralateral side.[4] The theory according to which primary ovarian cancers often develop simultaneously on both sides,[5] is rejected by most contemporary investigators.[6]

It is customary to distinguish the *scirrhous* carcinoma as a separate subgroup, characterized by the preponderance of a dense connective tissue stroma.[7]

The majority of the primary ovarian carcinomas are parenchymatous growths often described as "*medullary*" or "*encephaloid*" cancers.[8]

The subdivision of the solid carcinomas into the two main groups of fibrous (scirrhous) and parenchymatous (medullary or encephaloid) cancers is based mainly on the difference in the consistency of the two types, the former being hard, the latter, soft. Histologically, the former consist mainly of

[5] cont'd. 880, *Kempf* A88202/880, *Whitwell* A29333/880-1, *Schuchardt* A79004/881, A88374/882, *Margoniner* A88257/883, *Lukin* A40728/884, *Beattie* A40960/885, *Cohn* A78164/885, *Löhlein* A78625/886, *Jeoffroy* A92004/887, *Winter* A79215/888, A79214/888, *Gemmell* A42423/888, A92002/03, *Müller* A78739/889, A44210/892, A74637/04, *Gebhard* A78326/890, *Laue* A78581/890, *Villar* A74638/890, *Gottschalk* A45816/891, *Cullingworth* A45788/891, A91999/892, *Lafleur* A92009/891-2, *Monro* A78722/892, *Schaldemose* A44219/892, *Grenser* A78371/892, *Sturzenegger* A79079/892, *Thevenard* A79109/892, *Bucher* A78122/893, *Morris* A44849/894, *Steffeck* A44642/894, *Bode* A78070/895, *v. Mengershausen* A64793/895, *Eyrich* A78269/895, *Nisot* A92166/895, *Robischon* A78895/895, *Kötter* A78534/895, *Vignes* A47294/895, *Muret* A78745/896, *Gaiser* A78320/897, *Frank* A49044/897, A49083/897, *Pousson* A49132/897, *Rhein* A78882/898, *Lovrich* A50545/898, *Malcolm* A74636/899, *Jacobson* A78468/899, *Gramm* A92003/899, A50932/899, *Bourland* A92034/899, *Norris* A92167/899, A92017/05-6, *Jones* A92005/00, A74710/05, A92006/05-6, *Baily and Lord* A75281/00, *Opitz* A77057/00, *Scharlieb* A92023/00, *Verdelet* A92104/00, *Amann* A77973/01, A77972/01, A77983/08, *Nassauer* A78752/01, *Fairbairn* A78270/01, *Kossmann* A92008/01, *Everke* A78266/01, *Rosenfeld* A92169/01, *Sauter* A78947/01, *Dirner and Fonyo* A92000/02, *Deletrez* A74583/02, *Delore* A74584/02, *Mackenrodt* A78642/02, *Tannen* A76602/02, *Sutton* A92024/02, *Piollet* A78836/02, *Jellett and O'Sullivan* A78478/03, *Pilsky* A78835/03, *Wagner* A92174/03, A79164/06, A79166/29, *Thorne* A79112/03, *Arana y Chavarria* A91980/04, *Lockyer* A78623/04, A92013/05, *Kelly* A78510/04, A92049/04, A92051/05, *Boursier* A91997/04, *Hansemann* A78401/04, *Schmorl* A78989/04, A78990/06, *Weindler* A79188/05, *McIlroy* A78638/05, A78639/06, A78640/06, A75863/07, *Ziegenspeck* A92025/05, A92177/05, A79233/05, *Leopold* A78596/05, A78597/08, *Delaunay* A78201/05, *Glockner* A92040/05, *Schwarz* A79012/05, *Milian* A78710/05, *Macnaughton-Jones* A78643/05-6, *Cestan* A91998/06, *Tweedy* A79131/06, *Baumgarten* A78034/06, *Tate* A79091/06, *Ruge* A78931/07, A78929/29, *McIlroy* B13154/06, *Le Jemtel* A75847/07, A78590/08, *Duncan* B13177/07, *Rendu* B13272/07, *Cullen* A78179/08, *Mendels* A78688/08, *Sutton* A78062/08, *Groves* A78377/08-9, *Ferran* A78276/09, *Kehrer* A78504/09, *Brothers* A78111/09, *Penkert* A78819/09, *Schwab* A79009/09, *Stöckel* A79061/09, *Anderson* A77999/09-10, *Zalewski* A79231/10, *Bovin* A78087/10, *Bukojemsky* A78128/11, *Jellett* A66924/11, *Lindemann* A78614/11, *Moos* A78727/11, *Vanverts* A66932/11, *Bory* A75844/12, *Theilhaber and Edelberg* A79107/12, *Morian* A78728/12, *Schäffer* A78956/12, A78955/12, *Francuzowicz* A78300/13, *Fitzgibbon* A78279/14, *Boldt* A78073/14, *Godart* A66922/14, *Nacke* A78747/15, A78749/23, *Harbitz* A78402/16, *Haury* A66923/16, *Meyer* A64795/16, *Mills* A78712/17, *Strong* A79075/17, *Schwartz* B9357/19, *Keller* A78506/21, A78505/36, *Boettger* A75841/21, *Bentkowski* A78045/21, *Tedenat and Vinon* A75853/21, *Pribram* A78858/22, *Aubert* B8551/22, *Stein* A79053/23, *Bröse* A78110/23, *Strassmann* A79068/23, *Adam* A75843/24, *Iversen* A78463/24, *Bauereisen* A78032/25, *Koenig* A78530/25, *Raingeard* A78865/26, *Mann* A78656/26, *Schiller* A78976/26, *Thibaudeau* B8033/26, *Hornung* A64770/27, *Orsini* A78794/27, *Blumreich* A78067/29, *Rooy* A78904/29, *Heile* A78418/30, *Ribeiro* A65080/30, *Douglas* A66114/32, *Gupta and Mukhopadhaya* A62302/32, *Heimann* A78420/33, *Pazourek* A61573/33, *Baumgardner* A52253/34, *Dougal* A78220/34, *Soler* A52181/34, *Murphy* A27882/35, *Canizares Verson* A95054/37, *Mortimer and Crail* A97010/38, *Adams* A97031/38, *Holter* A97616/39, *Werneck and Junqueira* A97487/41.

[1] *Miller* A18279/37.

[2] *Bixby* A88275/874, *Clément* A78160/03, *Glockner* A78346/04, *Lockyer* A78621/04, *Haultain* A78410/10-1, *Rosinski* A78917/13, *Gemmell* A78332/14.

[3] *Massabuau and Etienne* A78671/20.

[4] *Gaiser* A78320/897, *Polano* A64823/04, *Miller* A18279/37.

[5] *Norris and Vogt* A78764/25.

[6] *Bucher* A78122/893, *Heinrichs* A78426/899, *Schlagenhaufer* A78977/02, *de Mora* A79507/31.

[7] *Castellier* A88292/815, *Leonard* A88341/829, *Pigne* A88363/841-2, *Pjasetzki* A43583/890.

[8] *Retzius* A92020/823, *Butterfield* A88291/845-6, *Van Buren* A87048/852, *Boscher* A88279/852, *Banks* A88269/857, *Brown* A69769/858, *Lallement* A88337/861, *Greene* A88317/863, *Emmert* A88305/865, *Richardson* A88370/865, *Collins* A87031/866, *Pepper* A88361/870-1, *Beecher* A88274/872-3, *Mears* A78685/874-5, *Wegscheider* A88386/875, *Johnson* A88330/875, *Keen* A87036/876, *Hjelt* A88326/877, *Amon* A65792/881, *Odebrecht* A78774/888, *Oliver* A45869/891, *Larnaudie* A78579/891, *Griffith* A78373/00, *Briggs* A78099/02, *Stolypinsky* A79063/04, *Levison* A78606/04, *Glockner* A92039/05, *Brewis* A78095/05-6, *Nagel* A78751/06, *Albertin* A77956/08, *Amann* A77990/10, A77991/11, *Barris* A78020/11-2, *Hoon* A78449/22, *Schwegler* A79014/23, *Stacy and Melson* A75852/23, *Müller* A78737/29, *Krauskopf* A59697/36, *Lacerda Filho* A95373/37, *Mocquot* A95295/37, *Hall* A96618/41.

epithelial, the latter of connective tissue elements. Some investigators recognize an intermediate third group, the "*carcinoma simplex*", in which epithelial and connective tissue structures are approximately equally represented. The ovarian cancers may also be subdivided according to the presence or absence of gland-like or adenomatous structures in them. It is true that adenomatous alveoli are microscopic cysts, but tumors which contain no macroscopically prominent cavities are generally not listed among the cystic growths. Some investigators are particularly preoccupied by the possible confusion of microscopically and macroscopically cystic tumors and prefer the term "massive carcinomas" or "macroscopically solid carcinomas" for all tumors which appear to be solid, as judged by naked eye inspection.[1] These may be subdivided into the adenocarcinomas which contain microscopically gland-like cystic cavities and the microscopically solid growths, containing alveolar, trabecular or diffuse epithelial elements.

The *adenocarcinomas* contain tubules with distinct lumina, usually lined by a single layer of more or less atypical epithelial cells. The latter may achieve different degrees of maturity and normal Graafian follicles are often detectable between the cancer cells. In other cases, the lining epithelium of the tubules is definitely stratified and the proliferation and stratification of the lining cells may be so pronounced that the lumen becomes comparatively inconspicuous. Sometimes, this proliferation may take the shape of papillomatous excrescences and many transitional types may develop; indeed even in the same tumor, certain areas may be tubular, while others are more or less massive or adenopapillary, so that the so-called "multiform carcinomas" result. The various modifications are well illustrated in the descriptions given by authors who published relevant case reports.[2]

In some instances the proliferation and stratification of the epithelia may reach such excessive degrees that the cell limits are no longer distinguishable and large syncytia develop, thus giving rise to what is often called a *giant cell carcinoma*.[3] Even the metastases of these tumors may exhibit typical giant cell formation. It has been claimed—we believe with doubtful justification—that the adenocarcinoma, the giant cell carcinoma and the chorionepithelioma are merely different stages in the development of the same blastoma type.[4]

The so-called *alveolar carcinoma* is apparently only a modification of the adenocarcinoma in which alveoli, with indistinct or no lumina, are particularly prominent.[5] The lining cells may show cilia and the stroma may contain phagocytes with pigment granules.[1]

The *plexiform* carcinoma of the ovary is characterized by the preponderance of solid cell columns which run more or less parallel with each other or form irregular interlacing patterns.[6] The frequently ovoid nuclei of the epithelial cells tend to arrange themselves perpendicularly to the axis of the cell columns.[7]

In the "*diffuse carcinoma*" of the ovary the malignant epithelial cells are more or less evenly disseminated throughout the ovarian tissue. It is rarely, if ever, a primary tumor and most of the supposedly relevant cases were probably Krukenberg tumors.[1]

The so-called "*melanocarcinoma*" or "*cancer melanodes*" of the old literature is a pigmented malignant growth[8] which has not been adequately characterized. Probably most of the supposedly relevant instances were actually melanosarcomas (see chapter on Melanosarcoma).

In the course of the malignant transformation of originally benign common cysts there may develop *solid carcinomatous areas within the cyst wall*. These may exhibit the characteristics of adenomatous, adenopapillary or even diffuse medullary carcinomas of the serous or pseudomucinous series.[9]

C. Carcinomatous Cystomas. The cystic carcinomas of the ovary are by far more common than the solid cancers. As has repeatedly been emphasized in this review, there is no convincing proof that ovarian cancers can develop as primarily cystic blastomas. Hence in order to avoid confusion, we shall refer to them as "carcinomatous cystomas" rather than "cystic carcinomas". Perusal of the numerous relevant case reports clearly indicates that, at least, in the vast majority of cases, the cystic carcinoma arose as a result of malignant transformation in an

[1] *Miller* A18279/37.

[2] *Heider* A88325/859, *Meek* A49071/897, *Ardouin* A50562/898, *Everke* A78265/898, *Stobbaerts* A50684/898-9, *Santi* A92021/02, *Martin Aguilar* A91972/05, *Rosenstein* A78908/05, A78909/05, A78913/12, A78912/12, *Macnaughton-Jones* A78644/05-6, A78645/06-7, *Zacharias* A79227/06, *Ihl* A78460/06, *Giles* A64876/09-10, *Brewis* A78097/10-1, *Patrick* B8680/22, *Stacy and Melson* A79049/23-4, *Delrez* A68001/29, *Buford* A65455/30, *Carpenter* A96614/40.

[3] *Leopold* A41747/887, *Glockner* A92038/05, *Dreyfus* A78223/07, *Massabuau* A78670/18-9, *Ley* A78607/19-20, *Massabuau and Etienne* A78671/20.

[4] *Massabuau* A78670/18-9.

[5] *Limnell* A70119/01, *Rosenstein* A78908/05, A78909/05, *McIlroy* A78640/06, *Rais and Faix* A78866/06, *Desurmont* A68504/11, *Schwartz* A79010/18.

[6] *Frankl* A76805/14, *Kamniker* A78492/29.

[7] *Glockner* A70014/05.

[8] *Gründer* A88319/858.

[9] *Amann* B11325/10, *MacCarthy and Caylor* A70804/22, *Schneider* A77798/27, *Miller* A18279/37, *Rauscher* A95097/37.

originally benign ovarian cystoma.[1] In some cases cyst formation is the result of liquefaction necrosis, but it should be kept in mind that many of the so-called cystic carcinomas described in the old literature have not been adequately examined as regards histologic structure, so that their exact classification is impossible. In other cases the derivation from a characteristic serous or pseudomucinous cyst is clearly demonstrable because the carcinomatous area is limited to a small circumscribed portion of an otherwise benign cystoma. It is especially noteworthy that in certain cases carcinoma formation appears to occur simultaneously and independently in several distinct areas of a benign cyst. This process of "Verkrebsung von mehreren Stellungen der Wandung"[2] suggests that the stimulus for malignant transformation is not necessarily limited to a small portion of the growth.

Carcinomatous Serous Cystomas. (*Synonyms:* Serous cysto-carcinoma, epithélioma germinatif). These are subdivided into three main groups according to the type of benign cystoma in which they develop. Thus, Miller[2] distinguishes the carcinomatous fibro-adenoma, simple cystoma and papilliferous cystoma.

Carcinomatous fibroadenomas are hard, nodular growths in which only small cystic cavities (having a diameter of a few millimeters) can be seen. While the cysts are usually lined by benign cylindric epithelium, certain solid or semi-solid portions assume the aspect of an adenocarcinoma. These cancers are comparatively rare.[3]

The *carcinomatous simple serous cystomas* are usually nodular tumors with an originally smooth surface in which the cancerous outgrowths tend to proliferate towards the lumen; the latter may eventually be completely filled by them. Only in later stages is there any marked invasion of the wall which leads to the spreading of blastoma cells towards the outside. Histologically, the epithelial components are polymorph, sometimes multinuclear cells, which may form tubular or plexiform patterns, but which, in some cases proliferate in a rather diffuse manner. Giant cells, with up to 15-20 nuclei, have been described in such tumors[4] but they are uncommon. Usually the malignant epithelial cells proliferate in the cyst wall, thus forming an increasingly stratified epithelium from which wart-like papillomas protrude into the lumen.[5] Occasionally, carcinomatous transformation may occur simultaneously in several areas of a serous cystoma.[6] A statistical survey of 69 relevant cases revealed that in 34 of them carcinomatous, serous growths developed bilaterally.[2]

The *carcinomatous papillomas* of the ovary are commonly of the serous variety. There are transitional forms between the carcinomatous simple serous cystoma and the carcinomatous papilloma since, as we stated above, wart-like papilliferous excrescences also tend to develop on the internal surface of simple cystomas. It is customary, however, to reserve the designation "carcinomatous papilloma" for tumors which macroscopically resemble the cauliflower-like benign serous papillomas. Although in some cases the anaplasia of the epithelial cells goes so far that it is impossible to differentiate between pseudomucinous and serous growths, it is undoubtedly true that the vast majority of the papillary carcinomas described in the literature belong to the latter variety.[7]

[1]*Glymer* A88296/843, *Reyer* A88369/847, *Kips* A88333/853, *Barth* A78023/856, *Bonvin* A78077/856, *Descroizilles* A78209/859, *Priestly* A88367/860, *Moxon* A88353/872-3, *Werner* A88392/873, *Thornton* A79113/873-4, *Weinlechner* A88389/877, *Brown* A88287/878, *Berthold* A87028/879, *Wouters* A88396/880, A88397/880, *Wagemann* A41575/882, *Goodell* A40390/882, *Flaischlen* A40043/882, *Ebermann* A40281/883, *Longaker* A40727/884, A88343/884-5, A40726/884-5, *Bokström* A45169/889, *Chipault* A43455/889, *Boldt* A43299/890, *Poncet* A69413/890, *Hanks* A45835/891, *Vysotski* A46581/893, *Ogorodnikoff* A44784/893, *Rädisch* A78864/894, *Zematski* A82160/895, *Popelin* A48360b/896, *Lavillauroy* A78584/896, *Pozzi and Beaussenat* A49007/897, *Westerfield* A48421b/897, *Ciechanowski* A78154/897, *Mauclaire and Pilliet* A49183/897, *Fränkel* A78298/897, *Lauro* A50640/898, *Lafarelle* A74586/898, *Henrotin and Herzog* A82168/899, *Mauclaire* A78677/00, *Debray* A82161/00, *Chekan* A82166/00, *Kelly* A82170/00, A82169/05, *Danel* A82167/02, *Kostelezky* A82171/02-3, *Clément* A78161/03, *Price* A82173/03, *Bernex* A78053/04, *Westenhoeffer* A74639/04, *Shoemaker* A79028/04, *Flatau* A78283/04, *Cerné* A82162/04, A82163/04, A82164/04, A82165/04, *Klein* A78521/05, *Nagel* A78751/06, *Cornil* A78173/06, *Czyzewicz* A78180/07, *Pichevin* B13361/07, *Lejars* A78588/08, *Ferguson* A78275/12-3, *v. Ulesko-Stroganoff* A79136/13, A79135/13, *Eylenburg* A78268/13, *Vance* B11872/18, *de Snoo* A79043/22, *Lendon and Champion de Crespigny* B11751/22, *de Francesco* A68512/24, *Perrotti* A78821/26, *Grove* B20793/26, *Guyot and Dubreuilh* A78387/28, *Tourneux* A79122/31, *Guyot and Courriades* A78385/32, *Ciceri* A78153/33.

[2]A18279/37.

[3]*Orthmann* A78797/06, *Frankl* A76805/14, *Moench* A61571/33, *Miller* A18279/37.

[4]*Vogl* A79156/896.

[5]*Ott* A70878/894, *Landerer* A47120/895, *Horney* A78451/13, *v. Ulesko-Stroganowa* A73003/13, *Penkert* A70882/24.

[6]*ten Berge* A66275/29, A66274/29, A96669/40.

[7]*Przhevoski* A81492/878, *Flaischlen* A29371/880, A78280/890, *Lee* A29399/880, *Kolisko* A40719/884, *Cohn* A42018/886, *Doran* A78215/887-8, *Latzko* A42309/888, *Cornil* A70632/890, *Poupinel* A43377/890, *Hofmokl* A44060/890-1, A44061/890-1, *Ludlam* A45697/891, *Rothenberg* A70931/893, *Pfannenstiel* A46568/893, *Simpson* A44837/894, *Krichner* A70770/895, *Robb* A49011/896-7, *Cestan and Pettit* A47992/898, *Beyea* A91995/899, A78055/00, *Burns* A78133/00, *Nedielski* A81471/00-1, *Bisch* A78059/01, *Witkiewicz* A79218/01, *Berger* A78049/02, *Knorr* A78526/03, *Pit'ha* A83498/03, *Seeligmann* A79018/03, A79019/04, *Taylor* A70981/04, *Massabuau* A70826/06, *Eden* A78234/07-8, *Arnaud* A78007/08, *Cuff* A70639/08, *Driessen* A78224/08, *Heil* A78417/09, *Hübner* A75846/10, *Meyer* A70832/10, *Koch* A78527/11, *Wells* A75854/13, *Nesselrode* A68494/14, *Schwartz* A79010/18, *Grad* A78367/18, *Blanc* A83387/21, *Miller and Viko* A70838/21, *Heinrich* A70856/21, *Goldberg* A78354/21, *Gibson and Findlay* A78338/23, *Rösch* A66930/24, *Watson* A79181/24-5, *Fitzgibbon* B7472/25, *Gittermann* A78342/27, *Marinescu-Slatina* A78660/27, *Deaver* A63506/28, A71391/28, *Frost* A63515/28, *Lipschütz* A65560/30, *Phaneuf* A64440/30, *Edwards* A78240/31, *Molin et al.* A78720/31, *Godlewski* A61407/33, *Stoian and Bogdan* A70970/33-4, *Hoesch* A61484/36, *Jones* A96619/41, *Meiser* A97496/41, *Lingley* A55501/42.

In a very large percentage of these cases psammoma bodies are found and hence the terms "*carcinoma psammosum*", "psammocarcinoma" or "malignant psammoma" are frequently used to designate such tumors.[1]

It must be emphasized that the papilliferous carcinomas of the ovary are among the most malignant tumors[2] and that a very large number of them are *bilateral*.[3] The actual figures concerning the incidence of bilateral development are subject to great variations. Some authors believe that the great majority of them are bilateral,[4] while others state that bilateral development is only about twice as frequent as unilateral.[5] A careful scrutiny of 427 cases revealed that only 199 of them were bilateral.[6] In another series of 63 carcinomatous papillomas (some cystic, some semisolid) 47% were bilateral;[7] yet another investigator gives the incidence of bilaterality as 40-50%.[8] Perhaps these discrepancies are, at least partly, due to the fact that the so-called "premalignant growths are included among the carcinomas by some investigators but not by others. Occasionally, two originally independent, papillary carcinomas unite as a result of secondary fusion.[9]

The so-called "*Klein's tumor*" is a serous papilloma of the ovary transformed by stroma edema into a false racemose growth. It is discussed in the section on the benign serous papillomas and it has been emphasized there, that these tumors are often malignant.

Carcinomatous Pseudomucinous Cystomas. Synonyms: Pseudomucinous cysto-carcinoma, myxo-epithelioma, epithélioma enteroid. These are far less frequent than the corresponding serous variety, because pseudomucinous papillomas are not as subject to malignant transformation as serous papillomas. In the old literature especially, these growths were frequently described as "colloid cancers", a term which was rather loosely applied also to Krukenberg tumors. Since the ovarian metastases of "pseudomucinous" tumors of the gastro-intestinal tract bear a striking resemblance to the carcinomas originating in pseudomucinous ovarian cysts, it is probable that many of the supposedly relevant case reports actually describe metastatic carcinomas. In the walls of true carcinomatous pseudomucinous cysts, solid portions may arise which are indistinguishable from Krukenberg tumors. This adds to the difficulty of the diagnosis (see passage on Solid Pseudomucinous Carcinomas).

The macroscopic appearance of the carcinomatous pseudomucinous cysts is not unlike that of the corresponding benign tumors. Microscopically, the epithelial elements appear as more or less anaplastic pseudomucinous cells which may form irregular tubules or papillae but occasionally grow rather diffusely. In many instances their secretion tends to become less and less tingible with mucin stains; occasionally metaplasia into stratified squamous epithelium is noted. The numerous varieties of these tumors are described in the relevant *case reports*.[10]

Bilateral development is less frequent among the pseudomucinous than among the serous cystic carcinomas. A review of 77 cases revealed 23 instances of bilateral carcinomatous pseudomucinous cystomas.[6] In another series 18% of these carcinomas were bilateral.[7] It is noteworthy that the *peritoneal metastases* of benign pseudomucinous cysts (see Pseudomyxoma peritonei) may also undergo malignant transformation.[11]

The *vascularization* of rapidly growing ovarian carcinomas is extremely good. In one case of a cystocarcinoma which weighed 14 lbs., 6900 cc. of blood was in the vessels of the growth as judged by hemoglobin determination on the washings of the blood vessel contents.[12] The muscularis of the ovarian arteries undergoes significant changes as a result of cystic carcinoma formation.[13]

D. Other Types of Carcinomatous Cystomas. In most cases of *squamous carcinoma*[14] of the ovaries there is reason to suspect the metastatic nature of the growth although partial squamous transformation may also occur in the lining of common cysts (see also Ovarian Metastases of uterine cancers).

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[1]*Risel* B13302/07, *Sannai* B20818/24.
[2]*Pfannenstiel* A70890/895, *Miller* A18279/37.
[3]*Eastman* B8194/28, *Kahr* A95265/37, *Brody* B6257/44.
[4]*Massabuau* A78670/18-9.
[5]*Pfannenstiel* A80267/05.
[6]*Miller* A18279/37.
[7]*Pemberton* 80890/40.
[8]*Kahr* A95265/37.
[9]*Werner* A73021/13, *Francuzowicz* A78300/13, *Buch* A78121/15.
[10]*Smyth* A88422/656, *Adams* A88401/849, *Rokitansky* A77077/853, A88421/878, *Perry* A88419/855, A88420/856, *Pisarski* A88399/857, *Page* A88416/861, *Hutchinson* A88409/866, *Peaslee* A88418/866-9, *Kidd* A88411/874, A92116/893-5, *Cossy* A88406/876, *Mossé* A88352/877, *Lapeyre* A88415/878, A88414/878-9, *Wischhusen* A79217/881, *Thiriar* A92123/884, *Griffith* A41847/887, *Hontang* A74585/887, *Shattock* A43442/888-9, *Hadjes* A42627/889, *Claisse* A78156/890, *Kelly* A46303/892, *Alimoff* A92105/892, *Berlin* A78051/893, A47398/895, *Amann* A77965/897, *Marien* A50673/898, *Cumston* A92110/898-9, *Anderson* A92106/898-00, *Vance* A92124/899, *Kostelezky* A77011/899, *Jones* A92114/899, A92115/899-00. *Bruce* A92108/02, *Vasilesco* A92126/02-3, *Martin* B13255/07, *Nicholson* A70872/09, *Dimmock* A78212/10-1, *Rosenstein* A78911/12, A78910/12, *Kerner* A78512/18, *Nossbaum* A78765/19, *Schickelé* A78970/22, *Durante and Le Filliatre* A78229/28, *Le Filliatre* A71407/28, B6029/28, *Schwarz* A64018/31, *Dambrin and Dambrin* A78181/33, *Latzke* A53175/33, *Mitchell* A97598/42.
[11]*Eiger* A77177/00, *Ahlström* A77952/12.
[12]*Engelbrecht* B8026/26.
[13]*de Francesco* A68512/24.
[14]*Boettger* A75840/19, *Morice et al.* A78729/30, *Williams and Bloom* A98092/42, *Rewell* A96877/42.

Most of the so-called *"round cell carcinomas"*[1] of the ovary were probably seminomas and are discussed in the chapter devoted to this latter tumor type.

The malignant variety of the *"epithelioma Wolffien"* has been discussed together with the corresponding benign type in the section on pseudomucinous cysts. *Carcinoids* similar to those of the appendix are very rarely found in the ovaries.[2] They probably represent one-sidedly developed teratoids (see also chapter on Teratoids).

SECONDARY CHANGES IN COMMON CARCINOMAS AND IN THE REMAINING OVARIAN TISSUE: A. Spread of Common Ovarian Carcinomas and Retrogressive Changes within the Tumor Tissue. The spread of ovarian carcinomas into neighboring organs by means of direct invasion has in part been considered already in the previous passage (see passage on Common Ovarian Carcinomas in Combination with Extra-Ovarian Cancers). It has been stated there that these tumors may invade the Fallopian tubes, the uterus and other peritoneal organs. In view of these marked invasive tendencies, it is hardly surprising that cancers of the ovary often cause very widespread adhesions.[3] Not infrequently ovarian cancers spread in the broad ligaments[4] and although the data concerning the frequency of this type of spread are rather contradictory, a review of 240 cases revealed that in 13% of them there was invasion of the broad ligament.[5] In rare instances marked and atypical invasive growth is seen. Thus in one case a cancer of the right ovary invaded the buttocks and right thigh as well as the pelvic bones, so that the hip joint and the head of the femur were destroyed.[6]

Primary ovarian cancers tend to form adhesions at a relatively early stage and it is comparatively rare to find them completely free at the time of operation. A survey of 176 cases published by 5 different investigators showed 66.5% to be involved in adhesions when first seen by the surgeon. The percentages given by the various investigators vary between 54.5% and 87.2%. As in the case of secondary cancers, invasion of adjacent organs, especially the oviduct, uterus and peritoneum is common.[5]

Among the degenerative changes, necrosis of the tumor tissue with subsequent liquefaction and cyst formation is a comparatively frequent occurrence. This may be followed by secondary infection and suppuration. In other cases, calcification, sometimes with subsequent ossification or hemorrhage, is seen in the degenerated and necrotic areas (see also chapters on Hemorrhage, Calcification, Ossification, Necrosis and Inflammation of the Ovaries in Sect IV, Vol. VI).

In *carcinomatous serous cystomas,* the formation of adhesions is likewise quite common and in a series of 75 cases published by 3 different investigators, adhesions were found in 47 instances. Among the carcinomatous serous papillomas adhesions are particularly frequent if the papilliferous growths break through to the peritoneal surface. Their incidence is estimated to be 65-70% or even higher.[5]

The spread of the carcinomatous serous cystomas hardly deserves special consideration. Suffice it to say that as in the case of other cancers, the adjacent organs, especially the oviduct, uterus and pelvic peritoneum are most frequently involved. A detailed analysis of the literature on the subject has been published by Miller.[7]

Carcinomatous pseudomucinous cystomas tend to produce adhesions and invade neighboring organs in approximately the same manner as the other ovarian carcinomas, but it is noteworthy that rupture of such carcinomatous cysts may cause the formation of a cancerous "pseudomyxoma peritonei".[8]

B. The Ovarian Remnant. That primary ovarian tumors tend to develop bilaterally and that extragonadal carcinomas often produce metastases simultaneously in both ovaries has already been discussed in the preceding paragraphs. Suffice it to say here, that if ovarian carcinomas have led to considerable emaciation, the remaining gonadal tissue undergoes atrophy even if it is not directly affected by the growth.[9] It is not surprising to find atrophic ovaries in the majority of carcinoma-bearing women because most of them are past the menopause; if the ovaries involute as the result of debilitating carcinomas in young women, their atrophy must be regarded as part of the general adaptation syndrome elicited by the non-specific damaging action of the tumor.

In some instances, on the other hand, ovarian function and structure does not seem to be severely influenced by the malignant growth. Thus, for instance, a well-developed corpus luteum may be found either in the contralateral ovary or even in the ovary bearing the carcinoma.[10] The comparatively frequent occurrence of pregnancy in ovarian carcinoma-bearing women (see part on Incidence in Pregnancy) indicates even more eloquently how well ovarian function may be preserved in spite of the tumorous growth. In the majority of the cases, however, the cancer destroys most of the ovarian tissue by the process of direct infiltration.

[1] *Szathmary* B12390/33.
[2] *Kakuma* B9414/07.
[3] *Papin* A78807/26, *Guyot and Dubreuilh* A78386/27.
[4] *Rüder* A78928/14.
[5] *Miller* A18279/37.
[6] *Lucarelli* A64184/31.
[7] A18279/37.
[8] *Ley* A78607/19-20, *Pemberton* 80890/40.
[9] *Golay* A78353/876, *Cantoni* A78142/20.
[10] *Molin et al.* A78719/31.

Ovarian carcinomas may have a well developed and elongated *stalk* but in some cases the latter may be entirely missing. In general, carcinomatous cysts tend to form a stalk, while primary solid cancers as well as ovarian metastases of primary extragonadal cancers usually have no pedicle. In the case of the carcinomatous cystomas, the stalk may develop between the normal ovarian tissue and the blastoma, but more frequently the entire gonad forms one mass with the tumor and the pedicle connects this mass with the broad ligament.[1]

COMMON CARCINOMAS IN COMBINATION WITH OTHER OVARIAN TUMORS: Not infrequently an ovarian carcinoma develops within the walls of common ovarian cystomas but in these cases—to which all the cystic carcinomas originally belong—we do not speak of multiple tumor formation but merely of malignant transformation. It is very doubtful that simultaneously developing primary *carcinomas of the ovary and broad ligament*[2] exist, and purportedly relevant cases are likely to be metastases of ovarian cancers. Development of a *solid carcinoma in one ovary and a cystic carcinoma in the other* has also been reported.[3] The simultaneous occurrence of *adenocarcinomas and dermoid cysts* in the same ovary is not exceptional.[4] Less frequently an *adenocarcinoma in one ovary and a dermoid cyst in the other* are found in the same patient[5] or there are *bilateral pseudomucinous adenocarcinomas and simultaneously a dermoid* on one side.[6] The carcinomatous degeneration of originally benign dermoids usually results in squamous or basal cell cancers and is discussed in the section on teratoid tumors. *Cystadenocarcinoma and ovarian struma* are rarely seen in the same ovary.[7] There are instances of ovarian *carcinoma* and *endometrioma* development in the same ovary.[8] In women in whom one ovary is the site of a pseudomucinous cystadenocarcinoma, the other ovary may contain a *Brenner tumor.*[9] Ovarian *carcinoma and fibroma*[10] or *carcinoma and sarcoma*[11] may also occur in combination.

The literature contains numerous references to the so-called *carcinosarcoma* (synonyms: carcinoma sarcomatodes, carcinomatous sarcoma, cancrosarcoma, sarcocarcinoma of the ovary), but in many of these cases there is some doubt concerning the true nature of the tumor, since certain regions in ovarian carcinomas frequently assume a sarcomatoid appearance; the possibility of a metastatic carcinoma deposit within a primary sarcoma, and vice versa, must also be kept in mind.[12]

COMMON CARCINOMAS IN COMBINATION WITH EXTRAOVARIAN CANCERS (including metastatic ovarian carcinomas and metastases of ovarian carcinomas: The combination of ovarian carcinomas with extraovarian tumors is very frequent and a voluminous literature has developed concerning the pathology of *ovarian metastases of extragonadal cancers.*[13] Metastases are disproportionately frequent in the functional ovaries of women during the childbearing period of life.[14]

On the basis of their histologic appearance the common types of metastatic ovarian carcinomas may be subdivided into the following groups:

1. Krukenberg tumors.
2. Solid adenocarcinomas.
3. Papillary adenocarcinomas.
4. Basal cell (usually squamous) carcinomas.
5. Carcinoma metastases in benign ovarian cysts.

Many investigators comment upon the comparative frequency of *bilateral* development among metastatic ovarian carcinomas.[15] One author[16] estimates that in about 50% of the cases, metastatic carcinomas are macroscopically visible in both ovaries, and upon histologic examination the percentage of bilateral

[1]*Miller* A18279/37.
[2]*Krug* A78549/891.
[3]*Amann* A77969/00.
[4]*Geyer* A73674/895, *Delaunay and Pilliet* A50567/898, *Peters* A76274/00, *Delaunay* A73480/05, *Brettauer* A73366/07, *Bircher* A78058/08.
[5]*Smiley and Auster* A32567/40.
[6]*Potherat and Potherat* B8709/20.
[7]*Rauchenberg* A97307/38.
[8]*Payne* A32556/40.
[9]*Geist* A64759/22, *Spencer* A64894/25-6, *TeLinde* A64447/30.
[10]*Tenconi* A53109/33.
[11]*Ladinski* A77616/898, *Simoff* A70958/01, *Andres* A76904/19, *Stein and Bloom* A70967/29, *Gery and Reeb* A66119/32, A66120/32.
[12]*Lippmann* A79944/05, *Schwartz* A79948/05, *Cullen* A79940/11, *Bell* A79939/11-2, A79938/11-2, *Rothacker* A66919/12, A79947/13, *Loomis* A66927/13, *Lanzarini* A66907/14, *Kleinschmidt* A79942/22, *Akimoto* A64724/25, *Vecchi* B7110/26, *Brakemann* A79258/29, *Quin* A68114/29, *Recek and Pavluk* A66194/31, *de Oliveira Sarmento* A96929/43.
[13]*Weichselbaum* A88387/886, *Arzamasskoff* A92031/892, *Nadig* A78750/00, *Kraus* A78544/01, *Sauter* A78948/01, *Kehrer* A78501/03, *Glockner* A78345/03, A78344/03, A78347/04, A92036/04, *Omori* A78787/04, *Papaioannou* A78806/04, *Amann* A77974/05, A77975/05, A79691/05, *Kamann* A78490/05, *Sutton* A78061/06, A78064/10, A78063/10, *Kaul* A78498/06, *Stickel* A79060/06, *Santschenko* A78945/07, *de Snoo* A79041/08, *Faure* B11303/10, *Cohn* A78166/10, *Rosenstirn* A78916/10, A78915/10, *Küster* A78554/11, A78553/11, *Kleinmann* A78523/11, *Vincent and Ferrari* A79151/12, A79152/12, *Paul* A78811/13, *Schauta* A78963/13, *Fairise and Heully* A78271/13, *Stone* A79066/16, *Frankl* A78303/16, A78305/20, *Kohlmann* A77600/17, A78535/17, *Heully* A78435/22, *van Dongen* A78214/22, *Schmidt* A78985/23, *Tedenat* A79098/24, *Kovacs* A78540/24, *Kutscherenko and Schwedkowa* A78562/27, *Malinin* B7156/27, *Maljeff* A78653/27, *Rosenzweig* A96707/28, *Anderes* A77998/29, *Charbonnel and Monglond* A78147/31, *Kückens* A78551/33, *Alfieri* A77961/33, *Simon* A79031/34, *Sardi and Ahumada* A97486/41.
[14]*Warren and Macomber* A27718/35.
[15]*Heinrichs* A78426/899, *Mayer* A78681/26.
[16]*Frankl* A76805/14.

involvement is considerably higher. Another worker[1] claims that in 90% of the cases of metastatic ovarian cancers both ovaries are affected and it has even been stated[2] that unilateral metastatic ovarian cancers are very rare. The percentual incidence of bilateral involvement is variously estimated by other investigators to be 52%[3] or 50%.[4]

The *metastases of primary ovarian cancers* are also of great clinical importance.[5] In many instances it is virtually impossible to distinguish these with certainty from the ovarian metastases of extragonadal carcinomas because in the presence of an ovarian and an extraovarian cancer there may be no criterion which would permit the identification of the primary growth. This is especially true of those cases in which both the primary tumor and the metastases are anaplastic and fail to retain the typical structure of the organ from which they are derived.

When ovarian carcinomas are found in combination with extragonadal cancers, the following pathogenetic possibilities must be considered:

1. The ovarian carcinoma is primary and the extragonadal tumor secondary.

2. The extragonadal carcinoma is primary and the ovarian tumor secondary.

3. Both the ovarian and the extraovarian carcinoma are primary growths, independent of each other.

4. Both the ovarian and the manifest extraovarian carcinoma are metastases of a third (sometimes not detectable) primary tumor.

5. A primary ovarian cancer spreads to another organ by direct invasion.

6. A primary extragonadal cancer spreads to the ovary by direct invasion.

Since the relationship between the tumors is frequently not evident from the published data the cases in which ovarian carcinomas developed simultaneously with extragonadal cancers will be considered conjointly in this section. By consulting the original papers, however, in many instances the reader will find at least suggestive evidence concerning the relationship between these growths.

Peritoneal carcinomatosis, when seen in conjunction with ovarian cancers, may be due to direct propagation of a primary ovarian growth or to the secondary involvement of the ovary and the peritoneum following a primary cancer of another organ. Frequently, a primary cancer of the gastrointestinal tract metastasizes simultaneously in the ovaries and the peritoneum.[6]

Carcinoma deposits in *lymph nodes* rarely cause any difficulty of interpretation since they are always secondary to the ovarian cancer.[7] In many cases the carcinoma metastases occur at some distance from the primary tumor e.g. in the *axillary or supraclavicular,*[8] *inguinal,*[9] *parametrial,*[10] *iliac,*[11] *lumbar,*[12] *mesenteric,*[13] *retroperitoneal,*[14] *renal,*[15] *mediastinal lymph nodes*[16] or the *lymph node accumulations around the portal vein.*[17]

Following surgical interventions designed to remove the carcinomatous ovaries, secondary development of cancer in the *abdominal scar* is a comparatively frequent complication unless great care is taken to avoid the implantation of cancer cells into the wound.[18] Occasionally a malignant tumor may

[1] *Major* A79780/18.
[2] *de Mora* A79507/31.
[3] *Schmid* A76478/26.
[4] *Ley* A78607/19-20.
[5] *Poupinel* A42085/886, *Lancial* A92055/890, *Odebrecht* A78775/895, *Landerer* A47120/895, *Buddenberg* A92026/897, *Graf* A78369/03, *Opitz* A78791/09, *Lejars* A78589/10, *Händly* A78391/15, *Schmid* A75842/19, *Kitain* A78518/22, *Levin and Joseph* B7965/25, *Tate* A65517/30, *Amreich* A65051/31, *Shaw and Johnston* A66063/31, *Hückel* A78455/35, *Prentice* A95418/38, *Turunen* A96647/40.
[6] *Gairdner* A88312/867, *Lelong* A88340/867, *Bristowe* A78106/869/70, *Petrina* A78824/872, *Bradbury* A78089/872, *Cossy* A78175/876, *Foulis* A34829/878, *Hobson* A69314/883-4, *Brieger* A78098/883, *Tillman* A79117/889, *Lancial* A43400/890, *Crombie* A78176/00, *Smith* A92098/01, *Seeligmann* A79018/03, *Combemale and Nayrac* A78169/29, *Roche* A78897/30, *Sampson* A64015/31, *Bertrand and Colson* A61918/33, *Broussy* A61402/33, *Vries* A79162/34.
[7] *Gibb* A78337/856-7, *Defontaine* A29348/879, *Talamon* A79088/880, *Troisier* A42574/888, *Simon* A79032/11, *Morosowski* A70518/12, *Keller* A78508/29, *Lambret and Razemon* A78571/29, *Ernst* A78256/31, *Sampson* A59476/36.
[8] *Dembo* A46317/892, *Emsheiner* A78248/896, *Villard and Murard* A79148/12, *Lahey and Haythorn* A78567/12, *Mallet* A66173/31, *Barany and Sala* A78017/33 *Schwimmer* A96880/43.
[9] *Busack* A78134/894, *Liebrich* A70797/895, *Semb* A70956/896, *Ohlmann* A78781/02, *Dührssen* A78225/11, *Erler* A77474/14, *Goldberg* A78354/21, *Neumann* A78758/28, *Leuriger* A78603/30, *Mayo and Fauster* A78682/32, *Philipp* A51977/34.
[10] *Aubert* A78012/22.
[11] *Kleinhans* A78522/896, *Ley* A78607/19-20, *Aubert* A78012/22.
[12] *Thornton* A79113/873-4, *Ley* A78607/19-20, *Cavour* A78145/20.
[13] *Karsner* A78496/10, *Buch* A78121/15, *Nörr* A78761/19, *Gibson and Findlay* A78338/23, *Lucarelli* A64184/31, *Vogt* A51987/33.
[14] *Stelzner* A76568/883-4, *Cohn* A42018/886, *Pfannenstiel* A70890/895, *Heinrichs* A78426/899, *Ottow* A78802/34.
[15] *Teichmann* A77847/888.
[16] *Teichmann* A77847/888, *Landerer* A47120/895, *Bruns* A65858/24.
[17] *Liveing* A78620/875, *Lerch* A45139/889, *Eichmeyer* A63507/28.
[18] *Liveing* A78620/875, *Marchand* A70821/879, *Griffith* A78372/886, *Larnaudie* A78579/891, *Dembo* A46317/892, *Rothenberg* A70931/893, *Sippel* A79033/894, *Landerer* A47120/895, *Sänger* A78937/897, *Pohorecky* A81486/899, *Davis* A7006/00, *Thorne* A79112/03, *Milner* A78713/04, *Opitz* A78790/09, *Boldt* A83396/11, *Strassmann* A79067/12, *Lahey and Haythorn* A78567/12, *Nörr* A78761/19, *Graebke* A83393/19, *Fleurent* A78288/21, *Villata* A79149/23, *Schiller* A78976/26, *Blumenthal* A78066/27, *Wagner* A79166/29, *Ruge* A78929/29, *Dvorak* A78231/30, *Masuhara* A78674/30,
Footnote cont'd.

develop in the abdominal wall even following surgical removal of an apparently benign cystoma.[1] In a few cases primary ovarian carcinomas were observed to spread to the *umbilicus*.[2]

Simultaneous development of cancer in the ovaries and the *Fallopian tubes* is not uncommon.[3] It will be recalled that carcinomatous serous papillomas may originate both in the ovary and in the oviduct; since most of the case reports concerning simultaneously developed ovarian and tubal carcinomas belong to this category, it is frequently impossible to determine the primary site of tumor development. It is assumed that a primary ovarian carcinoma may lead to metastases in the oviduct owing to implantation of cancer cells which migrate through the tube. Conversely, perhaps cells of a primary carcinoma of the oviduct may ascend and re-implant themselves upon the ovarian surface. This process is somewhat reminiscent of the current theory concerning the development of ovarian endometriosis by implantation of ascending endometrial cells upon the ovarian surface. It is also relevant to observe that in some cases, carcinomas developed simultaneously in the ovary, oviduct and uterus[4] presumably due to migration and reimplantation in the various parts of the genital passages. Not infrequently both tubes and both ovaries are affected. Solid ovarian cancers may also metastasize in the tube.[5] Occasionally the oviduct and ovary form a single, cancerous, so-called "malignant tubo-ovarian cyst."[6]

The association of ovarian carcinomas with cancers of the *uterus* is particularly common.[7] All the pathogenic possibilities which have been outlined above for the explanation of simultaneous ovarian and extragonadal cancers in general must be considered in these cases. An ovarian cancer may also secondarily produce a malignant growth of the endometrium due to the excessive production of folliculoid hormones by the tumor cells. In the section on the carcinomatous folliculomas it was emphasized that certain solid or micro-cystic serous carcinomas, hitherto classified among the common cancers, may

[18]cont'd *Barone* A64413/30, *Leutiger* A78603/30, *Ernst* A78256/31, *Baràny and Sala* A78017/33, *v. Numers* A52174/34, *Ottow* A78802/34, *Kraul* A78543/34, *Lazarus* A95374/38, *Benhamou et al.* A97601/39.

[1]*Heimann* A64454/30.

[2]*Küster* A88336/874-5, *Liveing* A78620/875, *Estor and Villa* B15981/23-4, *Leutiger* A78603/30.

[3]*Marchand* A70821/880, *Orthmann* A78795/888, A78796/06, A78797/06, *Lerch* A45139/889, *Pfannenstiel* A70890/895, *Sänger and Barth* A78938/895, *Meyer* A78701/897, *Heinrichs* A78426/899, *Knauer* A78525/01, *Limnell* A70119/01, *Stolz* A79064/02, *Morinaga* A78730/03, *Danel* B8896/03, *Cullen* A78178/05, *Pompe van Meerdervoort* A78847/05, *Edge* A78238/05-6, *Kehrer* A78503/08, *Bushnell and Kerawalla* A65860/08, *Boxer* A78088/09, *Benthin* A78044/09, *Tate* A79093/10, *Amann* A77989/10, A77988/10, *Glendining* A78343/10, *Weinbrenner* A79187/11, *Bubnoff* A78120/12, *Werner* A73021/13, *Ruge* A78930/16, *Thaler* A79105/16, *Boldt* A78074/17, *Dujarier and Khan* A78226/20, *Stanca* A79050/22, *Amreich* A77995/22, *Schäfer* A78954/23, *Lessing* A78602/23, *Beck* A78036/24, *Bültemann* A78126/27, *Barrows* A78021/27, *Jessen* A78479/27, *Wolfe* A79220/28, *Orzechowski* A78798/28, *Neumann* A78758/28, *Frankl* A78308/29, *Watkins and Wilson* A79179/30, *Holland* A78442/30, *Hirsch* A78440/31, *Winter* A79213/33, *Tenconi* A53109/33, *Beitzke* A78040/35, *Sampson* A97018/38, *Pastorini and Schlossberg* A98002/43.

[4]*Gebhard* A78327/891, *Peterson* A78823/03, *Taussig* A79094/07.

[5]*Pastorini and Schlossberg* A98002/43.

[6]*Edge* A78238/05-6.

[7]*Bauchet* A78027/853, *Reichel* A88260/856, A78876/888, *Blau* A78065/870, *Pistor* A78838/872, *Weber* A79180/873, *Goodhart* A78357/873-4, *Maunoir* A78678/875, *Lee* A29399/880, *Amadeo* A77964/884, *Löhlein* A78626/889, *Sänger* A78936/890, *Hilgenstock* A78438/890, *Littauer* A78618/891, *Gebhard* A78327/891, *Wehmer* A79182/894, *Kümmell* A78552/895, *Kleinhans* A78522/896, *Bäcker* A78014/897, *Meyer* A78701/897, *Heinrichs* A78426/899, *Amann* A77968/899, A77970/01, A77971/01, A77978/06, A77977/06, A77981/07, A77980/07, A77979/07, *Heitz and Bender* A78429/00, *Beyea* A78055/00, *Gottschalk* A78360/00, *Funk* A78319/01, *de la Volpilliere* A81305/01, *Böckelmann* A78069/01, *Krömer* A78546/02, A78547/08, *Riechelmann* A78889/02, *Peterson* A78823/03, *Goldenberg* A70728/03, *Labusquière* A78565/04, *Lockyer* A78622/04, *Jayle and Papin* A78473/04, *Willimsky* A79211/04, *Schmorl* A77797/04, *Borrmann* A78080/04, *Bauereisen* A78028/04, A78029/05, A78030/12, *Delaunay* A78200/05, *Brink* A78101/05, *Rais and Faix* A78866/06, *Jellett* A78474/06, *Hicks* A78437/06, *Albertin and Jambon* A77957/06, *Tate* A79092/07, *Taussig* A79094/07, *Schenk* A78966/07, *Brewis* A78096/07-8, *Winter* A79216/08, *Violet and Chalier* A79154/08, *Bircher* A78058/08, *Sitzenfrey* A79036/08, *Offergeld* A78777/08, A78778/09, *Eden* A78235/08-9, *Rieck* A78890/10, *Arzt* A78010/10, *Boldt* A65830/10, *Zalewski* A79231/10, *Scharlieb* A78959/10-1, *Gasarbekian* A78323/11, *Dührssen* A78225/11, *Schottländer* A78997/11, *Turner and Lockyer* A79130/11-2, *Mirabeau* A78714/12, A78715/12, *Schottländer and Kermauner* A79000/12, *Warstat* A79178/12, *Mériel* A78693/12, *Morosowski* A70518/12, *Braun* A78092/13, *Werner* A73021/13, *Bondy* A78075/14, *Litwak* A78619/14, *Bassani* A78024/15, *Weidman* A79186/17-8, *Anspach and Block* A78003/17-8, *Hartmann and de Jong* A79583/18-9, *Foulkrod* A78296/19, *Ruge* A78932/19, *Gerson* A78336/19, *Ley* A78607/19-20, *Savariaud and Butler-d'Ormond* A78949/20, *Kotzareff* A78539/20, *Cavour* A78145/20, *Frankl* A78305/20, *Goldberg* A78354/21, *Shaw* A79027/22, *Marino* A78662/22, *Rau* A78869/22, *Meigs* A78687/22, *Clivio* A78162/22, *Martzloff* A78667/23, A78668/27, *Küstner* A78555/23, A78556/23, *Grosse* A78376/23, *Lessing* A78602/23, *Norris and Vogt* A78762/24, *Ménétrier and Bertrand-Fontaine* A78690/24, *Bruns* A65858/24, *D'Allaines and Bertrand* A77963/24, A77962/24, *Burckhard* A78130/24, *Stübler and Brandess* A76588/24, *Frankl* A78307/25, *Davis* A78186/25, *Pribram* A77755/25, *Steiner* A79054/26, *Schmid* A76478/26, *Bengolea and Pavlovsky* B15631/26, *Halter* A78394/26, A78396/35, *Wolff* A79222/27, *Schmelz* A79385/27, *Sussex and Caylor* A79082/27, *Bell* A78042/27, *Keller* A78507/27, *Neumann* B8218/27, *Maljeff* A78653/27, *Laude and Cleuet* A78582/27, *Novak* A78766/27-8, B10773/27-8, *Neumann* A78758/28, *Zacutti* A79228/28, *Köncke* A78529/28, *Tesauro* B5941/28, *Klöpper* A78524/28, *Isbruch* A78462/29, *Pistuddi* A64937/29, *Pasquini* A78810/29, *Walter* A79173/29, *Zanardi* A68299/29, *Haultain* A78411/29-30, *Vanverts* A79138/30, *Burger* A78132/30, *Phaneuf* A64440/30, *Clauser* A67287/30, *Hauser* A78413/31, *Demuth* A78206/31, *Rochet et al.* A62255/32, *Shaw* A61532/32, *Offutt* A64399/32, *Wallbruch* A79172/33, *Warren* A79176/33, *Dougal* A78219/33, *Miginiac* A52167/34, *Tixier and Bertrand* A79118/34, *Howitt* A53042/34, *Sampson* A51981/34, *Harjola* A97380/39, *Barns* A97469/41.

actually represent malignant folliculomas producing carcinogenic, folliculoid substances. This possibility has not been proven as yet and it is offered merely as a hypothesis which may explain the comparatively frequent association of ovarian cancers with metropathia hemorrhagica and endometrial carcinomas. With regard to the route of propagation, it should be borne in mind that malignant cells may be transferred from the ovary to the uterus, and vice versa, either through the tube or through lymphatic channels. Although in many cases the histologic structure of the tumors gives some indication concerning their origin, in numerous instances the latter cannot be determined with certainty. Probably the majority of the squamous epithelium carcinomas seen simultaneously in uterus and ovaries are primary cancers of the uterine cervix which led to ovarian metastases.

In some cases "*adenoacanthomas*" are formed in the uterus; both these primary cancers and their ovarian metastases are characterized by a partly glandular and partly squamous type of epithelium.[1] Note, however, that the primary ovarian "epithélioma Wolffien" may exhibit a similar structure.

It is noteworthy that some ovarian cancers metastasize into benign uterine tumors such as fibromyomas[2] or endometrial polyps.[3]

In some instances the ovarian and uterine growths have an entirely different structure. Thus a carcinomatous papilloma of the ovary may develop simultaneously with a leiomyosarcoma of the uterus.[4] It has even been stated that Krukenberg tumors may develop in the ovaries as metastases of primary uterine cancers.[5]

Less commonly ovarian carcinomas are combined with cancers of the *vagina* and in these cases the same pathogenic possibilities exist as in those in which the ovarian epithelioma is combined with a uterine cancer.[6]

Invasion of the *vulva* by ovarian carcinoma is rather exceptional.[7]

The simultaneous occurrence of ovarian and *mammary* cancers is not particularly common. Here, again it may be difficult to ascertain in some cases which of the two tumors is primary.[8] Occasionally Krukenberg tumors of the ovaries sometimes develop simultaneously with mammary metastases in patients having a gastric carcinoma[9] and perhaps a primary mammary cancer may even produce Krukenberg-type metastases in the ovaries.[10]

Ovarian cancers occur with particular frequency in patients in whom carcinomas develop concurrently in various portions of the *gastro-intestinal tract*. In most of these cases, the ovarian cancer is secondary to a primary blastoma of the stomach or intestines.[11] Histologically, the structure of such metastatic ovarian cancers is variable and largely dependent upon that of the primary blastoma. Quite frequently, however, the ovarian metastases exhibit the characteristic appearance of the "*Krukenberg tumors*" with the formation of signet ring cells and mucoid material. The Krukenberg tumors represent a well-characterized pathologic entity and since they are not necessarily secondary to gastro-intestinal carcinomas, their specific characteristics will be discussed in a separate chapter. It may be mentioned here, however, that among 44 Krukenberg tumors observed at the Mayo Clinic the primary cancer was in the stomach in 20, the sigmoid in 7, the colon in 4, the cecum in 2, the jejunum in 2 cases, while in the remaining instances it was not found or located outside the gastrointestinal tract.[12] It is important to realize, however, that some of the cancers quoted in the present section may also belong to this category although the evidence reported in the original publication is not quite convincing.

Ovarian carcinoma metastases in the *esophagus*[13] are exceedingly rare.

Carcinomas of the *stomach and pylorus* frequently produce ovarian metastases. It is only in exceptional instances that there may be some reason to suspect that the ovarian growth was the primary site of tumor formation. In the vast majority of these cases, the data clearly indicate that the gastric

[1] *Schattenberg and Ziskind* A99193/40, *Beecham and Friday* A97779/42, *Simpson and Branch* B6311/44.
[2] *Kümmell* A78552/895, *Gottschalk* A78360/00, *Werner* A73021/13.
[3] *Arzt* A78010/10, *Bauereisen* A78030/12.
[4] *Major* A98166/43.
[5] *Leffel et al.* A37789/42.
[6] *Lerch* A45139/889, *Semmelink* A47983/898, *Ohlmann* A78781/02, *Gerson* A78336/19, *Goldberg* A78354/21, *Orsini* A78794/27, *Mallet* A66173/31, *Adler* A77951/31, *Fleiss* A78286/31, *Debiasi* A78188/32, *Shaw* A61532/32, *Numers* A52174/34, *Binstadt* A78057/34, *Clauberg* A78157/34, *Küstner* A61283/36, *Wenner* A54733/42.
[7] *Horney* A78451/13, *Viertel* A79144/35.
[8] *Luys* A88344/855, *v. Török and Wittelshöfer* A79119/880, *Paget* A94881/889, *Gendron* A78333/890, *Bramwell* A78090/894, *Sutton* A78060/02, *Wigham* A79207/03, *Weyl* A79199/05, *Montigel* A78726/06, *Sitzenfrey* A79035/07, *Hallauer* A78393/08, *Jellett* A78477/08, *Zalelsohn* A77914/11, *Lahey and Haythorn* A78567/12, *Schmincke* A78988/14, A78987/14, *Franqué* A78314/15, *Geipel* A78328/21, *Handley* A78399/22, *Köncke* A78529/28, *Marchand and Picard* A78658/28, *Espinos* A78257/29, A78258/30, *Taylor* A79096/31, *Eseen-Möller* A53033/33, *Scarpitti* A61498/33, *Warren and Macomber* A27718/35, *Saphir and Parker* B21788/41.
[9] *Graf* A78369/03, *Jackson and Babcock* A67743/30.
[10] *Larson* A97129/38, *Leffel et al.* A37789/42.
[11] *Römer* A78899/02, *Amann* A77987/10, *Metzger* A78695/11, *Bardon and Lescale* A83395/24, *Gauthier-Villars* A78324/27, A78325/28, *Clauser* A78158/28, *Franssen* A65150/30, *Klatten* A53047/34, *Verebely* A97746/38, *Piana* A97329/39.
[12] *Leffel et al.* A37789/42.
[13] *Janusz* A78472/26.

cancer was primary.[1] Less frequently, ovarian carcinomas are accompanied by cancers of the *small intestine*,[2] or *large intestine* (including the sigmoid flexure and the rectum); a considerable number of these latter cases arises from direct infiltration of the ovarian cancer into the intestine and vice versa.[3]

In cases in which carcinomas are simultaneously found in the ovaries and the *appendix*, the tumors are usually of the common pseudomucinous, adenocarcinomatous type[4] but they may also be carcinoids[5] or Krukenberg tumors.[6]

Ovarian carcinomas tend to produce *bone* metastases, which in some cases affect extensive portions of the skeleton so that blood formation may be disturbed.[7] In some Krukenberg tumors bone metastases are also found.[8]

If carcinomas develop simultaneously in the ovaries and the *liver or biliary passages* the identification of the primary blastoma may cause difficulties although generally the hepatic growths are secondary.[9] It has been stated that a primary cancer of the gall bladder may result in metastatic ovarian carcinomas of the Krukenberg type.[10]

It is comparatively rare that ovarian carcinomas are seen in patients in whom there develops simultaneously a cancer of the *pancreas*.[11] Some pancreatic carcinomas produce Krukenberg tumors in the ovaries.[12]

If the *spleen* is affected it is mostly the site of a hematogenous metastasis.[13]

The *pleural cavity*[14] and the *respiratory organs*—

[1]*Brinton* A78102/859, *Lolliot* A88413/867, *Villard* A79147/870, *Lange* A78575/877, *Ozenne* A78805/880, *Grawitz* A78370/881, *Menetrier* A82484/886, *Schrader* A79001/886, *Zahn* A79229/889. *Trekaki* A79123/890, *Lubarsch* A78631/891, *Dembo* A46317/892, *Welch and Smith* A79191/893, *Lévi and Claude* A78605/895, *Bode* A78071/896, *Lannois* A78577/896, *Tiburtius* A79114/899, *Buday* A78124/00, *Souligoux and Deschamps* A79044/01, *Rathert* A78868/01, *Gottschalk* A78361/01, *Borrmann* A78078/01, A78079/01, *Langlais* A78576/02, *Schlagenhaufer* A78977/02, *Selberg* A79020/02, *Kappeler* A78495/02, *Polano* A78843/04, *Heinemann* A78424/05, *Kehrer* A78502/05, *Amann* A77977/06, A77986/09, A77988/10, A77989/10, *Weyl* A79200/06, *Sternberg* A79058/06, *Schmorl* A78991/06, *Leriche* A78599/06, *Montigel* A78726/06, *Schauta* A78962/07, *Englehorn* A78251/07, B13190/07, *Brunner* A78115/07, A78116/08, *Sitzenfrey* A79034/07, A79037/08, A79038/09, *Bosquette and Laroyenne* A78082/08, *Sadewasser* A78934/08, *Schnitzler* A78994/09, *Runge* A78933/09, *Montanelli* A78724/09, *Müller* A78740/09, *Flaissier* A78282/09, *Fischer-Wasels* A78278/09, *Walther* A79175/10, *Lenormant* A78592/10, *Glendining* A78343/10, *Boeckel* B11299/10, *Hartmann* B11308/10, *Oberndorfer* A78771/10, A78770/10, A78773/11, A78772/11, *Herff* A78433/11, *Bobbio* A78068/11, *Mériel* A78692/12, *Lahey and Haythorn* A78567/12, *Wessling* A79198/13, *Bardy* A78018/13, *Bégouin and Bardon* A78038/14, *Stone* A79066/16, *Dengg* A78207/17, *Forssner* A78293/17, *Ley* A78607/19-20, *Frankl* A78306/22, *Rau* A78869/22, *Delannoy and Ausset* A78198/23, *Bouchut and Morenas* A78083/23, *Janusz* A78472/26, *Mayer* A78681/26, *Gauthier-Villars* A78324/27, A71395/28, *Duroselle* A78230/27, *Maljeff* A78653/27, *Lapointe* A78578/27, *Moure* A78735/28, *Pettinari* A78825/29, *Bräunig* A78094/31, *Cabot case* B21635/31, *Brisset* A78103/32, *Bell* A66142/32, *Werthemann* A79197/33, *Opitz* A27884/35. *Stebbins and Carns* A79051/35, *Warren and Macomber* A27718/35.

[2]*Adams* A77949/870, *Heinrichs* A78426/899, *Le Dentu* A78586/01, *Lahey and Haythorn* A78567/12, *Ley* A78607/19-20, *Pribram* A77755/25, *Roblee* A64719/29.

[3]*Weber* A79180/873, *Oswald* A78800/876, A88358/877, *Bardeleben* A88270/885, *Dembo* A46317/892, *Meyer* A78701/897, *Kayser* A78499/03, *Goullioud* A78363/03, A78362/03, *Jessett* A78480/07, *Malcolm* A78651/07-8, *Brunner* A78117/08, *Amann* A77984/08, A77985/08, *Bushnell and Kerrawalla* A65860/08, *Karsner* A78496/10, *Schottländer* A78996/10, *Richter* A78886/11, *Schmincke* A78988/14, A78987/14, *Truesdale* A79128/20, A79129/20, *Mayer* A78681/26, *Vambersky* B7165/27, *Neumann* A78758/28, *Fawcett* A78272/31, *Pohl* A62254/32, *Hunt and Budd* A61411/33, *Vogt* A51987/33, *Seelaus and Haskell* A51983/34, *Santy* A61163/36.

[4]*Swanton* A79084/07, B13366/07, *Tate* A79093/10, *Amann* A77990/10, A77991/11, *Held* A78430/12, *Edge* A78239/14, *René* A78880/20, *Bryant* B20991/23, *Harnik* A78405/24, A78406/24, *Völcker* A79155/29, *Driessens et al.* A97053/38.

[5]*Hopping et al.* A56455/42.

[6]*Stanca* A65182/30, A79838/33, *Lubin and Polayes* A33973/40.

[7]*Luys* A88344/855, *Küster* A88336/874-5, *Sternberg* A79057/896, A50479/898, *Cavour* A78145/20, *Rau* A78869/22, *Bankart* A78016/25-6, *Janusz* A78472/26, *Mayer* A78681/26, *Eichengrün and Esser* A78243/27, *Charles and Francfort* A78148/27, *Erdheim* A78254/29, *Copeland* A78170/31, *Lucarelli* A64184/31, *Schempp* A78964/33, *Ottow* A78802/34, *Kottmeier* A78538/35.

[8]*Dupont and Lièvre* A79722/29, *Terplan and Vaughan* A79846/34, *Stebbins and Carns* A79051/35, *Jarcho* A79763/36, *Simeck* A95130/37.

[9]*Barth* A78022/851, *Bristowe* A78105/851-2, A78104/851-2, A88283/859-60, *Gibb* A78337/856-7, *Weber* A79180/873, *Thornton* A79113/873-4, *Loomis* A78627/879, *Schuchardt* A79004/881, *Stelzner* A76568/883-4, *d'Antona* A43570/890, *Le Fur* A78587/894, *Sellheim* A79021/895, *Landerer* A47120/895, *Bellinger* A78043/897, *Griffon and Leven* A78374/899, *Lecornu* A78585/02, *Riechelmann* A78888/02, *Marie* A78659/02, *Kamann* A78491/06, *Noever* A92059/06, *Resinelli* A70922/06, *Goullioud* A78364/07, A78365/07, A78366/07, *Amann* A77980/07, A77981/07, A77993/12, *Karsner* A78496/10, *Morosowski* A70518/12, *Lahey and Haythorn* A78567/12, *Christiani* A78152/13, *Riwlin* A78892/13, *Cavour* A78145/20, *Maljeff* A78653/27, *Cabot* B10774/28, *Barone* A64413/30, *Bürger* A78132/30, *McWhorter and Cloud* A78646/30, *Demuth* A78206/31, *Lucarelli* A64184/31, *Gupta and Mukhopadhaya* A62302/32, *Barany and Sala* A78017/33, *Cabot case* B21766/41, B21765/41.

[10]*Starkus* A61898/32, *Leffel et al.* A37789/42.

[11]*Barth* A78022/851, *Adams* A77949/870, *Amann* A77977/06, *Schuster* A79007/08, *Forssner* A78294/17, *Rosner* A78918/23, *Erdheim* A78254/29, *Hirai and Nakagawa* A78439/31.

[12]*Boggino and Thompson* A98102/41, A98101/41.

[13]*Weber* A79180/873, *Bramwell* A78090/894, *Sellheim* A79021/895, *Schuster* A79007/08, *Gerson* A78336/19, *Eichengrün and Esser* A78243/27, *Maljeff* A78653/27, *Yokuhata* A79226/27, *Wilinski* A79210/30, *Egenolf* A78241/30, *Barany and Sala* A78017/33.

[14]*Bloch* A81325/875, *Boussi* A78086/877, *Arnozan* A78009/879, *Häckel* A78389/883, *Menetrier* A82484/886, *Le Jemtel and Esmein* A78591/06, *Bezzola* B13372/07, *Roubier and Chanaleilles* A78922/30, *Evans and Strachan* A66116/32, *Schwimmer* A96880/43.

specifically the larynx, bronchi and lung[1] are often involved and in some instances hematogenous cancer thrombi are detectable in the pulmonary vessels. It is noteworthy that gastric cancers may simultaneously lead to Krukenberg type metastases in the ovaries and more or less diffuse "lymphangitic carcinomatosis" of the lungs.[2]

The *heart and pericardium*,[3] various parts of the *nervous system*,[4] the *skin*,[5] the *kidney*,[6] the *urinary bladder and ureters*,[7] the *thyroid*,[8] the *adrenals*[9] and the *lacrymal glands*[10] may also be the site of cancerous growth in women with ovarian carcinomas.

In some of these cases, especially those in which the ovarian cancer was accompanied by carcinomatosis of the peritoneum, lymph-nodes, spleen, heart, kidney, endocrines and skin (as well as in many of the other cases mentioned above), there is good reason to believe that the extragonadal tumors were secondary either to the ovarian carcinoma or to an often minute and unrecognized primary growth. From the localization of some of these metastases (e.g. in heart, thyroid, lung) it is evident that although the lymphatic spread is more common, ovarian carcinomas can form hematogenous metastases as well.[11]

CHEMICAL COMPOSITION

Comparative little work has been done concerning the chemical composition of ovarian cancers.[12] The few relevant publications imply that close similarities exist between the chemical composition of carcinomatous and benign ovarian cysts (see also part on Chemical Composition in chapter on Common Ovarian Cysts).

INCIDENCE

General Incidence: Most of the statistical studies concerning the incidence of ovarian carcinomas are difficult to evalute because of inadequate identification of the tumors. Perhaps one of the greatest sources of error is the frequent confusion of metastatic and primary cancers. Hence the relevant statistical data must be evaluated with great caution.

Among 2,768 patients admitted to the Mayo Clinic for diverse surgical gynecologic diseases in 1943, there were 83 ovarian carcinomas.[13]

In reviewing the statistical data of 22 distinct carcinoma series, with an aggregate total of 28491 women suffering from various types of carcinomas, cancers of the ovary were found in 1321 cases, which equals an incidence of 4.6%.[14] Another statistical series records 282 ovarian carcinomas among 12417 cancerous women, that is an incidence of 2.3%.[15] These figures, as well as our own statistical calculations, lead us to believe that approximately 4% of all the cancers of women are ovarian carcinomas.

In order to show the comparative frequency of ovarian carinomas and other cancers of Müllerian derivates Miller[16] compared the figures given by various surgeons on 5009 cases of genital cancer subjected to surgical therapy. Among these 598 (11.73%) were ovarian carcinomas, 4120 carcinomas of the uterus, 29 of the oviduct and 262 of the vagina and vulva. (In the original publication the grand total of these cases is erroneously listed as 5099.) A similar computation on the basis of autopsy material led Miller to conclude that among 1607 pelvic carcinomas 211 (13.13%) were ovarian cancers, 1292 carcinomas of the uterus, 1 of the oviduct and 103 of the vagina and vulva. Our own statistical calculations agree with the figure of about 12% for the incidence of ovarian cancers among the carcinomas of the female pelvic organs.

The proportion of carcinomas among the ovarian blastomas in general is estimated to be about 15%, on the basis of 7646 observations made by different investigators.[17] In another series of 150 ovarian tumors (including cysts), 20 carcinomas were found.[18] This agrees fairly well with the above percentual incidence.

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[1]*Thornton* A79113/873-4, *Liveing* A78620/875, *Brown* A88285/879, *Stelzner* A76568/883-4, *Baader* A78013/895, *Emsheimer* A78248/896, *Resinelli* A70922/06, *Karsner* A78496/10, *Rollett* A78902/11, *Morosowski* A70518/12, *Nörr* A78761/19, *Cavour* A78145/20, *Bilz* A78056/23, *Gibson and Findlay* A78338/23, *Müller* A78737/29, *Barone* A64413/30, *McWorter and Cloud* A78646/30, *Roubier* A67264/30, *Roubier and Chanaleilles* A78922/30, *Lucarelli* A64184/31, *Ottow* A78802/34, *Vogt* A79160/34, *Kuhlmann* A78557/34, *Kirshbaum* A59695/36, *Schwimmer* A96880/43.

[2]*Beger* A96787/879, *Graf* A78369/03, *Jarcho* A79762/27, A79763/36, *Dupont and Lièvre* A79722/29, *Janow* A65158/30, *Terplan and Vaughan* A79846/34, *Stebbins and Carns* A79051/35.

[3]*Bucquoy* A78123/867, *Emsheimer* A78248/896, *Nörr* A78761/19, *Ley* A78607/19-20, *Maljeff* A78653/27, *Cain and Tran-Nhu-Lan* A97759/28, *Müller* A78737/29, *Erdheim* A78254/29, *Horanyi and Timcsak* A78450/35.

[4]*Muratow* A78744/895, *Emsheimer* A78248/896, *Kaul* A78498/06, *Dupont and Lièvre* A79722/29, *Cornil and Paillas* A94778/37.

[5]*Broca* A78107/850, *Linzenmeier* A78615/30, *Barone* A64413/30, *Bottler* B29/30, *Terada* A61577/33, *Philipp* A51977/34, *Ottow* A78802/34, A51975/34, *Willis* A94815/34, *Fleischmann* A95057/37, *Meyer* B7733/38, *Urbach et al.* A36658/41.

[6]*Adams* A77949/870, *Teichmann* A77847/888, *Dembo* A46317/892, *Steinhaus* A79055/10, *Rau* A78869/22, *Bruns* A65858/24, *Steiner* A79054/26, *Wilinski* A79210/30.

[7]*Pauchet* B13359/07.

[8]*Morosowski* A70518/12, *Hoffmann* A64161/31, *Shaw* A61532/32.

[9]*Gibb* A78337/856-7, *Teichmann* A77847/888, *Lahey and Hawthorn* A78567/12, *Janusz* A78472/26, *Maljeff* A78653/27, *Roubier* A67264/30.

[10]*Adams* A77949/870.

[11]*Simard and Gagnon* B10797/28.

[12]*Roncali* A92080/896, *Panting* A92120/00.

[13]*Counseller et al.* 85159/44.

[14]*Miller* A18279/37.

[15]*Heimann* A78423/899.

[16]A18279/37.

[17]*Miller* A18279/37. [18]*Scharlieb* A66931/09-10.

With regard to the percentual incidence of the various histologic types of ovarian carcinomas, it may be said that carcinomatous transformation was observed 69 times in a series of 1246 *simple serous cystomas* which is an incidence of 5.5%.[1] On the other hand, among the *papillary serous cystomas,* malignant changes are more frequent and are noted in about 50% of the cases.[2] The *carcinomatous pseudomucinous cystomas* are much less common and in most statistical reviews they represent only about 5% of the corresponding benign cystomas.[1]

Metastatic ovarian carcinomas are frequently seen in cases of primary uterine cancer where they are found in about 15% of the autopsy cases[1] while, in patients with other primary carcinomas, they are much less common.

Primary solid carcinomas of the ovary are comparatively rare. Thus in a series of 234 women who came to autopsy with various types of cancers, only 4 suffered from primary ovarian carcinomas, while 16 had metastatic cancers in the ovary.[3]

Krukenberg tumors are generally regarded as rare blastomas, thus up to 1943 Copland and Colvin[4] were able to collect only 155 relevant cases in the entire world literature. The many relevant publications quoted in this Encyclopedia (see chapter on Krukenberg Tumors) reveal, however, the existence of several hundred authentic cases and many more doubtful instances probably belong to this group.

AGE INCIDENCE: Numerous statistical studies are specifically concerned with the incidence of carcinoma formation in various age groups. It is frequently stated that by far the highest incidence occurs during the childbearing period of life. Although ovarian cancer may develop at any age, the literature perused in preparing this Encyclopedia strongly suggests that by far the greatest number of ovarian cancers develop at or after the menopause.

A statistical survey of 2083 cases of various types of ovarian cancer published by different investigators yields the following figures of age distribution:

Years	No. of Cases
0—20	41
21—30	133
31—40	299
41—50	700
51—60	633
61—70	210
71—80	32
81—90	1

In the remaining instances, the exact age of the patient was not known. The average age of the women bearing ovarian cancers is estimated by the various investigators to be between 49 and 52 years.[1]

In another series of 149 cases[5] the incidence was as follows:

Years	No. of Cases
20—30	4
30—40	17
40—50	46
50—60	47
60—70	28
over 70	7

Many additional case reports have been published on carcinomas of the ovary in *children.*[6] More specifically in children up to 5 years;[7] 5 to 10 years;[8] 10 to 15 years[9] and in *young women* 15 to 20 years[10] and 20 to 30 years[11] of age.

[1] *Miller* A18279/37.

[2] *Pfannenstiel* A80267/05. *Smith* A68121/29.

[3] *v. Mielecki* A78708/13.

[4] A56857/43.

[5] *Pemberton* 80890/40.

[6] *Wilde* A79209/892, *Bürger* A78127/893, *Leopold* A78595/894, *Baader* A78013/895, *Berent* A78048/01, *Rohde* A78900/04, *Karsner* A78496/10, *Holtz* A78447/14, *Oxmann* A78804/21, *Thadewald* A79104/24, *Hunt and Simon* A78459/28, *Wildbolz* A79208/31, *Mayo and Fauster* A78682/32, *Meyer* A59469/36, *Gutmann* B7706/38.

[7] *Wiel* A79203/05, *Rosanoff* A78905/11, *Knewitz* A83399/20, *Hunt and Simon* A78459/28, *Lanman* A68183/29, *Moench* A61571/33.

[8] *Palmer* A69790/875. *Olshausen* A41468/886, *Gussenbauer* A78383/893, *Krukenberg* A78550/893, *Leopold* A78595/894, *Baader* A78013/895, *Stolypinsky* A79063/04, *Parry* A78808/07, *Kermisson* A83398/09, *Vignard* A79145/10, *Karsner* A78496/10, *Morian* A78728/12, *Etienne and Aimes* A78262/13, A78263/20, *Perkins* A83402/13-4, *Gerson* A78336/19, *Lusinchi* A78634/20, *Potter* A78851/25, *Flessa* A78287/26, *Lanman* A68183/29, *Frank* 58775/32, *Mayo and Fauster* A78682/32, *Witzberger and Agerty* A95127/37.

[9] *Jackson* A78464/850, *Marjolin* A69787/861, *Cohn* A42018/886, *Leopold* A41747/887, A78595/894, *Guttmann* A78384/889, *Heimann* A78422/898, *Martin* A78665/899, *Heinrichs* A78426/899, *Kusnetzky* A78559/03, A75832/03, A92160/04, *Joüon* B13196/07, *Redlich* A78874/07, A78873/07, *Lindemann* A78614/11, *Lahey and Haythorn* A78567/12, *Knott* A83400/15, *Oliver* A83401/17, *Ridout* A79338/19, *Pélissier* A78816/20, *Krompecher* A64781/25, *Rosenberg* A64720/29, *Kieser* A78514/31, *Wildbolz* A79208/31, *Bertrand and Soustelle* A61917/33, *Bernardbeig and Sicard* A78052/33, *Polichetti* A78845/33, *de Sa* A59452/36, *Goldstein* B6252/44.

[10] *Binaud* A44797/894, *Fourrier* A92144/04, *Grunert* A78397/10, *Rauschmann* A78870/10, *Rastouil* A78867/11, *Strong* A79076/19, *Lusinchi* A78634/20, *Dickinson* A78210/24, *Guyot and Princeteau* A78388/25, *Zacutti* A79228/28.

[11] *Maunsell* A78679/06-7.

Ovarian carcinomas in *old women*[1] aged 60 to 70 years[2] or even 70 to 80 years[3] have also been reported.

It is noteworthy that many of the ovarian carcinomas of children, especially those described in the old literature, have not been adequately characterized from the histologic point of view, so that some doubt exists concerning their identity. Perusal of the histologic reports indicates that some of these supposedly carcinomatous growths were probably sarcomas and many purportedly primary carcinomas were actually Krukenberg tumors.

The age incidence of *solid,* presumably *primary, carcinomas* calculated on the basis of 534 cases collected from the literature[4] was as follows:

Years	No. of Cases
1—10	14
11—20	40
21—30	52
31—40	76
41—50	155
51—60	147
61—70	41
71—80	9

The average age of 77 women who underwent operations for solid adenocarcinomas in the Mayo Clinic, was 48 years.[5]

Among the *carcinomatous simple serous cystomas* the age distribution of 104 cases collected from the literature[4] was as follows:

Years	No. of Cases
1—20	0
21—30	7
31—40	8
41—50	37
51—60	33
61—70	17
71—80	2

In a series of 394 *carcinomatous serous papillomas* published by various investigators,[4] the age incidence was as follows:

Years	No. of Cases
1—10	1
11—20	4
21—30	22
31—40	50
41—50	64
51—60	58
61—70	70
71—80	13

Among the remaining cases, 35 occurred between 11-40 years and 111 were seen between 41-60 years although the exact age was not given.

The age distribution in 86 published cases of *carcinomatous pseudomucinous cystomas* was the following:[4]

Years	No. of Cases
11—20	4
21—30	7
31—40	19
41—50	23
51—60	18
61—70	12
71—80	2
81—90	1

The fact that *Krukenberg tumors* can develop in children has been definitely established on the basis of several authentic case reports.[6] However, the highest incidence of this tumor is found among women of the childbearing age. It has been suggested that at this time the connective tissue cells of the ovary are especially prone to react in an "extraordinary embryonic manner" to the presence of cancer cells in their neighbourhood.[7] Krukenberg tumors may also occur, however, in women past 65 years of age.[8]

From the various statistical surveys it is evident that the maximum incidence for all types of common ovarian carcinomas is at the end or shortly after the childbearing period of life. It must be kept in mind, however, that the total number of observations greatly diminishes after this time as we approach the end of normal life expectancy; hence

[1] *Jones* A92158/06, A93159/06.
[2] *Rose* A78906/05, *Prochownik* A78861/07, *Wiener* A79205/10, A79206/10, *Gibson* A78339/13.
[3] *M'Gibbon* A78637/07-8, *Maiss* A78649/08, A78650/09.
[4] *Miller* A18279/37.
[5] *Moench* A61571/33.
[6] *Scholz* A78995/886, *Goinard and Montpellier* A65069/31, *Kukin* A53174/33, *Heidler* A79750/36, *Sager* A33974/40.
[7] *Shaw* A79832/26.
[8] *Copland and Colvin* A56857/43.

there is no reason to believe that in a given number of cases the incidence would begin to decrease towards the end of normal life.

Pregnancy Incidence: The large number of case reports describing ovarian carcinomas in pregnant women would appear to indicate that there is a tendency towards the formation and proliferation of these growths during gestation.[1] Reliable statistical analyses concerning the incidence of ovarian carcinomas in pregnant, as compared to non-pregnant women have not been made. Some investigators believe that gestation does not actually constitute a predisposing factor.[2]

It has also been claimed that women who have had many children become predisposed to the development of ovarian cancers, but this is likewise doubtful as judged by a painstaking review of this subject.[2]

The above-mentioned case reports show that primary solid carcinomas, carcinomatous serous or pseudomucinous cysts, as well as various types of metastatic ovarian cancers, may develop in the course of gestation, and even if they are bilateral they do not necessarily interfere with the maintenance of pregnancy. The increased intra-abdominal pressure (which may lead to rupture, hemorrhage or torsion of the tumors), as well as the tendency of growths to interfere mechanically with normal delivery will, however, frequently cause complications during gestation. Perhaps it is owing to the occurrence of such incidental disturbances that so many ovarian cancers come to the attention of the clinician at the time of gestation.

Whether *Krukenberg tumors* are more common in pregnant than in non-pregnant women, is debatable.[3] Some investigators definitely deny an increased incidence during gestation. It is undeniable, however, that many instances of Krukenberg tumors in pregnant women are on record.[4]

Puerperal Incidence: Comparatively few ovarian cancers are seen during the puerperium.[5] This is probably due to the fact that in pregnant women such tumors would become manifest at, or even before, the time of delivery and hence would rarely first be seen by the clinician immediately after childbirth.

Racial Incidence: There is no very convincing proof of any racial predisposition for the formation of ovarian cancers, although some investigators published suggestive data in favor of this view.[6]

It has been claimed that among Jewish women the incidence of ovarian cancer is higher, while that of uterine cancer is lower than among Gentiles.[7] It is stated—without convincing statistical evidence—that Negro women are less subject to ovarian carcinoma formation than white patients;[2] ovarian cancers are not exceptional in colored patients, however,[8] and among 42 unselected cases of women treated for ovarian carcinoma at the New York City Cancer Institute, 8 were Negroes.[9] According to the report of the Cancer Institute of the Dutch East Indies (1934) during a 5-year period, 62 ovarian cancers were seen among the natives and 3 among Chinese.

Krukenberg tumors have repeatedly been observed among negroes.[10]

PATHOGENESIS

A. Carcinomatous Cystomas. A great deal of work has been done in an effort to elucidate the pathogenesis of the common ovarian carcinomas. Special attention was given to problems related to their *histogenesis*,[11] but for the majority of the relevant blastomas, namely the carcinomatous cystomas, this question is of secondary importance since it is now well established that cystic carcinomas do not develop primarily, but only as a result of malignant transformation in originally benign cystomas. The pathogenesis of the benign cystomas has been discussed in some detail in the section devoted to them. It will suffice to state here that the carcinomatous serous and pseudomucinous cystomas originate from the corresponding benign serous and pseudomucinous growths respectively. In some instances carcinomatous degeneration may be seen in very small cysts and there is no close relationship between the size of a cystoma and its tendency to become malignant.

[1] *Sabatier* A69881/787, *Gistrén* A69852/801, *Robie* A69879/855, *Mosler* A69870/860, *Holst* A78445/867, *Hempel* A78431/875, *Peabody* A41750/887, *Lotheissen* A78629/895, *Grube* A78378/01, *Schauta* A78960/06, *Zickel* A79232/07, *Weisswange* A79190/08, *Gobiet* A78349/09, *Hesselbach* A78434/11, *Fuchs* A78318/12, *Ströbe* A79073/13, *Jacobson* A78469/13, *Kosmak* A78537/14, *Luker* A78633/21-2, B11753/22, *Reid* A78877/22, *Schmid* A78982/22, A79983/24, *Peller* A78817/23, *Basu* A66920/24, *Armytage* A78006/25, *Pedersen* A78814/27, *Badie* A78015/27, *Kamniker* A78492/29, A68017/29, *Wegner* A79167/30, *Bau* A78026/31, *Nürnberger* A78768/31, *Schwarzkopf* A65084/31, *Meyer-Wildisen* A61422/32, *Szathmary* A61576/33, *Halter* A78395/34, *Stabler* A79048/36, A79047/36, *Bossert* A56572/42.

[2] *Miller* A18279/37.

[3] *Schmid* A78983/24.

[4] *Burdainsky* A78131/07, *Bell* A79698/27, *Guiroy and Jakob* A79747/28, A79746/28, *Esau* A80129/29, A61926/33, *Büttner* 5587/33, *Frankl* A61753/33, *Puppel* A61891/33, *v. Bud* A28145/35, *Hagstrom* A97147/38, *Watrin et al.* A97325/39, *Horta Barbosa et al.* A96692/40.

[5] *Nijhoff* A83403/19.

[6] *Theilhaber* A79108/10, *Abruzzese* A77948/34-5.

[7] *Theilhaber* A79108/10, *Peller* A78818/31.

[8] *Schwimmer* A96880/43.

[9] *Kaplan* A78494/33.

[10] *Major* A79780/18, *Gordon* A79740/24, *Jackson and Babcock* A67743/30, *Bacon* A79696/34, *Leffel et al.* A37789/42.

[11] *Nagel* A88239/888, *Tanaka* A92102/01, *Fleury* B7702/38.

Perhaps one of the smallest carcinomatous cysts, only a few millimeters in diameter, was found accidentally at an operation for uterine retroflexion. In this instance part of the cyst wall was transformed into adenocarcinoma tissue.[1]

With regard to the *functional pathogenesis* of ovarian carcinomas our knowledge is likewise extremely scanty. It has been claimed that parasitic protozoa may be found in certain ovarian cancers and that they may be responsible for the malignant growth.[2] Indeed, on the basis of such evidence the term "infectious carcinomatous papilloma" has been used to designate certain ovarian carcinomas,[3] but this theory has not been confirmed. It is also very doubtful whether there is any etiologic relationship between ovarian carcinoma formation and tuberculosis in patients who happen to suffer from both these conditions.[4]

Many investigators speculated concerning the possible role of sexual intercourse or abstinence upon the development of ovarian cancers. Neither this theory, nor the view that repeated pregnancies induce a predisposition to ovarian carcinoma formation, has received support from statistical analyses.[5]

The question of a hereditary predisposition was raised by the much quoted observation of ovarian carcinomas in a pair of twins. In both these women the same surgeon removed bilateral ovarian cancers and a myoma of the uterus within a two-year period. In one twin the cancers were cystic and papillary, while in the other they were free of papillae and rather solid adenocarcinomas. In general, however, simultaneous tumor formation is rarely seen in pairs of identical twins and as judged by the evidence in the section on "Racial Incidence" there is little to support the view of an important hereditary factor in the development of common ovarian carcinomas. The case of a carcinomatous papilloma in a little girl in whose family three women suffered from tumors of the genital region, has also been quoted as indicating a familial predisposition[6] but is hardly very convincing in itself.

The occasional development of a cancer in the remnant of a partially removed ovary[7] or the sudden growth of such carcinomas following radium or X-ray treatment[8] fails to supply any positive basis for the assumption that local stimuli are of great etiologic importance in producing carcinomas in the ovary.

B. Primary Solid Carcinomas. With regard to the origin of primary solid ovarian cancers three histogenetic possibilities deserve serious consideration.

It has been claimed that these growths arise *from the granulosa cells* of ovarian follicles.[9] Although in an early publication Massabuau[10] claimed that his facts "demonstrate irrefutably the follicular origin" of these tumors, Massabuau and Etienne[11] claim this to be an "impossible hypothesis". It is not uncommon to find follicle or ovum-like formations in solid ovarian carcinomas,[12] but these are not real ova or follicles.[13] They probably represent mere products of cellular degeneration as they may also be found in extraovarian cancers.[14] Although the follicular origin of the common solid carcinomas is refuted by most investigators,[15] the fact still remains that many of them bear a striking resemblance to the hormone-producing granulosa cell carcinomas and differentiation between the two is often difficult on the basis of histologic evidence alone.

A second group of investigators derive the primary solid ovarian cancers *from the germinal epithelium.*[16] This theory is based mainly on observations of very early stages in which the surface epithelium was found in a state of active, and often irregular, proliferation in the vicinity of the developing blastoma.

The possibility cannot be denied that these carcinomas do not necessarily always originate from the same cell type but may develop either from the surface epithelium or from that of primordial follicles.[17]

A third theory derives primary cancers *from the Wolffian body* or mesonephros. Indeed, some investigators go so far as to refer to them as "Wolffian epitheliomas".[18] It is customary, however, to limit this term to certain microcystic pseudomucinous cystadenomas and carcinomas. Both the benign and the malignant variety of this blastoma type have been discussed in a section on pseudomucinous cystomas and will not be reconsidered here. Apart from the fact that the theoretic basis of this histogenetic theory is not adequately proven, it should be kept in mind that in most cases only pseudomucinous growths are termed "Wolffian epitheliomas" and it only adds to the confusion created by this rather unfortunate designation if we follow the example of investigators who apply it both to pseudomucinous and serous carcinomas.[19]

[1] *Hornung* A78452/27, A78454/29.
[2] *Müller* A78742/895, *Miller* A92057/895.
[3] *Roncali* A92078/895, A92079/895, A78903/895.
[4] *Kermauner* 41623/25.
[5] *Miller* A18279/37.
[6] *Kermisson* A83398/09.
[7] *Reeke* A67259/30.
[8] *Abruzzese* A77947/32.
[9] *Müller* A44210/892, *v. Kahlden* A47460/895, *Pozzi and Beaussenat* A49007/897, *Schröder* A64835/01, *Limnell* A70119/01, *McIlroy* A78640/06.
[10] A70826/06.
[11] A78672/13.
[12] *Emanuel* A11546/893, *Kirchner* A70770/895, *Schröder* A64835/01, *Blau* A64734/07, A64735/26.
[13] *Wendeler* A96821/899, *Liepmann* A64788/04.
[14] *McIlroy* A78640/06, *Dreyfus* A78223/07.
[15] *Goodall* A73686/19-20, *Miller* A18279/37.
[16] *Limnell* A70119/01, *Glockner* A70014/05, *McIlroy* A78640/06, *Massabuau and Etienne* A78672/13.
[17] *Limnell* A70119/01, *Massabuau* A70826/06.
[18] *Masson* 79329/12, *Massabuau and Etienne* A78672/13, *Ley* A78607/19-20, *de Mora* A79507/31.
[19] *Ley* A78607/19-20, *Miller* A18279/37.

C. Krukenberg Tumors (including other metastatic ovarian cancers). The pathogenesis of Krukenberg tumors has been the subject of many investigations.[1] The formation of the peculiar and very characteristic mucus-containing "*Signet ring cell*" received special consideration by all those workers who were interested in problems pertaining to the histogenesis of this blastoma,[2] but in spite of much careful work, the formation of this cell type is still not fully explained. Some investigators[3] believe to have seen Krukenberg-type ovarian metastases in patients in whom the primary tumor was not mucus-producing; yet in the majority of cases, the signet ring cells must be regarded as derived from mucus-producing primary carcinomas in extragonadal tissues.

It is generally agreed that the great majority, if not all, the Krukenberg tumors are metastatic;[4] there is great uncertainty, however, concerning the pathways through which the carcinoma cells become lodged in the ovarian parenchyme. The possibility of a *spread through the lymphatic vessels* of the ovary has been demonstrated, not only for Krukenberg tumors but for various types of metastatic ovarian cancers, by the actual detection of carcinoma cell groups within the ovarian lymphatics.[5] Some advocates of this interpretation believe that the cancer cells reach the ovary by retrograde migration through direct retroperitoneal lymphatic communications between the stomach and the ovaries.[6] Others, who support the peritoneal theory of propagation, believe that the cancer cells first enter the free peritoneal cavity, but are subsequently taken up by the ovarian lymphatics through supposedly open stomas. In defense of this view it has been stated that india ink introduced into the peritoneum of the rabbit is taken up by the ovarian lymphatics and it was concluded that cancer metastases probably also enter through pre-existent lymphatic channels.[7] However, subsequent experiments on the guinea pig, mouse and rabbit failed to demonstrate any such migration either for intraperitoneally injected india ink or for bacteria. From this it was concluded that the ovarian surface epithelium, unless it is traumatized, protects the gonad against invading particles. It was evident from these experiments, however, that even the physiological lesions incident to ovulation make penetration of the particles possible.[8] Similar negative experiments with india ink led to the assumption that perhaps the ovary may have a special "biological affinity" for cancer cells.

Although the experimental work did not furnish any very convincing evidence for or against the possibility of a lymphatic spread, the fact remains that the above mentioned observations of cancer cells within the ovarian lymphatics definitely prove that this pathway of penetration can be of importance, at least in certain cases.

Other investigators stress the probable role of *peritoneal sedimentation* of cancer cells coming from other abdominal organs.[9] This possibility is all the more worthy of consideration since cancer cells are often found in the peritoneal fluid.[10] The formation of metastases through this mechanism can obviously not be operative in those Krukenberg tumors which arise from an extraperitoneal primary cancer.

Since carcinoma cells may be found in the pulmonary blood vessels in patients suffering from Krukenberg tumors, the possibility of a *hematogenous spread* to the ovary must not be disregarded.[11]

Extension *by continuity* from structures adjacent to the ovary, may also occur[10] but hardly plays a prominent role since in most cases of Krukenberg tumors the primary cancer is not in the immediate vicinity of the gonad.

There is no reason to believe that carcinoma cells can reach the ovary through only one of the above mentioned channels and it appears logical to assume that implantation may occur through any of the pathways discussed in the preceding paragraphs.[10]

Several cases of Krukenberg tumors have been described in which an extraovarian carcinoma was not detectable, so that the ovarian cancers were considered to be *true primary tumors*.[12] The authenticity of the so-called primary Krukenberg tumors is questioned by some investigators because so frequently these tumors were thought to be primary and yet a careful search discovered a minute, hardly recognizable, carcinoma usually in the stomach.[13]

[1] *Geremia* A79734/31, *Puhr* A52293/34, A28067/35, *Fernandez Ferreiros* A97545/41.

[2] *Wagner* A79853/02, *Ulesko-Stroganoff* A79132/10, A79133/10, *Schiller* A78974/25, *Duboucher and Montpellier* A68169/29, *Nicolo* A95080/37.

[3] *Jarcho* A79762/27, *Larson* A97129/38, *Novak and Gray* A96527/38, *Copland and Colvin* A56857/43.

[4] *Leffel et al.* A37789/42, *Copland and Colvin* A56857/43.

[5] *Sellheim* A79021/895, *Oltramare* A78786/04, *Schiller* A78975/25, *Shaw* A79832/26, *Armstrong and Wolfe* A53143/34, *Runyeon* A52298/34, *Novak and Gray* A96527/38, *Leffel et al.* A37789/42.

[6] *Vazzoler* A64208/31, *Armstrong and Wolfe* A53143/34.

[7] *Kraus* A78544/01.

[8] *Wolfheim* A79224/06.

[9] *Boyd* B128/29, *Saccone and Gordon* A52301b/34.

[10] *Leffel et al.* A37789/42.

[11] *Major* A79780/18.

[12] *Krukenberg* A79771/895, A79772/896, *Sternberg* 47578/01, *Schenk* A79824/04, *Glockner* A78347/04, *Rosthorn* A79818/06, *Fischer* A79727/09, *Krüger* A79770/09, *Outerbridge* A79803/11, *Marchand* A79784/19, *Frankl* A78305/20, *Frankenthal* A79730/21, *Neumann* A79797/24, *Miner* A79793/26, *Andrews* A52251/34, *Celentano* A62062/35, *Novak and Gray* A96527/38, *Uhlmann* A31683/39.

[13] *Stickel* A79060/06, *Sandrock* A79823/06, *Cohn* A78166/10, *Ulesko-Stroganoff* A79132/10, *Hussy* B60/11, *Hartmann and Metzger* B59/11, *Paul* A78811/13, *van der Perk* B58/21, *Kaufman* B61/29, *Terplan and Vaughan* A79846/34, *Simeck* A95130/37.

From these cases it is evident that great caution must be exercised before accepting a Krukenberg tumor as a primary carcinoma.

There is no reason to doubt, however, that the ovary, which is capable of giving rise to pseudomucinous cystomas, could give origin to the mucoid Krukenberg tumors. It is possible, furthermore, that carcinomatous transformation of an originally benign pseudomucinous cystoma may lead to the secondary invasion of the remaining ovarian parenchyme by mucus-producing cancer cells which then assume the appearance of the Krukenberg tumor. It will be recalled that in the section on carcinomatous pseudomucinous cystomas we emphasized the fact that certain solid areas in which the stroma is invaded by cancer cells exhibit the typical "signet ring cell type".

CLINICAL COURSE

Reviews: Martin A96824/899, Novak A63534/41, A94367/44, B109/44, Geist B6672/42.

The presence of a *mass in the lower abdomen* is usually the first sign of the disease and even this indication is frequently very late to come to the attention of the patient. It is usually noticed in the form of a "lump" in the lower abdomen often accompanied by heaviness and occasional pain although the latter two symptoms are apt to be lacking.[1]

The *menstrual cycle* frequently shows disturbances,[2] there may be *menorrhagias* and *metrorrhagias* of a severe nature both in patients of the child-bearing age and in post-menopausal cases.[3] The pathogenesis of these hemorrhages differs from case to case. Undoubtedly, in some instances, carcinomas develop simultaneously in the uterus and the ovaries as indicated in the morphologic section where the uterine metastases of ovarian cancers and the ovarian metastases of uterine carcinomas have been discussed. In other instances, secondary vascular lesions, due to mechanical presence of the ovarian growth, have been considered as the cause of uterine bleeding, especially in post-menopausal cases.[4]

The possibility of sex hormone production, even by some of the so-called common serous ovarian carcinomas, must also be kept in mind. It is noteworthy that the endometrium may fail to undergo senile involution in menopausal women bearing ovarian carcinomas, and in some relevant cases a concurrent metropathia hemorrhagica was cured by ovariectomy.[5] The possibility of such hormone production is further emphasized by the cases in which presumably simple medullary carcinomas of the ovary produced signs of *precocious puberty* and uterine hemorrhages in children.[6] In other patients, however, prepubertal development of a common ovarian cancer caused no histologically detectable change in the endometrium.[7] It must be admitted that in some, if not all of the cases with precocious uterine bleeding the tumor may have been an atypical granulosa cell carcinoma. But it is also conceivable that there is no fundamental difference between the carcinomas of the "granulosa cell type" and the more or less solid or microcystic serous carcinomas of the ovary.

Since *uterine fibromyomas* are often considered to develop under the influence of excessive stimulation by folliculoid hormones, it is perhaps significant that uterine fibroids are quite common among patients suffering from various types of serous and pseudomucinous ovarian carcinomas.[8] Because of the frequent occurrence of uterine fibroids in any group of gynecologic patients, it is not permissible, however, to consider their development in this group as necessarily due to the hormonal activity of the ovarian cancers. Careful statistical studies would be required to prove a greater frequency of fibromyomas among patients with ovarian cancers than among other gynecologic cases.

In some women ovarian cancers lead to amenorrhea with *involution of the uterus* and other sex organs.[9] This may be due to extensive destruction of the ovarian parenchyme by the infiltrating growth, or to the general emaciation which is so frequently seen in cancerous patients. Several investigators describe other less common uterine changes in women with cancers of the ovary.[10] It is noteworthy that large ovarian cancers may promote the *prolapse of the uterus* due to direct pressure upon this organ[11] and that *hydrometra* may develop concurrently with ovarian cancers,[12] but these complications are rather uncommon. Under the name of "Modifications plastiques du corps utérin en présence de tumeurs

[1] *Novak* A63534/41.
[2] *Maringer* A78661/28.
[3] *Alfieri* A77959/09, *Mendelssohn* A78689/20, *Schiffmann* A64830/25, A64832/27, A64833/29, *Aschner* A78011/26, *Tenconi* A79100/27, *Lahm* A64783/27, *Benthin* A79252/28, *Ahumada* A77953/28, A77954/28, *Hamant and Mosinger* A78398/28, *Frey* A78316/28, *Strauss* A64848/29, *Zweifel* A79235/29, *Douay* A67294/30, *Smit* A65085/31, *Adler* A77951/31, *Tietze and Mayer* A64022/31, *Brocq and Chabrut* A62286/32, *Cannon* A52089/34, *Logwinski* A64987/35.
[4] *Benthin* A79250/27, A79251/28.
[5] *Gessner* A79285/896.
[6] *Battye* A69764/860, *Thaler* A73172/22, *Flessa* A78287/26, *Frank* 58775/32.
[7] *Goldstein* B6252/44.
[8] *Weinlechner* A86318/879, *Lusk* A78635/880, *Edebohls* A43753/891, *Claisse and Dartiques* A78155/899, *Bouglé* A78084/00, *Torggler* A79120/04, *Jellett* A78476/06, *Giles* A78340/06-7, *Malcolm* A78652/14-5, *Shoemaker* A79029/17, *Tixier and Pollosson* B7524/25, *Delannoy* A78197/34, *Daniel and Caramzulescu* A95055/37.
[9] *Golay* A78353/876, *Danel* A78182/05.
[10] *Hayes* A78414/878, *Addressi* A65141/31.
[11] *Thiriar* A79111/890.
[12] *Finkelstein* A78277/31.

ovariques" Beuttner[1] described a peculiar *thickening and hardening of the uterus* which is macroscopically very obvious but is not accompanied by any clearcut histologic changes. It occurs not only in conjunction with ovarian cancers, but also in women with sarcomas or benign cystomas of the ovaries or broad ligaments.

Among other changes in accessory sex organs, hyperplasia of the *mammary glands*, sometimes accompanied by lactation, is occasionally mentioned in case reports of patients suffering either from primary or secondary ovarian carcinomas.[2] The pathogenesis of this rare manifestation has not as yet been clarified.

Virilization as a consequence of common ovarian carcinomas is exceptional. In the few supposedly relevant cases, there may be some doubt concerning the correct identification of the tumor or its causal connection with the pseudohermaphroditic traits.[3] In several cases signs of virilization were observed in the bearers of a Krukenberg tumor;[4] these signs may disappear following ablation of the bilateral ovarian tumors.[5] The theoretical interpretation of these findings is very difficult on the basis of present-day knowledge, yet they undoubtedly occur. A tumor described as a malignant arrhenoblastoma[6] which led to virilization may also belong to this group since the published microphotographs show typical signet ring cells which strikingly resemble those of Krukenberg tumors.

Fertility is definitely diminished by the presence of an ovarian carcinoma, mainly because the tumor destroys ovarian tissue and exerts an adverse effect upon the general well-being of the patient. In some cases ectopic pregnancies develop probably as a result of mechanical interference with the migration of the ova.[7] If pregnancy develops, however, it often tends to promote the growth of ovarian cancers, as indicated by the case reports quoted in the section dealing with the pregnancy incidence of ovarian carcinomas.

The *metastases* of ovarian cancers, as well as the ovarian metastases of extragonadal carcinomas, have been discussed in great detail in the morphologic part of this section. Suffice it to say here, that several investigators described cases of apparently independent *multiple primary tumor formation* in women bearing ovarian cancers.[8] In some of these cases the extraovarian tumor was a uterine sarcoma,[9] or a lymphangioma of the oviduct[10] etc., briefly, a growth which could not be a metastasis of the ovarian cancer. Such cases reinforce us in our suspicion that perhaps oncogenic substances (folliculoids?) may be formed by the cells of ovarian blastomas.

Ascites is comparatively common in women with ovarian cancers; it occurs especially in conjunction with papillary carcinomas and peritoneal cancer metastases. Sometimes it may be due to circulatory disturbances caused by partial torsion of the growth. The water accumulation in the abdomen may reach considerable proportions and tends to recur after paracentesis.[11] It is of diagnostic importance that in women having a great deal of ascites a carcinoma which is originally not palpable may become quite evident after paracentesis.[12]

Krukenberg tumors may also produce ascites; among 44 cases observed at the Mayo Clinic it was noted in 17 instances.[13]

Hydrothorax may likewise be caused by ovarian cancers.[14] Thus, in a case of a papillary cystadenocarcinoma there was in the pleural cavity a large fluid accumulation which disappeared upon removal of the tumor.[15] Hence it may be assumed that hydrothorax in patients suffering from ovarian carcinomas is not invariably an indication of pleural metastases. This fact is of obvious significance in determining the operability of such cancers. The pathogenesis of the pleural fluid accumulation is not known as yet, but these cases are reminiscent of the ovarian fibromas accompanied by ascites and hydrothorax (see chapter on Ovarian Fibroma).

The symptoms and signs of ovarian tumors elicited by their *metastases* need not be discussed here in detail since they may readily be visualized by perusal of the relevant passages in the part on the pathologic anatomy of these growths. Suffice it to say that nervous symptoms are not uncommonly produced by metastases involving the nervous system while bone and lung metastases may elicit radiologically detectable lesions etc.

The *anemia* characteristic of various types of carcinomas is generally not pronounced in ovarian cancer patients until the condition reaches its late

[1] A65601/29.
[2] *Pfannenstiel* A64886/08, *Polano* B12/11, *Sänger* A24463/12, *Schmincke* A78988/14, A78987/14, *Halban* 26394/25.
[3] *Davis* A7006/00, *Alberti* 37893/05, *Amann* B11295/10, *Stübler and Brandess* A76588/24, *Halban* 26394/25, *Parhon and Aburel* B75/29.
[4] *Esau* A80129/29, *Uhlmann* A31683/39.
[5] *Büttner* 5587/33.
[6] *Canello and Lisser* A30063/39.
[7] *Goldberger* A78355/28, *Molin et al.* A78720/31.
[8] *Lichtenstein* A78608/895, *Walter* A79174/896, *Nehrkorn* A78755/01, *Richter* A78885/05, *Warstat* A79178/12, *Lessing* A78602/23, *Jolkwer* A78484/29, *Orr* A78793/30, *Kulikowska and Hoerner* A27166/34.
[9] *Scudder and Fein* A52178/34.
[10] *Schiffmann* A78973/29.
[11] *Weinlechner* A40514/881, *Braun von Fernwald* A40965/885, *Balleray* A82133/886, *Planchard* A78840/888, *Prochnownik* A78862/07, *Jacobsthal* B8541/21, *Begouin and Massé* A78039/26, *Klempner* A59696/36.
[12] *Novak* A63534/41.
[13] *Leffel et al.* A37789/42.
[14] *Anderson* B10812/44.
[15] *Schenck and Eis* A31428/39.

stages. It is noteworthy, however, that especially in Krukenberg tumors with widespread skeletal metastases *Purpura thrombocytopenia* and *erythroblastosis* may develop.[1]

The association of "*acne papulosa*" with a Krukenberg tumor[2] is quite exceptional and probably coincidental.

Fever is an uncommon accompaniment of ovarian cancer, usually seen only if the tumor becomes necrotic or infected.[3]

Emaciation is generally not very prominent until the cancer is fairly well developed.[4]

COMPLICATIONS

Among the accidental circumstances which may complicate the clinical course of ovarian carcinomas, perhaps the most common is the *rupture* of carcinomatous cysts followed by flooding of the peritoneum with their contents.[5] The increased intra-abdominal pressure occasioned by gestation augments the tendency of carcinomatous cysts to rupture.[6] In the case of carcinomatous pseudomucinous cystomas such rupture may lead to the formation of a "*carcinomatous pseudomyxoma peritonei*" as stated in the part on pathologic anatomy. In some instances carcinomatous cysts may rupture directly into another hollow organ, following the formation of dense adhesions which protect the peritoneal cavity. Such *perforations may occur into* various parts of the *intestinal tract*,[7] or the *vagina*[8] and may establish vesico-vaginal fistulae.[9] The extreme gravity of direct perforation into the peritoneum hardly requires comment, since it is self-evident that a flooding of the entire peritoneal cavity with cancer cells is extremely likely to produce general peritoneal carcinomatosis and thus render the case inoperable.

Another frequent complication of ovarian cancers is the production of partial or complete *intestinal obstruction* either by the growth itself or by its metastases.[10] Thus, for instance, Krukenberg tumor metastases may cause a stricture of the rectum.[11]

Similarly carcinomas of the ovaries or their metastases may cause *occlusion of the ureters*[12] and lead to *anuria*.[13]

As a result of mere increase in their size, ovarian carcinomas may become *impacted in the pelvis*[14] and if cancers are allowed to grow they may lead to so pronounced an increase in the intra-abdominal pressure that they predispose to the formation of *herniae*.[15]

Vascular thromboses and *embolisms*, due to the cancer cells themselves or to circulatory disturbances caused by their pressure upon the blood vessels, have also been observed. They may occur in the lower extremities[16] and in rare instances lead to embolic gangrene necessitating amputation of a thigh.[17] Even pulmonary embolisms may thus be caused[18] and as we have seen in the section devoted to the metastases of ovarian cancers, tumor cell embolisms are commonly noted in various organs.

The combination of ovarian cancer with *tuberculous peritonitis*[19] or *tuberculous salpingitis*[20] is infrequent, but when it occurs may lead to diagnostic difficulties.

The comparatively frequent complication of ovarian cancers by *hemorrhage* (often subsequent to rupture), *torsion, abscess formation* etc. is discussed in the chapters specifically devoted to these latter lesions (see Sect. IV, Vol. VI).

DIAGNOSIS

The diagnostic criteria which prove to be of special help in the recognition of ovarian cancers have been reviewed by numerous investigators.[21] It has been particularly emphasized that in many cases early diagnosis is difficult or impossible because these tumors may remain "silent" and cause no symptoms until very late in the course of the disease.[22] Generally, a presumptive diagnosis is made on the basis of the pelvic findings, but the malignant nature of the

[1] *Terplan and Vaughan* A79846/34, *Stebbins and Carns* A79051/35, *Jarcho* A79763/36.
[2] *v. Bud* A28145/35.
[3] *Salomonson* A97216/38.
[4] *Oliver* A45869/891, *Prochownik* A78862/07, *Novak* A63534/41.
[5] *de Renzi* A81444/899, *Levi* A66985/04, *Jessett* A78481/07, *Jessett and Evans* B9270/07, *Amann* A77989/10, A77988/10, *Spencer* A79045/14-5, A79046/22-3, *Jaffé* A78471/27, *Anfänger* A78001/27, *Marsalek* A78664/29, *Oldfield* A78782/29, *Savescu and Steopoe* A78950/29-30, *Levi* A95059/37.
[6] *Nürnberger* A78768/31.
[7] *Bröse* A78109/895, *Dostert* A78216/02.
[8] *Aubert* A94795/37.
[9] *Studdiford* A79078/18.
[10] *Heath* A78415/864-5, *Danlos* A78184/875, *Barral* A88272/883, A88271/883, *Lotheissen* A78629/895, *de Rouville et al.* A75865/23-4, *Braun et al.* A78093/24, *Eichmeyer* A63507/28, *Pohl* A78841/31.
[11] *Runyeon* A52298/34.
[12] *Goldberg* A97199/39, *Lazarus* A96660/41.
[13] *Chavannaz* A74580/05, A74581/05, A74579/05.
[14] *Tourneux* A79121/26.
[15] *Rosenstein* A78909/05, A78908/05.
[16] *Philipson* A78831/877.
[17] *Weinlechner* A88388/876.
[18] *Trousseau* A79127/860, *Merklen et al.* B7336/26.
[19] *McWilliams* A78647/21.
[20] *Jentgens* A97202/39.
[21] *Thornton* A88383/876, *Sutugin* A40248/883, *Engelhard* A42499/888, *Lauro* A49241/897, *Cullingworth* A75282/04, A75283/04, *Davanzo* B7150/27, *Fleurent* A71428/28, *Forgue* A63511/28, *Andreeva* A65600/29, *Benthin* A64416/30, *Anspach and Montgomery* A65052/31, *Sannicandro* A61495/32, *Keith* A59415/36, *Papanicolaou and Traut* 84545/43.
[22] *Crossen* A56424/42.

condition is not evident until macroscopic and microscopic observation of the specimen is made possible by exploratory laparotomy. Ovarian carcinoma should be suspected if *pelvic examination* reveals a hard firm mass in the ovarian region, especially if the patient is middle-aged. Benign cystic tumors are generally softer and more elastic, having a smooth surface as compared to the more nodular, irregular and often adherent cancers. Solid benign tumors, such as fibromas, may lead to confusion with cancers but play a minor role because of their comparatively uncommon occurrence.[1]

The common association of ovarian cancers with *ascites* has been mentioned in the previous section, as well as the fact that peritoneal fluid accumulations may interfere with the palpability of the tumors so that paracentesis may be necessary before the growth can be felt. It must also be kept in mind that ovarian fibromas are likewise capable of producing a great deal of ascites and even pleural fluid accumulations. In some instances paraffin sections of centrifuged peritoneal exsudates proved of diagnostic value in patients with cancerous ascites.[2]

Post *menopausal bleeding* is generally caused by uterine carcinomas but may also be due to ovarian cancers. Although this possibility must be borne in mind, the preoperative differential diagnosis between ovarian and uterine carcinomas is of no great practical importance, since both of these conditions call for radical operations.[1] The diagnostic significance of "douleurs à heure fixé"[3] appears to have been somewhat over-rated.

In some instances, massive *peritoneal hemorrhage* is the first manifestation of an ovarian cancer.[4]

Cases in which the diagnosis of a Krukenberg tumor is possible from a biopsy specimen of the cervix[5] are great rarities.

Among the modern diagnostic procedures *peritoneoscopy* frequently proves of special value and may help early recognition of the condition.[6] Roentgenologic examination reveals "psammoma calcification" in many papillary cystadenocarcinomas, but this does not permit differentiation from benign psammomas.[7] X-rays may also help to distinguish ovarian cancers from calcified myomas.[8]

From a differential diagnostic point of view, *tubercular peritonitis* may cause difficulties both in the case of carcinomatous papillomas[9] and metastatic carcinomas of the Krukenberg type.[10]

In some cases it was difficult to differentiate ovarian carcinomas from *uterine fibromyomas*,[11] *pregnancy*,[12] *extrauterine pregnancy*,[13] *gastric tumors*,[14] *acute functional gastrointestinal disturbances*,[15] *carcinoma of the rectum*,[16] *coxitis*,[17] polycystic *floating kidney*,[18] *hypernephroma*,[19] or a *retroperitoneal sarcoma*.[20]

PROGNOSIS

Reviews: Kusnetzky A78560/10, Demuth A78206/31, Taylor A77845/31, Viertel A79144/35, Meigs A34255/40, Pemberton 80890/40.

The data concerning the prognosis of ovarian carcinomas are extremely variable[21] and *recurrences*, after what appeared to have been complete surgical removal of the tumors, are comparatively frequent.[22] Sometimes such recurrences are noted many years after ablation of the original tumor, following an interval of well-being which may last 5-10 years,[23] 10-15 years[24] or even more than 15 years.[25] In certain instances, carcinoma formation, after removal of the ovarian tumors, was seen in the uterus[26] or vagina,[27] but in some of these cases the later formed tumor could not be identified with certainty as a true recurrence of the earlier growth.

In any case the outlook for patients with common ovarian carcinomas is grave, especially because so frequently the growth is not recognized until its development has progressed very far. Thus among 154 cases of common ovarian carcinomas observed at the Massachusetts General Hospital, the average five-year survival rate was 15.5%, the prognosis being considerably better for women with cystic carcinomas (21.9% five-year survivals), than for those having solid ovarian cancers (9.7% five-year

[1] *Novak* A63534/41.
[2] *Mandlebaum* B21332/17.
[3] *Begouin* A59645/36.
[4] *Moiroud* A62251/32, *Vanverts* A62271/32.
[5] *Harms* A62069/36.
[6] *Meigs* A34255/40.
[7] *Lingley* A55501/42.
[8] *Schultze* A62949/32.
[9] *Rochard* A75858/07, *Guyot and Princeteau* A78388/25, *Nicoletti* A97628/30.
[10] *Ducuing and Wassal* A79721/31.
[11] *Schultze* A62949/32, *v. Mikulicz-Radecki* A97211/38, *Colmeiro Laforet* A97608/39.
[12] *Poulet* A78852/875.
[13] *Rothe* A88371/877, *Peters* A78822/29.
[14] *v. Pall* A62944/32, A62945/32.
[15] *Bernstein* A27860/35, *Zondek and Heifetz* 85121/43.
[16] *Kleckner* A97083/37.
[17] *Tenani* A75869/10-1.
[18] *Salvini* A61655/36.
[19] *Belmonte* A67019/32.
[20] *v. Mikulicz-Radecki* A65621/29.
[21] *Edge* A78237/04-5, *Guyot and Dubreuilh* A71397/28, *Fleischmann* A78285/30.
[22] *Terrillon* A40953/885, *Vincent* A79150/08, *Krömer* A78548/09, *Schempp* A78964/33, *Fleischmann* A95057/37.
[23] *Routier* A78924/11, *Villard and Murard* A79148/12, *Godart* A78350/13, *Spencer* A79045/14-5, A79046/22-3, *Nacke* A78748/19.
[24] *Odebrecht* A78776/897, *Vineberg* A79153/12.
[25] *Olshausen* B6885/02, *Arnold* A78008/28, *Pemberton* 80890/40.
[26] *Pfannenstiel* A44727/894, *Grimsdale* A78375/13.
[27] *Semmelink* A47983/898.

survivals).[1] In another series of 149 cases, operated on in the Free Hospital for Women (Boston), the survival rate was considerably better inasmuch as 32% lived 5 or more years after the operation. All investigators agree that with cystic tumors chance of survival is generally better than with the solid and semi-solid growths and that among the cystic cancers the adenopapillary variety is particularly malignant, especially if, after destruction of the capsule, the papillary excrescences reach the surface.[2]

It is important to realize that the estimation of the prognosis of any individual case must depend not only upon the macroscopic distribution and appearance of the tumor at the operation, but also upon its histologic and cytologic structure. In an effort to make the morphologic criteria of malignancy as objective as possible Broders[3] suggested the following *scale of gradation* based upon the cytologic characteristics of differentiation in the cancerous epithelium:

Grade 1: about 3/4 of the epithelium is differentiated, 1/4th undifferentiated.

Grade 2: differentiated and undifferentiated epithelium about equal in amount.

Grade 3: about 1/4th of the epithelium is differentiated and 3/4th undifferentiated.

Grade 4: no tendency to cell differentiation. It was found that although this method of grading was not designed specifically for ovarian carcinomas, it is a good indicator of the probable prognosis in this latter group inasmuch as the number of permanent cures and the average length of survival decrease progressively in the cancers graded "1" to "4" reaching a minimum in the latter.[4]

Other factors to be considered in grading carcinomas are the degree of lymphocytic infiltration, hyalinization and fibrosis. In the case of mammary cancers at least, these changes—if pronounced—are usually indicative of a comparatively low grade malignancy[5] but the value of these characteristics has not been established as yet for ovarian cancers.

It has been claimed that the size of the nucleolus in proportion to that of the nucleus rises parallel with the degree of malignancy so that large and especially multiple nucleoli may be taken as a sign of great malignancy.[6]

The prognosis of *metastatic ovarian carcinomas* is extremely grave but perhaps not quite as hopeless as some investigators believe.[4] Thus occasionally even metastatic Krukenberg tumors appear to be subject to therapy if both the primary growth and the ovarian metastases are removed (see part on Therapy). The frequently reported spontaneous regression of peritoneal carcinomatosis following partial resection or mere laparotomy[7] should be viewed with scepticism. Careful study of supposedly pertinent case reports leaves us with the impression that the diagnosis of malignancy was never beyond doubt in such instances. Usually the cases described under this heading, appear to have been instances of peritoneal papillomatosis or pseudomyxoma peritonei, sometimes in the so-called "pre-malignant" stage (see also chapter on Common Cystomas, part on Therapy).

Several cases are known where *pregnancy* ensued following conservative surgical therapy for ovarian carcinomas.[8] It must be remembered, however, that conservative interventions are far too dangerous to be recommended as they are almost invariably followed by recurrences. Of course in some instances a partial ovariectomy is performed merely because the malignant nature of the tumor was not recognized at the time of the intervention. The growth of an untreated ovarian cancer is frequently accelerated by a coexistent gestation and hence in view of the grave prognosis of such cases an immediate operation is to be recommended (see part on Incidence in Pregnancy).

THERAPY

Reviews: Lerch A92130/888, Freund A42635/889, Werder A51021/899, Meyer A78698/00, Meusel A78697/00, Pissemsky A78837/09, Mikulicz-Radecki A78709/31, Strassmann A61534/33, A79069/33, Gegenbach A78334/34, Norris A51973/34, Heimdal A97068/38, Crainz A97196/39, Benthin A97193/39, Pedewski A97213/39, Crainz and Schiemann A96602/40, Way A37518/41, Walter et al. A36076/41.

The most effective therapy of ovarian cancers is their *surgical removal.* Operation should be performed as early as possible and, irrespective of the histologic type of the tumor, it should be as radical as conditions permit. The literature cited in the part on prognosis as well as the publications quoted below, clearly indicate that the danger of recurrences is great and hence bilateral ovariectomy with removal of the Fallopian tubes and panhysterectomy give the best results. Even if peritoneal involvement is disclosed, removal of the ovaries is still indicated whenever technically feasible, since the secondary extensions tend to progress less rapidly after ablation of the

[1] *Meigs* A34255/40.
[2] *Bonamy and Goude* A95350/37, *Morton* A97569/39, *Arimitu* A97191/39, *Pemberton* 80890/40.
[3] B129/20, A98701/21, B130/22, B7683/25, A98702/25, B7684/26.
[4] *Dockerty and Masson* A38032/41.
[5] *Sistruck and MacCarty* A98703/22.
[6] *Page and MacCarty* A95087/37.
[7] *Codman* A70627/18, *Gucci* A70741/27, *Labhardt* B12402/28, *Taylor and Alsop* B21733/32.
[8] *Spencer* A79045/14-5, *Robinson* A78893/19, *v. Szathmary* A27891/35, A61659/35.

ovarian tumors.[1] Some clinicians claim that even the omentum should be removed routinely.[2]

The practice of puncturing cancerous cysts to facilitate their subsequent removal is to be discouraged because of the danger of implantation metastases.[3]

The surgical removal of ovarian carcinomas in children[4] and in pregnant women[5] may be fraught with special technical difficulties, but should always be attempted as long as the case is operable.

If the ovarian cancer invades other organs such as the intestine[6] or the urinary bladder[7] partial resection of these organs should be performed together with the radical operation for the ovarian growth itself.

Even in typical metastatic *Krukenberg tumors* it is advisable to attempt removal of the primary gastro-intestinal growth, together with the ovaries and uterus, since such radical operations have repeatedly yielded quite satisfactory results.[8]

It is especially important to remember that in every operation for gastric carcinoma the ovaries must be carefully examined, and conversely on the occasion of interventions for solid ovarian tumors the gastrointestinal tract should be scrutinized in order to detect possible multiple tumors. As stated elsewhere, either the primary (e.g. gastric) tumor or the ovarian Krukenberg tumors may be so small that they are hardly visible.

The *conservative surgical interventions* advocated by some clinicians[9] have no place in the therapy of any of the common ovarian cancers.

Among the *complications of operative interventions* special importance is attached to the implantation of carcinoma tissue with subsequent recurrence of the cancer in the abdominal scar. This has been discussed in the passage on Carcinoma Metastases. Another possible complication is the occurrence of post-operative ileus[10] or damage to the ureters, especially if the latter are involved in the carcinomatous mass.[11] In such cases an end-to-end anastomosis of the transcised ureter may be possible.[12] The unusual occurrence of paralysis in the lower extremities, due to faulty spinal anesthesia in cases of laparotomy for ovarian carcinomas, hardly deserves more than cursory mention.[13]

Deep *X-ray treatment* may be used as the sole therapeutic measure in inoperable carcinomas but its beneficial results are usually transitory. There is much to be said, however, for the prophylactic use of X-ray treatment following radical operations for ovarian carcinoma; it tends to prevent recurrences or at least delay their progress.[14] Some clinicians

[1]*Seutin* A87042/838, *Woyeikowski* A87051/847, *Meeker* A87038/859, *Turnbull* A87047/866, *Casswell* A87029/867, *Banon* A87027/867, *Kahrs* A87035/869, *Sklifasovski* A87043/869, *Storer* A88380/871, *Wilson* A87050/871, *Jessett* A74897/871, *Kidd* A74899/874, *Weinlechner* A87049/876, A86318/879, *Coates* A87030/876, *Buhl* A86335/876, *v. Rokitansky* A87041/878, *Demons* A87033/878-9, A92140/893, *Hensoldt* A78432/880, *Kaltenbach* A29513/880, *Fetherston* A29349/880, *Cabrera and Saavedra* A40186/882, A40704/884, *Allen* A40378/882, *Schustler* A40267/883, *Guillemet* A40942/884-5, *Polaillon* A40485/885, *Schramm* A79002/886, *Ludlam* A41652/886, *Guermonprez and Duhamel* A92153/888, A42443/888, *Girard* A92149/889, *Casuso* A42677/889, *Stratz* A92172/889, *Bruttan* A45244/889, *Johnson* A42609/889-90, *Sutugin* A45610/890, *Laakmann* A83650/890, *Michaux* A45734/890, *Hofmokl* A44061/890-1, *Schneider* A43982/891, *Krukenberg* A78550/893, *Denucé* A92141/893, *Binaud* A83334/893, *Busack* A78134/894, *Skene* A47508/895, *Odebrecht* A92168/897, *Duncan* A78228/897, *Geyer* A92128/897, *Dumont-Leloir* A78227/897, *Verstraete* A49221/898, *Marien* A50673/898, *Amann* A77968/899, *Werder* A92175/899, *Baldy* A50986/899, *Olshausen* A78785/00, *Estor and Puech* A78261/00, A92143/01, *Seeligmann* A79017/01, *Delobel* A83352/01, *Delaunay* A92139/01, *Jones* A92157/01-2, *Mackenrodt* A78642/02, *Barnsby* A74578/04, *Krebser* A92129/04, *Drucbert* B13161/06, *Tauffer* A75868/06, *Schmidlechner* A82394/08, *Vanvolxem* A79140/10, *Bongartz* A70592/13, *Bastian* A78025/13, *Erler* A77474/14, *Thaler and Frankl* A75870/16, *Wolffenstein* A79223/19, *Thies* A79110/20, *Schäfer* A78952/22, A78953/23, *Pribram* A77755/24, *Loubat* A75866/25, *Amreich* A77996/26, *Mayer* A99597/26, *Petit-Dutaillis* A70888/27, A64401/32, *Schleyer* A78978/28, *Ford* A78291/28, *Schmid* A64544/29, *Weibel* A79184/30, *Heyman* A99595/32, *Wintz* A62274/32, *Judd and Philips* A61412/33, *Strassmann* A61534/33, *Montgomery and Farrell* A52168/34, *Norris* A51973/34, *Schroeder* A27757/34, *Szymanowicz* A27760/35, *Fekete* A95209/36, *Kimbrough* A99596/36, *Siebke* A98181/42.

[2]*Pemberton* 80890/40.

[3]*Meigs* A34255/40.

[4]*Vignard* A79145/10, *Pélissier* A78816/20, *Etienne and Aimes* A78263/20.

[5]*Weisswange* A79190/08, *Stabler* A79048/36, A78047/36.

[6]*Goullioud* A92151/03, *Jessett* A94153/07.

[7]*Schustler* A40267/883.

[8]*Kratzenstein* A48445/897, *Schenk* A78965/05, *Schenk and Sitzenfrey* A78967/07, *Glinski* A79736/09, *Frankenthal* A79730/21, *Pribram* A78859/23, *Amreich* A79692/25, *Schmid* A78984/29, *Janow* A65158/30, *Comando* A52257/34, *Leffel et al.* A37789/42.

[9]*Küstner* A64431/30.

[10]*Koch* A44828/894.

[11]*MacKenrodt* A78641/00, *Ionescu* A78461/05.

[12]*Jonnesco* B13003/03-4.

[13]*Meyer* A78699/10.

[14]*Franqué* A78312/13, A78313/13, A78315/26, *Rauscher* A66929/13, *Orbaan* B21272/20, *Aubert* A78012/22, *Meurer* A78696/22, *Schäfer* A78953/23, *Zweifel* B8322/23, *Stübler and Brandess* A76588/24, *Schmitz* A75867/24-5, A97825/42, *Heyman* A78436/24-5, *Dreuschuch and Lovas* B20790/25, *Heinsius* A78427/26, *Holzknecht* A78448/26, *Jacobs* A78465/27, A53043/34, A67483/30, A64224/30, A66125/32, *Keene et al.* A78500/27, *Naujoks* A78753/27, *Ford* A78291/28, *Tesauro* A79103/28, *Cahen* A78138/29, A78137/29, *Vogt* A64566/29, *Meigs* A99598/30, *Gruss* A65469/30, *Kamniker* A66126/31, *Webster* A65090/31, *Wintz* A62274/32, *Heyman* A62304/32, A99595/32, *Weibel* A79185/32, *Bevan* A61308/33, *Fruchaud* A61755/33, *Joly* A61310/33, *Smith* A61533/33, *Kraul* A78543/34, *Gengenbach* A52110/34, *Montgomery and Farrell* A52169/34, A52168/34, *Moulonguet* A52164/34, *Schröder* A27757/34, *Harris and Payne* A27742/35, *Healy* A27872/35, *Kean* A27706/35, *Kimbrough* A99596/36, *Schinz and Zuppinger* A99599/37, *Jacobs and Stenstrom* A95220/37, *Burnam* A97194/38, *Crainz* A97195/38, *Gal* A97062/38, A95359/38, *May* A97208/39, *Okrainetz and Biller* A97508/39, *Meigs* A34255/40, *v. Delft* A98112/41.

claim that preoperative X-ray therapy may make some previously inoperable cases operable.[1] Walter et al.,[2] who reviewed the relevant literature as well as a large number of personal observations, came to the conclusion that post-operative deep X-ray therapy is of considerable value in improving the average length of survival and that maximal dosages should be employed whenever possible. Unlike many other investigators they feel that the major factor in the prognosis and in the determination of the type of therapy to be employed, is the clinical stage of progression and not the histologic gradation of the tumors. In Krukenberg tumors the value of X-ray therapy is very doubtful.[3]

Many investigators obtained encouraging results with *radium therapy,* especially when employed in combination with radical surgery or as a palliative measure in inoperable cases.[4] Others are in favor of combining *X-ray* and *radium therapy.*[5] It has been emphasized that a castrating dose of radium may cause complete disappearance of the endometrium. In one patient with an extensive bilateral papillary adenocarcinoma and postmenopousal bleeding this destruction of the endometrial lining "cured" the metrorrhagias but had no effect upon the growth of the ovarian neoplasm itself. The possibility of such a purely apparent cure following radium treatment for postmenopausal hemorrhages should always be kept in mind.[6]

In exceptional instances, on the other hand, rapid growth of an ovarian carcinoma may be seen following radiation therapy.[7]

The use of *testosterone propionate* has also been suggested, on the basis of a few cases of ovarian cancer in which pain was almost completely relieved and the patient's general condition improved as the result of this treatment.[8]

Among other attempted therapeutic procedures transfusion with *irradiated ascitic fluid* or *maternal blood,*[9] treatment with an ointment containing *lead* and *iodine,*[10] *isamine blue*[11] and *colloidal gold* therapy[12] should be mentioned but will hardly prove of value.

[1]*Pemberton* 80890/40.
[2]A36076/41.
[3]*Leffel et al.* A37789/42.
[4]*Ahlström* A77952/12, *Gosset and Wallon* A62301/32, *Vogt* A52190/34, *Gadek and Neugebauer* A52106/34, *Arneson* A99591/36.
[5]*Douay* A61555/33, *Vogt* A51987/33, *Heimann* A78421/34, *Coliez* A97172/38, *Counseller* A95352/38.
[6]*Brody* B6257/44.
[7]*Voyadzopoulos* A79161/31, *Abruzzese* A77947/32.
[8]*Beecham* A97167/43.
[9]*Whitehouse* A79202/26-7.
[10]*Micholitsch* A67245/30.
[11]*Bernhard* B8032/26.
[12]*Nowack* B20813/26.

PARA-OVARIAN COMMON CARCINOMAS

Although the para-ovarian region is not infrequently involved in secondary carcinomatosis of the pelvis, isolated para-ovarian carcinomas are comparatively rare. Most of them are cystic and are described in the literature as carcinomatous cysts of the broad ligament.[1] Occasionally, such carcinomatous para-ovarian cysts have been noted in patients who simultaneously suffer from cancers of the intestine or mesentery.[2]

A few instances are definitely designated as cancers of the parovarium.[3] It is extremely difficult, if not impossible, of course, to identify the parovarian origin of a malignant tumor in the ovarian region. Extreme caution is necessary, therefore, if an attempt is to be made to derive any malignant epithelial neoplasm from the embryonic vestiges of the para-ovarian region.

[1]*Wathen* A45855/891, *Heinsius* A91467/01, *Pluyette* A91475/16-7, *Bozzolo* A91545/33.
[2]*Lanelongue* A88678/891, *Franchini* A91466/06.
[3]*Talmey* A88679/00, *Pons* A88680/05.

OVARIAN COMMON CARCINOMAS IN ANIMALS

Ovarian carcinomas are probably much more frequent in the animal kingdom than is generally suspected.[1] Unfortunately, in many relevant cases, only superficial autopsies were performed so that the ovarian tumors cannot be adequately identified.

In *fish* ovarian carcinomas may apparently occur. Thus in one instance, an adenoma or adenocarcinoma was found in the ovary of a goldfish.[2]

In the *fowl* among all types of carcinomas, those affecting the ovary appear to be most common.[3] In a list of 37 cases reviewed from the literature, the ovary was the site of the primary tumor in 20 birds.[4]

In one instance, an ovarian carcinoma of a hen gave rise to generalized splanchnic, hepatic and peri-

[1]*Ball et al.* B6557/32, *Decaris* B6522/34.
[2]*Biesele* A98142/43.
[3]*Fujinami* B11921/, *Joest* B11891/27.
[4]*Joest and Ernesti* B11892/15-6.

toneal metastases.[1] In another series pedunculated carcinomas, in the region of the adrenal gland and ovary of adult hens,[2] gave rise to diagnostic difficulties because their origin—from ovary or adrenals respectively—could not be established. These tumors were not particularly malignant, although they gave rise to mesenteric and peritoneal metastases. Their histologic aspect was more suggestive of adrenal cortical than of ovarian carcinomas. One "carcinoma psammosum" of the fowl ovary proved to bear a rather striking resemblance to the corresponding neoplasms of human pathology.[3]

Ovarian carcinomas have also been found in the *turkey*[4] and the *dove*.[4]

In the *cat* an ovarian carcinoma produced numerous metastases.[5]

In *cattle* ovarian carcinomas may be solid, cystic or papillary. Not infrequently they give rise to widespread metastases throughout the abdominal cavity. Implantations may occur on the surface of the parietal and visceral peritoneum; although the regional lymph nodes are usually affected, the liver, spleen and kidneys seldom show more than superficial or subserous involvement.[6] Even bilateral ovarian cancers may occur in the cow.[7]

In the *guinea pig* the histologic characteristics of an "adeno-cystocarcinoma ovarii" have been described in some detail.[8]

In a *horse* an ovarian carcinoma was seen to produce extensive metastases.[9]

In the *monkey* ovarian cancers have rarely been observed,[10] probably because comparatively few autopsies have been performed in this species during the latter part of life, that is when a high incidence of ovarian cancers could have been expected.

In the *mouse* (CBA strain) a spontaneous ovarian carcinoma could be maintained for several years by successive transplantations. As judged by the continuous vaginal cornification and the mammary growth produced by such tumors, they appear to secrete folliculoid hormones. It has been established that the growth of the transplanted ovarian carcinoma depends upon the simultaneous presence of multiple mendelian factors and is also influenced by the internal secretions of the host. Histologically, extreme calcification and formation of "osteoid tissue" was very characteristic of certain areas of this neoplasm; in other regions it resembled papillomatous folliculomas.[11]

[1] *Pentimalli* B11895/15-6.
[2] *Mathews and Walkey* B11899/30.
[3] *Martius* A23103/13.
[4] *Joest and Ernesti* B11892/15-6.
[5] *Kitt* A92050/00.
[6] *Schlegel* B11911/, *Feldman* B11531/32.
[7] *Montpellier and Thieulin* A65169/31.
[8] *Montroni* B6621/30.
[9] *Ganselmayer* B7152/27.
[10] *Jung* B20936/24.
[11] *Strong and Hill* 68575/37, *Strong et al.* 68576/37, 83148/38.

PLATE XXIII

COMMON CARCINOMAS

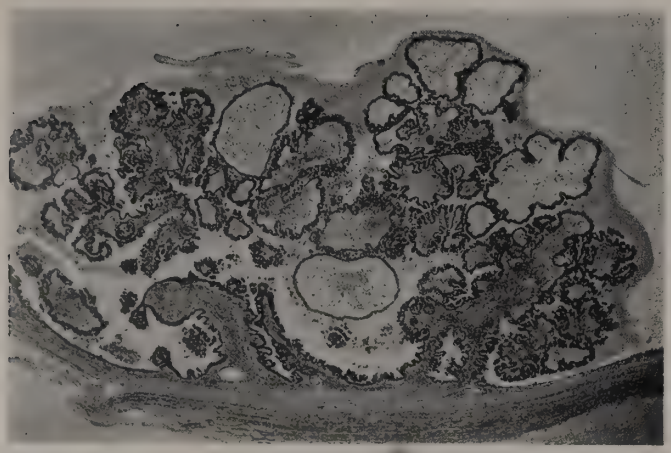

Fig. 1. SEROUS, PAPILLARY CARCINOMA (courtesy of Dr. L. Berger). Small papillary excrescences on inner surface of a cyst wall. In this region, the tumor is remarkably typical.

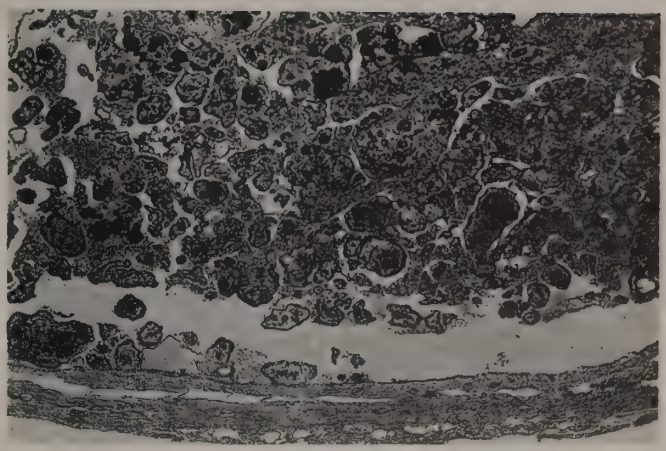

Fig. 2. SEROUS, PAPILLARY CARCINOMA WITH PSAMMOMA BODIES (courtesy of Dr. P. Masson). Note black calcified psammoma bodies within the papillary excrescences. As the neoplasm shown in Fig. 1, this papillary excrescence was also found within the cyst cavity. Both Fig. 1 and Fig. 2 are so oriented that the cyst wall is seen along the lower margin of the field.

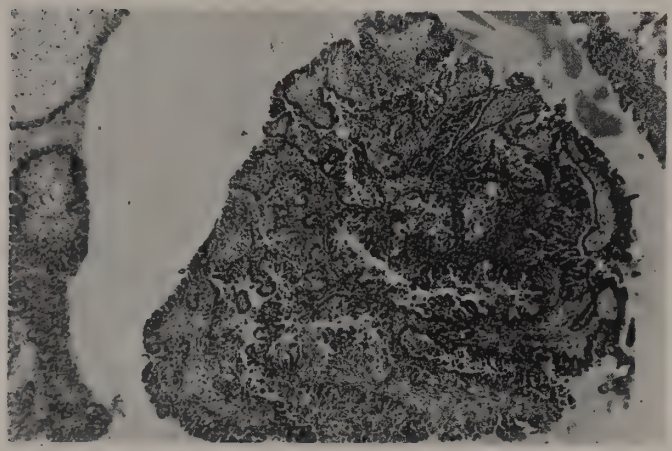

Fig. 3. SEROUS PAPILLARY CARCINOMA. Higher magnification of a region in the neoplasm shown in Fig. 1. Note the growth of the epithelium which invades the stroma of the papillae.

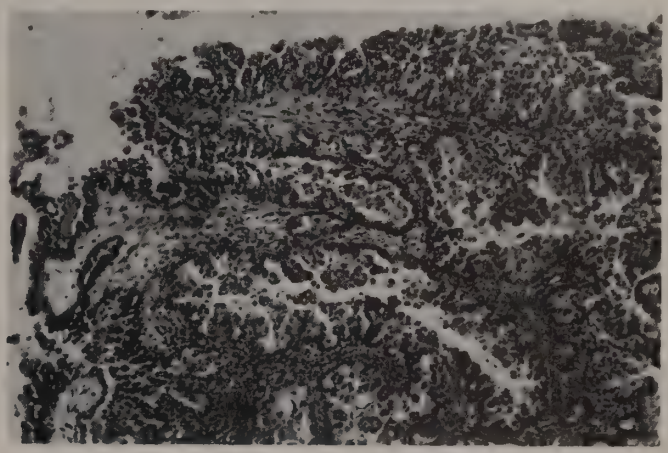

Fig. 4. SEROUS PAPILLARY CARCINOMA. Still higher magnification of a region in the tumor shown in Figs. 1 and 2. The invasive growth of the epithelium is clearly visible at this magnification.

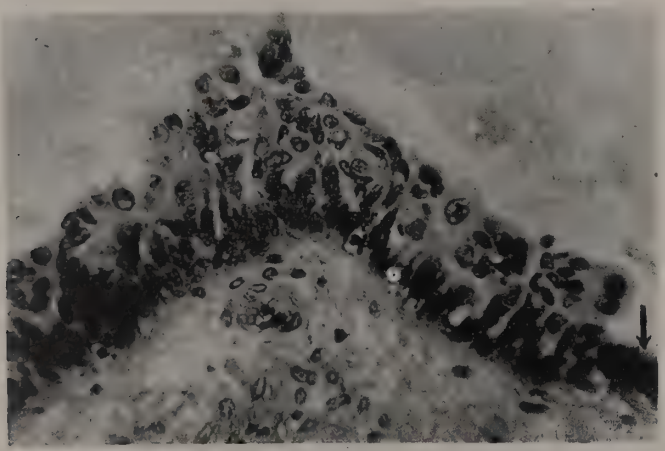

Fig. 5. SEROUS PAPILLARY CARCINOMA. A small field in the tumor shown in Figs. 1—4. Note the regular and typical appearance of a few cells lining this excrescence (marked by arrow). The remainder of the lining is stratified, irregular and definitely of a malignant character. The shape and size of the nuclei are very irregular (oil immersion).

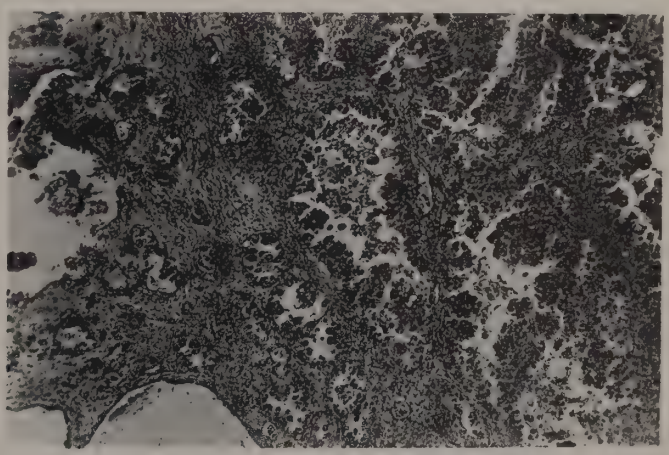

Fig. 6. SEROUS, PAPILLARY CARCINOMA (courtesy of Dr. L. Berger). A more massive type of serous, papillary cancer in which most of the epithelial cell masses grow inwards into the stroma and only small papillary excrescences are formed.

PLATE XXIV

COMMON CARCINOMAS

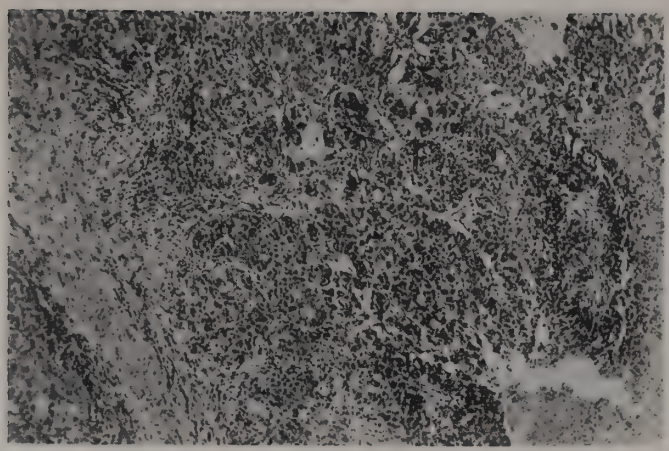

Fig. 1. SEROUS, SOLID CARCINOMA (courtesy of Dr. T. R. Waugh). Irreguar, solid mass of atypical cells. Some of the cellular elements form large syncytia (marked by arrow).

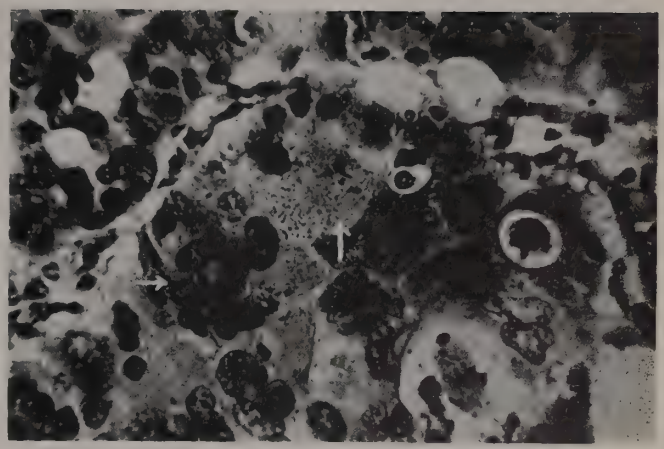

Fig. 2. SEROUS, SOLID CARCINOMA. A small region of the neoplasm shown in Fig. 1, under oil immersion. Note extremely irregular, polymorph nuclei and the central syncytium. The latter contains a cluster of nuclei (horizontal arrow) and a few irregular chromosomes (vertical arrow).

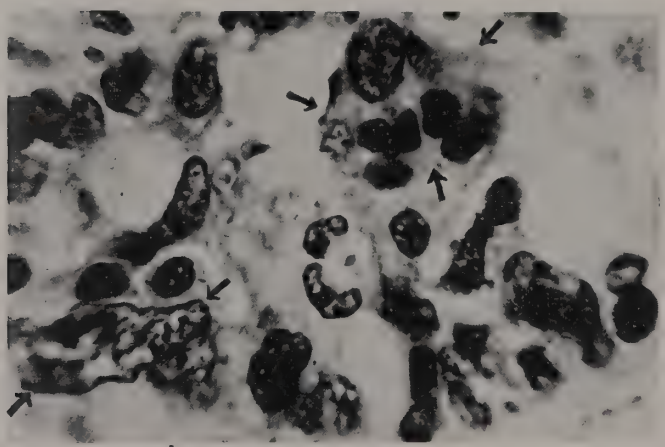

Fig. 3. SEROUS, SOLID CARCINOMA. Yet another field of the tumor shown in Figs. 1 and 2. Note large syncytial formation (outlined by three arrows) with several small and one very large nucleus. An oblong, bizarre shaped, giant nucleus is seen near lower left corner of the field (outlined by two arrows).

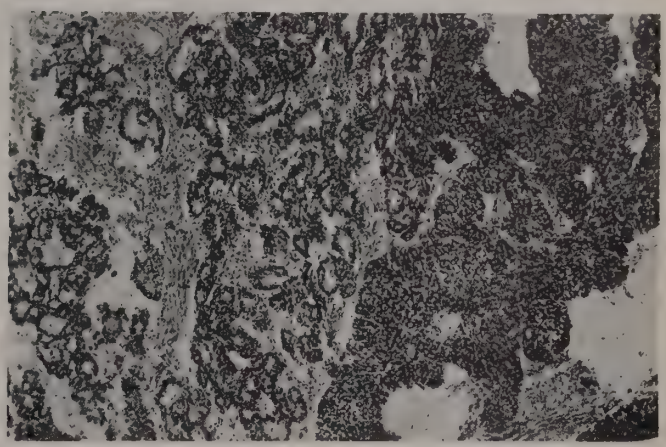

Fig. 4. SEROUS, PARTLY SOLID, PARTLY TUBULAR CARCINOMA. The tubular (left side of field) portion resembles malignant tubular adenomas and the more solid or microcystic portion (right side of field) is reminiscent of granulosa cell carcinomas.

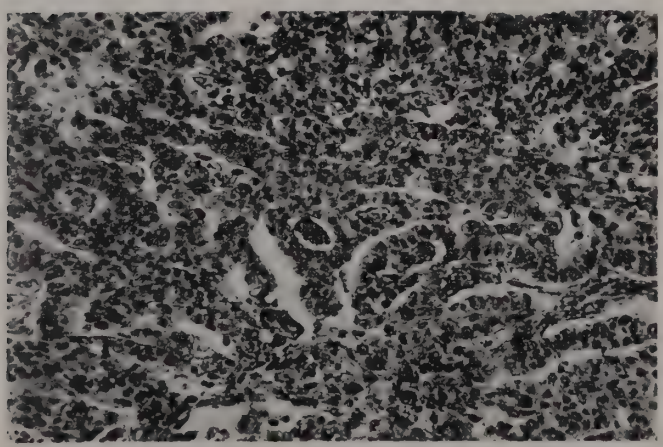

Fig. 5. SEROUS, PAPILLARY CARCINOMA (courtesy of Dr. L. Berger). Macroscopically this tumor was almost entirely solid, but microscopically, it exhibits a laminated appearance. The papillary formations are almost purely epithelial and contain negligible amounts of stroma.

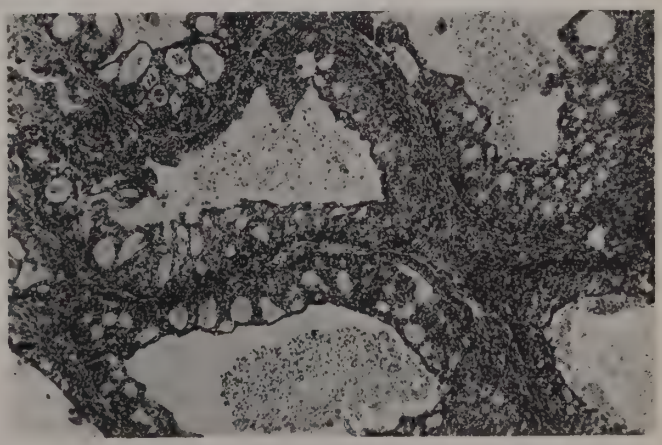

Fig. 6. PSEUDOMUCINOUS PAPILLARY CARCINOMATOUS CYSTOMA. Minute cysts in the macroscopically-solid portion of a pseudomucinous, carcinomatous cystoma. Note intra-epithelial cysts consisting of pseudomucin accumulations within the cells of the highly stratified epithelium. This appearance is rather characteristic of pseudomucinous carcinomas.

PLATE XXV

COMMON CARCINOMAS

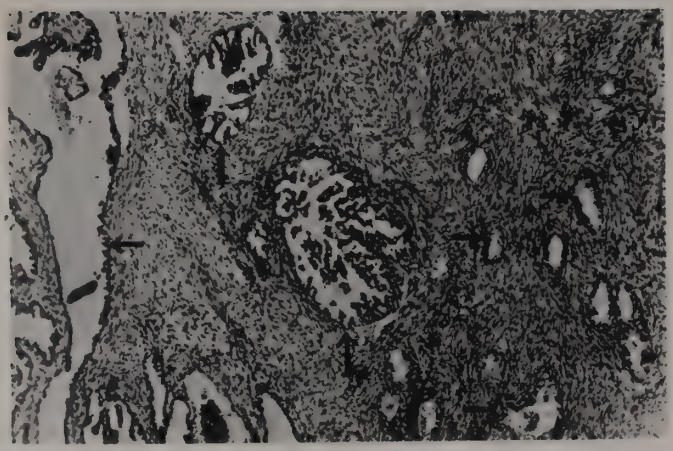

Fig. 1. **SEROUS, PARTLY PAPILLARY, PARTLY TUBULAR CARCINOMA** (courtesy of Dr. R. T. Waugh). The vertical arrows point to small cystlets with internal papillary excrescences. The horizontal arrows indicate tubular formations within the same neoplasm.

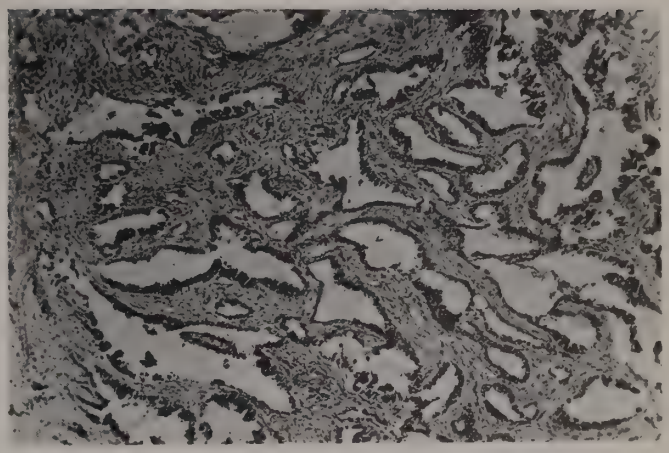

Fig. 2. **SOLID "ADENOCARCINOMA"**. Irregular tubular spaces, lined by a serous epithelium. This type is very reminiscent of the "malignant tubular adenomas" of the ovary.

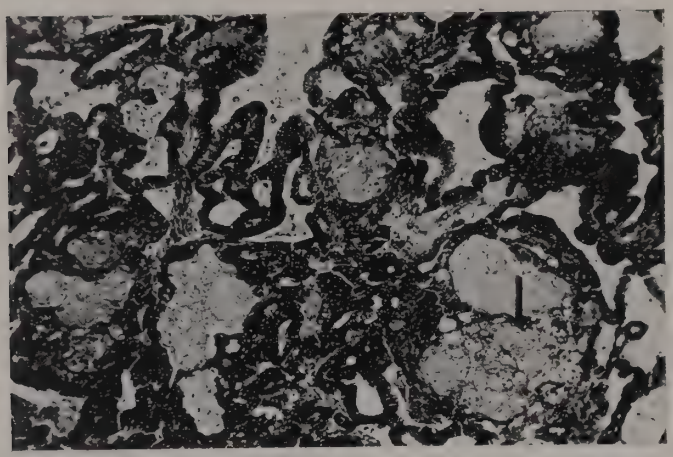

Fig. 3. **ADENO-ACANTHOMA** (courtesy of Dr. P. Masson). This tumor is often referred to as a "Wolffian epithelioma". It mainly consists of gland-like tubules, lined by a high cylindric epithelium, but throughout the tumor small islets of squamous carcinoma cell nests (indicated by arrows) tend to develop within its parenchyme. Such patchy transformations into squamous epithelium also occur in endometrial carcinomas, and hence this appearance is not indicative of a derivation from the Wolffian body.

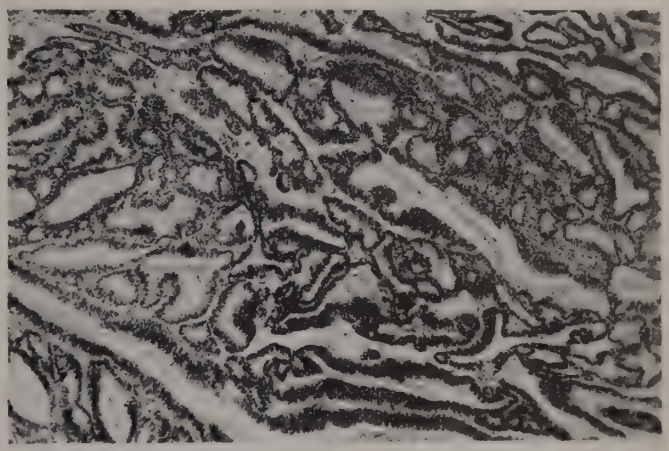

Fig. 4. **ADENOCARCINOMA** (courtesy of Dr. R. T. Waugh). Purely gland-like solid cracinoma of the ovary, similar to the tumor shown in Fig. 3 but devoid of squamous islets.

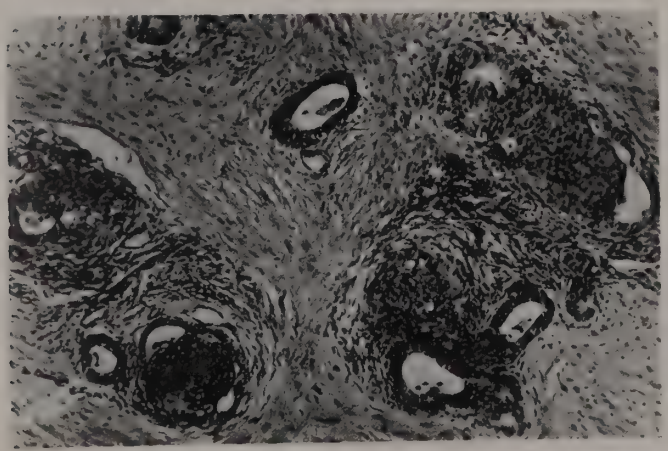

Fig. 5. **ADENO-ACANTHOMA** (courtesy of Dr. R. T. Waugh). A rather scirrhous tumor with tubular elements from the wall of which solid cell nests arise. The latter are not entirely differentiated into cornifying squamous, or basal cell islets, but appear to be developing in that direction.

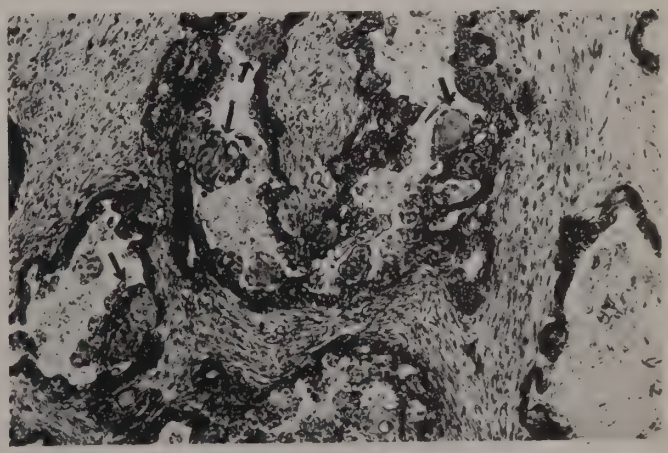

Fig. 6. **ADENO-ACANTHOMA** (courtesy of Dr. P. Masson). Another region of the tumor shown in Fig. 3. Note that here the dense stroma is much more preponderant. Only a few poorly-developed epithelial tubules are visible, but even they give rise to squamous cell pearls (indicated by arrows).

PLATE XXVI

COMMON CARCINOMAS

Fig. 1. KRUKENBERG TUMOR (courtesy of Dr. H. T. Karsner). General appearance of a Krukenberg tumor under low magnification. Note preponderance of fibrous connective tissue.

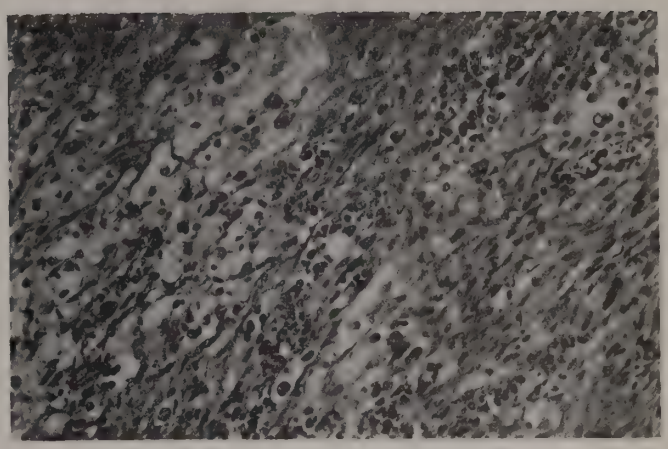

Fig. 2. KRUKENBERG TUMOR. Higher magnification of an area from the tumor shown in Fig. 1. Note that at this magnification, the epithelioid cells between the connective tissue fibers become clearly distinguishable.

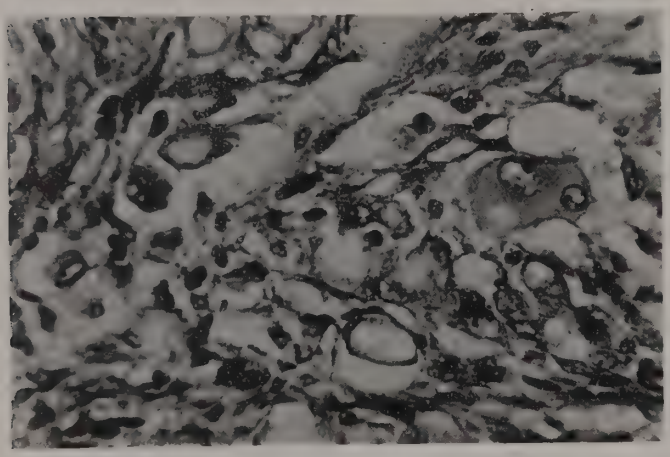

Fig. 3. KRUKENBERG TUMOR. Signet-ring cells and one bi-nucleated giant cell in a Krukenberg tumor with a comparatively loose cell arrangement (as seen under very high magnification).

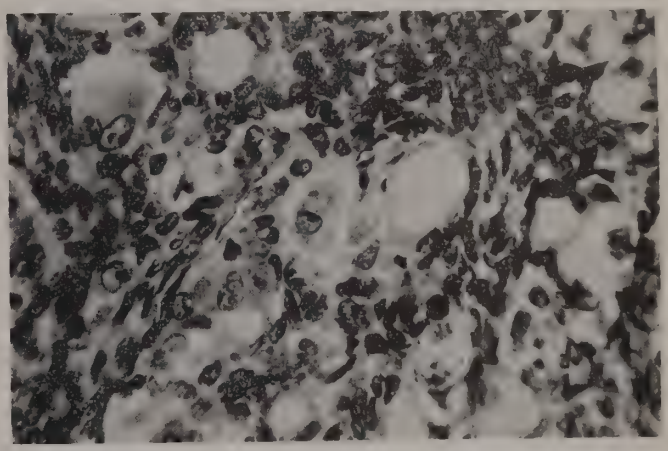

Fig. 4. KRUKENBERG TUMOR. Several large epitheloid cells which have not as yet developed a vacuole and some typical vacuolated signet-ring cells within a Krukenberg tumor whose stroma is extremely dense and cellular.

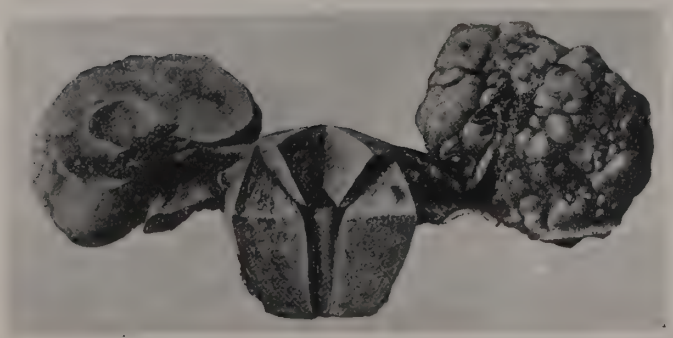

Fig. 5. GROSS APPEARANCE OF A BILATERAL KRUKENBERG TUMOR TOGETHER WITH THE TUBES AND UTERUS (after Novak B109/44). Note solid, nodular appearance characteristic of these tumors which are usually secondary to a carcinoma of the gastro-intestinal tract.

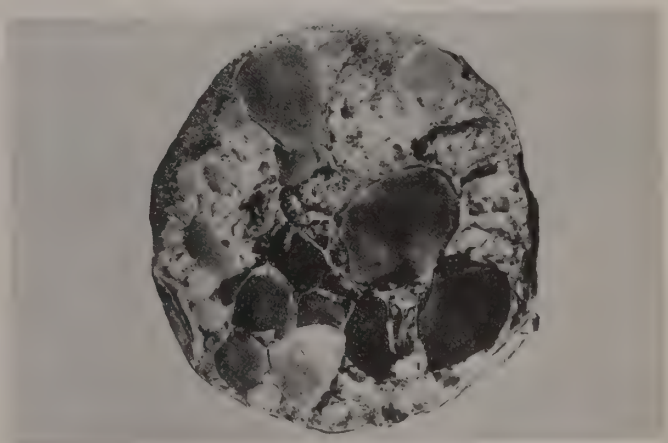

Fig. 6. GROSS APPEARANCE OF A PSEUDOMUCINOUS CARCINOMATOUS CYSTOMA IN A COW (after Feldman B11531/32). Note the colloid filled spaces clearly visible on this cross-section.

OVARIAN KRUKENBERG TUMORS

SYNONYMS: Fibrosarcoma ovarii mucocellulare carcinomatodes, carcinoma mucocellulare ovarii (Marchand), edematous fibroma with epithelial and gelatinous inclusions.

It is incorrect to describe these neoplasms as "Krükenberg" tumors (as so many workers do) since the "u" in this name takes no Umlaut.

REVIEWS

CZECH: Rubeska A92081/891, *Simeckova* A95228/37, A95227/37.

ENGLISH: Masson A53099/34, *Woodall* A33568/39, *Geist* B6672/42, *Leffel et al.* A37789/42, *Copland and Colvin* A56857/43, *Novak* B109/44.

FRENCH: Bourg A96766/28, *Bourg and Cordier* A96767/28, A79702/38, *Chavannez* A28082/35.

GERMAN: Sandrock A79823/06, *Marchand* A79783/13, *Mayer* A99597/26, *Sternberg* A64845/26, *Miller* A18279/37, *Bittmann* A97351/40.

HUNGARIAN: Kontsek A65613/30, *Stanca* A79838/33.

ITALIAN: Pizzetti A79806/22, *Massazza* A79785/25.

JAPANESE: Tanaka A92101/897.

POLISH: Wojtulewiczowna A79857/28.

ROUMANIAN: Daraban and Ioanitescu A79719/29-30, *Mandelstamm* A79781/31, *Peterburgsky* A79804/34.

PORTUGUESE: Santos A66202/32.

SPANISH: Sanchez y Arcas A79822/28, *Mazzini and Brachetto-Brian* A64434/30, *Santos* A61893/32, *Gallart-Esquerdo* B10819/43.

DEFINITION

The Krukenberg tumor is characterized by the presence of typical "signet ring cells" which contain some mucous material. They are spread out in a very cellular connective tissue stroma; this suggests a possible development from stroma cells. These tumors are almost always bilateral and secondary to a mucous carcinoma of the gastrointestinal tract, usually the stomach.

It should be emphasized that not all ovarian metastases of gastrointestinal tumors belong to this group and it is incorrect to designate as Krukenberg tumors (as some authors do) metastastic ovarian cancers which do not exhibit the above mentioned histologic characteristics. Krukenberg tumors are not known to produce any hormones.

HISTORY

Tumors probably belonging to this type were noted by many investigators during the latter half of the nineteenth century but were usually listed as metastatic carcinomas of the alimentary tract, sarcomas, endotheliomas, etc.[1] Krukenberg[2] was the first to describe them as a special tumor entity under the name of "fibrosarcoma ovarii mucocellular carcinomatodes". Under Marchand's direction he analyzed five personal observations as a basis for his doctor's thesis. It is of historic interest that this tumor which bears Krukenberg's name was known much before it was quite incidentally and inaccurately classified as a sarcoma by this medical student who subsequently became an ophthalmologist.

Later Marchand[3] rectified the error of his former pupil and admitted that the Krukenberg tumor is in reality a mucous cell carcinoma. A similar view had previously been expressed by Schlagenhaufer,[4] Wagner[5] and Römer[6] who emphasized that these tumors are usually secondary to gastro-intestinal carcinomas, a concept which is amply supported by many subsequent observations.

PATHOLOGIC ANATOMY

Macroscopically these tumors usually appear as bilateral growths of moderate size. Occasionally, however, they may be so small that they are overlooked at autopsy until the ovary is histologically examined;[7] conversely they may reach a weight of several kilograms.[8] Generally they maintain the normal shape of the ovary, although the latter is enlarged and sometimes lobulated or partly cystic. The capsule is usually smooth and does not tend to become involved in adhesions. The cut surface may be spongy, with myxomatous or gelatinous areas, and sometimes reveals necrotic and hemorrhagic patches. Contrary to common belief, the tumor is not very rare, as indicated by the large number of relevant case reports.[9]

[1] *Curgenven* A88298/861-2.
[2] A79771/895, A79772/896.
[3] A79783/13.
[4] A78977/02.
[5] 79853/02.
[6] A78899/02.
[7] *Copland and Colvin* A56859/43.
[8] *Krüger* A79770/09, A79773/10.
[9] *Kratzenstein* A48445/897, *Trovati* A74774/899, *Tiburtius* A92030/899, *Pflanz* A79805/898, *Lamoartner* A92027/01, *Lamparter* A77624/01, *Gottschalk* A78361/01, *Schmidt* A92096/01, *Henke* A92046/02, *Rispal and Gontier* A69414/04, *Orthmann* A79800/05, *Glockner* A70014/05, *Amann* A79691/05, A77992/10, *Sternberg* A79059/06, *Rosthorn* A79818/06, *Fischer* A79727/09, *Hussy* A79756/11, *Outerbridge* A78803/11, A79802/11, *Hall* A79748/12, *Kuhlhoff* A79774/12, *Meriel* A78692/12, A75856/14, *Schwartz* A79830/13, A79831/13, A66947/13, *Mandl* A79782/13, *Jacobson* A79761/13, *Bondy* A79701/14, *Filater* A66940/14, *Foulkrod* A79729/16, *Reel* A79815/17, A79816/21, *Major* A79780/18, *Ahlström* A79686/18, *Strong* A79844/19, *Chapman* A79707/20, *Frankenthal* A79730/21, *Wiebe* A79856/22, *Schröder* A79829/22, *Greil* A79744/22, *Bretschneider* A79703/22, *King* A79765/22, *Belozor* B8346/23, *Neumann* A79797/24, *Gräfe* A79741/24, *Gordon* A79740/24, *Miller* A79792/24-5, *Sacerdote* A79821/25, *Stevens* A79842/25-6, *Shaw* A79832/25-6, A79833/26, A79834/31, *Neumann*

Footnote cont'd.

Histologically, the most characteristic elements in the Krukenberg tumor are the mucus-containing "signet ring" cells. In some areas these invade the stroma diffusely, so that they actually appear to arise from the stroma. The stroma itself may be cellular and firm, or edematous, and the epithelial cells may be diffusely distributed in it or retain a more or less regular acinar arrangement. The view according to which acinus-forming metastatic ovarian tumors cannot be regarded as Krukenberg tumors is hardly tenable in view of the fact that certain acinus-like areas are detectable in the great majority even of those tumors whose bulk consists of the signet ring-type of cell. Some of these areas recognizably imitate gastric glands.[1] The mucoid material may break through the cell membranes and become scattered in the stroma, giving it a myxomatous appearance. Probably many of the so-called "ovarian myxomas" of the old literature belong to this type.

The *incidence* (including age, pregnancy and racial incidence) *pathogenesis, therapy and clinical course* of the Krukenberg tumor are discussed conjointly with the corresponding aspects of other ovarian cancers in the chapter on Common Ovarian Carcinomas.

[1] cont'd B8025/25-6, *Seidl* B11/26, *Miner* A79793/26, *Creyssel* A79717/26, *Matters* A79787/26, *Tapie* A79845/27, *Condamin* A79716/27, *Nishii* A78798/27, *Lutaud* A79779/27, *Jarcho* A79762/27, A97151/38, *Isbruch* A79758/28, A79759/29, *Hummer* A79754/28, *Gauthier-Villars* A71395/28, *Althabe and Colillas* A79690/28, *Lipschitz* A79777/28, *Leroux and Guérin* A68185/29, *Fallas* A68176/29, *Searight* A68118/29, *Dupont and Lièvre* A79722/29, *Moureau* A68110/29, *Allen* A79689/29, *Mercken* A79790/29-30, *Enzer* A64423/30, *Janow* A65158/30, *Babes and Pantzu-Lazarascu* A64412/30, *Albot and Michaux* A65598/30, *Stanca* A65182/30, *Mazzini and Brachetto-Brian* A67244/30, *Jackson and Babcock* A67743/30, *Tyner* A65674/30, *Cirio and Puntel* A64214/31, *Greenhill* A79743/31, *Diaz Garcia and Correa* A64217/31, *Ressine* A79817/31, *Ducuing and Vassal* A79721/31, *Barbanti-Silva* A79697/31, *Chalier* A79706/31, *Hundley* A64223/31, *Hyatt and Meigs* A79757/31, *Bennett and Douglass* A65144/31, *Schepetinsky* A62258/32, *Sierra* A62259/32, *Starkus* A61898/32, *Stephens* A61899/32, *Hamant* A62879/32, *Llinas* A66169/32, *Morikawa* A61886/32, *Godard* A66161/32, *Medina* A61913/33, *Finucci* A79726/33, *Desjacques and Leclerc* A61405/33, *Jeanneney and Rosset* A61758/33, *Offergeld* A61427/33, *Hunt and Budd* A61411/33, *Portes and Isidor* A62048/33, *Chisholm* A79709/33, *Vecchi* A79851/33, *Colombino* A79714/33, *Comando* A52257/34, *Vaptzaroff* A79850/34, *Weeter* A79854/34, *Scheuring* A79825/34, *Jeanneney* A52265/34, *Horsley* A52264/34, *Binkley* A53149/34, *Runyeon* A52298/34, *Saccone and Gordon* A52301b/34, A28172/35, *Mhitaroff* A79791/34, *Graff* A79742/34, *Groot* A79745/34, *Bacon* A79696/34, *Andrews* A52251/34, *Armstrong and Wolfe* A53143/34, *Freyberg* A79769/34, *Vitiello* A52314b/34-5, *Whitehouse* A79855/35, *Bicudo Netto* A62055/35, *Fernandez Ruiz* A61844/35, *Fennel* A28062/35, *Müller* A28125/35, *Crousse and Dupont* A28060/35, A28061/35, A79718/35, A95393/38, *Harms* A62069/36, *Delannoy et al.* A64750/36, *Tomasi* A95121/37, *Votta and Arrillaga* A95124/37, *Phillips* A95093/37, *Halbron et al.* A95261/37, *Santy et al.* A97155/38, *Mondor et al.* A97298/38, *Motta Maia and Duek* A96522/38, *Novak and Gray* A96527/38, *Gusmao* A96499/38, *Clerens* A95391/38, *Guibal et al.* A97279/39, *Kleine* A95444/39, *Aiello* A97252/39, *Monserrat* A97426/40, *Alexiu* A97344/40, *Crotty and Wood* A97357/40, *Castano and Reinecke* A96600/40, *Lubin and Polayes* A33973/40, *Del Genio* A98120/40, *Rodrigues* A96638/41, *Riveros and Boggine* A97517/41, *Fonseca Soares* A98114/41, *Nesler et al.* A97599/42, *de Angelis* A97775/42, *Francis* A97795/42, *de Oliveira Sarmento* A97816/42, *Cintra Franco* A98147/42, *Abreu* B10811/42, *Tisserand et al.* B10828/42, *Pecorone* A98171/42, *de Castro Teixeira* A96914/43, *Dominguez-Adama* B10817/44.

[1] *Gleize-Rambal and Robert* A79735/25.

PARA-OVARIAN KRUKENBERG TUMORS

In one case a primary gastric cancer metastasized into the right broad ligament giving rise there to an atypical para-ovarian Krukenberg tumor (Stochholm-Borresen B21673/31).

OVARIAN KRUKENBERG TUMORS IN ANIMALS

Typical Krukenberg tumors have not been found to occur in animals, but in a *fowl* an intestinal carcinoma metastasized into the ovary and produced a secondary deposit showing some—rather distant—resemblance to this type of growth (Feldman B8138/27).

OVARIAN MESONEPHROMAS

Synonyms: Papillo-endothelioma ovarii, teratoid adenocystoma.

REVIEWS

Schiller A30926/39, Jones and Seegar A33104/40, *Kazancigil et al.* A36304/40, *Stromme and Traut* A57588/43.

DEFINITION

The term mesonephroma is applied to ovarian tumors which resemble the embryonic mesonephros and have the following characteristics: 1) a glomerulus-like unit, consisting of a small cystic cavity which contains one capillary loop, covered with columnar epithelial cells whereas the cavity is lined with low endothelium-like cells; 2) solid areas consisting of proliferated endothelial cells, which appear stellate and are connected with each other by fine filiform projections. These two specific structures are definitely free from mucin. Limited production of a mucinous secretion can be found, however, in the small cystic cavities of the mesonephroma in some cases but the true mesonephroma never shows a mucinous secretion comparable to that of the parvilocular pseudomucinous cystoma. The tumor may be benign or malignant.[1]

HISTORY

The view that certain ovarian tumors may be derived from remnants of the mesonephros has been expressed by many investigators, and the pertinent extensive literature on "Wolffian epitheliomas", "mesonephric cystomas" and allied growths has been discussed at some length in connection with the microcystic pseudomucinous cystomas. It has been stated there that the blastomas described under these names are rather ill defined and may be either benign or malignant. It has also been emphasized that some investigators derive only pseudomucinous adenomas from the Wolffian body, while others take the opposite view, claiming that all relevant growths are of the serous variety. The question as to whether adenomas of the rete ovarii should also be included within this group has likewise been the subject of much debate. While there undoubtedly is a good deal of evidence indicating that certain adenomas and cystadenomas may be of mesonephric origin, it is evident from what was said above that the morphologic characterization of these growths is based on rather subjective and doubtful criteria.

In 1939 Schiller[2] described the so-called "mesonephroma ovarii" as a special tumor entity. He emphasized the similarity in the histologic structure of these growths to that of the normal mesonephros of human embryos and placed special emphasis upon the existence in the tumors of distinctly recognizable, though sometimes atypical, glomeruli. While many subsequent investigators agree that the mesonephroma is a special type of neoplasm, distinguishable from the common cystomas, some pathologists doubt its mesonephric origin (see part on Pathogenesis).

PATHOLOGIC ANATOMY

As stated in the section in which this tumor was defined, the outstanding feature of the growth is the presence of tubules and even glomeruli resembling those of the mesonephros. The tubules may contain varying amounts of mucin demonstrable by the commonly used mucin stains.[3] The irregular "hobnail-like" projections of cells into the lumen of the glomeruli is especially characteristic. Some of these tumors are almost entirely solid, containing only microscopic tubules and follicles, while others are partly macrocystic. Papillary formations are almost always prominent in these neoplasms but they may be "intracanalicular" and of microscopic size. In some growths the stroma is poorly developed, while in others it is abundant and partly hyalinized. It is noteworthy that a comparatively large number of the mesonephromas are very undifferentiated and manifestly malignant, though others are benign. Additional details concerning the structure of these growths will be found in the relevant *case reports*.[4]

INCIDENCE

It is difficult to estimate the incidence of mesonephromas since only comparatively few cases have been described as definitely belonging to this category. In one series of 350 unselected ovarian tumors 6 relevant cases were found.[5] However, in view of the fact that the very term mesonephroma was only coined a few years ago, it is probable that many relevant cases have previously been listed under other names. Doubtless many more cases will become known since it is not unlikely that a significant number of the so-called microcystic or adenomatous ovarian blastomas are mesonephromas.

The mesonephroma may apparently occur at any *age*, the youngest case described being 8 months, the oldest 69 years.[6]

[1] *Schiller* A57680/43.
[2] A30926/39.
[3] *Schiller* A57680/43, *Stromme and Traut* A57588/43.
[4] *Schiller* A30926/39, A38423/42, A57680/43, *Jones and Seegar* A33104/40, *Kazancigil et al.* A36304/40, *Tuta and Siebel* A36300/41, *Rosenblatt and Grayzel* A55550/42, *Jones and Jones* A37800/42, *de Silva Fialho* A99023/43, *Jensik and Falls* B10136/43, *Stromme and Traut* A57588/43.
[5] *Jones and Seegar* A33104/40.
[6] *Schiller* A30926/39, *Rosenblatt and Grayzel* A55550/42.

PATHOGENESIS

Although it is still doubtful whether the tumor is really of mesonephric origin, several investigators feel that its structure justifies, at least, the tentative assumption of its derivation from this source.[1] Others, who failed to find any recognizable mesonephric glomeruli, reject this interpretation and discuss the possibility of regarding the tumors as "angioendotheliomatous neoplasms"[2] or "teratoid" growths belonging to the group of pseudomucinous cystadenomas.[3]

While we do not as yet wish to draw any definite conclusions concerning the pathogenesis of the mesonephroma, the evidence presented appears to indicate that this neoplasm is a specific variety of the pseudomucinous microcystic adenomas and adenocarcinomas, which deserves to be treated as a separate entity.

CLINICAL COURSE AND THERAPY

It is evident from the published case reports that the course of the mesonephroma is devoid of any specific characteristics which would permit its clinical differentiation from other ovarian tumors of equal size and comparable growth rate. It produces no detectable endocrine disturbances. For this reason the diagnosis could hardly be made without biopsy. In view of the frequently high degree of malignancy, radical surgery is indicated and even if bilateral ovariectomy and panhysterectomy are performed the prognosis is doubtful since recurrences are common.[4]

Some mesonephromas respond well to radiation therapy, but this should only be used following radical operation as a prophylactic measure against recurrences.[5] Even this combination therapy does not appear to prolong the lives of patients having the less differentiated type of mesonephroma.[3]

[1] *Jones and Jones* A37800/42, *Schiller* A38423/42, *Rosenblatt and Grayzel* A55550/42, *Jensik and Falls* B10136/43.

[2] *Kazancigil et al.* A36304/40.

[3] *Stromme and Traut* A57588/43.

[4] *Jones and Seegar* A33104/40, *Tuta and Siebel* A36300/41, *Rosenblatt and Grayzel* A55550/42, *Jones and Jones* A37800/42, *Jensik and Falls* B10136/43, *Stromme and Traut* A57588/43.

[5] *Jones and Jones* A37800/42, *Jensik and Falls* B10136/43.

PLATE XXVII

MESONEPHROMAS

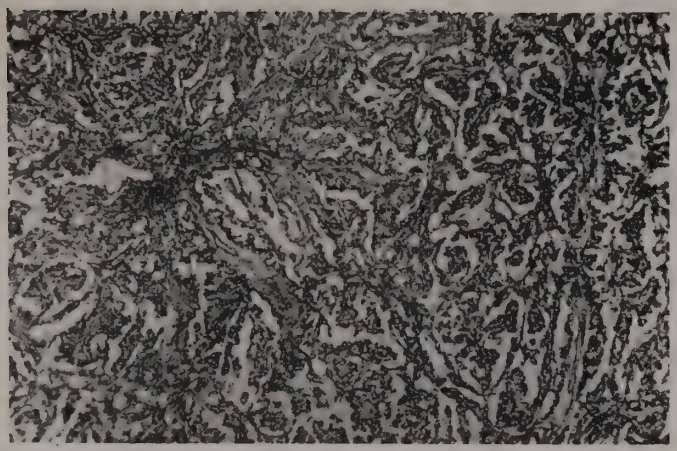

Fig. 1. MESONEPHROMA (after Schiller A30926/39). Microcystic tumor showing papillary structure.

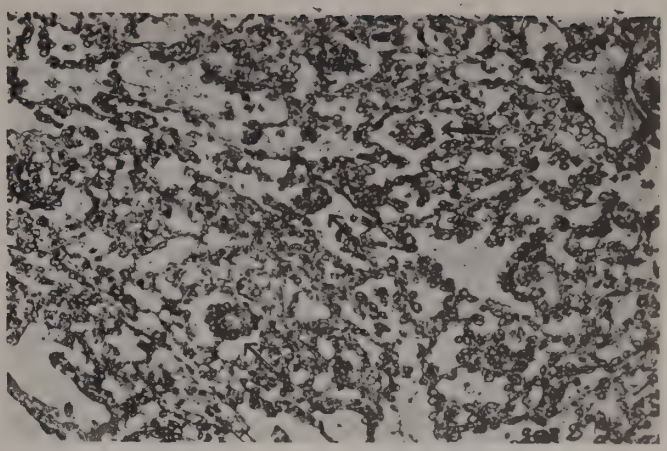

Fig. 2 MESONEPHROMA (after Schiller A30926/39). Loosely arranged parenchyme with small "glomeruli" (marked by arrows).

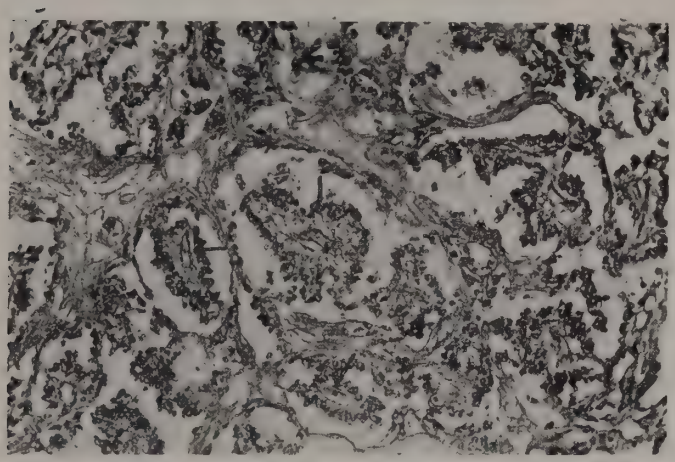

Fig. 3 MESONEPHROMA (after Schiller A30926/39). The tumor parenchyme consists of small cystic spaces corresponding to "glomeruli". Each cystlet contains a capillary loop (marked by arrows).

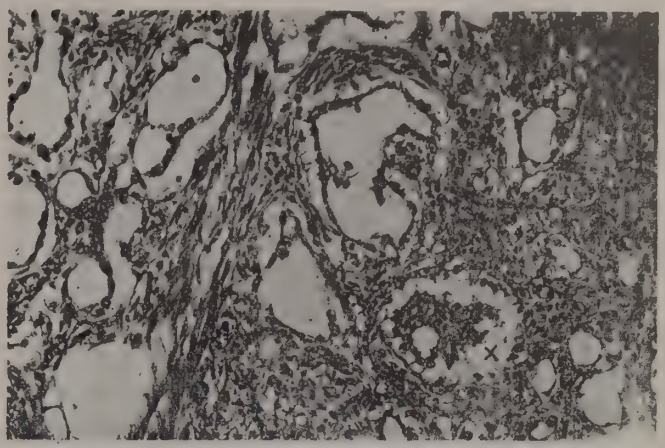

Fig. 4. MESONEPHROMA (after Schiller A30926/39). Note again irregular tubules and one large "glomerulus" (X). It must be emphasized that the "glomeruli" of the mesonephromas bear only a remote resemblance to those seen in fetal kidney tissue.

OVARIAN BRENNER TUMORS

Synonyms: Fibroepithelioma mucinosum benignum, oophoroma, oophoroma folliculare, fibroma ovarii adenocysticum, Brenneroma.

It must be kept in mind in connection with the terminology of this tumor that many relevant cases have been described in the literature as folliculomas or adenofibromas. These terms can no longer be regarded as synonymous with Brenner tumors since they are now definitely reserved for blastomas of a different character.

REVIEWS

CZECH: Tachezy A95331/36.

ENGLISH: Gaines A59888/36, *Schiller* A70266/36, *Schattenberg and Harris* A32319/39, *Robertson* A97586/39, *Walton* A64896/39, *Karsner* A32285/40, *Dockerty* A96679/41, *Geist* A6672/42, *Fox* A38432/42, *Novak* B109/44.

FRENCH: Varangot 68667/37, A68826/38.

GERMAN: Krompecher A73107/24, *Sternberg* A64845/26, *Kermauner* A64880/32, *Freund* A53159/33, *Reiner* A73123/35, *Sikl* A73130/35, *Wolff* A73143/36, *Miller A18279/37, Geissler* A98119/41.

ITALIAN: Freund A73100/34.

PORTUGUESE: Rodrigues A96539/37, *Lordy* A98164/42.

DEFINITION

The Brenner tumor is a benign, partly fibrous and partly epithelial growth of the ovary. The relative proportion of epithelial and stroma tissue is extremely variable, but quite frequently the latter prevails. The epithelial component consists of solid or cystic aggregations of cells not unlike those seen in the basal layers of stratified squamous surface epithelia. If cystic cavities are formed, the innermost lining cells tend to produce pseudomucin.

HISTORY

In 1907, under the name of "oophoroma folliculare", Brenner[1] described the tumor which now bears his name. Historically it is noteworthy that tumors of identical structure had previously been described by a large number of investigators[2] under a variety of different names such as "Fibroma papillare superficiale carcinomatosum ovarii", "solid carcinoma of the ovary with egg-formation", "adenofibroma cysticum carcinomatosum", "adenofibroma colloides ovarii" or merely "solid ovarian tumor". Almost simultaneously with Brenner's description and quite independently of the latter, Ingier[3] published a case under the name of "folliculoma ovarii". Perusal of his description clearly indicates, however, that he dealt with what is now known as a Brenner tumor and it is rather unfortunate that he chose the term "folliculoma" since this designation is now applied to the granulosa and theca cell tumors. A study of the literature indicates that many early workers not only described relevant cases before Brenner's time, but clearly recognized this tumor as a special pathologic entity which must be delimited from the other ovarian growths. In order to avoid further confusion, however, we shall retain the term "Brenner tumor" as it is so generally in use.

PATHOLOGIC ANATOMY

Before entering into a detailed discussion of the morphologic characteristics of Brenner tumors, it must be clearly stated that the evidence now at hand fully justifies the view that these growths are a pathologic entity different from other ovarian tumors. This is emphasized because the superficial resemblance of the Brenner tumor to granulosa cell tumors, and in some cases to squamous cell carcinomas, of the ovary occasioned many misunderstandings in the literature. Indeed, v. Werdt [4] believed this tumor to be identical with the so-called granulosa cell tumors and even with the so-called "large cellular ovarian carcinomata" while Sternberg[5] used the terms "folliculoma", "oophoroma" and "granulosa cell tumor" as synonyms.

Macroscopically the Brenner tumor is usually round or oval in shape with a smooth or slightly nodular surface. Its *size* is generally small but may reach considerable dimensions.[6] Among the largest tumors of this group are those which weighed 15 lbs.[7] and 18 (Engl.) lbs.[8] respectively. Many of the other tumors were extremely small, measuring only a few millimeters in diameter and it is occasionally difficult to draw a line between large "Walthard rests" and small Brenner tumors. Probably because of the large amount of fibrous tissue in their stroma, these tumors tend to be of a hard, cartilaginous or rubber-like *consistency*, resembling common fibromas. In the majority of cases they have a definite *pedicle*. On the *cut surface* they exhibit a grey, but sometimes distinctly yellowish tinge and within their predominantly solid substance, minute cystic cavities are distinguishable. In these there is a thick colloid-like material similar to that found in pseudomucinous cysts. Occasionally, larger cysts may be found and, as we shall see later, Brenner tumors are often at-

[1] A26963/07.
[2] *v. Mengershausen* A64793/895, *Macnaughton-Jones* A64884/898, *Orthmann* A96831/899, *Gottschalk* A64878/899, A76814/899, A64879/02, *Amann* A64726/899, *Schröder* A64835/01, *Lönnberg* A64883/01, *Fothergill* A64755/02, *Voigt* A64860/03, *Liepman* A64788/05.
[3] A79295/07.
[4] A64866/14.
[5] A64845/26.
[6] *Reel and Foster* A96936/43.
[7] *Davison and Neiman* A64871/34.
[8] *Giles* A64876/09-10.

tached to the walls of various types of ovarian cystomas. About 70% of all Brenner tumors belong to the solid fibroma-like variety. The *capsule* which covers these tumors is not very characteristic as its thickness and structure are subject to great variations.[1]

A comparatively large percentage of the Brenner tumors are *bilateral*.[2] It is somewhat difficult, however, to arrive at reliable statistical figures since some of these tumors are so small that they are not detected unless careful attention is given to the possibility of bilateral involvement. Dockerty and MacCarty[3] reported 10 cases, and Novak and Jones[4] 14 cases, among which not a single one was bilateral. According to Fox[5] who reviewed 170 cases described in the literature, 13 were definitely known to be bilateral, 57 involved only the left, and 67 only the right ovary, while in the remaining cases there is no mention of the side affected.

Occasionally the tumors were *multiple*. Thus in one patient observed[6] the main tumor occupied one ovary, while in the hilum region of the other ovary, which was atrophic, there were two small Brenner nodules. In another woman[7] there were two separate Brenner tumors, the larger one of which was situated in the ovary proper and the smaller in the Fallopian tube. Several additional instances of multiple small Brenner nodules—discovered by serial sections—have been reported.[8]

Microscopically the Brenner tumors are characterized by their usually abundant, fibroma-like, dense connective tissue *stroma* within which there is a variable amount of epithelial tissue in the form of irregular islets and bands. The connective tissue tends to form sheaths around the epithelial islets and this has often been compared with an abortive attempt at theca formation.[9] In most cases the connective tissue is poorly supplied with blood vessels and tends to undergo hyaline degeneration.[10] Occasionally smooth muscle cells have been noted within the stroma.[11]

The *epithelial nests* are frequently roundish or oval and consist of comparatively chromophobe, polygonal cells with distinct cell membranes. In their general aspect they resemble a stratified *squamous epithelium*. It is particularly noteworthy that, unlike the cells of the so-called granulosa tumors or folliculomas, the epithelial components of the Brenner tumors are very poorly tingible and the few granules seen in their cytoplasm are comparatively pale. Some of these epithelial nodules or strands are massive, while in others small "folliculoid" cavities are detectable. These resemble the Call-Exner bodies of the normal granulosa and give the epithelial accumulations the aspect of follicles. The contents of these folliculoid spaces are occasionally swollen and degenerated *cells which resemble ova;* this led to the designation of these tumors as "oophoromas". Several investigators gave special attention to these egg-like structures.[12] If the follicular antrum reaches a certain size it becomes filled with a gelatinous material similar to that seen in pseudomucinous cystomas and at the same time the epithelial cells lining the cavity assume the characteristics of a *mucous epithelium*. It is noteworthy in this connection that both within the body of the pseudomucinous cells and within the cyst-like cavities, *mucicarmin positive material* has been demonstrated.[13] This adds to the resemblance between the Brenner tumor and the mucous cyst. Upon further growth of the cystic cavity, the structures may acquire an appearance which seems to justify the view, held by some investigators, that direct transitions between Brenner tumors and pseudomucinous cystomas can occur. It is of particular interest that the *nuclei* of the epithelial cells usually possess a distinct longtitudinal groove or fold which gives them a coffee bean-like appearance.[14] It has been emphasized[15] that with regard to this peculiar nuclear pattern, the Brenner tumor resembles Walthard's rests, testicular Sertoli cells and certain pseudomucinous cystadenomas.

In general the epithelial islets resemble undifferentiated stratified squamous epithelium in their peripheral part and columnar pseudomucinous epithelium in the layer adjoining the central cavities, whenever such are present. In some instances, however, the inner layer may differentiate into a more or less typical squamous epithelium.[16] Significant amounts of *lipid* granules are not detectable in Brenner tumors,[17] although occasional fat granules have been found in some cases,[18] *Glycogen* has also been demonstrated in the form of dust-like small particles within the cytoplasm of the epithelial cells.[19]

[1] *Miller* A18279/37, *Fox* A38432/42.
[2] *Ingier* A79295/07, *Josefson et al.* A62932/32, *Kraus and Weinzierl* A73106/33, *Weinzierl* A61818/33, *Maury and Schmeisser* A53055/34, *Proescher and Rosasco* A64888/36, *Fox* A38432/42, *Peale* A55812/42.
[3] A31394/39.
[4] A33609/39.
[5] A38432/42.
[6] *Schiffman* A62948/32.
[7] *Smith* A28069/35.
[8] *Bettinger* 5539/33, *Plaut* A64887/33, A61889/33.
[9] *Brenner* A26963/07, *Geist* A64759/22, *Seifried* A73129/23, *Neumann* 42642/27, *Esser* A64752/28.
[10] *Meyer* A66176/32.
[11] *Lahm* A64784/14, *de Lemos* A64787/19.
[12] *Fothergill* A64755/02, *Liepman* A64788/04, *Ingier* A79295/07, *Blau* A64734/07, *De Lemos* A64787/19.
[13] *Schiffmann* A64832/27, A62948/32, *Meyer* A66177/32, *Freund* A53159/33, *Held* A97148/38, *Teilum* A96644/41.
[14] *Varangot* 68667/37, A68826/38.
[15] *Danforth* A55575/42.
[16] *Plate* A61859/35, *Ayre and Kearn* A63380/43.
[17] *Schiffmann* A64832/27, *Esser* A64752/28.
[18] *Neiman* A61849/36.
[19] *Schiffmann* A64832/27.

It is especially noteworthy that in spite of their superficial histologic resemblance to carcinomas, the Brenner tumors are clinically benign since they neither infiltrate into other organs nor metastasize.

The literature on this tumor is quite extensive and many additional facts concerning the characteristics of the Brenner tumor will be found upon perusal of the relevant *case reports*.[1]

SECONDARY CHANGES IN BRENNER TUMORS AND IN REMAINING OVARIAN TISSUE: Brenner tumors rarely cause extensive adhesions. They are not infrequently the site of hyalin degeneration (as stated above), but actual necrosis never affects any significant portion of the tumor tissue (for hemorrhage, calcification and torsion see corresponding sections). The ovarian remnant is rarely the site of any significant change apart from the mechanical damage caused by the mere presence of the tumor tissue.

BRENNER TUMORS IN COMBINATION WITH OTHER OVARIAN BLASTOMAS: It is a characteristic feature of the Brenner tumor that it tends to occur in combination with other ovarian blastomas. As mentioned above, certain parts of the typical Brenner tumor may resemble pseudomucinous cystomas, a fact which led to the assumption that the latter may arise from the former. In this connection it is of interest to note the great frequency with which Brenner tumors develop in the walls of *pseudomucinous cystomas* (see chapter on Common Cystomas). Less frequently they also occur, however, in combination with *fibromas*,[2] *endometriomas*[3] *dermoids*,[4] *serous cysts, struma ovarii,* etc. (see corresponding chapters).

Occasionally a Brenner tumor in one ovary is accompanied by the simultaneous development of another blastoma in the contralateral gonad, for instance a fibroma.[5]

INCIDENCE

The *general* incidence of the Brenner tumor is difficult to estimate as a large number of relevant blastomas have erroneously been listed as fibroadenomas, folliculomas etc. It should also be recalled that, as we stated above, it is not easy to draw the line between very small Brenner tumors and large Walthard rests. One author[6] collected 170 cases from the literature, but this number is considerably increased if we include the many additional instances which can be identified as Brenner tumors although they were originally described under different names. Probably any sizable series of benign solid ovarian tumors usually contains a few examples of the Brenner tumor if carefully examined from this point of view.

The *age* incidence has been considered by several previous reviewers all of whom were unanimous in stating that post-menopausal women are most frequently affected.[7] The youngest patient with a typical Brenner tumor was 20 years,[8] the oldest 77 years[9] of age. The data given by one reviewer[6] may be summarized as follows:

Age in years	Number of Cases
0—10	0
11—20	1
21—30	11
31—40	26
41—50	41
51—60	47
61—70	27
71—80	5
not stated	12
TOTAL	170

The incidence during *pregnancy* cannot be estimated on the basis of the few published instances of Brenner tumor development during gestation.[10]

The *racial* incidence is likewise difficult to determine, but it may be said that a comparatively large number of these tumors occur among negroes,[11] al-

[1]*Hedinger* A73103/11, *Desaux and Masson* A73092/12, *Seifried* A64837/23, *Krompecher* A64781/25, *Spencer* A64894/25-6, *Stevens* A73137/25-6, *Blau* A64735/26, *Esser* A64752/28, *Richter* A64826/29, *Stein* A64895/31, *Mandelstamm* A66174/32, *Meyer* A66176/32, A66177/32, *Muller* A61425/32, A64810/34, *Derichsweiler* A73091/33, *Plaut* A64887/33, *Bettinger* 5539/33, *Lascano Gonzalez and Sammartino* A28159/34, *Frankl and Klaften* A28154/34, *Ewald* A52260/34, *Herlant* A62070/34, *Wolfe and Kaminester* A53080/34, *Reist* A64890/34, *Reimann and Brown* A64889/35, *Wallart and Scheidegger* A28079/35, *Fauvet* A27998/35, *Delannoy and Bédrine* A62064/35, *Proescher and Rosasco* A64888/36, *Tachezy* A95331/36, *Meeker* A64885/36, *Neiman* A61849/36, *Bassal and Fabre* A59875/36, *Christidi et al.* A95388/37, *Gnassi* A64877/37, *Eleizegui* A97104/38, *Mocquot and Varangot* A97115/38, *Plate* A97117/38, *Chiray et al.* A33669/39, *Walton* A64896/39, *Timmerberg* A95455/39, *Lemgruber* A97584/39, *Smith and Pettit* A31418/39, *Siegel* A64892/40, *Angel Etcheverry and de Hoz* A96664/40, *Sjövall* A96641/40, *Grayzel and Friedman* A37324/41, *Hicks* A98125/41, *Antunes and Hoeppner Dutra* A98135/42, A98136/42, *Hartz* B10820/43, *Tavares* B10826/43, B10827/43.

[2]*Bettinger* A73087/33. [3]*Novak and Jones* A33609/39.

[4]*Schiller* A73127/34, A52305b/34.

[5]*Plaut* A61889/33, *Freund* A73100/34.

[6]*Fox* A38432/42.

[7]*Abraham* A73085/33, *Bettinger* 5539/33, *Dockerty* A33546/40.

[8]*Plaut* A61889/33.

[9]*Marwil and Beaver* A55549/42.

[10]*Siegel* A64892/40, *Rogers* A58774/43.

[11]*Davison and Neiman* A64871/34, *Novak and Jones* A33609/39, *Danforth* A55575/42.

though the majority of the cases published are in the white race.

PATHOGENESIS

Brenner[1] originally interpreted the tumor as being derived from *Plüger's tubes* which do not contain ovogonia. Muller[2] actually describes his case under the name of "epithélioma pfügérien"; it is very unlikely, however, that there is any equivalent of Pflüger's tubes in the human being and consequently neither the Brenner tumors nor the so-called "pflügeromas" or "pflügeroblastomas" of the literature[3] can originate from this source.

Plaut[4] derived these tumors from the peritoneum, or *germinal epithelium,* covering the ovary, because on serial sections of one case he was able to demonstrate connections with the latter. Arey[5] studied serial sections of two very small Brenner tumors and found stalk-like connections between these blastomas and the surface epithelium of the ovary. These observations support the view that Brenner tumors may develop directly from the germinal epithelium. It has also been suggested[6] that both the Brenner tumor and endometriosis arise from the same primordium—namely the celomic epithelium. This assumption was based mainly on the observation of a case of Brenner tumor in one ovary with endometriosis of the contralateral Fallopian tube. We wonder what would happen to our views concerning the pathogenesis of ovarian tumors if this type of reasoning were extended to all instances of multiple oncogenesis quoted in this Encyclopedia!

It has been argued[7] that in some cases the tumor may arise from cells related to *epoophoron* paraovarium and the rete because of the supposed resemblance of Brenner tumors to certain types of transitional epithelia in urinary passages. A similar view[8] had been previously expressed in connection with an "unusual ovarian tumor" apparently derived from *Wolffian duct inclusions.*

The fact that pseudomucin granules are often demonstrable in the epithelial elements of Brenner tumors (see above) led to the view that close pathogenic connections exist between the latter and *pseudomucinous cystomas.*[9] This view receives strong support from the frequently made observation of Brenner tumors which appear to develop in the walls of pseudomucinous cystomas (see chapter on Common Cystomas).

The opinion, occasionally voiced, that the tumors arise from the *granulosa* has been strongly contradicted by Meyer[10] who advanced the theory that they are derivatives of *Walthard's rests.* This view is consonant with the previously expressed hypothesis[11] that all ovarian cysts are of this origin. Many contemporary pathologists subscribe to the Walthard rest theory[12] which has perhaps been strengthened by the observation that the supposedly typical coffee bean-like nucleus of the epithelial cells in the Brenner tumor is very similar to that of Walthard rest cells. Since this same nuclear pattern occurs in many pseudomucinous cystadenomas, the assumption of a relationship between these, the Brenner tumor and the Walthard rest is rather suggestive.[13] On the other hand, it must be admitted that this nuclear pattern is not entirely specific, since in addition to Walthard's rests and Brenneromas it is also found in the Sertoli cells and the lining epithelium of the rete testis.[14]

CLINICAL COURSE

It is generally assumed that the Brenner tumor produces no hormones and no symptoms other than those due to its physical presence in the ovary. Thus Novak and Jones[15] state that " . . . . the uterus in old women with Brenner tumors has often been described as typically senile and atrophic. When the tumor occurs during the menstrual life, no characteristic effect upon menstruation is noted, as I have previously mentioned." Careful perusal of the relevant literature, however, shows that although in most instances Brenner tumors are hormonally "silent", they may occur in associaton with changes known to be caused by hormonal factors. It appears justified to assume, therefore, at least in certain cases, that the Brenner tumor may produce hormones. In support of this view attention is called to the frequent association of these ovarian neoplasms with various *menstrual disturbances,*[16] especially *postmenopausal uterine bleeding,*[17] *hypermenorrhea* or *metrorrhagia,*[18] *uterine fibroid polyps,*[19] *adenomyosis*[20]

[1]A26963/07.
[2]A61425/32.
[3]*Masson* A64790/23, *Zuckermann* A97450/40, A97727/40.
[4]A61889/33.
[5]A98139/43, 84700/44.
[6]*Abraham* A61914/33, A73085/33.
[7]*Schiller* A73127/34.
[8]*Stein* A64895/31.
[9]*Held* A97148/39, *Teilum* A96644/41.
[10]A66176/32, A66177/32.
[11]*Richter* A64825/27.
[12]*Novak and Jones* A33609/39, *Lordy* A98164/42, *Peale* A55812/42.
[13]*Danforth* 82840/41, A55575/42.
[14]*Arey* A98139/43.
[15]A33609/39.
[16]*Votta* A96468/38.
[17]*Schiffman* A62948/32, *Abraham* A73085/33, *Freund* A53159/33, *Schiller* A52305b/34, A73127/34, *Fauvet* A27998/35, *Kleine* A64881/37, *Novak and Jones* A33609/39, *Marwil and Beaver* A55549/42.
[18]*Frankl* A64756/27, *Smith* A28069/35, *Danforth* A55575/42.
[19]*Macnaughon-Jones* A64884/898, *Frankl* A64756/27, *Richter* A64826/29, *Meyer* A66176/32, *Plaut* A61889/33, *Weinzierl* A61818/33, *Smith* A28069/35, *Neiman* A61849/36, *Danforth* A55575/42.
[20]*Meyer* A66176/32.

PLATE XXVIII
BRENNER TUMORS

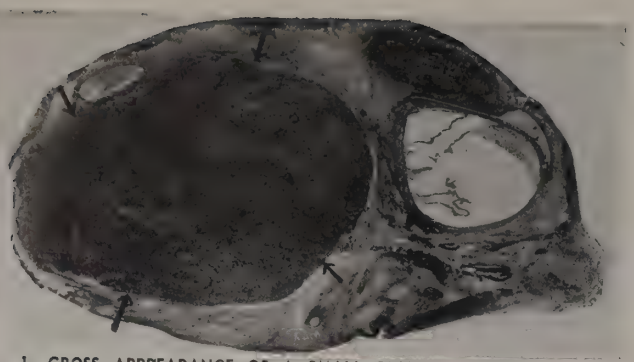

Fig. 1. GROSS APPPEARANCE OF A SMALL BRENNER TUMOR (courtesy of Dr. L. Berger). General appearance of a solid Brenner tumor (marked by arrows) within the ovary which contained it.

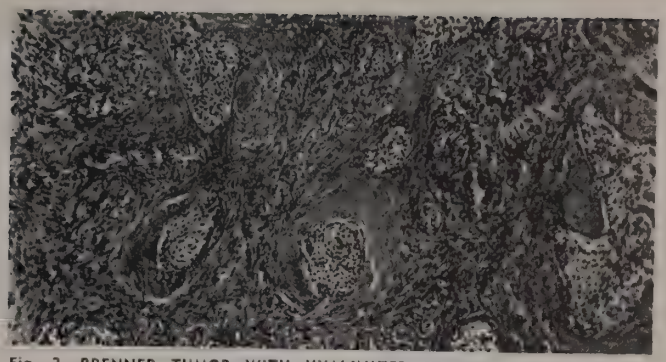

Fig. 2. BRENNER TUMOR WITH HYALINIZED STROMA. Higher magnification of a small area from within the tumor represented in Fig. 1. Note solidity of epithelial cells within a very dense connective tissue stroma. The connective tissue in the immediate vicinity of the epithelial masses is entirely hyalinized and of an homogeneous appearance.

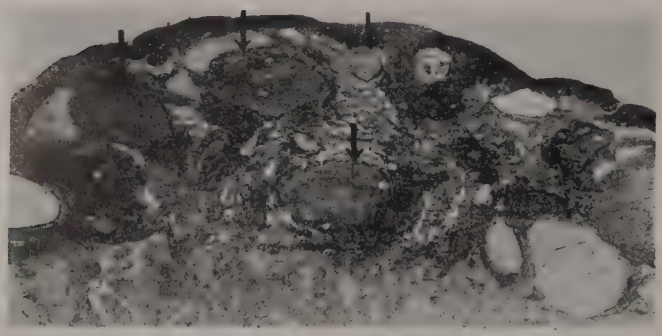

Fig. 3. MULTIPLE, APPARENTLY INDEPENDENT BRENNER TUMORS (courtesy of Dr. L. Berger). Both ovaries of this 45-year-old patient contained multiple nodules (those in this field are indicated by arrows) of typical Brenner tumor tissue. The remaining ovarian parenchyme was approximately normal.

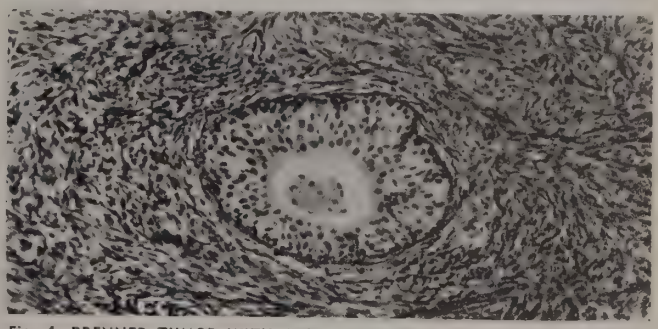

Fig. 4. BRENNER TUMOR WITH CYST FORMATION. Small cystic epithelial cell groups within the dense connective tissue stroma, characteristic of Brennerom.as. Note that the innermost layer of the stratified epithelial lining is high cylindric and of a pseudomucinous type. Some pseudomucin and cell debris has accumulated within the cyst lumen.

Fig. 5. SOLID BRENNER TUMOR (courtesy of Dr. H. T. Karsner). This picture illustrates the most common type of a Brenner tumor. The connective tissue is extremely dense and excessively developed, the epithelial cell groups are solid and consist of light cells.

Fig. 6. CYSTIC BRENNER TUMOR? Note multiple, small cystic formations within an excessively-developed connective tissue stroma. From the individual cysts, pseudomucinous material appears to infiltrate into the stroma (at points indicated by arrows). Small cysts with a stratified lining are not uncommon within Brenner tumors (see Fig. 4 on this Plate); it is uncommon, however, to find all epithelial masses transformed into cysts with a comparatively low, often only unicellular lining, as in this tumor. Hence, the identity of this neoplasm should not be considered as definitely established.

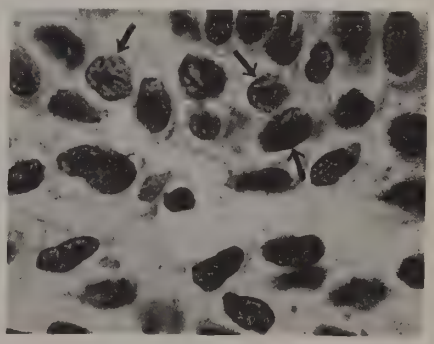

Fig. 7. CHARACTERISTIC "COFFEE BEAN" NUCLEI IN BRENNER TUMOR. Nuclei of the epithelial cells from a region of the tumor illustrated in Figs. 1 and 2, shown under oil immersion. Note longitudinal fold, or indentation, characteristic of the Brenner tumor nuclei (some typical cells indicated by arrows).

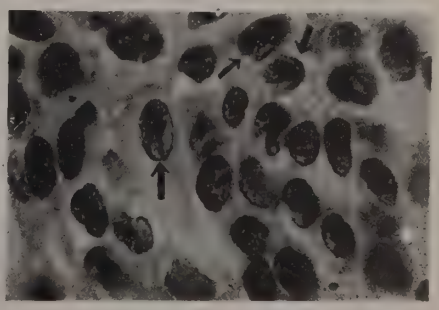

Fig. 8. CHARACTERISTIC "COFFEE BEAN" NUCLEI IN A BRENNER TUMOR. Another region of the tumor shown in Fig. 7.

and even *carcinoma of the uterus;*[1] occasionally the tumor may lead to prolonged periods of *amenorrhea.*[2] In some cases marked hirsutism and other signs of *virilization* were noticeable.[3] It should be specially mentioned that in one case[4] removal of the ovaries containing typical bilateral Brenner tumors, led to disappearance of the virile characteristics. All these observations strongly suggest that functionally the Brenner tumor resembles the folliculomas and arrhenoblastomas although it is less frequently active as a hormone-producing tissue. It must be remembered, however, that histologically typical folliculomas may also be hormonally "silent". In our morphologic description we tried to emphasize the differences between the Brenner tumors, folliculomas and tubular adenomas (arrhenoblastomas) because it is on the basis of their dissimilarities that these tumors have to be distinguished from each other. Yet the fact remains that there are close histologic relations between these blastoma types and it appears that clinical experience supports the view of a close association between them. We believe that the possibility of hitherto unsuspected intimate connections among morphologically dissimilar tumor types deserves serious consideration even if it is contrary to the orthodox and generally accepted views concerning their histogenesis.

In one instance[5] a Brenner tumor was found in a woman suffering from thyroid atrophy, nephrosclerosis, and what the authors call a "polyendocrinocirrhotic" syndrome, but since this is merely a single case the association of the lesions may well be coincidental.

Ascites may also occur in women suffering from Brenner tumors[6] but this symptom is comparatively rare. In one typical case of Meigs' syndrome with peritoneal and pleural effusions,[7] a Brenner tumor was the causative agent since the syndrome disappeared after ablation of the growth.

COMPLICATIONS

Brenner tumors may give rise to complications due to torsion of their pedicle, hemorrhage (see chapters on Torsion and Hemorrhage in Sect. IV, Vol. VI) or during pregnancy by mechanical interference with the birth mechanism (see case reports listed in passage on Pregnancy Incidence).

DIAGNOSIS

The clinical diagnosis of Brenner tumors cannot be made with certainty. They present themselves as medium-sized, usually mobile, solid, ovarian tumors which may cause some pain and generally develop very slowly. Only histologic study of a specimen permits the definite identification of this neoplasm.

PROGNOSIS

The growth of the Brenner tumor is almost invariably very slow and the blastoma is usually completely ignored by the patient for many years. It never becomes malignant nor has it been known to regress spontaneously.

THERAPY

The only logical therapy is surgical removal of the tumor. As previously stated, Brenner tumors are frequently bilateral (or multiple in the same ovary), hence if the real nature of the disease is suspected during operation, it is essential to give special attention to this possibility. In the case of complete removal, there is no danger of recurrence.

[1] *TeLinde* A64447/30, *Bettinger* A73087/33, 5539/33, *Freund* A53159/33.
[2] *Neumann* 42642/27.
[3] *TeLinde* A64447/30, *Josefson et al.* A62932/32.
[4] *Josefson et al.* A62932/32.
[5] *Chiray et al.* A33669/39.
[6] *Fothergill* A64755/02, *Novak and Jones* A33609/39.
[7] *Kelemen* A71800/44.

PARA-OVARIAN BRENNER TUMORS

In exceptional cases Brenner tumors may apparently be formed in the para-ovarian region. Thus in one patient[1] a small Brenner nodule was discovered in the Fallopian tube.

[1] *Smith* A28069/35.

OVARIAN BRENNER TUMORS IN ANIMALS

In the fowl a growth was described under the name of oophoroma folliculare[1] which appears to have been a counterpart of the Brenner tumor.

[1] *Seifried* A73129/23.

ENDOMETRIOSIS

(See also Vicarious Menstruation in Sect. IV, Vol. VI).

Synonyms: Endometriosis, endometrioma, endometriomyoma, endometrioid heterotopia, adenoma endometrioides, adenomyohyperplasia, adenosis benigna, adenomyosis, adenomyoma, endometriomyoma, adenofibrosis endometrioides, ectopic endometrial cysts, peritonitis adenoides, adenomyometritis, adenomyositis seroepithelialis, hysteroadenosis metastatica, ectopic Müllerianoma, adenoma of Menge, Sampson's tumor, solenoma, chocolate cysts, haematocystis picea, Teercysten, kystes menorrhagiques, kystes hematiques, ovarian hematomas of endometrial (Müllerian) type, salpingitis isthmica nodosa.

Terminology: It should be noted that some of the terms listed above are not strictly speaking synonymous inasmuch as they denote particular localizations of the endometrioma. All of them, however, refer to the proliferation of endometrial tissue in an abnormal location. The terms internal, direct, or primary endometriosis and adeno-myosis uteri are synonymously used to denote endometriomas which develop in direct continuity with the endometrium and invade the uterus from the inside; the designations external, indirect, secondary, migratory or metastatic endometriosis are reserved for all other endometriomas. The name "endocervicosis" is sometimes used to describe "cervix erosions" with manifestly endometrial lining, while the designation "salpingitis isthmica nodosa" refers to endometriosis in the isthmus of the oviduct.

It is regrettable that some investigators persist in employing the term endometriosis as synonymous with external endometriosis, while others use it as a generic term which includes both the external and internal types. This ambiguous usage led to a great deal of confusion and must be kept in mind in evaluating the relevant literature.

In this Encyclopedia we shall employ the term "endometriosis" to designate the underlying pathologic process (in analogy with tuberculosis or lymphogranulomatosis) and the term "endometrioma" for the individual focus of abnormal growth (in analogy with "granuloma"). Unlike some other investigators e.g. Homma,[1] we do not consider the ending "-oma" inappropriate in this instance; firstly, because custom does not restrict it to "true" neoplasms (e.g. granuloma) and secondly, because we are not convinced that endometriomas differ essentially from the "blastomas". On the contrary, we feel that they are sufficiently similar to the latter to indicate this fact by their name.

REVIEWS

CZECH: *Stolz* B5613/28, *Janota and Recek* A68015/29, *Zubrzycki* B7019/35.

DANISH: *Aagard* B6712/28, *Aaberg* B20181/38, *Franck and Ohlsen* B10010/39.

DUTCH: *Muller* A68493/22, *v. Dongen* B10906/27, *v. Dongen and Hammer* B10907/27, *Hartz* B10909/31, *Lawick and van Pabst* B10916/37, *Rombach* B5441/38, *de Snoo* B20163/38.

ENGLISH: *Schwarz* B20561/15, *Bailey* B7448/24, *Donald* B11221/25, *Sampson* B11226/25, *Nicholson* B7407/26, *Branch* B10896/27, *Fraser* B10908/27, *Goldstine* B10650/28, *King and Fiddes* B6115/29, *Keene and Kimbrough* B6114/29, B5673/30, B5699/30, A74165/33, *Hosoi and Meeker* B6111/29, *Smith* B6082/29, *Maxwell* B5702/31, *Hill* B10911/32, *Allen* B5812/33, *Harbitz* B5819/34, *Kitzmiller* B10915/34, *Tyrone* B5859/35, *Sutton* A74130/35, A94406/44, *Hosoi* B10632/36, *Wigham* B10620/36, *Stewart and Claye* B10925/37, *Smith* B10924/37, *Crile* B10297/37, *Dougal* B20191/38, *Scrivner* B20161/38, *Jones* B10913/38, *Watts* B10927/38, *Phillips* B5436/38, *Lartschneider* B5412/38, *Morris* B5496/38, *Wakefield* B5517/38, *Counseller* B5342/38, B15045/39, *Clark* A33569/39, *Bertner* A32321/39, *Sherwood* B15074/39, *Moss* B15073/39, *Colcock* A34414/40, *Dreyfuss* A32551/40, *v. Geldern* B5057/40, *Bland* B20491/41, *Tigert* B20502/41, *Gillespie* B20512/41, *Sutton* B20522/41, *Hurd* A36560/41, *Geist* B6672/42, *Haydon* A55562/42, *Holmes* A37770/42, *Meigs* B20531/42, *Sanders* B10889/42, A57436/43, *Goodall* B6649/43, *Pascoe* A57789/43, *Wolford* B10883/43, *Linder* B10879/43, *Willis* B10874/43, *Jenkinson and Brown* A58687/43, *Masson and Cariker* B10842/44.

FINNISH: *Peterson* B6889/31, *Kärki* B6837/32, *Turunen* B5058/39.

FRENCH: *Louis* B11077/08, *Rulle* B10665/28, *Jayle* B11044/28, *Nathan* B6874/29, *Michon* A64438/30, *Moulonguet* B10917/32, *Portes and Isidor* B20316/33, *Bizard et al.* B20333/35, *Leuret* B5847/35, *Delannoy et al.* B20353/36, *Brocq and Palmer* A95238/37, *Okincsyc* B20148/37, *Gricouroff* B15573/37, *Rocmans and Petitfrere* B15616/37, *Cadenat* B85602/37, *Cotte and Mathieu* B15044/38, A31795/39, *Gosset et al.* B10014/39, *Brocq and Varangot* B5067/40, B20509/40, *Bland* B20507/41, *Gerin-Lajoie* B6646/45.

GERMAN: *v. Rosthorn* B11130/05, *Haeuber* B20606/24-5, *Meyer* B20552/25, B6856/30, B6866/30, *v. Oettingen* B10946/27, *Albrecht* B6715/28, *Heim* A76990/29, *Vogt* B5740/31, *Schmid* B20287/32, *Lacour* B10931/32, *Spickmann* B10894/32, *Rosenloecher* B20275/32, *Seitz* B11008/32, B20288/32, B5769/32, B5793/33, B10923/34, B15088/39, B11009/39, *v. Jaschke* B20313/33, *Neumann* B5787/33, *Goldham* B20300/33, *Hüssy* B10912/33, *Niermann* B10932/33, *Mankin* B20315/33, *Heidler* B5821/34, *Philipp* B5803/34, B20152/37, *Kleine* B5828/34, *Matyas* B5830/34, *Bayer* B10928/35, *Karlin and Osjakina* B5844/35, *Stickel* B5856/35, *Hellmann* B10630/35, *Benthin* B10895/36, *Boch* B11011/36, *Novak* B10340/37, *Miller* A18279/37, *Heidler* B10936/37, *Lohmann* B5091/39, *Petri* B10037/39, *v. Mikulicz-Radecki* B10031/39, *Philipp and Huber* B10947/39, *Turunen* A34212/40.

HUNGARIAN: *Stefancsik* B11064/30.

ITALIAN: *Cetroni* B10900/26, *Scontrino* B10949/28, *Seitz* B5791/32, *Giaccone* B5818/33, *Alteri* B5771/33, *Garufi* A93982/38, *de Palo* A99262/40.

NORWEGIAN: *Semb* B6928/26, *Sunde* B10950/35, *Harbitz* B10628/36, *Clemetsen* B10007/39.

POLISH: *Maczewski* B11001/28, *Schusterowna* B10948/35, *Czyzewicz* B10904/37.

[1] A32080/39.

PORTUGUESE: *Facanha* B5815/33, *Correa da Costa* B10296/36, *de Aquino Salles* B10274/37, *de Almeida and da Silva Horta* B10001/39, B10002/39, *Paes Barreto* A98169/42, *di Paola* B10882/43.

ROUMANIAN: *Daniel* B13319/07.

SPANISH: *Garcia Orcoyen* B7151/27, *Bolanos and Aleman* B5716/31, *Seitz* B5792/33, *Borras et al.* B20292/33, *Luque and Fernandez-Ruiz* B59340/35, *Gonzalez Marmol* A27741/35, *Risolia and Brea* A95317/37, *Potenza* B20499/40, *Pou de Santiago* A98088/41, *Baldi and Masciottra* A98100/41, *Lopez de Nava* B10864/42, *Achard* A10884/42, *di Tursi* B10871/43, *Labandibar* B10863/43.

SWEDISH: *Marcus* B5743/31-2.

UKRANIAN: *Levinsky* B11000/34.

DEFINITION

Endometriosis is a condition in which endometrial tissue proliferates in an ectopic location.

It is customary to distinguish between internal (direct) and external (indirect) endometriosis, depending upon whether the endometrial tissue proliferates within the uterus, [by growing into the muscle directly from the inside] or whether it grows outside the uterus [on the surface of the ovary, within the oviduct, on the outside surface of the uterus or oviduct, in the pelvic peritoneum, the intestinal serosa, etc.]. Internal endometriosis has often been designated as "adenomyosis", a term which is no longer necessary since now it is fairly generally accepted that the internal and external types of endometriosis are essentially identical conditions.

The ectopic endometrium may lead to cyst formation and if menstruation occurs from the ectopic endometrium, the menstrual blood is usually retained within the cyst cavity, giving rise to the so-called "chocolate cysts" or "tarry cysts". In some publications, hemorrhagic follicular or corpus luteum cysts have also been designated as "chocolate" or "tarry cysts", but it is no longer necessary to use these noncommittal and confusing terms since the endometrial structure of the cyst lining definitely identifies the formation as an endometrioma.

HISTORY

The history of endometriosis has repeatedly been reviewed.[1]

It is almost certain that many cases of "vicarious menstruation" (see Sect. IV, Vol. VI)—known to physicians and laymen since time immemorial—were the result of bleeding from an ectopic endometrium. The same is true of the "tarry" or "chocolate cysts" in the ovary and the pelvic peritoneum frequently described early in the nineteenth century. v. Rokitansky[2] was probably the first to recognize internal endometriosis as an independent form of disease. Later Babes[3] described "epitheliale Geschwülste in Uterusmyomen". Russell[4] was the first, however, to recognize endometrial tissue in the ovary. This discovery was later confirmed by other investigators[5] and it is generally accepted now that the structure of the tissue in such growths is essentially the same as that of the uterine lining. Although the interpretation of the pathogenesis of such cysts is still subject to much controversy, it may be said that Sampson's[6] classical investigations convinced most workers that at least in some, if not in all cases, ectopic endometrium grows in the pelvis because it is regurgitated there through the oviducts at the time of menstruation.

The term "endometrioma", which is now commonly in use, was proposed by Bell;[7] it was later suggested that "endometriosis" is a preferable designation[8] since it stresses the resemblance of the structure to endometrium, without characterizing it as a true neoplasm. The term "adenomyosis" had been in use at an even much earlier date to designate the internal type of endometriosis.[9]

Many additional early references are of historic interest.[10]

CLASSIFICATION

The various types of endometriosis may be classified according to different viewpoints. We may distinguish between the usual benign and the rare malignant type of endometriosis.

Goodall[11] proposes the following classification in which endosalpingiosis and endocervicosis are also included:

- Endometriosis
  - 1. Mixed
    - Benign
    - Malignant
  - 2. Stromatous
    - Benign
    - Malignant
- Endosalpingiosis
- Endocervicosis

[1] *Clark* A33569/39, *Goodall* B6649/43.
[2] B6901/860.
[3] B6719/882.
[4] A51017/899.
[5] *Cullen* B6676/08, B6655/20, *Wagner* B9451/18.
[6] B8682/21, A81410/21, A80395/22, A80394/22.
[7] A68506/22.
[8] *de Josselin de Jong and Snoo* B107/25, *Sampson* B6664/25.
[9] *v. Recklinghausen* B6405/896, *Cullen* A48333/896.
[10] *Wullstein* B6798/893, *Kranzfeld* B6836/897, *Kossmann* B6835/897, *Borst* B6732/02, *Füth* B6767/03, *Meyer* B6863/03, B6864/19, *Schickele* B6909/13, *Hueter* B6816/18.
[11] B6649/42.

It is debatable whether that type of endometriosis which happens to occur in the cervix uteri deserves a special designation, instead of being termed "endometriosis of the cervix", in analogy with other localizations to which we merely refer as endometriosis of the rectum, sigmoid etc. It is likewise questionable whether endosalpingiosis should or should not be classified as belonging to the group of endometriosis. Obviously, it would also be possible to subdivide the various types, purely on the basis of the location of the endometriomas into ovarian, tubal, uterine, diffuse, pelvic, generalized peritoneal, etc., endometriosis. Such a purely topographical system of classification is of little practical use, however, and indeed, there does not appear to be any real need for a subdivision of endometriosis upon a purely morphologic basis.

From the clinician's view-point, the following classification has been suggested:[1]

1) That of a uterine tumor.
2) That of obstruction or invasion.
3) That of a tubo-ovarian mass.
4) The symptomatic type, where symptoms only predominate.
5) The postoperative scar type, which is very rare.

Although these subdivisions are sometimes very clear-cut, it is not uncommon to find one or more types present in the same individual; hence at times, such a classification is not particularly valuable even from a purely clinical point of view.

PATHOLOGIC ANATOMY

MACROSCOPIC CHARACTERISTICS: Upon naked eye inspection, the endometriomas usually appear in the form of small masses, surrounded by adhesions. They are found on either one or both sides of the pelvis, not infrequently on the posterior surface of the uterus or in Douglas' space. Upon loosening the adhesions, a "tarry", "chocolate" or rust colored fluid escapes. Not infrequently, careful inspection shows several similar areas in the pelvis. They form rather puckered hemorrhagic reddish or bluish areas on the uterosacral ligament, the anterior surface of the sigmoid and the rectum; not infrequently, such endometrioma areas are found diffusely throughout the pelvic peritoneum.[2]

The *size* of the endometriomas varies from small nodules of only a few millimeters to larger cysts measuring up to about 5-10 cm. in diameter. True endometrioma cysts rarely, if ever, become larger than this,[3] and it is doubtful whether such cases as that of an "adenofibromyoma" of the ovary weighing 13¾ lbs. should be regarded as belonging to this group.[4] If the endometriosis is diffuse, the entire pelvis may be completely filled by a rather solid mass consisting of the adenomyomatous uterus, which is firmly adherent to the Fallopian tube and fixed in extensive endometrial adhesions connecting it with the rectum, the sigmoid and the broad ligament. The invading endometrial tissue tends to progress far into the rectovaginal septum and, upon first inspection, the surgeon may gain the impression that there is an extensive invasion of the internal sex organs by a malignant growth.[5]

The *position* of the endometrial nodules is extremely variable.[6] Sometimes, they are limited to the uterus or the ovarian surface. In many instances, however, the ovary as well as extra-ovarian structures, or only the latter are involved.

The *comparative frequency of endometriosis in various organs* may be estimated from the following statistical surveys:

In a series of 80 histologically-confirmed cases of external endometriosis, the distribution of the lesions, expressed as a percentage of the organs involved (164 organ lesions), was the following:[7]

Organ	% of Organs Involved
One ovary (30 cases) } Both ovaries (28 cases) }	35.3
Pelvic peritoneum	4.2
External surface of uterus	2.4
Rectovaginal septum	14.0
Bladder	1.2
Fallopian tubes	1.2
Sigmoid	1.8
Round ligament	0.6
Uterosacral ligament (with adherent rectum)	21.2
Uterovesical peritoneum	7.1
Vaginal vault behind cervix	2.4
Broad ligament	6.0
Inguinal canal	0.6
Laparotomy scar	0.6
Intraligamentous endometrial cyst	0.6
Infundibulopelvic ligament	0.6

In another series in which 260 cases of internal and external endometriosis were analysed, the distribution of the lesions, again expressed as a percentage of the organs involved (361 organ lesions), was the

[1] *Green-Armytage* B5778/33.
[2] *Novak* A63534/41.
[3] *Schwarz and Crossen* A80892/24, A7570/24, *Terasaki* B6085/28, *Novak* A63534/41.
[4] *Zimmerman and Cochran* B15514/27.
[5] *Novak* A63534/41, B109/44.
[6] *Tausch* A31669/39.
[7] *Holmes* A37770/42.

following:[1]

Organs	% of Organs Involved
Uterus	44.8
One ovary alone (53 cases) } Both ovaries (31 cases) }	23.2
Pelvic peritoneum	14.2
Rectovaginal septum	4.4
Bladder	3.0
Sigmoid	2.8
Fallopian tubes	1.6
Small intestine	1.4
Round ligament	1.1
Uterosacral ligament	0.83
Abdominal wall, p.o. scar	0.83
Appendix	0.56
Umbilicus	0.56
Infundibulopelvic ligament	0.28
Stump of cervix	0.28

It will be noted that in this series, which includes internal endometriosis, the uterus was most frequently affected.

In yet another series, comprising 307 patients with external endometriosis, the distribution of the 343 major organ lesions (minor lesions were not listed) was as follows:[2]

Organs	% of Organs Involved
One ovary	36.0
Both ovaries	28.0
Cul-de-sac	25.0
Fallopian tubes	3.2
Tubal stumps	1.1
External surface of uterus	2.0
Broad ligament	1.4
Rectovaginal septum	1.1
Umbilicus	1.1
Cervix	0.25
Appendix	0.25
Bladder	0.25
Laparotomy scar	0.25

All these statistical surveys indicate that outside the uterus—which may be affected both by the external and the internal form of endometriosis—the ovaries and the pelvic peritoneum (especially Douglas' space) are the most common sites of endometrioma formation.

Numerous case reports specifically dealing with endometriosis of the *ovary* furnish material concerning the diverse manifestations of the disease in this location.[3] It is evident from these case reports, as well as from the statistical surveys mentioned above that ovarian endometriosis is frequently *bilateral*.[4] Thus among 55 cases in one series 35 were unilateral and 20 bilateral;[5] most surveys are in agreement with the assumption that the ratio of unilateral to bilateral ovarian involvement is about 2:3.

The *multiple* small surface endometriomas of the ovary are likewise quite common and of a very characteristic appearance.[6]

Perusal of the case reports and statistical surveys listed above indicates, furthermore, that in a very large number of cases, ovarian endometriosis is accompanied by the development of similar lesions either in the uterus or, more frequently, in the pelvic peritoneum especially Douglas' space.

The morphology of the ovarian endometrioma is essentially the same as that of external endometriosis in other sites, but depending upon the degree of involvement, the following classification has been suggested for this particular localization of the disease:[7]

1) Ovarian endometriomas consisting of large, usually coherent, blood cysts of the typical "chocolate cyst" type, without other external endometriomas.

[1] *Fallas and Rosenblum* A33798/40.
[2] *Payne* A32556/40.
[3] *Boeckel* A68331/861, A68332/861, A68333/864, *Emmet* A87113/876, A87114/879, *Bender* B8838/03, *Jones* B8885/03, *Isojama* B12804/04, *Rabinovitz* A68495/17, A68496/17, *Schwarz* A68498/20, *Norris* A80887/20-1, *Shaw and Addis* B11711/22, *Donald* B11653/22, *Nyström* B11762/22, B21062/23, *Bell* A68506/22, *Meigs* A68521/22, *Frankl* A68513/23, *Schwarz and Crossen* A80892/24, *Vogt* A68527/24, *v. Oettingen and Linden* B6702/24, *Kirscht* A68505/25, *Schindler* B6915/25, *Wieloch* 26305/25, *Stübler and Haeuber* B20624/25, *Keene and Norris* B7990/25, *Kitai* B7491/25, *Magner* A68520/25-6, *Keene* B8055/26, *Hendricks* B20795/26, *Stevens* B7993/26, *Dawson* B7379/26, *Stacy et al.* B7353/26, *Davis and Cron* B11016/26, B6745/26, *Branch* B20725/26, *Llewellyn* B20805/26, *Cordua* B7325/26, *Pischzek and Schmidt* B7345/26, *Ballin* B15642/27, *ten Berge* B10644/27, *Brakemann* B15634/27, *Castano* B10646/27, B15466/27, B7148/27, A68132/29, *Keene and Kimbrough* B15669/27, *Higuchi* B5591/28, *Stout* A96738/28, *Benetazzo* A68131/29, *Ballin and Morse* A66271/29, *Brühl* A78113/29, *Engelhard* A68172/29, A68173/29, *Hertz et al.* A68013/29, *Lee* B6119/29, *Sampson* A64542/29, *Palazzo and Sammartino* B5682/30, *Berard and Croizat* A67279/30, *Breuer* A67281/30, *Joachimovits* A64427/30, *Toptchieff* A64450/30, *King* A61565/33, *Heimann and Königshoefer* A53167/34, *Seguy and Isidor* B5854/35, *Möschel* B11073/35, *Isidor* A96044/36, *Bertone* B10623/36, *Staehler* A95327/36, *Frosch* B10625/36, *Daniel and Gerota* A95246/37, *Gutierrez* A96500/37, *Kulikowska* A95272/37, A95273/37, *Okinczyc* A95306/37, *Perez Olivares* A95092/37, *Philipp* A95311/37, *Posatti* A95312/37, *Rhamy et al.* A97400/40, *Santa Cruz Pacheco* A96578/40, *Lobsenz* A96631/41, *Canizares et al.* B10132/43, *Casanovas* A96913/43, *Pravia* B10848/43, *Freire* B10818/43, *Gerin-Lajoie* B6646/45.
[4] *Okinczyc and Parturier* B5788/32, *Muller* A52170/34, *Staehler* A95327/36.
[5] *Beutler* B115/37.
[6] *Cotte and Mathieu* A31795/39, *Novak* B109/44, *Arostegui and Leon Blanco* B10830/44.
[7] *Cotte and Mathieu* A31795/39.

2) Multiple small endometriomas limited to the ovarian surface though sometimes involved in adhesions.

3) Multiple external endometriomas involving both the ovaries and other structures.

It is rather doubtful that a classification of this kind could be of much practical value although it emphasizes the variability of the growth and spread of endometriomatous foci.

One of the most frequent extra-ovarian localizations of external endometriosis is the *oviduct*. Apart from the fact that in generalized pelvic endometriosis, the external, subserous, surface of the oviduct may be the site of endometriomas, it is of importance to note that the lining of the Fallopian tube is also frequently the site of heterotopic endometrial mucosa patches.[1]

The occasional occurrence of *free endometrial tissue in the lumen* of the oviduct[2] is of special pathogenic interest, since it indicates that, at least under certain conditions, the endometrial tissue may regurgitate into the tube, where implanation could then occur. Salpingographic studies show that retrograde peristalsis is quite common in the human oviduct.[3] All of these observations suggest that endometrial tissue particles could regurgitate through the entire length of the tube to its fimbrial end and implant themselves either upon the ovarian surface or upon other pelvic tissues.

Menstruation from tubal endometriosis islets may lead to the formation of a hematosalpinx or to so-called "*tubal menstruation*".[4]

It has been claimed that fertilized ova have a predilection for implantation in tubal endometrium and thus may give rise to extra-uterine *tubal gestation* (see also passage on Pregnancy Incidence in part on Incidence).

Small nodules of endometriosis in the isthmus of the oviduct are sometimes caused by invasion of the muscular layer, by tubal or uterine mucosa. They may give rise to the condition designated as "endosalpingiosis of the cornua" or, more often, "*salpingitis isthmica nodosa*" ("Tubeneckenendometriose" of the German; "endometriome des cornes uterines" of the French investigators).[5]

The *uterus* is likewise very frequently the site of endometriosis.[6]

The *cervical endometriosis* is readily detectable, upon inspection through a vaginal speculum, as a red or brownish-red growth either on the anterior cervical lip or on the side of the external os. It may be mistaken for a cancerous erosion until its true nature is established by histologic control. True endometriosis of the portio vaginalis and cervix[7] is rare and should not be confused with the common "cervix erosion" or "pseudo-erosion of the cervix". The latter is not a true erosion but covered by an epithelium typical of the cervical, not of the fundus region.[8] Cases of secondary invasion of the cervix by endometriomas of the rectovaginal septum etc. are likewise not considered to be true examples of cervical endometriosis in the common sense of the term.

It is perhaps debatable whether the so-called "decidua tumors of the portio vaginalis"[9] also belong to this category.

As indicated above, it is customary to sharply distinguish *internal endometriosis (adenomyosis)* from all other types, inasmuch as its clinical and morphologic features are sufficiently different from those of external endometriomas, to give it the character of a separate disease entity. In the case of internal endometriosis, the glandular tubules of

[1] *Martinotti* B8990/03, *Jones* B12743/03, *Nadory* B13027/04, *Varaldo* B11141/05, *Zweifel* B9492/18, *Boribarn-Wetchagit and Ellis* B9364/20, *Mahle* B21155/21, *Schridde and Schoenholz* B6921/24, *Schindler* B6915/25, B20622/25, *Kitai* B7393/26, *Novak* B6883/26, *Schiffmann* B7349/26, *Meyer* B10657/27, B15487/27, *Lahm* B6840/27, *Hammer and van Dongen* B15476/27, *Mestitz* B10656/27, *Szamek* B5614/28, *Higuchi* B5591/28, *Castano* A68132/29, *Neumann* B5631/29, *Hamant et al.* B5625/29, B5668/30, *Shmatok* B5686/30, *Breuer* A67281/30, *Parfenoff* B5657/30, *Weiss* B5741/31, *Seitz* B20289/32, *Cruz* A62292/32, *Sampson* A62750/32, *Cornil et al.* B20297/33, *Canizares Verson* B5835/35, *Séguy and Tsidor* B5854/35, *Barsony* B6993/36, *Held* B11043/39, *Huber* B15061/39, *Rodriguez* B5117/39, *Philipp and Huber* B10039/39, *Marchetti* A99258/40, *Heim* A99255/40, *Rintelen* A99265/40, *Keller* B10862/42.

[2] *Jägerroos* A21931/12, *Lahm* A68517/25, *Cordua* B20727/26, B6738/26, *Hosoi and Meeker* B6111/29, *Baer* B5772/32, *Sampson* A35245/40.

[3] *Bakke and Romke* B6732/26, *Bakke* B6722/27.

[4] *Minard* A89002/889, A89001/889, *Bond* A85995/898, *Tomson* A89006/898, *Thomson* A89004/898, *Moltzer* A85993/02, *Findley* A85996/03, *Bland* A85994/03, *Montgomery* A89003/04, *Thorn* A89005/04, *Goffe* A86000/04, A85999/04, *Gosmann* A85992/04, *Fitch* A85998/04, A85997/04, *Czyzewicz* B6742/08, *Delporte* A89885/09-10, *Jägerroos* A21931/12, *Albrecht* B6714/24, *Behrend* A89884/25, *Schmid* A89887/25, *Müller* A89886/25, *Lahm* B6840/27, *Hosoi* B6815/32, *Kraul* B10939/33.

[5] *Chiari* B10844/887, *Schauta* B6907/888, *Schickele* B6908/02, *Meyer* B11116/03, *Funke* B12962/03, *Chiarabba* B12976/04, *Hoehne* B10845/05, *Lockyer* B9583/16, *Consoli* B20574/23-4, *Michon and Labry* B7023/27, *Rubin* B6903/28, *Neumann* B5653/29, *Douglass* B12229/29, *Frankl* B21749/29, *Sampson* B5684/30, *Haselhorst* B5762/32, *Pugliatti* B5853/35, *Delannoy et al.* B6998/35, *Gonzalez Marmol* B5842/35, *Casco and Salerno* B10289/37, *Philipp and Huber* A32108/39, B20498/40, *Salaber and Nogues* B20534/41, *Torzsay-Kiss* B10870/42.

[6] *Correa da Costa* B5756/32, *Frankl* B20270/32, *Thiessen* B20346/36, *Pemberton* B10359/37.

[7] *Volk* B8827/03, *Samuel* B8075/25, *Fels* B10648/28, *Rushmore* B5738/31, *Frankl and Kraul* B5840/35, *Fobe* B6958/40, *v. Torzsay-Kiss* B20503/40, *Henriques* B6959/41, B20527/42, *Hobbs and Lazar* B6960/41, *Lash and Rappaport* B10840/43.

[8] *Hinselmann* B10640/28.

[9] *Göbel* B21456/39.

the endometrium invade the myometrium from the inside. Sometimes they reach deep into the substance of the uterine musculature, penetrating the latter throughout its entire width to the subserous layer. While such far-reaching invasion is comparatively infrequent, a considerable degree of loosening of the myometrium due to endometrial proliferation is quite common in the internal type of endometriosis.[1]

In general the internal type of endometriosis tends to invade the uterine muscle more or less diffusely. In some instances, however, large *cystic cavities* are formed within the myometrium[2] and occasionally *pedunculated,*[3] *polypous,*[4] cystic internal endometriomas of the uterus develop, which may occlude the vagina. There appears to be a close relationship between the typical internal endometriosis in which the mucosa grows outward into the uterine muscle, and the various forms of endometrial adenomas, endometrial polyps, cystic polypous fibroids, in which growth occurs inwards towards the lumen.

The endometrial tissue which invades the myometrium usually participates in the cyclic structural variations of the orthotopic endometrium[5] (see also Microscopic Characterization below).

As a special subdivision of internal endometriosis, its combination with *carcinoma of the uterus*[6] may be mentioned; this type is often interpreted as a malignant variety of internal endometriosis (see also Carcinomatous Endometriosis below).

It has been attempted to create another subdivision of internal endometriosis, under the designation "*adenomyosis uteri interna tuberculosa*"[7] and it is undoubtedly true that in many instances internal endometriosis and genital tuberculosis develop simultaneously.[8] The casual correlations between the two diseases—if any—are still unknown.

Endometriosis of the outside surface of the myometrium belongs to the group of "endometriosis externa"[9] as do the other types of pelvic endometriosis.

It is noteworthy that *endometriosis interna and externa* may co-exist.[10] In a group of 44 patients, with external endometriosis, 8;[11] in another similar group of 204 patients, 14,[12] and in a third group of 80 patients, 7[13] instances of simultaneous internal endometriosis were found. Another series of observations deals with 260 patients, among whom 129 showed internal, 95 external and 36 both types of endometriosis in combination.[14] All these observations are in agreement with the concept that the internal and external types of endometriosis are closely related and probably due to a common pathogenic agent. Our own survey of numerous additional case reports, indicates that in patients with external endometriomas, the incidence of concomitant internal endometriosis is approximately 10%. This is all the more noteworthy since many other authors are not in agreement with this interpretation. Thus in a group of 224 cases of internal and/or

[1]*Caudron* B11202/873, *Löhlein* B11209/889, *Fraipont* B11206/889, *Coe* B11204/891, *Cullen* B11096/896, B11097/897, B11061/03, B11098/08, B20576/19, *Switalski* B11136/00, *Pick* B11124/00, *Hirst* B11110/00, *Lichtenstern* B11114/01, *Baldy and Longcope* B11086/02, *Füth* B6767/03, B11102/04, *Nebesky* B11120/03, *Tietmeyer* B11082/03, *Santi* B11132/04, *Cameron and Taylor* B11092/04, *Meyer* B11117/04, B11119/05, *Cameron and Leitch* B11091/04, *Williams* B11143/05, *Taylor* B11139/05, *Tate* B11137/05, *Semmelink and Josselin de Jong* B11135/05, *Polano* B11126/05, *Augier and Delassus* B11085/05, *Kudoh* B11076/05, *Roche* B11129/06, *Graves* B11104/06, *Jessup* B11111/06-7, *Lockyer* B11115/07, *Rutstein* B11080/07, *Kerr* B11112/07-8, *Grünbaum* B11105/08, *Ernst* B11062/08, B11075/08, *Sutton* B11090/08-9, *Wells* B11142/09, *Yamasaki* B11144/10, *Taussig* B11138/10, *Schumann* B11133/10, *Pybus* B11127/10, *Roux* B11131/11, *Lamacchia* B11113/11-2, *Roblin* B11079/12, *Fornero* B11100/12, *van der Hoeven* B20607/12, *Frankl* B6764/13, B20580/16, B20581/22, B6765/25, B5759/32, B11018/37, *Schwartz* B11134/13, *Hellier and Stewart* B11109/13, *Bazy* B11088/13, *Warner* B20630/15, *Cullen* B11926/16, *Panning* B20540/17, *Luban* B20598/18, B20597/18, *Maxwell* B20550/20, *Schwarz* B20562/20-1, *Cranstoun* B20575/21-2, *Horn* B6811/22, *Westmann* B20570/22, *Letulle and Delater* B20615/22, *Fitzgibbon* B20578/22, *Abell* B20543/22, *Schwarz and McNalley* B20563/22, *Herzog* B20585/23, *Frank* B20579/23, *Linden* B11224/24, *Ahumada* B20545/24, B20544/24, *Robins* B20559/24, *Artusi* B7446/24, *McGehee* B11225/24-5, *Kitai* B20590/25, *Jakubowitz* B20539/25, *Jordan* B7488/25, *Spirov* B11063/26, *Burg* B10992/26, *Meigs* B7335/26, *Langen* B10940/26, *Stavely* B11026/26-7, *Talalaiev* B11065/27, *Lahm* B10997/27, *Dorsch* B20537/27, *Burns* B11015/27, *Wittich* B20542/28, *Armanini* B8161/28, *Viana* B8170/28, *Panettiere* B8153/28, *Higuchi* B5591/28, *Wenzel* B20600/29, *Haselhorst* B10935/29, *Baltzer* B11030/29, *Roffo* B11057/29, B21625/29, B11058/30, *Cotte and Martin* B12161/30, *Nikultzeff* B5705/30, *Ossiakina* B11053/30, *Migliavacca* B11048/30, *Baillat and Bertrand* B11029/30, *Hunter and Adams* B11020/31, *Mazza and Lucena* B11047/32, *Cotte and Trillat* B11036/33, B11037/34, *Castano* B10897/33-4, *Placeo* B11056/34, *Helepenstell* B10930/34, *Charbonnel and Darmaillacq* B11032/34, *Albin* B10892/34, *Feurer* A93978/34, *Guercia* B11041/35, B11042/35, *Cotte* B11033/35, B11034/36, B11035/38, *Fernandez Ruiz* B20354/36, *Lapeyre* B11046/36, *Hollstein* B15575/37, *Lapeyre et al.* B10941/38, *Pressly* B20500/41, *Mukherjee* B20517/41, *Holmstrom* B20495/41, *Canizares et al.* B10833/43, *Aparicio* B10859/43, *Brines and Blain* B10877/43, *Reich et al.* 85466/44.

[2]*Mátyás* B11022/34, *Palacios Costa et al.* B11054/36, B11055/37.

[3]*Saylor* B11060/28, *Montaldo* B11049/37.

[4]*Schiffmann* B7349/26, *Nagy* B11050/36.

[5]*Dreyfuss* A32551/40.

[6]*Skamnakis* B20162/38.

[7]*Lartschneider* B10025/39, *Köberle* B15065/39.

[8]*Archambault and Pearce* B11084/06, *Costantini* B11095/13, *Johnstone* B20588/23-4, B20589/24, *Ahumada and Contreras Ortiz* B10952/31, *Vaux* B10959/32, *Stewart* B10958/33, *Rigdon* B10956/33, *Lash* B10955/34.

[9]*Cullen* B20577/21, *Palazzo and Sammartino* B5682/30, *Jürgens* B7009/37, *Turunen* B15620/37, B5516/38.

[10]*Herly* B20935/24, *Schiffmann* B7349/26, *Nigrisoli* B11051/28, *Stankus* B12245/29, *Schereschewsky* B5710/31, *Dellepiane* B11038/33.

[11]*Witherspoon* B5860/35.

[12]*Payne* A32556/40.

[13]*Holmes* A37770/42.

[14]*Fallas and Rosenblum* A33798/40.

external endometriosis, the myometrium was affected in 152, the serosa of the uterus in 7 and the ovary in 41 cases, while in the remaining patients, endometriomas were found outside the ovary or uterus. In this series, there were only 6 instances in which internal and external endometriosis co-existed; the author concluded that "this rarity of the combination is another factor in suggesting a different origin".[1] Nevertheless, only few other investigators subscribe to this view. The great variability in the statistical figures listed above may perhaps, at least partly, be due to the fact that in a group of patients with manifest external endometriosis, the incidence of an accompanying internal endometriosis is greater than in the converse situation. Consequently, the combination type is more common in statistical series in which patients with external endometriosis are surveyed than in groups consisting of women with internal endometriosis.

More or less generalized *pelvic* endometriosis is likewise comparatively frequent.[2] In some instances, the endometriomas are entirely, or almost entirely, limited to *Douglas' space* whence they tend to infiltrate into neighboring organs. These are often designated by special terms emphasizing their topography, such as "paravaginitis", "adenokolpitis nodosa", "adenomyoma fornicis", "seroso-adenomyosis recto-uterina", "serositis fibroadenomatosa rectocervicalis", "adenomyosis and adenofibrosis rectocervicalis", "parametritis posterior" or "recto-uterine" endometriomas.[3]

In some instances the infiltration proceeds farther caudad thus giving rise to the so-called *recto-vaginal* endometriomas.[4]

Occasionally, endometriomas develop more or less selectively in the *utero-sacral ligaments*[5] and a statistical study of 164 cases of endometriosis[6] showed that in 21.2% the utero-sacral ligaments were affected and the rectum was adherent; in 14% of the cases there was a localized endometriosis in the recto-vaginal septum and in 2.4% the endometriosis was on the external surface of the uterus. In this same series, endometriosis of the Fallopian tubes (1.2%) or the sigmoid (1.8%) was rare, but endometriosis of the utero-vesical peritoneum (7.1%) or the broad ligament (6.0%) was comparatively common.

The *vagina* may likewise be the site of endometriomas. The anterior and much more frequently the posterior wall of the vaginal tube or the vaginal fornix ("blue dome cysts") may be involved. Vaginal endometriosis cysts tend to be painful and tender to touch, especially, during the menstrual phase of the cycle. In some of these cases, the vaginal endometriomas were apparently formed as a result of direct implantation upon the mucosa but most of them arose due to spreading of endometriomatous tissue from Douglas' space through the recto-vaginal septum.[7] Some endometriosis cysts actually perforate into the lumen of the vagina.[8]

Endometriosis of the vagina has occasionally been seen to develop during pregnancy[9] or following vaginal hysterectomy,[10] in the latter case presumably due to implantation of the endometrium on the vaginal surface during the intervention. Trauma due to surgical interventions or childbirth probably plays a role in many of the case reports quoted above and it is perhaps not inappropriate to speak of a vaginal scar endometriosis as a lesion comparable to the much more common analogous condition in abdominal scars.

The *vulva*[11] and the *perineum*[12] may also exhibit endometriomas. In some cases, so-called perineo-anal endometriomas were formed owing to the spread of ectopic uterine mucosa throughout the perineum to the anal region.[13]

Following perineal tears or episiotomies scar endometriomas may also develop in this region.[14]

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[1] *Dreyfuss* A32551/40.

[2] *Handley* B8951/03, *Donald* B7646/23, *Herd* B11223/25, *Branch* B20725/26, *Ballin and Morse* A66271/29, *Novak* B5735/31, B10609/36, *Cotte and Grangette* B5692/31, *Crossen* B20267/32, *Mussey and Butsch* B10966/34, *Butsch* B10964/35, *Malcolm* B10605/36, *Perez Olivares* B15610/36, *Frosch* B10625/36, *Gardner* B10012/39, *Payne* A99263/40, *Anderson* A99244/40, *Kellar* B20496/41, *Lucas* B20515/41, *Knowles* B20529/42.

[3] *Meigs* B7130/27, *Collins* B7149/27, *Ahumada* B8125/27, *Payne* B15530/27, *Maczewski* B7012/28, *Mattina* B6063/29, *Stefansik* B1065/32, *Lucas* B11072/32, *Haselhorst* B5780/33, *Albrecht* B5811/33, *Chydenius* B6997/35, *Batizfalvy* A32124/39, *Opazo* B20533/41.

[4] *Kellogg* B21349/17, B21289/19, *Heineberg* B21346/17, *Cullen* B21344/17, *Krakowsky* B11684/22, *Shaw and Addis* B11711/22, *Lochrane* B11686/22, *Pincsohn* B7665/23, *Herly* B20935/24, *Collins* B16105/27, *Bancroft and Jessup* B8127/28, *Tixier and Pollosson* B12194/30.

[5] *Davis and Cron* B6745/26, B11016/26, *Israel* B10325/37.

[6] *Holmes* A37770/42.

[7] *Curtis* B11791/18, *Donald* B11653/22, *Boerma* B7455/25, *Palmer* B6887/25, *Davis and Cron* B11016/26, B6745/26, *Schoch* B8078/26, *Derocque* B11068/26, *Heineberg* B6807/27, *Hinselmann* B8200/27, *Schuster-Kadisch* B8158/27, *Iraeta* B10651/28, *Palazzo and Sammartino* B5682/30, *Halter* B6/85/30, *Meyer* B6866/30, *Sachs* B5708/31, *Buiko and Lissowetzky* B5753/31, *Uebermuth* B5713/31, *Heim* B5690/31, *Michon and Condamin* B5734/31, *Murray* B6873/32, *Lissowetzky and Buiko* B5763/32, *Hellendall* B5822/33, *Zacherl* B12399/33, *Harbitz* B5819/34, *Penkert* B5801/34, *Geist* B7004/34-5, *Hay* B10018/39, *Dannreuther* A36032/41, *Ahumada et al.* B10885/42.

[8] *Hermstein* B6022/29.

[9] *Portes et al.* A33236/39.

[10] *Kasprzyk* B10021/39.

[11] *Henry* B116/27, *Skorpil* B5855/35, *Jeffcoate* B15577/37, *Schulz* A32083/39, *Gigl* A99252/40, *Ahumada and Sammartino* B10875/42.

[12] *Palmer* B6887/25, *Prager* B5766/32, *Peltier de Queiroz* B21722/32, *Harbitz* B5819/34, *Skorpil* B5855/35, *Weiss and Synephias* B5518/38, *Jessing* B20514/41.

[13] *Weis and Fobe* B20348/36.

[14] *Violet* B6950/27, B7020/28, *Neumeiler* B6880/26, *Micholitsch* B7013/33, *Sjövall* B15765/40.

More or less *generalized peritoneal endometriosis* is comparatively rare and usually results either from the rupture of a large endometriosis cyst (occasionally perhaps also from massive regurgitation of menstrual fluid into the peritoneum), which can give rise to generalized peritoneal re-implantations of uterine mucosa tissue. This type—sometimes designated by the French investigators "péritonite cataméniale"—may give rise to severe peritonitis-like symptoms during the menstrual period.[1]

Endometriomas may also be found on the surface of *various intestinal loops*,[2] the most frequent intestinal localization being the *rectum, sigmoid and pelvic colon*.[3] The average incidence of recto-sigmoid involvement in a series of 613 cases of external endometriosis was 26%.[4] Occasionally, isolated patches of endometrioma tissue have also been found in the *cecum*,[5] *appendix*[6] *small intestine*[7]—especially its ileum portion[8]—or the *omentum*.[9]

The *urinary bladder*, though not frequently affected, may show proliferating surface endometriomas which sometimes penetrate to the mucosa; they frequently originate as "vesico-vaginal endometriomas".[10] This localization is of special clinical importance inasmuch as it tends to give rise to cyclic disturbances of micturition. Gross hematuria was noted in 13 among 46 cases of bladder endometriosis in one carefully examined series of patients.[11]

Endometriosis of the *ureter* has only rarely been described,[12] but it is probable that other instances of this condition have escaped recognition and were erroneously diagnosed as ureteral tumors. Several cases are known in which ureter compression and hydronephrosis resulted from a diffuse pelvic endometriosis[13] and in one patient an endometrioma was located in the uretero-vesical orifice.[14] In another instance an ovarian "chocolate cyst" was so closely adherent to the ureter that following removal of the cyst a fistula developed between the ureter and the abdominal wound (later this closed spontaneously).[15]

Endometriosis of the *anterior abdominal wall*, generally in the region of the *umbilicus*, is of special interest inasmuch as it is difficult to explain this particular localization on the basis of reimplantation. Conversely, the metaplasia theory (see part on Pathogenesis below) would permit a rational interpretation, inasmuch as remnants of celomic epithelium are frequently found in the umbilicus, and through metaplasia these could conceivably give rise to endometrial tissue.

Umbilical endometriosis generally appears in the form of small nodules which, if they approach the surface, may give the skin a bluish tinge. These nodules become tender and painful at the time of menstruation and if they break through to the skin, periodic bleeding may occur from the umbilical

[1] *Duclos* A85660/889, *Pichevin* A85229/01, *Johnson* B8342/23, *Sampson* B10666/28, *Koerner* B6116/28, *Pallares* B5633/29, *Novak* B5765/31, *Mussey and Butsch* B5849/35, *Möschel* B11073/35, Sturgis B10890/42.

[2] *Monat* B7405/26, *Branch* B20725/26, *Oberling and Hickel* B10661/27, *Biebl* B7147/27, *Schuler* B5711/31, *Damm* B5722/31, *Göbel* B11069/32, *Döderlein* B20268/32, *Möschel* B11073/35, *Neumeyer* B20343/36, *Hepburn* B10321/37, *Seidl* B11074/37, *Lemare et al.* B5411/38, *Graff* A99254/40.

[3] *Scharpenack* B8925/03, *Sitzenfrey* B12405/09, *Füth* B11103/10, B20583/17, *Forssner* B11101/11, *Forgue and Massabuau* B11099/12, *Raspini* B11128/12, *Renisch* B11078/12, *Sutton* B11089/13, *Leitch* B20594/13-4, B20595/14, *Simiam* B20541/14, *Fries* B20538/14, *Yeomans* B21340/17, B11822/18, *Violet* B20566/21, B20567/24, B11066/28, *Miles* B20554/21-2, B7159/27, B7131/27, *Tobler* B6945/23, *Judd and Fouldes* B6827/23, *Gross* B20740/25, *Michon and Comte* B7337/26, *Michael* B10658/27, *Graves* B6780/27, *Sharples* B7140/27, *Thuy Ba* B20599/27, *Iraeta* B10651/28, *Dawson* B5622/29, *Berard and Croizat* A67279/30, *Matry* B5677/30, *Oehlecker* B20284/32, *Allen* B5812/33, *Kirchner* B20307/33, *Harbitz* B5819/34, *Masson* B117/35, *Konjetzny* B5846/35, *Bartlett* B5832/35, *Maclean* B20341/36, *Bertone* B10623/36, *Friedman* B10624/36, *Okinczyc* B20344/36, *Cattell* B10290/37, *Schofield and Bacon* B5509/37, B20159/38, *Dukes* B20192/38, *Bazy et al.* B15033/38, A31926/39, *Henderson* A32451/39, *Josefsson* B10020/39, *Bergeret and Rachet* B10005/39, *Papin* B15082/39, *Mayo and Miller* B5097/40, *Colcock* A34414/40, *Henschen* B20528/41, *Lefrançois* 80889/41, *Blaikley* B20506/41, *Patton and Patton* B20519/41, *Bunch* B10860/43, *Smith* B10869/43.

[4] *Jenkinson and Brown* A58687/43.

[5] *Keller and Fobe* B15578/37, *Leroux and Malgras* B15071/38, *Bustos and Brachetto Brian* B10886/42.

[6] *Dougal* B7647/23, *Outerbridge* B7591/25, *Seelig* B7617/25, *Jayle* B7155/27, *Milone* B5689/30, *Baillat* B6721/30, *Breuer* A67281/30, *Harbitz* B5819/34, *Kulikowska* A95273/37, A95272/37, *Votta* B20174/37, *Gauthier-Villars and Marthe-Lamy* B7003/39, A31917/39, *Reis and Sinykin* A33975/40, *Milnor and Tilden* A56571/42.

[7] *de Josselin de Jong* B6823/13, B6824/19-20, *Haufler* B5697/31, *Behrendt and Neumeyer* B6994/36, *Aronsson* A99246/40, *Milnor* B20516/41.

[8] *Jayle* B7155/27, *Starr* B5636/29, *Kahn* B5730/31, *Gallo and Pozzo* A99251/40, B20492/41, *Glenn and Thornton* A34487/40, *Waters* A36005/41.

[9] *Frosch* B10625/36, *Yamada and Sasaki* B10378/37.

[10] *Stickney* B20564/15, *Judd* B121/21, *Brady* B7456/25, *Keene* B6830/25, *Keene and Norris* B7990/25, *Whitehouse* B119/26, *Frommolt* B11242/27, B20271/32, *Müller* B11245/27, B10608/36, *Morson* B11244/27-8, *Ottow* B5632/29, B5656/29, B11247/30, *Plaut* B5658/29, *Oehlecker* B5654/30, *Keene and Kimbrough* B5673/30, *Ruiz and Roncoroni* B11059/30-1, *Döderlein* B20268/32, B20299/33, *Eberhard* B20269/32, *Cilento* B5775/32, *Köhler* B20308/33, B6838/33, *Haselhorst* B5820/33, *v. Sauer* B5790/33, *Settergren* B5808/33, B5807/33, *Kamniker* B11243/34, *Harbitz* B5819/34, *Weijtland* A52980/34, *Perlmann* B11534/34, *Phillips* B5802/34, *Perard and Elbim* B5852/35, *Henriksen* B118/35, *Chauvin* B15603/36, *v. Mikulicz-Radecki* B10606/36, *Mark* B10336/37, *Adams* B5321/38, *McClelland* B10028/38, *Homma* B11533/38, *Stoeckel* B11535/38, *Gregoire and Couvelaire* B15053/39, *Reynolds* A32230/39, *Mabuti* B10027/39, *Waters* 80981/40, *Dreyfuss* A32551/40, 78385/40, *Nixon* A32894/40, *Kahle et al.* A37134/41, *Hennig* B20526/41, *Baker and Brewer* B20524/41, *Rubritius* B10868/42, *Williams* B10873/43.

[11] *Moore et al.* A56725/42.

[12] *Stickney* B20564/15, *Randall* A37554/41.

[13] *Morse and Perry* B5607/28, *Haselhorst* B5781/33, *Hauser* B20199/38.

[14] *Williams* B10873/43.

[15] *Rongy and Seley* B11450/44.

region.[1] It is rather probable that the so-called "vicarious menstruation" of the umbilical region, frequently reported in the ancient medical literature, is likewise due to umbilical endometriosis.

Various investigators noted that in the immediate vicinity of umbilical endometriomas "myxomatous" tissue, similar to Wharton's jelly,[2] tends to develop and the sweat-glands undergo hyperplasia, perhaps due to humoral stimuli emanating from the ectopic mucosa.[3]

Meyer[4] was apparently the first to show that endometriomas sometimes develop in laparotomy scars. Among 576 women operated on for endometriosis in the Mayo Clinic from 1923 to 1934 ten instances of this complication were noted.[5] These scar endometriomas may reach a considerable size and sometimes show characteristic menstrual swelling or, if they communicate with the outside, actual bleeding at the time of menstruation. At the time of the menses they become tender and painful. Such endometriomas in laparotomy scars are probably responsible for the vicarious menstruation in scar tissue frequently described in the old literature. In agreement with the implantation theory, it was originally thought that these endometriomas develop only after operations on the uterus which would be likely to cause transplantation of endometrial tissue into the scar. Conversely, some workers[6] insist that scar endometriosis may occur after any type of laparotomy and that actually it is comparatively uncommon *after episiotomy* (see above, under perineal endometriosis) *hysterectomy, appendectomy* or *cesarean section,* although a sizable group of such cases has been observed (see below under functional pathogenesis).

Salpingiectomy[7] and *ventral fixation of the uterus* are especially often followed by scar endometriosis.[8]

In view of the comparatively great importance of scar endometriosis in clinical medicine, it may be well to summarize here a series of relevant observations collected by one reviewer:[9]

Laparotomy with ventrofixation of the uterus (often combined with some other operation on the sex organs)	81
Operations on the adnexa	14
Abdominal cesarean section, at term	14
Abdominal cesarean section in cases in which duration of pregnancy is not stated	9
Abdominal cesarean section, done early in pregnancy (hysterectomy and evacuation)	28
Laparotomy for perforation of the uterus during induced abortion	2
Laparotomy with opening of non-pregnant uterus	14
Laparotomy for ruptured tubal pregnancy	7
Laparotomy for appendicitis	15
Laparotomy for unknown reason	9
Total number of cases observed	193

It is evident from this statistical survey, that endometriosis of the abdominal scar occurs with particular frequency, following interventions on the uterus, although in a noteworthy number of instances the eliciting operation was performed for appendicitis.

As regards the *pathogenesis of scar endometriosis,* it is most probable that in the cases in which the intervention affected the internal sex organs, dissemination of endometrium or tubal mucosa occurred either by direct inoculation or by spread through adhesions. The ventrofixation methods in which the corpus uteri is directly sutured to or into the abdominal wall, are particularly apt to give rise to endometriosis in the abdominal scar. The operations on the adnexa, which are often simultaneously performed, may also play an important part in the pathogenesis of such cases. The fact that all types of transitions are observed between direct uteroparietal fistulae, fistulae with surrounding endometriosis and isolated endometriomas in the anterior abdominal wall—with only traces of endometrial tissue passing into the uterine cavity—are in agreement with the above-mentioned interpretation.[9]

Endometriosis of the abdominal scar, following *appendectomies,* was most frequently seen in patients

[1] *Mintz* B6871/899, B6872/09, *Green* B6781/899, *Pfeiffer* B6891/04, *Herzenberg* B6808/09, *Ehrlich* B6756/09, *Cullen* B6740/16, *Hedinger* B6804/23, *Tobler* B6946/23, *Andrews* B7531/25, *Edwards and Spencer* B7469/25, *Danforth* B11233/25, B6743/26, *Schiffmann and Seyfert* B6911/26, *Stacy et al.* B7353/26, *Jeanneret* B6822/26, *Föderl* B7124/26, B6768/27, *Hornung* B6814/27, *Pratt* B7137/27, *Köhler* B15529/27, *Maes* B6856/27, *Palmén* B6886/27, *Oberling and Hickel* B10661/27, *Lelièvre and Montpellier* B10652/27, *Roques* B10664/28, *Frachtman* B7001/28, *Frero* B5649/29, *Baltzer* B21736/29, *Schauffler* B12243/29, *Holm* B12169/30, *Enzer* B5665/30, *Habbe* B5695/31, *Brown* B5718/31, *Rieck* B5736/31, *Thompson* B5748/31, *Eha* B5725/31, *MacFee* B11238/31, *Kleinberg* B11236/32, *Siedentopf* B6933/32, *Spitz* B1064/32, *Longwood* B5764/32, *Hoersen* B11070/33, *Herberz* B20303/33, *Lanos and Busser* B20309/33, *Schwarz* B5806/34, *Harbitz* B5819/34, *Galasso et al.* B5817/34, *Tølbøll* B5857/35, *Knoflach* B5845/35, *Vanderzypen and van Bogaert* B10617/36, *Strongin* B10614/36, *Vartan* B10374/37, *Pasternack* B10358/37, *Boggs* B5333/38, *van Dongen* B15076/39, *Berman* B15034/39, *Chapman* A99249/40, *Aronsson* A99246/40, *da Silva Pereira* B20501/41, *de Moraes* B10880/42, *Marquardt* B10865/42, *Werneck* B10872/43.

[2] *Heim* 3898/33, *Harbitz* B5819/34.

[3] *Ehrlich* B6756/09, *Cullen* B6740/16, *Baltzer* B10643/27, *Föderl* B6768/27, *Schiffman and Seyfert* B6911/26, *Butomo and Schereschewsky* B5642/29, *Habbe* B5695/31, *Siedentopf* B6933/32, *Harbitz* B5819/34.

[4] B11241/03.

[5] *Masson* B117/35.

[6] *Novak* A63534/41.

[7] *Dougal* B6750/26, *Harbitz* B5819/34, *Sutton* A94406/44.

[8] *Amos* B6718/05, *Fraas* B6761/19, *Lochrane* B6850/23, *Döderlein* B6752/27, *Harbitz* B5819/34.

[9] *Harbitz* B5819/34.

in whom it was necessary to drain the abdominal wound. It has been pointed out that the appendectomy scar is situated within the "Streuungskegel" of the tube or ovary (the latter may contain endometriomas) as is the appendix itself. It will also be kept in mind that the appendix may be the site of external endometriosis as stated above.[1] Still, it must be admitted that scar endometriosis, following operations which do not involve the internal sex organs, is rather difficult to reconcile with the implantation theory, although even such instances are not incompatible with this concept, especially if we admit that uterine and tubal mucosa may regurgitate into the peritoneal cavity.

Not infrequently, a long *lapse of time* is recorded between the laparotomy and the subsequently developing scar endometriosis. In 28 relevant cases of one series this time interval was 4.2 years on the average.[2] In another series of 89 cases, scar endometriosis developed after the operation within one year in 59%, within one to four years in 21%, while in the remaining cases the endometriomas appeared in the scar five to eleven years after the laparotomy.[1]

Many *case reports deal with* special problems presented by *scar endometriomas*.[3]

The development of endometriosis in the *inguinal and crural regions*[4] or in the sac of *inguinal or femoral herniae*[5] is likewise difficult to interpret on the basis of the implantation theory. Some investigators[6] express the view that their occurrence in these locations could better be explained on the basis of lymphatic propagation; occasionally, however, endometriomas are found as low down as the junction between the upper and middle third of the thigh[7] and such localizations do not find any rational explanation on the basis of what is known concerning the course of the pelvic lymphatics. In a few instances, inguinal endometriosis, especially endometriosis in the inguinal hernial canal, could perhaps be regarded as due to direct growth of pelvic endometrial tissue through the inguinal canal, (see also chapter on Para-Ovarian Tumors, part on Pathogenesis, paragraph on Endometriosis of *Round Ligaments*).

Among the rarest localizations of endometriomas—but from a pathogenic point of view, also among the most interesting—we should mention their occasional occurrence in the *lung*.[8] It is evident that the transplantation of endometrial tissue into the lung could only be explained on the basis of hematogenous metastasis, but even if the endometrioma is benign it is not inconceivable that, occasionally, it could be transported through the blood stream. Similarly, the exceeding rare occurrence of an endometrioma in the *arm*[9] can only be explained on this basis. In one such case[10] endometriosis occurred in a twenty-five year old woman who suffered from a large nodule in the right elbow region. This nodule became large and painful at the time of the menses. Corpus luteum extract was shown to postpone both the swelling and the pain for as long a period as it postponed the actual menstrual bleeding. Here the hormonal treatment showed a close physiologic relationship between the orthotopic and ectopic endometrium.

The occasional finding of endometrioma tissue in *lymph nodes*,[11] especially those of the inguinal region, has repeatedly been used as an argument in support of the lymphatic dissemination theory, but the validity of this interpretation has been strongly contested (see below under Pathogenesis).

The considerable number of relevant *case reports* illustrates the manifold distribution patterns of the

[1] *Harbitz* B5819/34.
[2] *Wyrens and Randall* 81818/41.
[3] *Andrews* B11229/10, *Klages* B6832/12, *v. Franque* B6766/16, *Danforth* B11232/19, *Schaanning* B6906/21, *Brewer* B11230/21, *Cahn* B11231/22, *Hedinger* B6804/23, *Tobler* B6946/23, *Ladwig* B11237/24, *Skajaa* B6935/24, B6936/26, *Vassmer* B20565/24, B6948/25, *Neugebauer* B6878/25, *Lemon and Mahle* B6845/25, *Keller* B6831/25, *Mark* B20616/25, *Rosenstein* B6902/25, *Beer* B11228/26, *Berkeley* B6727/26, *Bonney* B6729/26, B6730/31-2, *Nicholson* B6882/26, *Michelmann* B6868/27, *Polano* B6894/27, *Pratt* B6897/27, *Roeder* B10985/28, *Ballin* B10642/28, *Goullioud et al.* B6778/28, *Douglass* B6751/28, *Bonney and Davidson* B6731/28, *Ehrenpreis and Letulle* B6999/28, *Haeusermann* B6782/28, *Versé* B6949/28, *Moench* B11240/28-9, *Legerlotz* B6843/29, *Baumgart* B11067/29, *Williams* B6797/29, *Meigs* B11239/29, A65620/30, *Krebs* B5674/30, *Coggi* B6737/30, *Haselhorst and Otto* B6800/30, B6801/30, *Damm* B5757/31, *Ingraham* B11235/31, *Barzillai* B11227/31, *Bárdosi and Habán* B6724/32, *Harbitz* B6787/32, *Strauss* B7030/32, *Brodsky* B5774/33, *Stultz* B6942/33, *Kranzfeld* B7011/33, *Krieger* B11071/33, *Pfleiderer* B6892/33, *Sengupta* B10986/33-4, *Schumann and Parke* B7017/34, *Harbitz* B5819/34, *Geist* B10312/37, *Kraul* B5410/38, *Goulart de Andrade* B5397/38, *Briscoe* B6996/39, *Hewitt* B7007/39, *Funck-Brentano et al.* B7002/39, *Machado* B10030/39, *Santa Cruz Pacheco* A96578/40, *Wespi and Kletzhändler* B20505/40, *Wyrens and Randall* A56034/42.
[4] *Steichele* B6711/, *Hollmann* B20746/25, *Shaw* B7513/25, *Christopher* B6736/27, *Schmitz* B120/27, *Baillat* B6721/30, *Neuffer* B5703/31, *Adams-Ray* B20264/32, *Hilgenfeldt* B5823/34, *Harbitz* B5819/34, *Fürst and Skorpil* A52990/34, *Knoflach* B5845/35, *Fagioli* B5839/35, *Staehler* A95327/36, *Froehlich* B10011/39, *Rousselin* B10042/39, *Machado* B10030/39, *Dickinson* A33601/39, *Ahumada et al.* A99241/40, *Milnor and Tilden* A56571/42.
[5] *Sampson* B6664/25, B7015/26, B6666/26, *Lemon and Mahle* B6710/25, *Laroyenne et al.* B5650/30, *Knoflach* B5845/35, *Mátyás* B5098/40, *Petri* B5109/40, *Donovan* B20511/41 *Patterson et al.* A36043/41.
[6] *Holmes* A37770/42.
[7] *Mankin* B5848/35.
[8] *Thomson and Lamb* B20625/25, *Schwarz* B172/38, *Hobbs and Bortnick* A32506/39, 79767/40.
[9] *Biebl* B20183/38.
[10] *Navratil and Kramer* B15608/36, *Navratil* A31122/39.
[11] *Geipel* B6770/17, *Lüthy* B6852/24, *Halban* B6650/24, *Bungart* B6651/25, *Hollmann* B6652/26, *Mestitz* B10655/27, *Wolff* B5688/30, *Hansmann and Shenken* B5779/33, *Gricouroff* B15605/36.

external endometriomas.[1]

MICROSCOPIC CHARACTERISTICS: The ectopic endometrial mucosa, characteristic of endometriosis, resembles the normal lining of the uterus both histologically and physiogically. It usually—though not always—responds to the same hormonal stimuli which regulate the development and menstrual shedding of the normal, orthotopic endometrium in the uterine cavity. As a result of repeated menstrual bleeding, the surface of the endometrioma—or the central cavity in the cystic variety of this growth—frequently contains menstrual blood. In cystic endometriomas, this blood tends to accumulate and distend the cyst, compressing its epithelial surface. As a result of secondary changes in the blood, its color becomes gradually darker, with a brownish tinge and its consistency becomes thickened; this is why these cysts have been designated as "tarry" cysts.

Owing to pressure by the accumulated menstrual blood, the surface lining may eventually be completely destroyed so that the cysts are not lined by any surface covering. In such instances, the wall of the cyst consists merely of connective tissue with numerous blood pigment-containing macrophages. Sometimes these macrophages contain lipid material and are then described as "*pseudoxanthoma cells*". They resemble those seen in the walls of old ovarian abcesses (see chapter on Inflammation in Sect. IV, Vol. VI). It is probable that some of the so-called "fibroxanthomas",[2] "pseudoxanthomas"[3] and "xanthogranulomas"[4] of the ovary may have been endometriomas or old ovarian abscesses with numerous "pseudoxanthoma cells". These pseudoxanthomatous endometriomas have frequently given rise to the erroneous diagnosis of corpus luteum cysts, since their cellular constituents resemble those of the corpus luteum. Especially in the case of the hemorrhagic variety of corpus luteum cysts, the differential diagnosis may be quite difficult even with the aid of a microscope. In the endometrioma cyst, however, careful search of various regions of the cyst wall almost invariably reveals some evidently endometrial epithelium and stroma which permits the diagnosis.[5] Of course the differential diagnosis between corpus luteum cysts with central hemorrhage and endometrioma cysts with pseudoxanthomatous lining cells comes into consideration only in the case of ovarian endometriosis.

Smooth muscle cells are sometimes observed in external endometriomas although it is difficult to explain their presence outside the uterus. A survey of the relevant literature shows that most muscle cells are fairly common in inguinal and umbilical endometriomas but comparatively rare in other locations.[6]

Special attention was given to the *elastic fibers* in the vicinity of endometriomas since the endometrial stroma cells appear to exert a special histolytic action upon them.[7]

The predominance of stroma cells in certain endometriomas led to the differentiation of the "*stromatous endometriosis*" (also designated as "endometrioma interstitiale" or "stromal endomet-

[1]*Bouzol* B6733/884, *Meyer* B6867/03, *Stratz* B6941/05, *de Besche* B6728/08, *Amann* B6717/15, *O'Keefe and Crossen* B6884/17, *Davidowsky* B6746/20, *Liepmann* B6848/20, *Mahle and MacCarty* B6857/20, *Forssner* B6760/21, *Petitpierre* B6890/23, *Schlink* B6916/23, *Whitehouse and Featherstone* B6795/23, B6796/26, *Abbott* B6713/24, *Komocki* B20591/24, *King* B20938/24, *Albrecht* B6714/24, *Bailey* B6720/24, *Crossle* B6739/24, *Gaifami* B6769/24, *Graves* B6779/25, *Gerlach* B6775/25, *Stübler* B20623/25, *Letulle et al.* B6847/25, *Mandl* B6858/25, *Pankow* B6888/25, *Heim* B11222/25, B5669/30, *Morozov* B20555/25. *Russel-Andrews* B6904/25, *Josselin de Jong and Snoo* B107/25, *Shaw and Addis* B6931/25, *Jayle* B10/26, *Waegeli* B20629/26, *Dossena* B6749/26, *Davis and Cron* B6745/26, *Danforth* B6744/26, *Frank* B6763/26, *Ferraciu* B6757/26, *Heaney* B6803/26, *Jeanneret* B6822/26, *Te Linde* B6944/26, *Natvig* B6875/26, B6876/32, *Neuweiler* B6880/26, *Polster* B6895/26, *Sampson* B6905/26, *Schiller* B6914/26, *Schwarz* B6924/26, *Semb* B6929/26, B6930/26, B6078/28, *Baltzer* B10643/27, *Lahm* B5600/27, *Josselin de Jong* B10914/27, *Davies* B10905/27, *Jayle* B7154/27, *Döderlein and Hornung* B6753/27, *Dellepiane* B6747/27, *Geipel* B6771/27, *Spirito* B6940/27, *Isbister* B5596/28, *Terasaki* B6085/28, *Roques* B10920/28, *Gross* B6107/28, *Bullock* B10645/28, *Shirer* B10667/28, *Jacobson* B5597/28, *Shige-Fukui* B6932/28, *Isbruch* B5960/29, *Jayle* B21590/29, *Moench* B5937/29, *Tigert* B5660/29, *Schulz* B5659/29, *øwre* B5655/29, *Turvey and Boyd* B5638/29, *Burnam* B6735/29, *Horn* B6813/29, *Maczewki* B6855/29, *Schultze* B6923/29, *Shallenberger* B5685/30, *Hector* B5698/30, B10910/30, *Benson* B5641/30, *Gile* B5666/30, *Baumm* B6726/30, *Loewenstein* B6851/30, *Matthias* B6860/30, *Schmechel* B6917/30, *Sellheim* B6927/30, *Vogt* B6790/30, *Wagner* B6791/30, *Kliman* B5700/31, *Eha* B5725/31, *Dougal* B5724/31, *Derichsweiler* B5723/31, *Schwalbe* B10893/31, *Roncoroni and Picena* B5737/31, *Lewinski* B5733/31, *Peterson* B6889/31, *Stetson and Moran* B5746/32, *Goodwin* B5761/32, *Isaacs* B20276/32, *Hill* B20274/32, *Hosoi* B6815/32, *de Snoo* B6938/32, B6939/33, *Ruiz* B10921/33, *Schonbauer* B6926/33, *Briquet* B20293/33, *Leonard* B5798/34, *Pilcher* B11025/34, *Nielsen* B7014/34, *Peple* B5851/35, *Attygalle and Misso* B20331/35, *Barsony* B5831/35, *Thiessen* B10926/35, *Correa da Costa* B5836/35, *Crowley* B5837/35, *Lee and Linder* B10942/35, *Castano* B10898/35, *Moss* B10607/36, *Hay* B10604/36, *Frawley* B10601/36, *Walker* B10619/36, *van der Merwe* B20347/36, *Grier* B15572/37, *King* B15579/37, *Nelson* B15609/37, *Pumphrey* B15611/37, *Pirest* B10360/37, *Cerqua* B10899/37, *Frankl* B10307/37, *Rocmans* B10363/37, *van Tongeren* B10372/37, *Zahedi* B7029/37, *Cromer* B10298/37, *Itibere de Castro Caiado* A97176/38, *Hooper* B20201/38, *Bendixen* B20182/38, *Hurley* B20202/38, *Williamson* B20177/38, *Claye* B10902/38, *Ottobrini Costa and Guerrero Cocuzza* B15070/38, *Flores* B10008/39, *Büngeler and Silveira* B5068/39, *Mocquot et al.* B10033/39, *Counseller* B10903/39, *Küss* B10022/39, *Goodall* A33352/40, *Block* B5065/40, *Madsen* A99257/40, *Graff* B20493/40, *Bradford* A99247/40, *Schultze* B5167/40, *Pearson* B20520/41, *Waugh* B20504/41, *Salgado* B10850/43, *Pou de Santiago* B10847/43.

[2]*Martinez Olascoaga and Castro* A97596/41.

[3]*Bulliard and Douay* A83388/25.

[4]*Cauchois and Isidor* A97577/39.

[5]*King* A65476/30.

[6]*Harbitz* B5819/34.

[7]*Migliavacca* B11023/32.

riosis") as a separate sub-group,[1] although it is doubtful whether this distinction is sufficiently fundamental to warrant a special designation. It has been stated that the presence of typical endometrial stroma is an important characteristic in all cases of endometriosis; this alone distinguishes them from the "adenoses" which consist of invading tubules only. Examples of the latter are the gastric mucosa glands which invade the muscularis of the stomach, Luschka's ducts in the gall bladder and cervical glands which sometimes penetrate deep into the collum uteri. These adenoses are—with debatable justification—regarded as due to mere hypertrophy[2] (see also part on Pathogenesis below).

As we said before, the ectopic endometrial tissue is responsive to the same type of hormonal stimuli which regulate the development of the normal uterine mucosa, hence, it is not surprising that it exhibits the usual histologic changes characteristic of the various phases of the menstrual cycle[3] and that in the presence of an active corpus luteum (e.g. pregnancy) it may also undergo the decidual type of *progestational proliferation*[4] (see also passage on Pregnancy Incidence below).

Finally it should be re-emphasized here that in cases of umbilical endometriosis the sweat glands in the vicinity of the ectopic endometrium tend to undergo marked hyperplasia while the connective tissue may undergo myxomatous transformations (see Umbilical Endometriosis above.)

Circumscribed patches of decidua vera are occasionally described in puerperal uteri under the name of "*endometritis decidualis tuberosa*"[5] but their possible relationship to endometriosis is still in doubt.

SECONDARY CHANGES IN ENDOMETRIOMAS AND IN THE OVARIES OF ENDOMETRIOMA BEARERS: Among the secondary changes which may develop in endometriomas malignant transformation is rare, although several purportedly relevant cases of *carcinomatous endometriosis* ("malignant adenomyoma" or "malignant endometriosis")[6] have been observed both in the uterus and more frequently in the ovary. The presence of endometriosis tissue in lymph nodes (see above) is not necessarily indicative of malignancy, since even benign endometriosis may perhaps be propagated through lymphatic channels. When endometriosis interna occurs concomitantly with a uterine carcinoma[7] or when endometriosis of the recto-sigmoid region is found in a woman with a carcinoma of the rectum[8] or the sigmoid,[9] it may be difficult to decide whether the cancer developed from an originally benign endometrioma or whether the two growths originated independently. The same doubt arises if ovarian cancers are accompanied by ovarian endometriosis (see chapter on Common Carcinomas of the Ovary).

There are a few instances in which a *sarcomatous transformation* ("adeno-myosarcoma" or "adenomyoma sarcomatosum" uteri) of a usually internal endometrioma has been suspected.[10] It must be kept in mind, however, that the so-called "stromatous endometriosis"[11] with its irregular connective tissue elements, may strikingly resemble a sarcoma and that differentiation between primary sarcomas of the uterus (particularly those arising from orthotopic endometrial stroma) and sarcomatous transformation of an internal endometrioma is often impossible.

Minor *metaplastic changes,* such as myxomatous transformation of the stroma ("myxo-adenoma" formation),[12] or squamous metaplasia of small foci within the epithelium of an internal endometrioma[13] are also very rare.

It is noteworthy that endometrial cysts are not infrequently associated with manifestations of *tuberculosis,* but the relationship between these two diseases is not as yet sufficiently clarified to justify a detailed discussion.[14]

The most common secondary change in external endometriomas is the almost constant formation of generally extensive *adhesions.* Repeated irritation by the recurring cyclic menstrual shedding of the surface causes an inflammatory reaction which leads

[1]*Goodall* A33352/40, B6649/43, *Robertson et al.* A37809/42, *Middlebrook* B10866/43.
[2]*Homma* A32080/39.
[3]*Butomo and Schereschewsky* B5642/30, *Tonkes* B5687/30, *Schereschewsky* B5768/31, *Schaanning* B5767/31.
[4]*Amos* B9037/05, *Lochrane* B11467/22, *Winestine* A68502/24, *de Snoo* B8070/25, *Schiller* B6913/25, *White* B20829/26, *de Josselin de Jong* B6825/26, *Harbitz* B5819/34, *Weller* B11013/35, *Fingerland* A94275/36, *Holtz* B15060/38, *Batizfalvy* A32124/39, *Waters* A36005/41, *Novak* A63534/41.
[5]*Richter* A32085/39.
[6]*Andrews* B20546/21, B21122/21, *Tixier and Bonnet* B20626/23, *Sampson* A78939/24, A78941/25, A78940/25, *Reeb* B20558/25, B20620/25, *Thomson* B110/26, *Borowski* B10953/29, *Smith* B6082/29, *Höppner* B1012/31, *Braine* B20266/32, *Seitz* B5769/32, *Migliavacca* B11024/33, *Bräuner* B10951/33, *Cirio* B20295/33, *Roczen* B10963/34, *Lockyer* B111/36, *Vogt* B10618/36, B10960/37, *Hanser* B20355/36, *Bertone* B10623/36, *Winterton* B10962/36-7, *Reinhardt* B15613/37, *Silva* B7765/38, *Tuthill* A97187/38, *Smith and Masson* B10957/39, *Batizfalvy* B21401/39, *Castano* A99248/40.
[7]*Eerland* B5838/35, *Heynemann* A32122/39.
[8]*Braine* B20266/32.
[9]*Jose and Hanson* B20278/32.
[10]*Bauereisen* B11087/04, *Drips* B12163/30, *Orlandi and Meda* B11052/32, *Tudhope* B113/34, *Schrank* B11012/38, *Nylander* B20147/38, *Goodall* B21457/39, A99253/40, *Fienberg* A35379/40, *McDonald et al.* B112/40, *Robertson et al.* A37809/42, *Cotte et al.* B7847/42.
[11]*Goodall* B6649/42.
[12]*Braman* B11203/890.
[13]*Pistofidis* B15085/38.
[14]*Ahumada and Ortiz* B5751/31, *Teräsvuori* B5747/31, *Stewart and Oldfield* B5796/32, *Pugliatti* B5853/35, *de Almeida and da Silva Horta* B5062/39.

to the defensive proliferation of connective tissue.[1]

As indicated in the passage on the age incidence of endometriosis, marked retrogressive changes occur at the time of the menopause.

Torsion[2] is a very rare complication in the case of endometriosis cysts since they do not tend to form a pedicle and are usually fixed by adhesions.

The *ovarian remnant* and the *contralateral ovary* show no characteristic changes in patients with ovarian endometriomas, although they may contain persistent follicles and these are also common in women in whom endometriomas develop outside the gonads.[3] Normal follicles or corpora lutea are rarely found in patients with ovarian endometriomas; this, it was claimed, may account for the high incidence of sterility among these patients[4] (see chapter on Follicle Cysts).

ENDOMETRIOSIS IN COMBINATION WITH OVARIAN TUMORS: Since folliculoid hormones appear to be necessary for the growth of endometrioma tissue, it is understandable that the endometriosis incidence is highest among patients with folliculomas, persistent follicle cysts and small cystic degeneration of the ovaries (see relevant chapters of this volume). The so-called carcinomatous and sarcomatous transformation of endometriomas (see above) may give rise to doubt concerning the possible confusion of these growths with benign endometriomas and co-existent, but pathogenetically independent, malignant blastomas.

INCIDENCE

The *general incidence* of endometriosis is undoubtedly very high, although the figures given by different investigators vary somewhat, depending upon the thoroughness with which the cases were scrutinized. Since endometriosis often manifests itself merely in the form of small inconspicuous nodules or adhesions in the pelvic peritoneum, it is evident that unless careful histologic checks are routinely made, numerous instances will escape attention and will be listed as nonspecific nodules or adhesions.

In one series of 1,453 gynecologic laparotomies, the incidence of external endometriosis was given as only 0.96%, but it was admitted that no careful search for endometriomas was undertaken;[5] in another series of 4,500 diverse gynecologic operations the incidence was 10%;[6] in a third of 4,763 gynecologic patients taken at random, the incidence of endometriosis was 3.0%, of these, 80 were operated upon so that the diagnosis could be confirmed by histologic control. The so-called "chocolate cysts" of the ovary were not included in the series, unless evidence of pelvic endometriosis was demonstrable elsewhere as well. Internal endometriosis (adenomyosis) was likewise excluded unless accompanied by external endometriosis. Since these 80 instances of proven endometriosis occurred among a total of 307 gynecologic laparotomies, the incidence among the surgically-treated cases was 26.0%.[7] This figure agrees fairly closely with those given by other investigators who estimate the incidence of endometriosis among women requiring abdominal operations to be about 30.0%[8] or 21.8%.[9]

In discussing these statistical data at a meeting of the Association of Obstetricians, Gynecologists and Abdominal Surgeons, Meigs[10] stated that in a recent series of 400 private patients necessitating abdominal surgery for gynecologic diseases, 28.0% had endometriosis. At the same time, of 400 gynecologic patients of the Massachusetts General Hospital, who required abdominal surgery, only 5.8% suffered from endometriosis; hence, the author concluded that in private practice the incidence of endometriosis is much higher than in a charity hospital. He added that 50.0% of the private patients upon whom he operated during a period of four months have had endometriosis. On the basis of these statistical studies, the author was able to formulate the conclusion that: "There must be something wrong somewhere." Be this as it may, it is almost generally accepted that endometriosis is more common among the well-to-do than among poor women.[11]

A survey of several large series of case reports indicates that "endometriosis develops in approximately 15% of all women during their active menstrual life."[12]

Additional statistical data concerning the incidence of endometriosis will be found in relevant surveys.[13]

Perusal of the Mayo Clinic's material revealed 114 instances of endometriosis among 2768 patients who underwent surgical operations for gynecologic disturbances.[14]

With regard to the *age incidence* of endometriosis, all investigators may be said to agree that this is a disease primarily affecting women during the childbearing period of life. In one series of observations, 75% of the cases occurred in women aged 30-50 years.[15] In another series of 307 cases[16] the age distribution

[1] *Miller* A18279/37, *Goodall* B6649/42, *Haydon* A55562/42.
[2] *Mazer and Hoffman* A64928/29.
[3] *Miller* A18279/37.
[4] *King* A64228/31.
[5] *Long and Strecker* A32314/39.
[6] *Haydon* A55562/42.
[7] *Holmes* A37770/42.
[8] *Meigs* B173/38, *Goodall* B6649/42.
[9] *Sampson* B6648/27, A64572/29.
[10] A3777Oc/42.
[11] *Fallas and Rosenblum* A33798/40, *Meigs* A37925/41.
[12] *Jenkinson and Brown* A58687/43.
[13] *MacCarty and Blackman* B20549/19.
[14] *Counseller et al.* 85159/44.
[15] *Keene and Kimbrough* B5673/30, B5699/30.
[16] *Payne* A32556/40.

was as follows:

Years	%
Less than 20	0.25
20-30	19.0
30-40	41.0
40-50	37.5
50-60	2.0
Over 60	0.25

In a series of 80 histologically confirmed instances of endometriosis externa[1] the incidence at various ages was:

Years	%
20-28	8.7
29-33	23.7
34-38	27.5
39-43	18.7
44-48	13.7
49-53	5.0
54-63	2.4

A survey of 260 cases, operated on in a private hospital, shows the relative incidence of internal and external endometriosis, as well as the fact that the external type usually requires surgical treatment at an earlier age than the internal:[2]

Years	% Internal	% External	% Combined
Less than 20	0.0	0.0	0.0
20-24	0.0	2.1	5.5
25-29	5.4	17.9	11.1
30-34	10.0	34.8	13.9
35-39	19.3	23.2	25.0
40-44	27.1	11.6	22.2
45-49	24.0	8.4	19.4
50-54	10.9	1.0	2.8
55-59	2.3	1.0	0.0
60-64	0.8	0.0	0.0
Over 60	0.0	0.0	0.0
Total No. of Cases	129	95	36

It is rare to observe endometriosis in women less than 20-23 years of age. A few cases have been reported, however, in women of 16-20 years.[3] No definitely identified instance of prepubertal endometriosis was found in our survey of the entire world literature.

The so-called "congenital adenomyosis"[4] is probably a different entity as regards its pathogenic mechanism; in most cases it appears to be a true malformation or ectopy of endometrium. Alternately during fetal life maternal hormones, which pass through the placenta, can influence the growth of the embryonic endometrium, and it is not inconceivable —though hardly probable—that they may cause endometriosis in the fetus.

The occasional occurrence of postmenopausal endometriosis in elderly women of 67 years[5] or even 78 years[6] is in apparent contradiction with the otherwise well established fact that the ectopic endometrium is dependent upon ovarian hormones. It has even been claimed that a special polypous form of "Menge's adenoma" is typical of the postclimacteric period.[7] In such cases the possibility of a pathologic source of folliculoids (e.g. folliculomas, adrenal cortex) or atypical growth of the endometrioma should be considered. In general, however, the ectopic endometrium involutes at the menopause.[8]

Latent internal endometriosis is not rare in postmenopausal women. In one series of 203 cases, the incidence in patients over 50 years of age was 10%. There was no evidence of an increased folliculoid hormone production, but the endometriosis was invariably asymptomatic and in a state of regression.[9]

The *pregnancy incidence* of endometriosis is low. This is not surprising in view of the fact that endometriosis is usually associated with sterility. Furthermore, if gestation does ensue in a woman suffering from endometriosis, the disease may remain asymptomatic during the pregnancy period because the ectopic endometrium—just as the normal uterine mucosa—does not undergo any cyclic menstrual variations at this time. Conversely, internal endometriosis may so weaken the uterine muscle that delivery is impeded by atony and severe postpartum hemorrhages ensue. The relevant case reports indicate, however, that both internal and external endometriosis can occur in pregnant women,[10] some of them involving the ovary itself.[11] In one of these

[1] *Holmes* A37770/42.
[2] *Fallas and Rosenblum* A33798/40.
[3] *Drips* B11039/27-8, *Meigs* A65620/30, *Payne* A32556/40, *Haydon* A55562/42, *Jenkinson and Brown* A58687/43.
[4] *Weyeneth* B20322/33, B10991/33.
[5] *Jenkinson and Brown* A58687/43.
[6] *Haydon* A55562/42.
[7] *Montaldo* B11049/37.
[8] *Sampson* A80394/22, *Schiller* B20560/24, *Gross* B20740/25.
[9] *Frank and Geist* A56288/42.
[10] *Meyer* B108/05, *Cullen* B6676/08, *Schäfer* B101/17, *Aschheim* B20547/23, B20548/23, B7026/29, *Ulesko-Stroganowa* B106/24, *Josselin de Jongh and Snoo* B107/25, *Schugt* B102/26, *Sampson* B6667/27, *Schweitzer* B103/27, *Szenes* B104/28, B105/28, *Haufler* B5697/31, *Haselhorst* B5780/33, B100/33, *Martin et al.* B6859/33, *Franqué* A52989/34, *Holzbach* B7027/34, B7028/35, *Szymanowicz* B10616/35, *Olson and Hansmann* B10611/36, *Portes et al.* A33236/39, *Batisfalvy* A32124/39, *Portes and Varangot* A33778/40, *Fallas and Rosenblum* A33798/40, *Sackett* B20521/41, *Holmes* A37770/42, *Scott* B10852/44.
[11] *Peralta Ramos* A98085/40, A96573/40, A96572/40.

cases an ovarian pregnancy developed in association with ovarian endometriosis.[1]

Histologic examination of the endometrioma tissue indicates that it participates in the usual gestational changes of the uterine lining. If pregnancy develops in a woman with marked internal endometriosis, spontaneous rupture of the uterus may ensue during labor as a result of the weakening effect which the endometrial invasion has upon the myometrium.[2] In one case, decidual nodules were visible in the mucosa of the cervical portion of the uterus during pregnancy[3] and in a few instances the ectopic decidua nodules were in the ovaries.[4]

As has already been mentioned in the paragraph dealing with the tubal localization of endometriosis, it is not uncommon to find ectopic tubal implantation of fertilized ova in women with endometriosis of the Fallopian tube.[5] Such observations, as well as the above mentioned occurrence of ovarian pregnancy in association with endometriosis of the ovary, have led to the belief that ectopic endometrium in the mucosa of the oviduct may be responsible for many, if not all, instances of tubal gestation (see also passage on ectopic pregnancy in part on Clinical Course).

Experimental observations also confirm the fact that the ectopic endometrium participates in the usual pregnancy changes of the uterine mucosa.[6]

The *puerperal incidence* of endometriosis is likewise low probably because of the same reasons which were mentioned above in explanation of its low pregnancy incidence. It should also be remembered that only in few cases are the manifestations of endometriosis likely to receive special attention during the puerperium.[7]

Almost nothing is known concerning the *racial incidence* of endometriosis, other than that the statistics of American hospitals show no striking difference between its frequency in white and colored women.

Other races are likewise subject to endometriosis, which has been shown to occur, for example, among the Chinese[8] and the natives of the Netherland Indies;[9] one case of internal endometriosis, associated with an adenocarcinoma of the uterus, was described in a Javanese woman.[10]

PATHOGENESIS

REVIEWS: Timofeyeff B11140/11, *Castano* B20572/19, B20573/20, *Lauche* B10999/26, *Michon and Comte* B11004/26, *Spirito* B6940/27, *Klee* B11045/28, *Moench* B11005/29, B11006/29, *Dietzmann* B20596/30, *Jagau* B10988/31, *Gonzalez Marmol* B10995/35, *Scultetus* B10990/35, *Poppek* B10989/36, *Levander* B20530/41, *v. Numers* B20518/41.

Histogenesis: The much debated data concerning the histogenesis of endometriosis have frequently been reviewed on the basis of information derived from human material[11] as well as on the basis of experimental work on animals.[12]

The most generally accepted histogenetic interpretation of endometriosis is the *implantation theory* first proposed by Sampson.[13] According to this investigator, particles of uterine mucosa may regurgitate through the Fallopian tubes into the peritoneal cavity, at the time of menstruation. These particles may then implant themselves either upon the surface of the ovary or at some distance from it upon the peritoneal mesothelium, and there form secondary foci of endometrial tissue. Especially the ovarian foci, which tend to become cystic and comparatively large, may give rise to additional secondary implantations by spreading endometrial particles upon the peritoneum subsequent to rupture of the ovarian cysts. Extra-ovarian endometriomas may also give rise to additional deposits and thus further spread the disease. In some cases, however, the ovaries are not involved, although the peritoneum contains several endometriomas; this indicates that it is not absolutely essential—as had originally been thought—for the endometrial tissue to implant itself first upon the ovarian surface before it can extend to the peritoneum. Under certain circumstances, it reaches the peritoneum directly without passing through the stage of an ovarian endometriosis cyst.[14]

This implantation theory was extensively discussed in the literature[15] and in its support it was pointed

[1] *McKenzie* A98165/43.
[2] Stone B20166/38.
[3] Hinselmann B20275/32.
[4] *Winestine* A68502/24, *Fingerland* A94275/36.
[5] *Ossiakina and Schmatok* B5850/35, *Vara* B15621/36, *Frankel and Schenck* B15571/37, *Isidor* B15606/37, *Morales* B10034/39, *Garcia and Tisne* B5082/39.
[6] *Piccone* B20345/36.
[7] *Szymanowicz* B10616/35.
[8] *Nixon* A32894/40.
[9] *Wreksoatmodjo* B5052/40.
[10] *Eerland* B5838/35.
[11] *Spahn* B11081/06, *Meyer* B11336/21, *Robinson* B20621/25, *Mestitz* B10655/27, *Ferracciu* B10649/28, *Clarke* B5663/30, *Molinengo* B5651/30, *Everett* B5726/31, *Tonkes* B5770/32, *Massazza* B20280/32, *Mankin* B20315/33, *Francois and Isidor* A53122/34, *Delannoy and Bedrine* B11017/35, *Harbitz* B10603/36, *Cadiz Oyarzun* A97073/37, *Tronci* A97318/39, *Reich* B15086/39, *Philipp and Huber* A15084/39, *Young and Feder* B10090/39, *Gricouroff* B10015/39.
[12] *Dellepiane* B6747/27, *Sodano* A68120/28, *Marabotto* B5629/29, *Wolff* B5688/30, *Fumagalli* B5694/30, *Schmid* B5805/33, *Brakemann* B5813/33. *Zocchi* B5810/33.
[13] A81410/21, A80395/22, A80394/22, B6663/22, A78939/24, A78940/25, B6664/25, B6665/25, B6666/26, B6667/27, B6648/27, A78942/28, B5611/28, A64542/29, B5684/30, A62750/32, A35245/40.
[14] *Sampson* A35245/40.
[15] *Vogt* B20627/24, B20628/25, *Koerner* B15483/27, *Sengupta* B10979/33.

out[1] that in the vast majority of women with peritoneal endometriosis, the oviducts are patent, so that menstrual blood could enter the peritoneum through them. At the occasion of laparotomies during menstruation, it has been shown that in fact *menstrual blood regurgitates through the oviducts* into the pelvic cavity. This occurs in patients both with and without peritoneal endometriosis. Particles of apparently normal uterine mucosa, surrounded by blood, were found free in sections of surgically removed oviducts. In this connection the numerous instances of "tubal menstruation" reported in the old literature are especially instructive (see passage on endometriosis of the oviduct in part on Pathologic Anatomy).

In the exceptional cases of pelvic endometriosis, in which the tubes were not patent and the ovaries did not show endometriosis cysts, there was reason to believe that the oviduct became occluded as a result of tubal endometriosis, since it was transformed into large hematosalpinx. The pelvic deposits were presumably formed prior to the obstruction of the oviduct in these patients.[2]

The fact that the *endometrioma tissue is essentially uterine mucosa* has likewise been amply substantiated. It resembles the normal endometrium not only in its histologic structure but, during the normal menstrual cycle, it responds essentially in the same manner as the orthotopic endometrium. The surface layers of the mucosa are cast off at the time when the patient menstruates and this shedding of the surface layer is accompanied by bleeding. It is actually this repeated bleeding from the ectopic endometrium which irritates the adjacent peritoneum and causes both the adhesions with the neighboring organs and the central hemorrhagic fluid accumulations so characteristic of the endometrioma cysts.[2] Further data concerning the functional resemblance of endometriosis and endometrial tissue will be found in the passage on functional pathogenesis in connection with our discussion of hormonal influences regulating the growth of endometrioma tissue. These observations have received ample support from subsequent clinical observations which are most readily explicable on the basis of the regurgitation and peritoneal re-implantation theory.[3]

It has also been shown that the cast-off *menstrual endometrium contains apparently well-preserved epithelial cells* which may partly retain their glandular arrangement[4] and remain *viable* for some time. Human endometrium obtained by curettage is even capable if life, following *explantation*,[5] but this has not been demonstrated as yet for endometrium spontaneously discharged with the menstrua. Even Meyer,[6] who strongly opposes the implantation theory, agrees that when we prove the viability of the discharged endometrium "dann wird die ganze Frage restlos zu Gunsten Sampson's entschieden sein". The growth of human[7] or rabbit[8] endometrium is stimulated in vitro by the addition of hormones to the culture medium; this fact should be borne in mind by those who study the problem with the aid of tissue culture technics.

The occurrence of endometriosis in women suffering from congenital or acquired *obstruction of the uterine cervix or vagina* (gynatresia)[9] is also most readily explained by the peritoneal "spill" and implantation theory; it is evident that if the menstrual blood cannot be eliminated through the normal channels, it is likely to regurgitate through the Fallopian tubes into the pelvic peritoneum. A similar pathogenic mechanism may also be operative in cases of external endometriosis in women with a *uterus bicornis or duplex*[10] or as well as in association with *other uterine malformations*[11] which can cause disturbances in the elimination of the menstrual fluid (see also passage on Retention of Menses in Sect. IV, Vol. VI).

Numerous *animal experiments indicate that endometrial tissue can be transplanted* without great difficulty. Probably the first effort along these lines was the successful homoio-transplantation of an endometrial particle into the anterior chamber of a rabbit's eye in 1874,[12] shortly after it had been demonstrated that various other tissues can readily be transplanted into this site.[13] Observations showing that uterine mucosa can grow in the peritoneal cavity—or even at a great distance from the uterus, in various other regions of the body—are likewise in agreement with the concept that endometrium, accidentally implanted upon various organs in women, could give rise to tumor-like endometrial proliferations. It is noteworthy that in animals such experimentally transplanted endometrial tissue islets tend to persist indefinitely without degenerating and are normally responsive to ovarian hormones, their

[1] *Schiller* B6912/22, *Vogt* B6951/24, *Cordua* B6738/26, *Heim* B6805/27, *Candela* B5643/29, *Sampson* A35245/40.
[2] *Sampson* A35245/40.
[3] *Lahm* A68517/25-6, *Wyatt* A34532/39.
[4] *Lindler* B6849/22, *Harbitz* B5819/34.
[5] *Mayer and Heim* B6861/26, *Cron and Gey* B15710/27, *Heim* B6806/28, *Caffier* B10635/28, 53130/31, *Traut* B5615/28, *Geist* B5777/33, *Hirsch and Jones* B5782/33.
[6] B6866/30.
[7] *Corinaldesi* 29078/34.
[8] *Vercesi* 31116/34, *Guercio* 34188/35, *Guercio and Arnone* 34187/35.
[9] *Anspach* B11083/04, *Rieck* B5804/33, *Rauramo* B15612/36, *Portes and Landrieu* A95417/38, *Jacobi* A99256/40.
[10] *Weyeneth* B20322/33, *Frosch* B10625/36, *Kraul* B5410/38, *Fallas and Rosenblum* A33798/40, *Frank and Geist* A56288/42, *McDonald* A59015/43.
[11] *Cirio* B11093/03, *Williams* B20571/23-4.
[12] *Goldzieher* B6777/874.
[13] *van Dooremal* B6748/873.

growth being especially enhanced by folliculoids.[1]

In the literature considerable importance is attached to experiments on three monkeys which, by virtue of this fact, deserve special consideration. In the first animal hysterectomy was performed on the first day of menstruation and the uterine contents were spread over the peritoneum. 56 days later no endometrial tissue could be discoverd in ectopic positions. In the second monkey human menstrual fluid, taken on the first day of menstruation, was transplanted in different places within the abdominal cavity. A second laparotomy 46 days later revealed no "take". In the third monkey the fundus uteri was resected on the first day of menstruation and its hemorrhagic contents were placed in a peritoneal pouch. The uterine wound was left open so that a fistula was formed between the lumen of the uterus and the peritoneal cavity. The animal was killed 39 days later, at which time no endometrial tissue could be discovered within the numerous adhesions formed in the abdominal cavity. In connection with these experiments it was pointed out[2] firstly, that the time of observation (2 months) was too short; secondly, heterotransplants from man to monkey are not likely to "take" especially if—as was the case here—the tissue is kept on ice for some time before implantation; thirdly, the establishment of a fistula between the uterus and the peritoneal cavity was not successful, since, at autopsy 36 days later it was completely closed. The author introduced some "Hormovar" directly into the abdominal cavity which may have had a detrimental instead of a stimulating effect upon the transplanted tissue.

It may incidentally be mentioned in connection with the implantation theory, that the frequent formation of cysts in both internal and external endometriomas is in agreement with what is known about the behaviour of lining epithelia in general (e.g. squamous, transitional epithelia) when they are experimentally transplanted into the interior of solid organs.[3]

In clinical medicine *autotransplantation of endometrium is sometimes practised in women* to re-establish menstruation in the case of complete obliteration of the uterine lumen (transplantation into the artifically recanalized myometrium) after subtotal hysterectomy (transplantation into the cervical canal), or even after complete hysterectomy (transplantation into the vaginal fornix).[4] This transplanted endometrium is comparable to a spontaneous endometrioma and the fact that it grows and functions, as the latter does, gives further support to the now rather widely accepted[5] view that endometriomas can form as a result of heterotopic implantation.

The concept of *endosalpingiosis* also developed along the lines of the implantation theory. It was found that following tubal resection, islets of oviduct mucosa may appear on the abdominal wall, the surface of the ovary or the surface of intestinal loops and this misplaced tubal mucosa tends to retain its original structure. We are, therefore, probably dealing with a condition similar to endometriosis but for the fact that it is tubal, not uterine, mucosa tissue which implants itself in an atypical location. Since in some instances this tubal mucosa appears to have shown a tendency to transform itself into the endometrial type, it has been assumed that endosalpingiosis is only a modification of endometriosis.[6]

The *lymphatic dissemination theory* of Halban[7] accepts the basic tenet of the implantation theory, namely, that particles of endometrium can re-implant themselves in abnormal locations. It assumes, however, that these particles are disseminated through the lymphatic vessels of the uterus into which endometrial cell groups could enter at the time of menstruation. This interpretation has been accepted by some subsequent workers[8] and the fact that lymph nodes may contain endometrial tissue (see part on Pathologic Anatomy) appears to give support to this interpretation.

It should be noted that the possibility of lymphatic dissemination had been considered even before Halban,[9] but it had been pointed out[10] that the so-called "lymphatic metastases" of endometriosis always occur in the inguinal lymph nodes and do not have any obvious uterine mucosa stroma, hence, they may perhaps merely represent swollen lymphatic sinus endothelia. It has also been stated—without much justification—that internal and external endometriosis are rarely found in combination, although according to the lymphatic spread theory, cases with marked internal endometriosis should be predisposed

[1]*Nichols* B6881/04-5, *Hesselberg et al.* B6809/18, *Jacobson* B6818/22, B6819/23. B6820/24, B6821/26, B20277/32, B5784/33, *Dossena* B20604/24, *Katz and Szenes* B6829/24, B10977/26, *Ferracciu* B10971/26, *Hunter* B6817/27, *Michon* B6869/27, B10978/27, *O'Keefe and Crossen* B7161/27, *Allen and Bauer* B5581/28, *Dahl-Iversen* A63504/28, B5647/29, A66290/29, B5646/29, *Kristensen* A67774/28, *Manzi* B5602/28, *Lanford* A5628/29, *Neumann* 16049/29, 6879/32, *Schochet* B6077/29, *Gleave* B5667/30, *Molinengo* B5652/30, *Cogliandro* B5691/31, *Brakemann* B6734/33, *Brea* B10982/33, *Harbitz* B6788/33, B5819/34, *Markee* A33632/33, 79332/36, *Cheval* B10983/34-5, *Hagino* B5398/38, B15056/38, B15057/38, *Gonzalez Marmol* B10973/38, *Mascia* B11003/38, *Greene* B10974/39, *Hobbs and Bortnick* A32506/39, *Weinstein et al.* A35207/40.

[2]*Harbitz* B5819/34.

[3]*Zimches* B6799/31.

[4]*Schmid* B20287/32, B5805/33, B6918/33, *Serdukoff* B5794/33, *Cheval* B10984/35, *Nürnberger* B6671/35, *Cirio and Murray* A61585/36, *Fuchs* B15604/37, *Bastiaanse* A32081/39, *Fox* B10837/43.

[5]*Rieck* B6899/30.

[6]*Sampson* B5611/28, B5709/30, B5684/30.

[7]B6650/24, B6783/25.

[8]*Holmes* A37770/42.

[9]*Schindler* B6675/06, *Sampson* B6663/22.

[10]*Meyer* B6668/25, B6670/25.

to show lymphatic external "metastases". It is also noteworthy that most of the lymph vessels which drain the endometrium, travel through the parametria and the few lymphatics which may reach the ovary enter through the hilum; yet the parametria and the hilum region of the ovary are rarely affected by endometriosis, while the surface of the gonad, which is not in direct communication with the endometrium, is a common site of endometriosis.[1] These and similar considerations induced a large number of investigators to refute the possibility of a lymphatic dissemination.[2]

In support of the lymphatic dissemination theory, on the other hand, it should be mentioned that occasionally the actual invasion of oviduct lymphatics by endometriosis tissue[3] has apparently been observed and that, at least in one case,[4] an isolated endometrioma was found in a lymph node of a woman who showed no other foci of this condition.

The concept of a *hematogenous dissemination* of endometrial tissue[5] was originally based on the purported observation of endometrial particles within the lumen of myometrial veins.[6] Although the endometrial nature of these intravenous particles has been contested,[7] the fact remains that no other theory could explain the occurrence of endometriomas in the arm or lung (see part on Pathologic Anatomy).

Experimental work gives no definite support to this possibility inasmuch as repeated efforts to produce endometriomas by intravenous injection of endometrium in rabbits failed, although direct implantation of endometrium outside the uterus gave very good results in this species.[8] It is true that some workers[9] claim to have produced pulmonary endometriosis by the intravenous injection of endometrial scrapings (taken from estrone pretreated animals) in the rabbit; yet in our opinion, the published microphotographs do not permit the certain identification of the pulmonary foci as endometriomas, although the original histologic preparations may have been conclusive.

The *celomic metaplasia theory* (or serosa-epithelial theory) generally credited to Iwanoff[10] had previously been considered by Fabricius.[11] The former claimed that, perhaps under the influence of a serous inflammation, glandular tubules arise from the peritoneal mesothelium of the oviduct or broad ligament and invade the musculature of the underlying structures, thus causing the development of cysts and glandules not unlike those of the endometrium. According to this metaplasia theory, aberrant endometrium develops as a result of abnormal differentation either in the pelvic peritoneum or the germinal epithelium of the ovary, both of which are embryologically related to the celomic epithelium as is the endometrium itself. In other words, it is assumed that in the celomic serosa, especially its caudal (cloacal) portion, there are diffusely distributed epithelial cells which remain bi-potent inasmuch as they can either develop into normal serosa epithelium or into the typical lining cells of the Müllerian duct derivatives; an embryonic potentiality which would be retained during postfetal life. Numerous subsequent investigators subscribed to this interpretation.[12] According to a slightly modified concept of this theory, we are not dealing with metaplasia but "prosoplasia" of the celomic epithelium.[13]

It is noteworthy, however, that one of the most enthusiastic proponents of the celomic epithelium metaplasia theory[14] subsequently completely abandoned this interpretation and considered this pathogenic possibility highly improbable. Miller,[15] on the other hand, mentions in defence of this theory, that the squamous epithelium of the portio vaginalis uteri may undergo complete transformation into a glandular cylindric epithelium of pseudopapillary type under certain conditions, a transformation which is much more extensive than that which would be needed to produce endometrioid tissue from peritoneal serosa. It appears to us that although metaplasia is a comparatively common biologic phenomenon, great care must be exercised if we are to depend on it for the interpretation of histogenetic problems, since it could explain the transformation of any one tissue into any other tissue and thus deprive pathology of all other possibilities of a rational interpretation concerning the histogenesis of abnormal growth.

It has been stated on the basis of embryologic studies that endometriosis in all known locations (including the extremities) could originate from local tissues, since developmentally even the non-epithelial structures of the celomic walls and extremities are related to the Müllerian ducts.[16] Here again we are

[1] *Heim* A76990/29.
[2] *Pischzek* A7555/24, *Kitai and Meyer* B6669/24, *Kitai* A77005/25, *Schiller* A76475/26, *Walz* B5617/28, *Rullé* B10665/28, *Terasaki* B6085/28, *Heim* A76990/29.
[3] *Sampson* A80395/22.
[4] *Wolff* B5688/30.
[5] *Philipp and Huber* A32123/39, A38522/40.
[6] *Sampson* B6648/27, *Aschheim et al.* B10003/39.
[7] *Meyer* A64800/30.
[8] *Jacobson* B6818/22, B6819/23, B6820/24, B6821/26, B20277/32, B5784/33, *Gleave* B6776/30.
[9] *Hobbs and Bortnick* A32506/39, 79767/40.
[10] B6697/898.
[11] B6698/896.
[12] *Gross* A46395/892, *Bailey* A74644/896, *Menge* A76110/01, *Meyer* B11118/05, *Lockyer* A70121/18, *Lauche* A7601/23, *Jacobson* B5597/28, *Rullé* B10665/28, *Mazer and Hoffman* A64928/29, *Heim* A76990/29, 3898/33, *Behring* 6455/31, *Tonkes* B5770/32, *Neumann* B5787/33, *Albrecht* B5811/33, *Harbitz* B5819/34, *Meigs* A37925/41.
[13] *Meyer* B6674/25.
[14] *Lauche* B6699/24, B6700/24, B6701/24.
[15] A18279/37.
[16] *Gruenwald* A56299/42.

on dangerous ground indeed! If this argument be carried to its logical conclusion, we would have to admit that all tissues of the body are embryologically related to all other tissues since they develop from the same fertilized ovum. This fact could be used to explain the abnormal development of any tissue in any location, but we doubt that pathology would profit from such a dialectic approach.

The strongest argument in favor of the metaplasia theory is the purported observation of transitional forms between the flat germinal epithelium on the surface of the ovary or the peritoneal mesothelium elsewhere in the pelvis, and the glandular, endometrioid epithelium characteristic of endometriomas. It is claimed that such transitional forms are frequently found in early stages of endometriosis and that the invagination of the surface serosa epithelium with the formation of tubular structures can actually be followed on microscopic preparations.[1] Meyer[2] admits, however, that he was unable to demonstrate any transitional stages between the normal ovarian stroma and the endometrioid stroma in the supposedly intermediate types, or early stages of so-called metaplasia.

For the particular case of urinary bladder endometriosis it has been claimed that it arises due to *metaplasia of transitional epithelium* into endometrium perhaps under the influence of hormonal stimuli.[3] This theory, even if it were accepted, would shed no light upon the histogenesis of endometriomas in other locations.

A modification of the metaplasia theory is the concept according to which endometriosis could develop owing to *metaplasia of lymphatic endothelia.*[4] This interpretation was refuted by subsequent investigators.[5]

Among the histogenetic possibilities which have but few proponents, it may be mentioned, for the sake of completeness, that certain authors believed endometriosis could develop from the abnormal growths of the *Wolffian body or parovarium*[6] or from aberrant remnants of the *Müllerian duct* epithelium.[7]

Other investigators do not believe in a unitarian interpretation of all instances of endometriosis,[8] and it is indeed quite possible that *endometriosis may result from diverse causes.* Herd[9] assumes that endometriomas may develop as a result of any one of the following five pathogenic mechanisms:

1. Implantation of endometrial particles regurgitated through the oviduct.

2. Direct invasion of the myometrium by endometrial glands which penetrate through the entire thickness of the muscles and reach the peritoneal surface in this manner.

3. Metaplasia of oviduct mucosa near the ostium with subsequent invasion of the ovary or adjacent structures.

4. Metaplasia of celomic epithelium.

5. Proliferation of misplaced embryonic primordia.

On the basis of our own observations and a review of the relevant literature, we are strongly tempted to agree with the interpretation that endometriosis may result through various and entirely different pathogenic mechanisms. It is certainly tempting to assume, on the basis of the many data supporting the implantation theory, that at least the great majority of the relevant cases are due to peritoneal implantation of regurgitated endometrial particles which enter the peritoneum through the oviduct at the time of menstruation. This would explain the great prevalence of endometriosis in the vicinity of the ovary and on the ovarian surface itself. On the other hand, the occurrence of endometriomas at a great distance from the ovary, for instance in the lung or the arm, could not be explained by any theory except that of hematogenous metastases. The possibility of lymphatic dissemination does not appear to be too far-fetched since so many cases have been described which appear to fit in with this concept (e.g. endometriomas breaking into lymphatic vessels or endometriomas in lymph nodes). Endometriosis of the umbilicus, on the other hand, is most readily explicable on the basis of the celomic metaplasia theory. The only concept compatible with all observations known to us at the present time appears to be, therefore, that various mechanisms may lead to the formation of endometriomas although some (e.g. trans-tubal regurgitation with peritoneal implantation) are certainly much more frequently the cause of this condition than others (e.g. hematogenous metastases). On the other hand, some theories (e.g. derivation from the parovarium) must now be regarded as obsolete.

FUNCTIONAL PATHOGENESIS: As regards the functional pathogenesis it is very likely that endometriosis is primarily an *endocrine* problem[10] and to be more specific, many gynecologists believe that an excess of folliculoid hormone production favors its development.[11]

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[1] *Pick* A10566/05, *v. Oettingen* A7552/24, *v. Oettingen and Linden* B6702/24, *Schiller* A76475/26.
[2] B6703/30.
[3] *Dreyfuss* 78385/42.
[4] *Schiller* A76475/26.
[5] *Terasaki* B6085/28.
[6] *v. Recklinghausen* B6405/896, *Pick* B11123/897, B11125/00, *Neumann* B11121/899, *Forssner* B11330/17, *Lockyer* A70121/18, *Katzenstein* A62093/36.
[7] *Cullen* A48333/896, *Kitai and Meyer* A6669/23, *Isidor* A96046/37, *Roulland and Isidor* B10365/37, B15617/37.
[8] *Lauche* A7601/23, B6709/24-5, *Jayle* B10/26.
[9] B6705/
[10] *Meyer* B6674/25, *Graves* B10996/25, B20584/25, *Philipp and Huber* A32108/39, *Campbell* A37770b/42, *Novak* A63534/41, *Goodall* B6649/43.
[11] *Jeffcoate* B174/34, *Witherspoon* B5860/35, A29216/35, *Meigs* A37770c/42, *Goodall* A37770d/42.

The occurrence of endometriosis in women with *granulosa cell tumors*[1] substantiates this view. In a series of patients with external endometriosis only 9.2% proved to have metropathia hemorrhagica but this sign of *hyperfolliculoidism* was noted in 25% of the women with endometriosis interna. From this it was concluded that only in the latter group do we have sufficient evidence to warrant the conclusion that hyperfolliculoidism is of etiologic importance.[2] It is of interest in this connection that following *ovariectomy* the endometriomas tend to involute (see part on Therapy) and that *menstrual changes in the endometriomas* develop parallel with those of the orthotopic uterine mucosa (see part on Pathologic Anatomy). These facts clearly substantiate the view that the same hormones, which are responsible for the periodic growth of the uterine lining, regulate the development of endometriomas.

It has likewise been demonstrated that *pregnancy, pseudopregnancy,*[3] gonadotropic hypophysoid hormones[4] and *corpus luteum extracts*[5] cause progestational changes in the experimental endometrial transplants of the rabbit and that treatment with *folliculoids* enhance their growth.[6] Some investigators described invasion of the uterine mucosa by endometrium in folliculoid treated guinea pigs[7] and rabbits.[8] In this connection, the reader is also referred to the discussion of the effect of ovarian hormones upon transplanted endometrium in the volume concerned with the physiology of ovarian hormones.

Although, in our opinion, the above-mentioned facts prove that ovarian hormones exert an influence upon the growth of endometriomas, it should be emphasized that they shed no light upon the histogenesis of this condition. It is evident that the hormonal, as well as any other functional stimulus which could promote the growth of endometrioma tissue, may do so through diverse histogenetic mechanisms. Thus, for instance, folliculoids may promote the regurgitation and implantation of endometrial tissue or its invasive tendencies, but they may conceivably also stimulate the metaplasia of celomic epithelium into endometroid tissue etc.

The fact that *trauma* favors the development of endometriosis is most readily reconcilable with the transplantation theory. As stated above, endometriosis tends to develop in abdominal scars. This is sometimes seen even after laparotomies which do not involve an endometrial trauma, for instance after *appendectomy,*[9] and *hysterectomy*[10] but its occurrence in the scar following *cesarian section,*[11] *laparotomy for perforation of the uterus* during induced abortion[12] and *other surgical interventions on the uterus,*[13] especially *ventral fixation* (see scar endometriosis in part on Pathologic Anatomy), and *laparotomy for ectopic pregnancy*[14] would find a natural explanation in the assumption that uterine mucosa is transplanted into the abdominal wound during the intervention.

Endometriosis following endometrial or endosalpingeal trauma and dislocation caused by *utero-tubal insufflation,*[15] *salpingectomy*[16] or even the use of *pessaries*[17] may be explained in a similar manner. The low incidence of endometriosis after interventions on the uterus compared to the high incidence (76%) after salpingectomy "suggests that uterine mucosa is not so invasive as tubal mucosa".[18]

Endometriosis in locations other than laparotomy scars is also frequently observed after laparotomies of any kind. Thus in one group of 119 women with pelvic endometriosis, 32% had undergone a pelvic operation at an earlier date[19] and 151 cases in a group of 260 women with endometriomas had previously been subjected to abdominal operation; but here again the incidence was not greater after interventions involving the uterus than after other surgical procedures.[20]

The possible eliciting role of *inflammatory lesions* has frequently been considered.[21] This is not surprising since owing to the irritating nature of the menstrual changes which occur in endometriomas, some inflammatory reaction is almost constantly present in the adhesions which develop around them. It has been emphasized, however, that it would be entirely inadmissible to consider endometriosis itself an inflammatory process, although it was conceded

[1] *King* A68133/29.
[2] *Henderson* A37331/41.
[3] *Zaleski* A31673/39.
[4] *Zaleski* B10379/37.
[5] *Zaleski* A15079/38.
[6] *Hobbs and Borthnick* 79767/40.
[7] *Buño et al.* 81382/41.
[8] *Pierson* A50759/34, A1697/36, A9222/37.
[9] *Cahn* B11231/22, *Harbitz* B5819/34.
[10] *Brewer* B11230/21, *Sullivan* B10987/28.
[11] *Hartmann and Loeschcke* B6789/13, *Geller* B6772/25, *Heaney* B6802/25, *Lützenkirchen* B6853/25, *Schwarz and Paddock* B6925/25, *Schwarz* B7018/27, *Rieck* B6898/28, *German* B6774/28, *Williams* B21820/29, *Sampson* B5684/30, *Nebesky* B6877/30, *Edwards* B6754/32, *Mengert* B6862/32, *LaMariana* B6841/33, *Green* B20301/33, *Harbitz* B5819/34, *Tyler* B7760/38, *Kaufman and Wilensky* B7010/38, *Caughlin* B10887/41.
[12] *v. Franqué* B6766/16, *Cullen* B6655/20.
[13] *Michelmann* B7158/27, *Allen* B11028/28, *Harbitz* B5819/34, *Wolff* B11014/36, *Philipp and Huber* A32123/39, *Hurd* A36560/41, *Wyrens and Randall* 81818/41, A56034/42.
[14] *Tobler* B6946/23, *Walz* B6793/26, *Polano* B6894/27, *Labry* B6839/29, *Haselhorst and Otto* B6800/30, *Meyer* B6866/30.
[15] *Kok* B6833/25, B6834/26, *Davis and Cron* B6745/26, *Spirito* B6940/27, *Rubin* B5683/30, B5707/30.
[16] *Dougal* B6750/26, *Sampson* B10922/28.
[17] *Eberhard* B20269/32.
[18] *Sutton* A94406/44.
[19] *Colcock* A34414/40.
[20] *Fallas and Rosenblum* A33798/40.
[21] *Herd* B6705/, *Claisse* B11094/00, *Hueter* B6816/18, *Meyer* B6864/19, *Strong* B21182/21, *Tobler* B6946/23, *v. Gierke* A77187/26, *Goldstine* B10650/28, *Ballin* B10642/28, *Mestitz* B10655/27.

that inflammatory changes may have an eliciting role in predisposed individuals.[1] It is perhaps noteworthy, in this connection, that in one series of 260 surgical interventions for endometriosis, the incidence of concomitant, chronic pelvic inflammatory disease was 17.3%.[2]

While it cannot be denied that *hereditary predisposition* plays a part inasmuch as endometriosis tend to affect several members of the same family,[3] the importance of this factor has not as yet been adequately investigated. The association of external endometriosis with congenital malformations of the uterus has been discussed above in connection with the implantation theory, although several pertinent observations have been thought to support the view that hereditary, or at least congenital factors, play an important role. Thus it appears that small foci of internal endometriosis have repeatedly been noted in combination with various malformations in newborn infants.[4] In connection with the genetic prerequisites of endometriosis, it will also be recalled that there is a case of congenital internal endometriosis on record which developed in the malformed uterus of a true hermaphrodite[4] although the disease has never been observed in men. It should also be kept in mind that some of the instances of endometriosis which developed in conjunction with severe malformations of the Müllerian derivatives (see above) may have resulted from congenitally misplaced endometrial particles.

Finally, it should be mentioned in connection with the functional pathogenesis of endometriosis interna that, whatever the eliciting etiologic agents may be, they are not necessarily always of the folliculoid hormone type. Adenomyomas can also develop from the mucosa of the gastrointestinal tract[5] or the gallbladder[6] whose proliferation is not selectively stimulated by folliculoid hormones. In these latter instances it is very suggestive to consider the possibility that the mucosa particles may invade the muscularis due to a developmental error and there is no reason to disregard a similar mechanism as of possible importance in the development of certain cases of endometriosis. Some workers insist, however, in distinguishing the above mentioned gastrointestinal and gallbladder anomalies as "adenoses" from the true adenomyoses (see part on Pathologic Anatomy).

The *tissue metabolism* of endometriomatous foci has been studied with a view to obtaining some information concerning the biochemic changes responsible for their invasiveness. The slight but consistent increase in anaerobic glycolysis which was found was not considered sufficient to explain the histolytic activity of endometriomas. The findings were similar in merely hyperplastic endometrium. During the luteal phase there was a moderate decrease in anaerobic glycolysis.[7]

CLINICAL COURSE AND COMPLICATIONS

The investigators who *reviewed* the clinical course of endometriosis[8] agree that there is no symptomatology truly characteristic of this disease as such, since the symptoms and signs presented by the patient are entirely dependent upon the particular localization of the ectopic endometrial growths in the case under consideration. Most of the patient's complaints are attributable to the direct action of the misplaced endometrial tissue and hence the special symptomatology in any one case principally depends upon the topography and extent of the endometriomas. Thus almost all the manifestations of the disease enter into the group usually considered as complications of an abnormal growth; hence, we shall discuss the clinical course and the complications of endometriosis conjointly in this chapter.

The multiformity of the symptomatology of endometriosis is clearly shown by the statistical surveys in which the *incidence of the chief complaints* is listed. Thus, in one series of 80 histologically-confirmed instances of external endometriosis[9] the incidence of the major complaints was the following:

Complaint	%
Dysmenorrhea	66.2
Menorrhagia	31.2
Metrorrhagia	10.0
Polymenorrhea	8.7
Uterine bleeding (brownish discharge pre- and postmenstrual)	15.0
Elevation temperature, leucocytosis	8.7
Lower abdominal pain	42.5
Pain in inguinal region	3.7
Pain in thighs	10.0
Sacral back pains	28.7
Rectal pains	7.5
Bladder symptoms	15.0
Gastrointestinal symptoms	18.7
Upper abdominal reflex pains	6.1
Dyspareunia	7.5
Amenorrhea	7.5
Headache	8.7
Sensation of pressure in pelvis	20.0
Nervousness	21.2
Constipation and obstipation	30.0
Pain referred to area of kidneys	11.2

[1] *Lauche* A7601/23.
[2] *Fallas and Rosenblum* A33798/40.
[3] *Goodall* B6649/43.
[4] *Weyeneth* B20322/33.
[5] *Stewart and Taylor* B7515/25, *Taylor* B7141/27.
[6] *Biancalama* B7121/26, *Nicod* B7132/27, *Weidlinger* B8249/28.
[7] *Dreyfuss* B5078/40.
[8] *Colcock* A34414/40, *Geist* B6672/42, *Goodall* B6649/43, *Novak* B109/44, *Sutton* A94406/44.
[9] *Holmes* A37770/42.

In a larger series of 307 patients with pelvic endometriosis,[1] a total of 596 chief complaints were listed together with the frequency of their occurrence:

Chief Complaint	%
Abnormal menstrual periods	56.0
Intermenstrual discomfort and pain	40.0
Dysmenorrhea	35.0
Backache	21.0
Dysfunction of contiguous organs	17.4
Pelvic tumor	12.5
Marital and fertility difficulties	6.6
Miscellaneous	7.5

Another series of 260 patients included cases of both internal and external endometriosis.[2] Here the number of patients with the various major complaints (not their percentual incidence) was listed as follows:

Complaint	Internal	External	Combined	Total
Menorrhagia	66	18	19	103
Metrorrhagia	23	17	12	52
Polymenorrhea	21	1	1	23
Uterine hemorrhage*	3	1	0	4
Dysmenorrhea	40	54	19	113
Lower abdominal pain	34	44	12	90
Backache	24	9	2	35
Abdominal tumor (noted by patient)	10	11	5	26
Vaginal discharge	9	9	1	19
Bladder symptoms	7	4	2	13
Rectal pain	2	3	2	7
Postmenopausal bleeding	4	0	1	5
Gastrointestinal upsets	0	1	4	5
Dyspareunia	0	3	1	4

* It is not quite clear to the reviewer what distinguished "uterine hemorrhage" from metrorrhagia.

Perusal of these statistical surveys re-emphasizes the great variability in the symptomatology of endometriosis. There are, however, also a few *manifestations characteristic of endometriosis as such* irrespective of its localization. Thus, the frequently noted exacerbation of the pain (wherever situated) at the time of menstruation is rather typical of endometriosis and readily explicable on the basis of a menstrual shedding of the ectopic endometrium and the consequent irritation of adjacent tissues. Another characteristic factor is the tendency of patients suffering from endometriosis to show other signs of hyperfolliculoidism, (e.g. metropathia hemorrhagica, uterine fibroids, etc.).

With regard to the general course of the disease, it may be said that in most instances it is chronically progressive, although some cases of so-called "*acute endometriosis*" have been observed.[3] In such cases, the clinical picture may be that of an acute abdominal emergency and is frequently confused with acute peritonitis, acute appendicitis,[4] or a ruptured ectopic pregnancy.[5] The available evidence indicates that such instances of acute endometriosis are almost invariably due to the rupture of a peritoneal (generally ovarian) cystic endometrioma with the spreading of its contents upon the peritoneum.[6]

Because of the above-mentioned dependence of the symptomatology upon the topographic distribution of the endometriomas, it is most instructive to discuss separately the clinical course of each major localization of the disease. The order of presentation in this clinical section will be the same as that followed in the part on pathologic anatomy to which the interested reader is also referred. There he will find an extensive survey of the literature dealing with each of the major localizations, as well as a discussion of the purely morphologic considerations which arise from them. Dysmenorrhea, dyspareunia and sterility, which are all manifestations seen with various types of endometriosis, will be discussed with the uterine type only in order to avoid repetition.

The *ovary* appears to be especially well adapted for the implantation and growth of endometrial particles, as judged by the fact that it is particularly often affected by external endometriosis. Small surface endometriomas of the ovary may remain asymptomatic for a long period, although owing to their great tendency to irritate the adjacent peritoneum and to form adhesions, this is rarely the case. The large ovarian endometriomas, on the other hand, which develop in the form of the typical "chocolate cysts" or "tarry cysts", almost invariably produce marked functional disturbances. They usually produce very extensive adhesions which tend to be the cause of severe dysmenorrhea. If the adjacent organs are severely involved in the connective tissue reaction which develops around the ovarian tumor, symptoms due to disturbance of these neighboring organs (ureter, rectum, sigmoid, etc.) may dominate the clinical picture. Interference with follicle maturation, ovulation and corpus luteum formation

[1]Payne A32556/40.
[2]*Fallas and Rosenblum* A33798/40.
[3]*Sutton* A94406/44.
[4]*Bernstein* 81760/38, *Cattell and Peacock* A96915/43.
[5]*Forlini* A97274/38.
[6]*Sampson* A81410/21, *Errard and Fournier* B8757/21, *Novak* B5765/31, *Hampton* A61387/33, *Hallberg* A95362/38, *Hatleberg* A97614/39.

probably accounts for a large percentage of the instances of sterility so common in women with this localization of the disease. It should be recalled, in this connection, that operations upon the Fallopian tubes are frequently followed by the development of ovarian endometriosis, a fact which is in agreement with the assumption that implantation of uterine or tubal mucosa upon the ovarian surface is a major factor in the pathogenesis of this condition.[1]

It should be kept in mind that large endometrioma cysts develop in the ovary more frequently than in other locations and hence, endometriosis accompanied by rupture and acute dissemination of endometrial tissue is likely to be of ovarian origin. Even a small ovarian endometrioma can probably act as a "hotbed" for further dissemination, and is hence frequently accompanied by "metastases", especially in Douglas' space and in other parts of the pelvic peritoneum. This is seen even without any preceding manifestations attributable to the sudden rupture of a large cyst or the condition known as "acute endometriosis". It is also of clinical importance to remember that ovarian endometriomas often show bilateral development and that their diameter rarely, if ever, exceeds 10-15 centimeters; they frequently reach a size of 5-10 centimeters, however, and thus tend to become larger than endometrioma cysts in other locations. These facts, which have been discussed in more detail in the part on Pathologic Anatomy, are often of diagnostic importance in evaluating a specific case.

Changes in the *uterus* are very frequently observed in patients suffering from endometriomas partly because the internal type of endometriosis is especially common and partly because *uterine fibroids* and *metropathia hemorrhagica* tend to develop in patients who suffer from endometriosis of any kind. This is probably due to a common hormonal etiology of (external and internal) endometriosis, uterine fibroids and metropathia hemorrhagica.

Thus in one series of 44 cases, it was found that (ovarian and uterine) endometriomas were associated with endometrial hyperplasia and uterine fibroids in 64% of the cases.[2] The common factor in this triad appears to be an increase in the endogenous production of folliculoid hormones, yet, there must be some additional pathogenic influences which are responsible for the fact that in one patient the one, and in another patient, another of these manifestations is either exclusively, or at least predominantly manifest.

In another series, comprising 224 cases of internal and external endometriosis, the internal type was manifest in 70% of the cases, which illustrates its comparative frequency. Among these 224 patients, internal endometriosis was found simultaneously with uterine fibroids in 61 cases; with hyperplasia of the myometrium in 44 cases and with fibroids and myometrial hyperplasia in 40 cases; in 7 patients there was postmenopausal atrophy of the uterus, but a normal myometrium was never observed. (A myometrium of more than two centimeters in thickness was considered hyperplastic). Endometriosis of the ovary was combined with uterine fibroids in 70% of all cases.[3] In a series of 307 patients with external endometriosis, the incidence of uterine fibroids was 63.9%.[4] In a group of 260 cases of internal and external endometriosis,[5] uterine fibroids were seen in 52 of the internal and 34 of the external endometriosis cases. In this series there were only 36 patients with combined external and internal endometriosis but 22 of these exhibited uterine fibroids. If all these cases of internal, external and combined endometriosis are considered conjointly, it may be said that uterine fibroids were present in 108 of these 260 patients, that is in 41.5%. The incidence of metropathia hemorrhagica was 10.7% and that of endometrial polyps 8.0% in this same group of patients. A carcinoma of the body of the uterus was observed in 2 and a carcinoma of the cervix in 1 case, all three of these cancers having occurred in conjunction with the internal type of endometriosis.[5] In yet another group of 80 histologically-confirmed cases of external endometriosis, the incidence of uterine fibroids was 53.7% and that of metropathia hemorrhagica 21.2%.

The high incidence of metropathia hemorrhagica[6] and uterine fibroids[7] is equally evident in other statistical surveys dealing with internal and external endometriosis. The above mentioned observations clearly indicate the existence of close relationships between endometriosis, uterine fibroids and metropathia hemorrhagica.

Data concerning the incidence of simultaneously-occurring internal and external endometriosis are somewhat contradictory (see part on Pathologic Anatomy), but in the author's opinion, not incompatible with the assumption of a common etiologic factor.

As indicated by the statistical surveys, in which the chief complaints were listed (see above) *metrorrhagia* and *menorrhagia* are very prominent among the manifestations of endometriosis. This is true of both internal and external endometriosis.[8] As indicated

[1]Sutton A94406/44.
[2]*Witherspoon* B5860/35.
[3]*Dreyfuss* A32551/40.
[4]*Payne* A32556/40.
[5]*Fallas and Rosenblum* A33798/40.
[6]*Dreyfuss* A32551/40, *Holmes* A37770/42.
[7]*Keen and Kimbrough* B5673/30, *King* A64228/31, *Rockstroh* A62171/36, *Dreyfuss* A32551/40.
[8]*Davis* B11205/882, *Mathias* B10945/27, *Chydenius* B20294/33, *Fallas and Rosenblum* A33798/40, *Payne* A32556/40, *Haydon* A55562/42.

above, such menstrual disturbances may arise in patients suffering from endometriosis because of a variety of reasons. Firstly, the condition of hyperfolliculoidism, which is probably present in the majority of these women, tends to cause functional bleeding from a hyperplastic endometrium; secondly, endometriosis is frequently accompanied by uterine fibroids, which in themselves are likely to cause bleeding; thirdly, in the event of internal endometriosis, the structure of the uterine lining is such that even slight irritation can readily elicit hemorrhages. As a result of one or the other of these factors, the incidence of excessive uterine bleeding in the form of menorrhagia or metrorrhagia is at least 50% among women suffering from endometriosis, as indicated in the statistical surveys mentioned above and in numerous additional case reports.

The *size of the uterus* is also notably influenced, especially by the internal type of endometriosis which tends to produce a permanent uterine enlargement.[1]

The *position of the uterus* has received much attention in connection with the pathogenesis of endometriosis. It has beeen found that retroflexion or retroversion is particularly common in patients suffering from this disease.[2] In one series, consisting exclusively of women with pelvic endometriosis, the incidence of uterine retrodisplacement was only 6.9%,[3] but in another series in which instances of both internal and external endometriosis were included, some type of retroposition was found in 52.6%[4] of the cases; in general, it may be said that mechanical factors preventing the normal discharge of the menstrual blood, appear to predispose to the development of endometriosis. The combination of hematometra cervicalis with pelvic endometriosis[5] likewise supports this concept and it will be remembered that malformations of the uterus have repeatedly been seen in combination with pelvic endometriosis (see Pathogenesis).

In connection with the uterine type of endometriosis, we may also consider the *dysmenorrhea* which, though not always present, is still one of the most characteristic symptoms of the disease.[6] In the event of internal endometriosis, it is probably due to engorgement of the endometrial proliferations within the myometrium and their distention subsequent to menstrual shedding and bleeding into the glandular cavities. The uterus could react to the presence of such distended endometrial cysts in the same manner as to a foreign body and the contractile effort to expel the tumor may result in pain of the same type as that seen at the attempted expulsion of a submucous myoma or a foreign body. It is also possible, however, that the pain is purely due to mechanical interference with the muscular contractions of the uterus.[7] In patients with external endometriosis, dysmenorrhea is more common and mainly due to menstruation of the ectopic endometrium.

A statistical survey of 80 histologically-confirmed instances of pelvic endometriosis revealed that dysmenorrhea was the chief complaint in 66.2% of the patients. The type of dysmenorrhea in this series[8] is illustrated by the following table:

Type of Dysmenorrhea	%
Pre- and intramenstrual pain	25.0
Dysmenorrhea all of menstrual life	21.1
Acquired dysmenorrhea	11.2
Premenstrual pain	15.0
Postmenstrual pain	8.7
Normal periods	18.6

In another series consisting of 105 patients with pelvic endometriosis,[3] the types of dysmenorrhea observed were as follows:

Type of Dysmenorrhea	Endometriosis Plus Allied Conditions (57 cases)	Endometriosis Alone (48 cases)
Primary	28%	20%
Aggravated	25%	39%
Acquired	47%	41%

As to the time of dysmenorrhea this same material was classified as follows:

Type of Dysmenorrhea	%
Premenstrual	18.0
Pre- and intramenstrual	25.0
Intramenstrual	50.0
Intra- and postmenstrual	4.4
Postmenstrual	1.3
Intermenstrual	1.3

All these, as well as many other[9] observations, indicate that endometriosis is usually accompanied by pre- and/or intramenstrual dysmenorrhea and the pain is rarely of the postmenstrual or intermenstrual ("Mittelschmerz") type.

[1] *Goodall et al.* B20525/42.
[2] *Watkins* B10961/37, B7767/38, *Haydon* A55562/42, *Fallas and Rosenblum* A33798/40.
[3] *Payne* A32556/40.
[4] *Fallas and Rosenblum* A33798/40.
[5] *Lifvendahl* B20314/33.
[6] *Bazterrica* B11031/26.
[7] *Sutton* A94406/44.
[8] *Holmes* A37770/42.
[9] *Browne* A33953/40, *Goodall* B6649/43.

When the uterosacral ligaments are involved, the dysmenorrhea is often referred to the rectum, the lower sacral or coccygeal regions.[1]

The influence of endometriosis upon *fertility* has also been the subject of many statistical surveys. It has been found that women with pelvic endometriosis are frequently sterile, while internal endometriosis is often accompanied by an unusually high incidence of fertility.[2] The high incidence of sterility among women with pelvic endometriosis has subsequently been confirmed by many investigators.[3] These observations indicate that in general the percentual incidence of sterility among married women with pelvic endometriosis varies between 40 and 50%, while the occurrence of barren marriages is recognized to be approximately 12% in the general population. From this it was concluded that external endometriosis increases the incidence of sterility approximately 4 times. This high incidence of sterility is probably due to several factors, which receive attention elsewhere in this chapter, such as the simultaneous development of metropathia hemorrhagica, uterine fibroids, persistent follicles, retrodisplacement of the uterus, dyspareunia and a tendency for ectopic or otherwise abnormal gestations.

Conversely, the comparatively low sterility index among women with internal endometriosis should not be regarded as an indication that this disease actually raises fertility but is probably due to the fact that multiple pregnancies enhance the development of internal endometriosis and hence, the disease is more prevalent among women who have had many children.[4]

Another very common complaint is *dyspareunia*.[5] This is most frequently observed in women with endometriosis of the rectovaginal septum or the vagina itself, and is probably due to the great tenderness of the vagina where it is in direct contact with ectopic endometrial tissue or with adhesions resulting from the latter.

The comparatively frequent occurrence of *ectopic pregnancy* in women with endometriosis of the Fallopian tubes, the ovaries or the pelvic peritoneum[6] led to the view that endometriosis is an important factor in the pathogenesis of ectopic gestations in general. It is conceivable that the ectopic and decidually-transformed endometrial islets in the peritoneum or the Fallopian tubes represent a particularly suitable territory for the implantation of fertilized ova. It has even been considered probable that all ectopic pregnancies, regardless of location, are due to nidation in ectopic endometrial foci which would attract the ovum perhaps chemotactically.[7]

Interstitial pregnancy, that is, invasion of the myometrium by the gestation sac, may occur on the basis of marked internal endometriosis and entails the danger of uterine rupture.[8]

As a special complication of internal endometriosis during gestation, *rupture of the uterus* should be mentioned.[9] Occasionally, internal endometriosis may be the cause of other complications of gestation such as, for instance, perforation of the uterus during a curettage performed for the purpose of inducing abortion,[10] atony during delivery which necessitates the performance of cesarean section,[11] life-endangering postpartum hemorrhage,[12] or mechanical interference with delivery owing to excessive proliferation of internal endometriosis tissue.[13] External endometriosis, on the other hand, generally does not interfere with the progress of pregnancy and delivery as indicated by a number of relevant case reports.[14]

Endometriosis of the *oviduct* may present itself under diverse pathologic pictures (see part on Pathologic Anatomy). The condition of "salpingitis isthmica nodosa" (or "endosalpingiosis of the cornua") is one of the most common types of tubal endometriosis and has been discussed in more detail elsewhere. It probably arises from direct invasion of the muscularis by the mucosa of the oviduct itself, or by endometrium which invades the Fallopian tube through the isthmus. Such cornual lesions are rarely diagnosed pre-operatively, except by uterosalpingography and are of little clinical significance, except that they may cause sterility or a tendency towards ectopic implantation of fertilized ova.[15] The oviduct may also be invaded by free, regurgitated endometrial particles, either from the lumen side or—if these endometrial particles are discharged into the free peritoneal cavity—from the serosa surface. It is obvious that endometriosis of these types will also interfere with the free passage of fertilized ova through the tube and may result in sterility or ectopic pregnancy.

The clinical manifestations of *peritoneal endometriosis* are again mainly dependent upon the particular position and degree of development of the ectopic

[1] *Novak* B109/44.
[2] Sutton A94406/44.
[3] *Payne* A32556/40, *Meigs* A37925/41, *Holmes* A37770/42, *Haydon* A55562/42, *Pascoe* A57789/43.
[4] *Dreyfuss* A32551/40.
[5] *Payne* A32556/40, *Novak* B109/44.
[6] *Schmorl* B6919/897, *Hammer and van Dongen* B15476/27, *Ossiakina and Schmatok* B5850/35, *Vara* B15621/36, *Isidor* B15606/37, *Turunen* B5516/38, *Huber* B15061/39, *Votta* B20523/39, *Brachetto-Brian and Casco* B20508/41, *Torzsay-Kiss* B10870/42, *Uzategui* B10891/42.
[7] *Schoenholz* B6920/26, *Frankel and Schenck* B15571/37.
[8] *Curtis* B11791/18.
[9] *Schäfer* B101/18, *Herrera and Salaber* B10954/37.
[10] *Schugt* B102/26.
[11] *Schweitzer* B103/27.
[12] *Szenes* B104/28, B105/28.
[13] *Josselin de Jong and de Snoo* B107/25.
[14] *Cullen* B6676/08, *Ulesko-Stroganowa* B106/24, *Sampson* B6667/27, *Haselhorst* A5780/33, *v. Franqué* A52989/34.
[15] *Sutton* A94406/44.

endometrial transplants. As stated elsewhere (see part on Pathologic Anatomy), the pelvic organs are most frequently affected and a more or less diffuse, often plastic pelvic peritonitis may result from an extensive peritoneal endometriosis. From Douglas' space the endometriosis tends to grow downwards towards the vagina or the perineum and, as stated above, this rectovaginal endometriosis is the most frequent cause of dyspareunia in women suffering from external endometriosis. In some instances, the endometrial mucosa actually reaches the vaginal surface and there causes the formation of frequently painful submucous cysts. At the time of menstruation these cysts tend to become particularly painful and engorged, while at other times their size and sensitivity decreases.[1] In some cases a pelvic or ovarian endometrioma may perforate into the vagina and henceforth cause periodic bleeding through the fistula thus established.[2] The so-called "blue dome cysts" are very small cystic endometriomas situated near the upper portion of the vagina. They grow just underneath the surface through which their dark color is clearly distinguishable (see part on Pathologic Anatomy). They apparently arise through direct implantation of the discharged menstrual blood and are not necessarily in contact with any invasive pelvic endometrioma. In themselves, these small cysts are of no great clinical importance.[3]

Endometriosis of the *intestines* is of special clinical importance, mainly because it so frequently results in intestinal obstruction.[4] In such cases the symptomatology depends largely upon the localization of the intestinal endometriomas which are most frequently found in the rectum and sigmoid, but sometimes also in other parts of the intestinal tract, for instance, the appendix or ileum (see part on Pathologic Anatomy). It is of great clinical significance to localize the site of obstruction and to recognize the true nature of the disease, because its recognition as endometriosis modifies the surgical procedure to be used. The therapeutic aspects of intestinal endometriosis will be considered in another part of this chapter. Suffice it to say here, that X-ray examinations are of great value in making an accurate diagnosis of their position and that it is particularly important to distinguish them from intestinal carcinomas which require much more radical surgical interventions.[5]

Endometriosis of the urinary *bladder* is a noteworthy condition as regards its pathologic anatomy, diagnosis and therapy; it is discussed in more detail under these headings. Its clinical course has repeatedly been described.[6] If the growth is large, it may be palpated on vaginal examination and at the same time other manifestations of endometriosis are generally present. There is frequency of urination, hematuria and dysuria, all these symptoms being periodic and coincident with menstruation.

Endometriosis constricting the *ureter* is a rare condition whose clinical interest lies mainly in the fact that it may cause obstruction of the ureter with subsequent formation of hydronephrosis.[7]

Endometriosis of the *umbilicus* may lead to regular menstrual bleeding from the navel[8] and such "supplementary" or "vicarious menstruation" has also repeatedly been noted in the case of *scar* endometriosis which developed following laparotomy.[9] It is rather probable that the majority of the cases of so-called "vicarious menstruation" are due to endometriosis, although there are some instances (e.g. epistaxis) which could better be explained by other pathogenic mechanisms, for instance, by vascular disturbances at the time of menstruation (see chapter on Vicarious Menstruation in Sect. IV, Vol. VI).

The other localizations of endometriosis are not of sufficient clinical interest to deserve discussion here, especially since their clinical manifestations are almost exclusively conditioned by their location. In all these instances the presence of nodules or cysts, which undergo cyclic variations in size and show signs of periodic bleeding coincident with the menstrual cycle, are characteristic of the ectopic endometrial mucosa islets.

DIAGNOSIS

Numerous *reviews* deal with the diagnosis of internal and external endometriosis.[10]

Among the special diagnostic technics the value of *X-ray* studies in the diagnosis of both internal[11] and external[12] endometriosis has repeatedly been emphasized. In the case of cystic endometriomas situated in Douglas' space, *diagnostic puncture* may be helpful in certain instances,[13] while direct *biopsy*

[1] *Sachs* B5708/31.
[2] *Hermstein* B6022/29.
[3] *Dannreuther* A36032/41.
[4] *Mouat* B7405/26, *Graves* B6780/27, *Gale* B5760/31, *Schuler* B5711/31, *Behrendt and Neumeyer* B10621/36, *Hepburn* B10321/37, *Josefsson* B10020/39, *Papin* B15082/39, *Glenn and Thornton* A34487/40, *Milnor* B20516/41, *Blaikley* B20506/41, *Patton and Patton* B20519/41, *Hulten* B20513/41, *Grigsby* B20494/41, *Morrin* A10881/42, *Harte* B10878/43, *Ben-Asher* B6301/44, *Lukins and Lukins* B10841/44.
[5] *Bartlett* B5832/35, *Catteil* B10290/37, *Dukes* B20192/38, *Jenkinson and Brown* A58687/43.
[6] *Adams* B5321/38, *Nixon* A32894/40.
[7] *Morse and Perry* B5607/28, *Haselhorst* B5781/33, *Hauser* B20199/38.
[8] *Boggs* B5333/38, *Kraul* B5410/38, *van Dongen* B15076/39.
[9] *Goulart de Andrade* B5397/38.
[10] *Lahm* B20613/24, *Rivett* B10968/27, *Hufnagl* B11234/29, *Keene* A65160/31, *Cuizza* B5721/31, *Kleine* B5785/33, *Halban* B20302/33, *Leuret* B10965/35, *Brocq and Palmer* A96005/36, *Pugsley* B10967/38, *Murphy* B20144/38, *Cotte and Mathieu* A31795/39, *Hooper* A32797/40, *Dörr* B5076/40, *Colcock* A34414/40, *Allen* B5061/40, *Forti* B10835/44.
[11] *Dionisi* B5074/39, B5075/40, *Philipp and Huber* B10038/39.
[12] *Jenkinson and Brown* A58687/43.
[13] Heynemann A32122/39.

facilitates the recognition of internal endometriosis[1] and its differentiation from uterine cancer.[2] The few available data concerning characteristic changes in hormone metabolism are not sufficiently precise to be used for diagnostic purposes, but some preliminary attempts[3] have been made in this direction.

Unfortunately, there are no symptoms which could be regarded as pathognomonic of endometriosis, since the symptomatology in any particular case is so greatly dependent upon the position of the endometriomas. Furthermore, as stated in other parts of this chapter, endometriosis tends to develop simultaneously with other disturbances, especially, uterine fibroids, metropathia hemorrhagica and follicle cysts which obscure the clinical picture. For this reason, in many instances a pre-operative diagnosis is impossible, to give but one example, in a group of 280 carefully examined cases of pelvic endometriosis almost two-thirds of the pre-operative diagnoses were incorrect.[4]

There are, however, certain *general symptoms* which, though not constant, are sufficiently common in women with endometriosis to raise the suspicion of this disease. Among these common manifestations dysmenorrhea, especially the premenstrual and intramenstrual type, as well as menstrual pain referred to the rectum, the lower sacral or coccygeal regions, is especially characteristic. The dysmenorrhea is generally acquired or represents an accentuation of a pre-existing complaint. There may also be a constant "bearing down" sensation ("as if everything were falling out of the pelvis"), pain referred to the groins, hips and thighs or menstrual headaches.[5] Similarly, dyspareunia is frequently noted, especially in patients with endometriosis of the rectovaginal septum or the vagina itself. Menorrhagia and metrorrhagia are likewise exceedingly common.[6]

In some cases, nodular thickenings due to endometriomas in the uterosacral ligament can be palpated from the vagina while masses in Douglas' space are often more readily palpated from the rectum. The endometriomas are sometimes small nodules but occasionally they are several centimeters in diameter. These findings, when noted in a woman who otherwise exhibits the usual symptoms and signs of chronic pelvic inflammation, should suggest at least the probability of endometriosis, a suspicion which is usually verified at operation. Retroflexion of the uterus is frequently found in patients with endometriosis but there are so many exceptions to this, that one cannot regard it as being of diagnostic significance.[7]

Endometriosis of the *ovary* may be confused with ovarian carcinomas and other tumors which tend to produce implants in the cul-de-sac. However, other signs of malignancy such as ascites, loss of weight, asthenia, secondary anemia and an "omental cake" are generally absent in endometriosis.[8]

If internal endometriomas become very large it may be impossible to dsitinguish them from submucous *uterine fibroids,* especially since both these conditions tend to cause menorrhagia and sometimes internal bleeding.[8]

The clinical manifestations are frequently the same as those of *chronic adnexitis,* inasmuch as on one or both sides of the pelvis or in the cul-de-sac, irregular tender masses are palpable, which consist of the tube and the ovary surrounded by adhesions. An adherent retroflexed uterus, without a history of inflammatory disease, is always suggestive of endometriosis.[8]

From a differential diagnostic point of view, endometriosis of the *intestine* is also of importance, since it frequently led to diagnostic errors with tragic consequences for the patient. Endometriosis of the intestinal tract is most frequently confused with a carcinoma of the bowel and especially of the sigmoid and the rectum.[9] In some of the instances, extensive intestinal resections have been performed simultaneously with an ovariectomy and hysterectomy, thus unnecessarily endangering the life of the patient. The rather typical macroscopic appearance of the intestinal nodules exposed at operation, as well as a history of cyclically exacerbating pain, cyclic intestinal bleeding and the frequent association of the intestinal condition with uterine fibroids, metropathia hemorrhagica and other manifestations typical of endometriosis, should always raise the suspicion that we are dealing with this condition.[10]

The roentgenologic characteristics of rectosigmoid endometriosis include a filling defect approximately 4-7 inches; a sharp demarcation of this filling defect similar to that seen in carcinomas; little evidence of disorders in other portions of the colon; an otherwise essentially intact mucous membrane and fixation as well as tenderness to palpation during fluoroscopic examination.[11]

The practical importance of endometriosis in the rectosigmoid region, is evident from the statistical surveys which show that the incidence of this complication in patients with pelvic endometriosis, is about 15-40%.[12]

[1]*Kakushkin* B20612/23, *Alvarez* B10858/43.
[2]*Tesauro* B10969/28.
[3]*Salaber et al.* B10867/43.
[4]*Payne* A32556/40.
[5]*Holmes* A37770/42.
[6]*Sutton* A94406/44, *Novak* B109/44.
[7]*Colcock* A34414/40, *Holmes* A37770/42, *Novak* B109/44.
[8]*Sutton* A94406/44.
[9]*Jenkinson and Brown* B10861/43.
[10]*Metz* B5679/30, *Friedman* B10624/36, *Henderson* A32451/39, *Graff* A99254/40.
[11]*Jenkinson and Brown* B10861/43, A58687/43, *Ben-Asher* B6301/44.
[12]*Jenkinson and Brown* A58687/43.

Endometriosis of the urinary *bladder* often leads to confusion with carcinoma or papilloma of the bladder, perforated pyosalpinx, salpingitis, fibroids and appendix abscesses. The diagnostic criteria of endometriosis in this location include a palpable mass in the uterovesical pouch combined with frequency of micturition, dysuria and hematuria at the time of menstruation, as well as a rather typical cystoscopic picture of blue-black cysts and blue folds of edema, the so-called "endometriotic edema" of the mucosa. At the time of menstruation it is generally impossible to obtain a clear view by cystoscopy because of the presence of blood in the bladder. Of course, hemorrhages into the bladder will only occur if the endometrial cyst actually penetrates through the mucosa.[1]

Among the conditions which rarely cause diagnostic difficulties, we might mention for the sake of completeness that endometriosis of the round ligament may be confused with a hernia[2] and endometriosis of the *umbilicus* with urachus tumors.[3]

Rupture of an ovarian endometrial cyst may present itself under the picture of an acute peritonitis, ruptured ectopic pregnancy, acute appendicitis, torsion or rupture of an ovarian cyst etc.[4] In doubtful cases, the various unusual localizations of endometriosis, discussed in the part on Pathologic Anatomy, should also be kept in mind.

PROGNOSIS

In untreated cases of endometriosis the disease is usually progressive although, in some cases, its progress is very slow. In general it may be said, however, that spontaneous regression or amelioration of the condition cannot be expected until the menopause, when ovarian function ceases and the endometriotic lesions become dormant.

Following surgical or X-ray therapy, on the other hand, the prognosis is good. There has been a great deal of discussion concerning the advisability of conservative versus radical surgery.[5] It is undoubtedly true that following partial resection, if the ovaries, or at least if one functional ovary is left behind, recurrences are comparatively common,[6] in one instance as late as 22 years after the operation.[7] It may be said in favor of conservative interventions, however, that if the endometriosis is not very widespread and all the visible endometriomas are removed, it is possible to ameliorate the condition of the patient considerably, or even to cure her by partial resection. In many relevant cases normal pregnancies ensued.[8] In view of these favorable results, early intervention has been recommended, since even in the case of ovarian endometriosis this will give the surgeon the greatest opportunity to conserve an adequate amount of normal ovarian tissue and thus to preserve fertility.[9]

If we consider one series of 73 patients with pelvic endometriosis as an example, we find that 12.6% of the women treated conservatively became pregnant subsequently, and two of these were barren eleven and twelve years respectively prior to the operation. In this same series, it was found that only 12.6% of the patients required additional irradiation treatment for relief of symptoms, following the conservative interventions. From this it appears that excision of major ovarian lesions, correction of tubal adhesions and associated retrodisplacement, etc., increase the chances for conception, at least, in a certain number of cases. The results in this particular series[10] may be summarized as follows:

	Conservative Uterus and One or Both Ovaries Conserved	Conservative Hysterectomy One Ovary Conserved	Radical Hysterectomy Bilateral Oophorectomy
Number of patients with adequate follow-up	24	35	14
Relief of chief complaints	29.1%	71.4%	85.7%
Partial relief	54.1%	25.7%	7.1%
Extreme nervous symptoms	0.0%	11.4%	64.2%
Pregnancies	12.6%	0.0%	0.0%
Subsequent treatment Irradiation	12.6%	0.0%	0.0%
Surgery	0.0%	0.0%	0.0%

In another series of 569 patients operated upon for endometriosis 503 retained their ovarian function following conservative interventions and a total of 83.3% remained symptom free. There were 19 pregnancies subsequent to operation.[11]

[1] *Nixon* A32894/40.
[2] *Dickinson* A33601/39.
[3] *Brady* B16103/27.
[4] *Sutton* A94406/44.
[5] *Read and Rogues* B5634/29, *Payne* A32556/40.
[6] *Kuehner* B20593/21, *Read and Rogues* B7024/29, *Keller and Fobe* B15578/37, *Movers* A99261/40.
[7] *Hart* B11108/12.
[8] *Claye* A95390/38, *Faber* A95397/38, *Cotte and Mathieu* A31795/39, *Haydon* A55562/42.
[9] *Heynemann* A32122/39.
[10] *Holmes* A37770/42.
[11] *Haydon* A55562/42.

THERAPY

The main points to be considered in connection with the therapy of endometriosis have frequently been *reviewed*[1] and special attention has been given to the various *surgical technics* which are to be recommended.[2] As we said in the part on prognosis, *conservative resection* of endometriomatous tissue frequently gives excellent results and hence, conservative interventions are to be recommended, especially in the case of young women who are anxious to remain fertile.[3] In this connection, it is well to remember that in many cases endometriosis is a symptomless condition which does not cause any inconvenience to the patient. Frequently, small endometriomas are accidentally encountered by the surgeon in the course of operations for other indications. In such instances, it is best merely to destroy the nodules with the cautery or to excise them.[4] Even if one ovary contains a good deal of endometriomatous tissue, it is best to perform a unilateral ovariectomy if the patient is still young and anxious for future pregnancy. In many such patients, no recurrences have been observed following unilateral ovariectomy, while in others in whom a second, more radical operation became necessary because of a later recurrence, the patient had one or more children in the interval and considered the inconvenience of a second intervention worthwhile.[4] Some surgeons advocate presacral neuractomy as part of all conservative interventions for endometriosis in which the uterus is preserved.[5]

In the case of umbilical or abdominal scar endometriosis mere excision of the visible nodules may be attempted, but recurrences are rather common and, especially if the internal organs are simultaneously involved, more extensive surgical procedures become necessary.[6]

In older women and especially in patients in whom the endometriosis is very extensive and the uterus or several of the adjacent organs, such as the intestine and bladder, are severely involved, it is best, however, to perform *radical operations*, removing the ovaries together with the uterus and the tubes.[7] Unless the patient insists on retaining her (generally slight) chance of becoming pregnant it is unnecessary, however, even in the most severe cases, to practice extensive resection of adjacent organs, such as the rectum, sigmoid or bladder, since following complete ovariectomy, endometriomas in these organs, tend to regress or, at least, remain dormant and symptomless.[8] Cases in which the infiltration of the rectum is so pronounced that complete obstruction results, may require immediate colostomy and the postponement of the radical pelvic operation to a later date.[4]

There has been a great deal of discussion concerning the value of *X-ray* therapy in the treatment of endometrosis.[9] It is particularly useful when it is impossible to remove all ovarian tissue because of the extent of the pelvic metastases and adhesions. In less severe cases it is considered inadvisable, however, since X-rays tend to aggravate the adhesions; furthermore, they appear to act merely by destroying ovarian function, and this is unnecessary in patients in whom a conservative surgical intervention would give equally satisfactory results and preserve fertility.[10] The value of direct irradiation of scar endometriomas (without exposing the ovaries) is doubtful.[6]

The comparatively great resistance of ectopic endometrial tissue to the direct effect of X-rays has also been demonstrated in the experimental endometriosis of the rabbit.[11]

The indications of *radium* therapy, which is used only by few clinicians,[12] are approximately the same as those outlined above for roentgen therapy. Intra-uterine applications of small doses of radium (400-600 mg. hr.) have been employed successfully in young women with early lesions to alleviate the dysmenorrhea. In some of these women pregnancies ensued subsequently. The greatest value of radiation is in the treatment of recurrences following conservative surgery, or of the lesion reactivated by the folliculoid hormones which have to be given occasionally to control the menopausal symptoms after castration.[13]

While some investigators agree that intra-uterine radium therapy may be effective, at least, in the treatment of internal endometriosis,[14] others state that failure of radiation therapy is actually of diagnostic value, inasmuch as if ordinary doses of X-ray or radium remain ineffective in a patient with negative pelvic findings, including diagnostic curettage, the possibility of a direct endometriosis of the

[1] *Walz* B5617/28, *Panettiere* B21601/30, *Allen* B5061/40, *Delannoy* B20510/40, *Stephenson and Graffagnino* B20535/42, *Novak* B109/44, *Sutton* A94406/44.
[2] *Dietlein* B10934/27, *v. Canstein* B10929/28, *Albrecht* B5811/33, *Sullivan* B5797/33, *Fürst and Skorpil* B5816/34, *Masson* B10943/35, B10944/35, *Dougal* B20190/38, *v. Pallos* B5106/39.
[3] *Wharton* B6090/29, *Meigs* A65620/30, *Cattell and Swinton* B20352/36, *Colcock* A34414/40, *Payne* A32556/40, *Haydon* A55562/42.
[4] *Novak* B109/44.
[5] *Colcock* A34414/40.
[6] *Harbitz* B5819/34.
[7] *Colcock* A34414/40, *Fallas and Rosenblum* A33798/40.
[8] *Nixon* A32894/40, *Dannreuther* A36032/41, *Jenkinson and Brown* A58687/43.
[9] *Füth* B20583/17, *Katzareff* B20592/20, *Mazer and Hoffman* A64928/29, *Albrecht* A67315/30, *Heyman* B5670/30, *Cruz* B7021/35, *Nixon* A32894/40, *Payne* A32556/40, *Movers* B20532/41.
[10] *Cotte and Mathieu* A31795/39, *Novak* B109/44, *Sutton* A94406/44.
[11] *Zaleski* B15080/38.
[12] *Herly* B20935/24, *Heineberg* B6807/27, *Tuxen* B7025/34.
[13] *Sutton* A94406/44.
[14] *Dannreuther* A36032/41.

uterine wall should be considered.[1]

In the case of recto-vaginal endometriosis, direct radium irradiation has been recommended,[2] but the value of this procedure cannot be accurately assessed on the basis of the few cases in which it was tried.

Only little is known, as yet, about the effectiveness of *hormone* therapy in the treatment of endometriosis. Progesterone has apparently contributed to the comfort of some young women suffering from endometriosis and especially the resulting dysmenorrhea.[3] It should also be kept in mind that testoid compounds, especially methyl-testosterone and testosterone propionate, enjoy some popularity in connection with the treatment of dysmenorrhea due to unknown causes. In view of the fact that testoids induce an atrophy of the orthotopic endometrium, it is possible that when such treatment alleviates dysmenorrhea, it does so by virtue of its effect on the endometrium. Some preliminary clinical trials have already been made in this direction.[4] They open a new possibility for therapeutic efforts with steroids which cause atrophy of the endometrium, either by virtue of their direct action upon it or because they inhibit the folliculoid hormone production of the patient's ovaries.

Ovarian autografting has been recommended following castration for endometriosis in cases where part of the ovarian tissue appears to be normal and hence can be transplanted, for instance, into the abdominal wall. Among 68 patients so operated upon, 44% of the grafts remained functional,[5] but there is a definite danger of recurrence either in the graft or elsewhere under the influence of hormones produced by the graft.

Since endometriosis frequently develops following surgical interventions and other types of trauma to the internal genital organs, an increasingly great emphasis is placed upon the *prophylaxis* of endometriosis. In this connection, the following recommendations have been made.[1]

1) Whenever avoidable pelvic examinations should not be made at or about the time of menstruation.

2) The Rubin inflation test or uterosalpingography should be avoided, near the end of menstruation or immediately following a curettage.

3) Diagnostic curettage and other intra-uterine manipulations should not be performed near the time of menstruation.

4) Misplacement of the uterus should be corrected to ensure better drainage of menstrual blood.

5) Cervical obstruction should be corrected for the same reason.

6) Violent exercise, during menstruation, should be avoided as it may favor the regurgitation of menstrual blood through the oviduct.

7) In young women, the introduction of radium into the uterine cavity should be preceded by a thorough dilation of the cervix to avoid the piston-like action of the capsule which may push material into the peritoneum through the oviduct.

8) Treatment with folliculoid hormones should be avoided in women suspected of endometriosis, and in patients who have undergone an operation for this condition in the past.

9) Ventral fixation of the uterus is contra-indicated in young women, because of the dangers of postoperative endometriosis of the abdominal wall.

10) A complete hysterectomy should be performed, whenever possible, in women requiring bilateral salpingectomy, in order to avoid post-operative endosalpingiosis.

11) Plastic operations upon the oviduct should only be performed in selected cases, since they frequently result in postoperative endosalpingiosis.

12) It is inadvisable to transplant endometrial tissue into various pelvic organs to aid in the preservation of ovarian function. Such endometrial transplants repeatedly required secondary operations because of the ensuing endometriosis.

In connection with this last prophylactic measure, we should like to emphasize, furthermore, that operations of this kind are all the more inadvisable since there is very little, if any, evidence that endometrial transplants help to preserve ovarian function (see Sect. IV, Vol. IV). The transplantation of endometrium into the fornix of the vagina after hysterectomy or into an obliterated uterine cavity after surgical recanalization (to preserve menstruation), likewise entails the danger of postoperative endometriosis.

[1] *Sutton* A94406/44.
[2] *Heineberg* B6807/27.
[3] *Dannreuther* A36032/41.
[4] *Salaber and del Castillo* B10888/42.
[5] *Counseller and Wrork* A33418/40.

PARA-OVARIAN ENDOMETRIOSIS

Para-ovarian endometriosis will not be discussed in a separate chapter, since this condition never originates from the para-ovarian embryonic vestiges. Readers are referred to the discussion of pelvic endometriosis in the preceding chapter, and to the passage on endometriosis and endosalpingiosis in the part on Pathogenesis in the chapter on Para-Ovarian Tumors in general.

ENDOMETRIOSIS IN ANIMALS

The fact that endometriosis can be produced experimentally in animals has been discussed at some length in connection with the pathogenesis of this disease in the preceding chapter.

It is important to realize, however, that endometriosis sometimes occurs spontaneously in the animal world.[1] Thus, more or less typical endometriomas have been observed in the *dog*.[2]

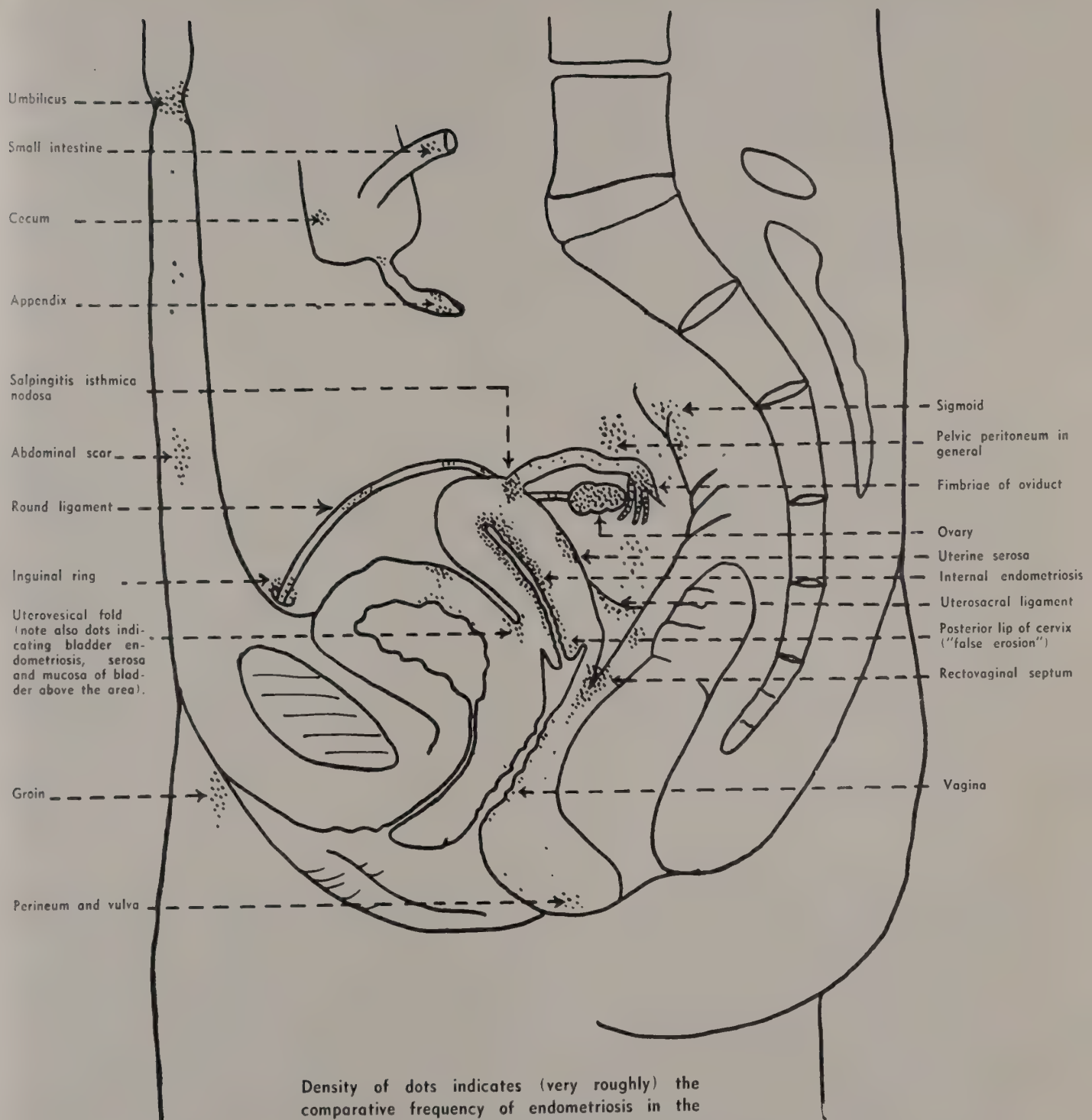
In one rhesus *monkey*[3] both internal and external—intestinal, mesenteric, pelvic—endometriosis occurred spontaneously and there was also a large endometrioma of the umbilicus. In a wild specimen of the Javanese Pithecus fascilularis mordax Thomas Wroughti (or Macacus irus Cuvieri)[4] spontaneous ovarian endometriomas were seen, and other individuals of this same strain proved to have spontaneous "adenomyosis externa uteri".

In the *rabbit* spontaneous endometriosis is not very exceptional.[5]

[1] *László* B11021/36.
[2] *Letulle and Petit* B6598/28.
[3] *Fraser* B5623/29.
[4] *Joachimovits* A64427/30.
[5] *Witherspoon* B5520/38.

PLATE XXIX

DISTRIBUTION OF ENDOMETRIOSIS



Density of dots indicates (very roughly) the comparative frequency of endometriosis in the various regions. The most exceptional localizations in ureter, lung, arm and lymph nodes are not represented in the drawing.

PLATE XXX

ENDOMETRIOSIS

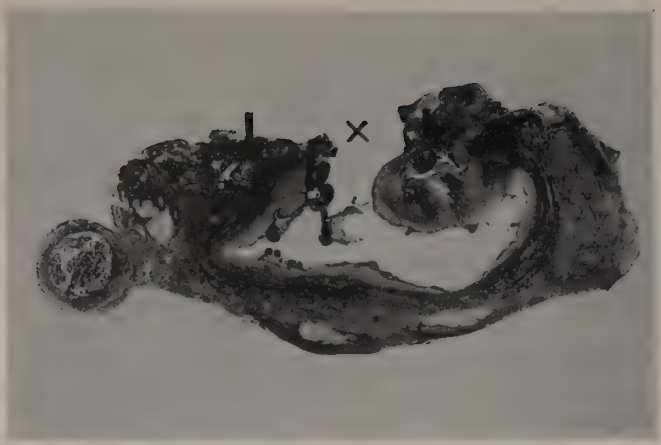


Fig. 1. **RUPTURED ENDOMETRIOMA OF THE OVARY** (courtesy of Dr. L. C. Simard). Endometriosis cyst which ruptured toward the surface (at point marked X). It is lined by more or less typical endometrium which tends to invade the ovary and form glandular masses in its substance, even at some distance from the cyst lining (at point indicated by arrows).

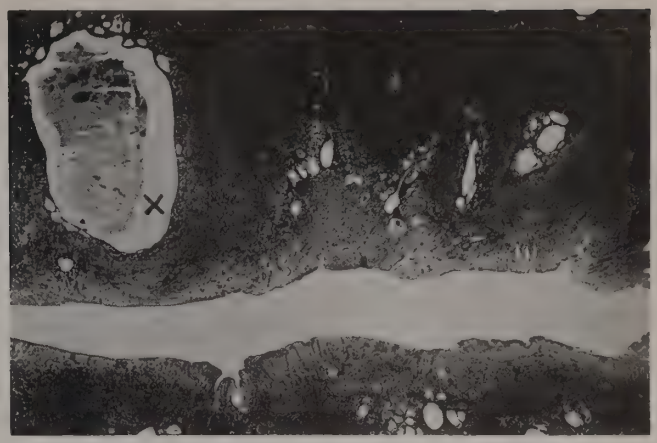


Fig. 2. **INTERNAL ENDOMETRIOSIS** (courtesy of Dr. L. Berger). Cross-section through the uterus, showing the endometrium which lines the cavity and fairly large portions of the myometrium which are invaded by tubules and cysts of endometrial tissue. One fairly large endometrial cyst is visible in the upper, left corner of the field (X).

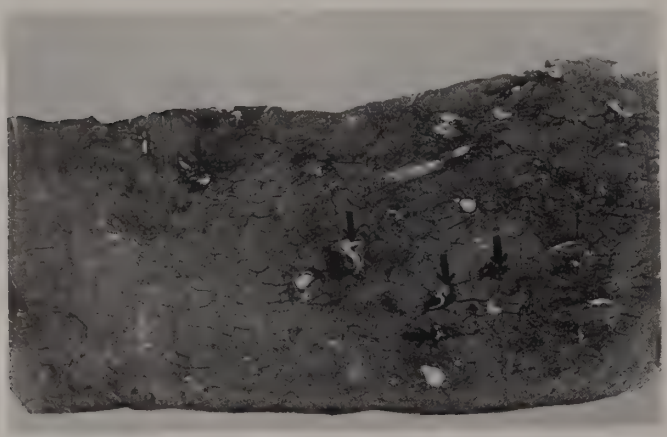


Fig. 3. **DIFFUSE ENDOMETRIOSIS OF THE MYOMETRIUM** (courtesy of Dr. L. Berger). This 42-year-old patient suffered from metrorrhagia and dysmenorrhea. At operation a thecoma of the ovary was found. Note diffuse infiltration of the myometrium by endometrial glands, each of which is surrounded by a dark halo of stroma (indicated by arrows).

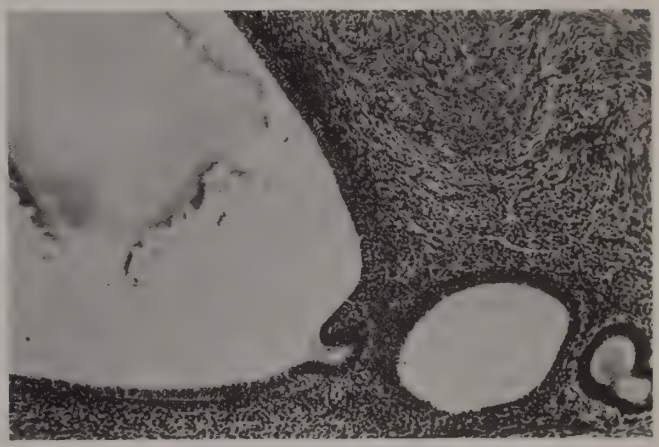


Fig. 4. **INTERNAL ENDOMETRIOSIS.** Higher magnification of an endometrial islet within the myometrium, shown in Fig. 3. Note typical endometrial epithelial lining and surrounding endometrial stroma.

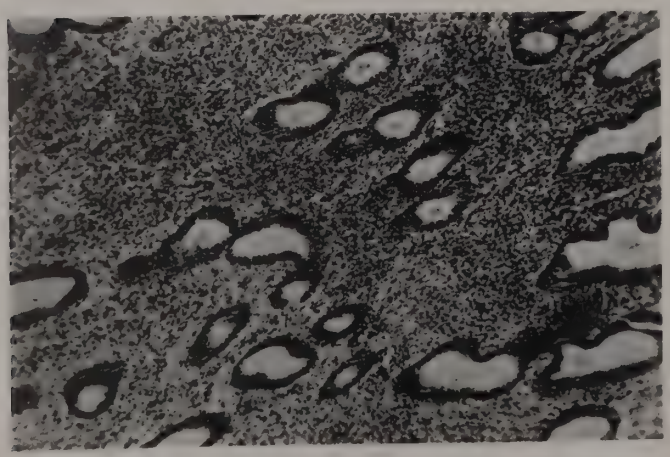


Fig. 5. **ENDOMETRIOSIS OF THE OVARY.** Well-developed endometrium found within the substance of an ovary, containing several endometriomas. Note that the aspect of the gland is characteristic of the follicular phase of the cycle.

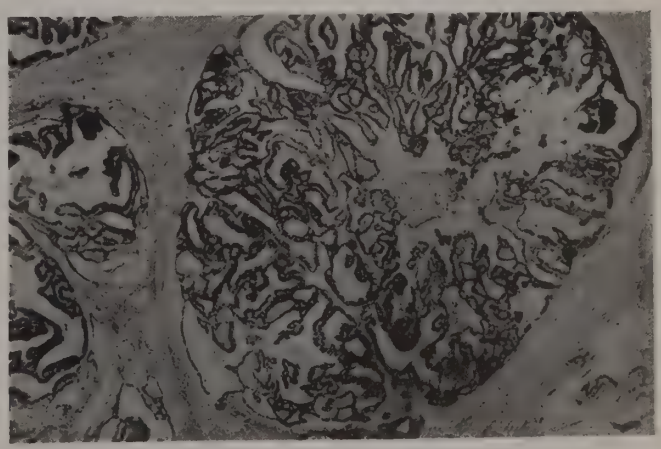


Fig. 6. **CARCINOMATOUS ENDOMETRIOSIS** (after Dannreuther A36032/41). Papillary, cystic adenocarcinoma formed in the wall of a large "chocolate cyst". The papillae are covered with several layers of columnar epithelium. Multiple endometriomas were present in other fields.

PLATE XXXI

ENDOMETRIOSIS

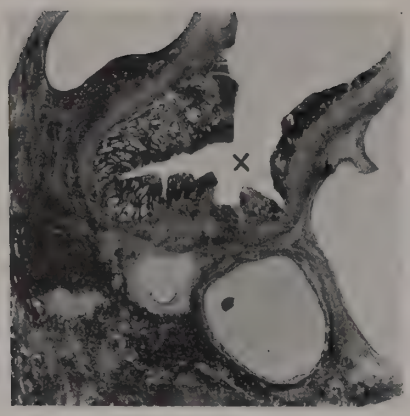


Fig. 1. ENDOMETRIOMA OF THE OVARY. Among the several cystic cavities in this field one (X) is lined by a well-developed endometrium in which the glandular spaces are clearly distinguishable even at this low magnification.

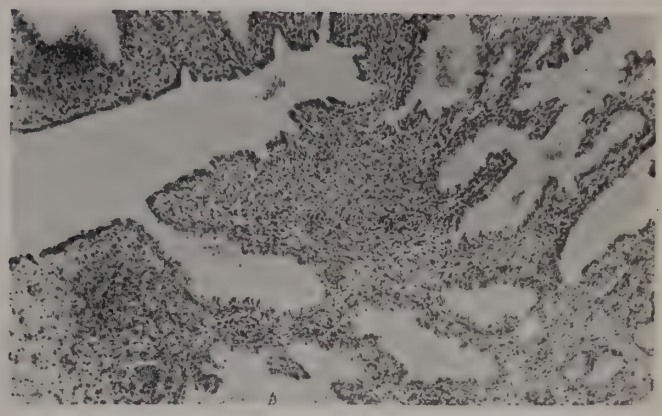


Fig. 2. ENDOMETRIOSIS OF THE OVARY. High magnification of the endometrium in the ovarian endometrioma, represented in Fig. 1. Note the typical aspect of the mucosa which, in this instance, shows signs of progestational proliferation.

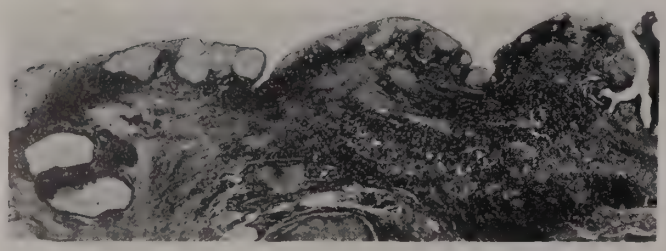


Fig. 3. ENDOMETRIOSIS OF THE OVARY. Note light islets of decidually-transformed endometrium along the entire surface of this ovary. At this low magnification the decidual tissue is recognizable only because of its light coloring.

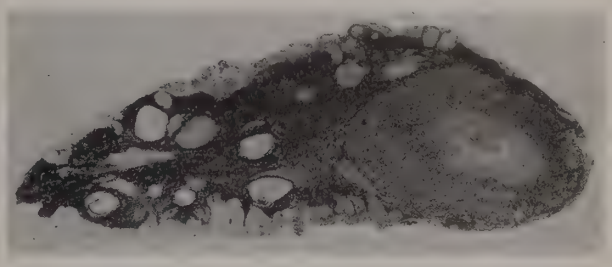


Fig. 4. ENDOMETRIOSIS OF THE OVARY. Low magnification of a section through the entire ovary of a case similar to that shown in Fig. 3. Here a large corpus luteum is visible in the right side of the gonad and the entire surface is encircled by light endometrial tissue which underwent decidual transformation.

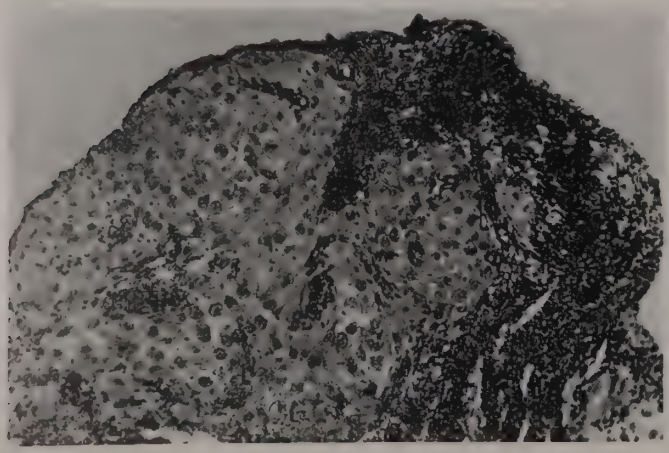


Fig. 5. ENDOMETRIOSIS OF THE OVARY. High magnification of a field in the ovary shown in Fig. 3. Note large typical decidual cells underneath the surface epithelium.

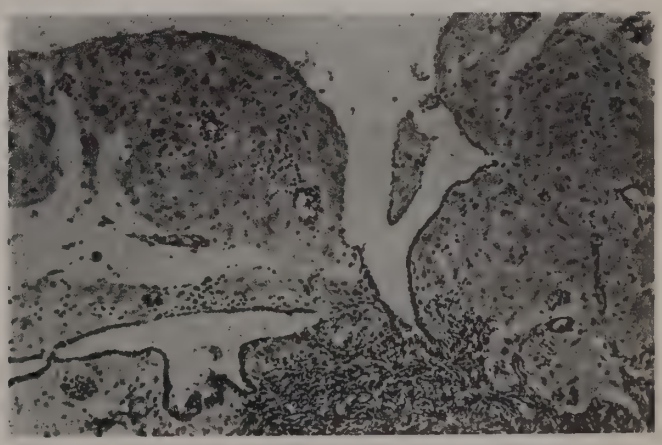


Fig. 6. ENDOMETRIOSIS OF THE OVARY. High magnification of a field in the ovary shown in Fig. 4. Note that here again the entire subcapsular region is transformed into decidua. This case is especially instructive since in conjunction with Fig. 4, it demonstrates the transformation of the endometrioma under the influence of the corpus luteum tissue.

PLATE XXXII

ENDOMETRIOSIS

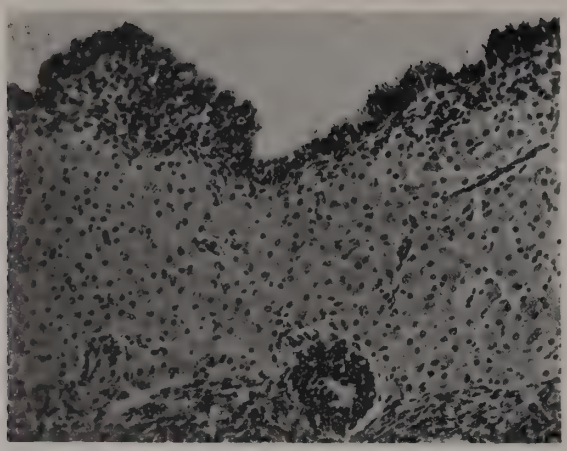


Fig. 1. PSEUDOXANTHOMA CELLS IN ENDOMETRIOMA (after Novak B109/44). Note large pseudoxanthoma cells which are rich in cytoplasm but have a small nucleus. These have sometimes been confused either with corpus luteum cells or with decidua cells.

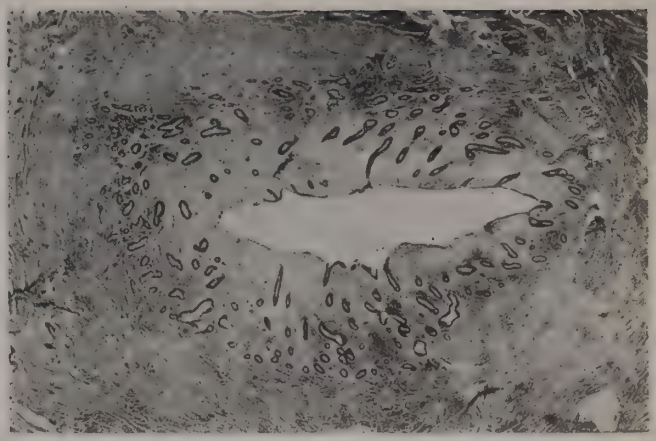


Fig. 2. ENDOMETRIOMA OF THE ROUND LIGAMENT (after Dannreuther A36032/41). Note well-formed, rather typical endometrium lining the cyst cavity.

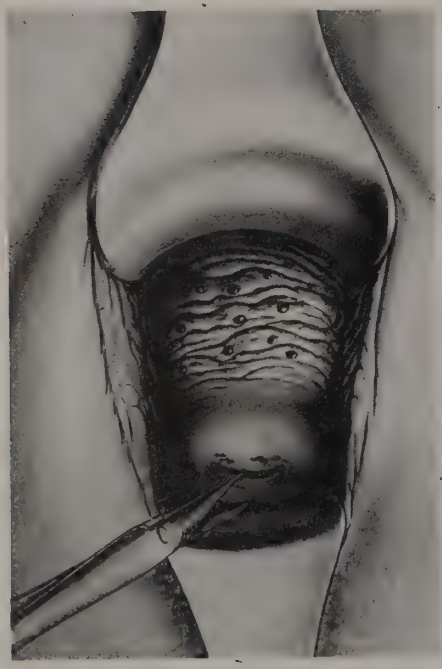


Fig. 3. BLUE DOME CYST (after Dannreuther A36032/41). Note charactersitic appearance of small endometrial nodules on vaginal fornix. These are called "blue dome cysts" because the menstrual blood accumulating in the cystlets gives them a bluish hue.

Fig. 4. ENDOMETRIOSIS OF THE UTERO-SACRAL LIGAMENT AND RECTO-VAGINAL SEPTUM (after Sutton A94406/44). This is the lesion which usually results from peritoneal endometriosis in the posterior cul-de-sac. After invasion of the posterior wall of the uterus, the anterior wall of the rectum and the right paracervical tissue, the endometrioma has extended downward between the rectum and the vagina, forming a tumor lateral to and below the cervix. This tumor was readily palpable prior to the operation.

OVARIAN TERATOID TUMORS (DERMOIDS, SOLID TERATOMAS, EMBRYOMAS)

SYNONYMS: Dermoid, dermoid cyst, cholesteatoma of the ovary, kyste pileux, kyste pileux et dentaire, kyste mixte de l'ovaire, cystic teratoma, kyste ovarique sebacé, compound (or mixed) ovarian tumor, bidermoma or tridermoma of the ovary, teratoma, teratoid tumor, embryoma, dysembryoma, fetus in feto, rudimentärer Ovarialparasit, Organom, Wundergeschwulst or wonder growth (teras=wonder, or miracle).

The terms listed here are not exactly synonymous. Some are employed to designate simple dermoid cysts consisting—exclusively or almost exclusively—of skin tissue, while others are used for more complex growths with predominant development of one or another organ-like structure, the most complex being an almost fully developed embryo. Differentiation between the individual groups is often difficult, however, because there are many transitional types and hence all designations used for the teratoid group of ovarian tumors are listed conjointly.

In common English medical usage it is not customary to designate each variety of tumor by a special name depending upon the prevailing tissue or organ. The term dermoid cyst is generally used for cystic tumors consisting only of skin, or of skin and its appendages (hair, nails, teeth and skin glands) and the term teratoma is employed for more complex, usually solid, tumors containing a variety of tissues and organs. Occasionally the terms embryoma or dysembryoma are employed to designate teratomas which resemble incompletely formed, but clearly recognizable embryos.

The use of the term "dermoid cyst" was proposed by Leblanc[1] a veterinarian who noted such a cyst in the cranium of a horse.

REVIEWS

CZECH: *Novy* A50942/898.

DANISH: *Vogelius* A76698/03.

ENGLISH: *Ritchie* A76396/865, *Byford* A69350/876, *Wells* A40376/882, *Thornton* A41601/883, *Cameron* A46296/892, *Price* A46376/892-3, *Wenning* A48429/896, A76731/896, *Shattock* A5717/08, *Lukins* A68571/18, *McClellan* A76037/21, B8749/21, B21211/21, *Eden and Lockyer* A73529/28, *Curtis* A63170/30-42, *Müller* A28165/35, *Kuzma* B7718/38, *Geist* B6672/42, *Novak* B109/44.

FRENCH: *Maunoir* A76092/861, *Parmentier* A76255/861, *Cousin* A69336/877, *Trevoux* A76655/888, *Charrier* A46387/893, *Fraikin* A68652/897, *Maystre* A76099/02, *Masson* A68474/22, *Peyron* A79520/22.

GERMAN: *Rokitansky* A76409/842, *Wells* A76729/874, *Lebert* A73963/875, *Rohn* A76408/881, *Olshausen* A41468/886, *Nördlinger* A76225/887, *Mantel* A46318/892, *Neunhöffer* A76207/892, *Milbradt* A76136/893, *Voigtel* A76700/895, *Mühlenbein* A76167/898, *Novy* A76230/899, *Wilms* A76753/899, *Sänger* A76445/899, *Vatter* A76680/01, *Nauwerck* A76194/02, *Saxer* A76464/02, *Meyer* A76122/03-5, A76129/12, A76130/24, *Schmid* A76479/02, *Rothe* A76429/03, *Askanazy* A73220/05, A73221/07, *Jung* A68514/05, *Borst* A73338/07, *Schwalbe* A76504/07, *Krömer* A70091/08, *Kehr* A82735/09, *Marchand* A76066/10, *Nyström* A76231/11, *Schwalb* A76503/12, *Lippert* A76005/13, A76006/13, *Rosenstein* A76418/13, A76419/13, *Luftspringer* A76031/18, *Miller* A76140/24, *Stübler and Brandess* A76588/24, *Sternberg* A64845/26, *Mayer* A99597/26, *Mandelstamm* A68104/29, *Miller* A18279/37.

ITALIAN: *Savaré* A80282/10, A80283/11, *Maurizio* A97425/39.

PORTUGUESE: *Wolff Netto* A97327/38.

RUSSIAN: *Zarkevich* A68643/899, *Thomson* A76624/04, *Klénitzky* A80234/30.

SPANISH: *Recasens* A48450/897.

SWEDISH: *Sjövall* A82750/08, *Hansson* A80209/13.

DEFINITION

Ewing[2] defines the *teratomas* as growths composed of tissues and organs of one, two or three germinal layers, designating them respectively as monodermal, bidermal or tridermal types. The embryoma is composed of tissues derived from all three germinal layers, in more or less orderly imitation of a fetus. In this manner these growths are distinguished from simple *mixed tumors* which are composed of more than one type of irregularly arranged neoplastic tissue named according to composition as in "chondro-epithelioma", "osteo-chondromyosarcoma" etc.

In the sense of these definitions, both the cystic and solid teratoid tumors have to be regarded as ovarian teratomas, among which the *dermoid cyst* deserves special consideration only because of its frequency. The simple mixed tumors are of an entirely different nature and do not belong to the teratoid growths. In this Encyclopedia, dermoids and the more complex teratomas will be discussed conjointly under the heading of teratoid tumors, since the many transitional types between them make strict classification into two distinct groups practically impossible. It should be kept in mind, however, that malignant transformation of dermoids is comparatively rare, while teratoid tumors (except organized embryomas) are usually malignant. The relevant case reports will therefore be roughly separated into these two main groups.

HISTORY

Dermoids and teratomas of the ovary attracted the attention of physicians hundreds of years ago. This is not surprising, since these tumors undoubtedly

[1]A94501/831.

[2]A64873/42.

are among the most curious freaks of nature. The first detailed description of the ovarian dermoid which I was able to find is that of Scultetus[1] who in the middle of the 17th century published a small monograph on this subject, entitled "Trichiasis admiranda sive morbus pilaris mirabilis." Martin Luther (as quoted by Greil[2]) referred to it as "Ausgeburt des Teufels" or "offspring of the devil".

Teratomas with recognizable and sometimes almost complete embryos have generally been regarded as singular ovarian pregnancies.[3] As we shall see later, differentiation between true ovarian pregnancies and ovarian teratomas of the embryoma type is difficult and frequently leads to confusion even at the present time. It soon became evident, however, that if such growths are to be interpreted as abnormal types of gestation they must result from "immaculate conception" since they occur in new-born infants and even in embryos. Prochaska[4] discussed this in a publication "___über die mit einem zweyten Fötus schwanger geborenen Kinder, oder über den Fötus in Fötu.".

The frequent inclusion within these tumors of teeth, hair, sebaceous material and various other organs and tissues, as well as the clinically important complications of such growths (torsion, perforation into internal organs or to the outer skin etc.) were all known to ancient physicians as indicated by the numerous relevant early descriptions.[5]

CLASSIFICATION

It is evident from the previous paragraphs of this chapter that a strict classification of the teratoid tumors is almost impossible, owing to the many transitional types between the main classes. For practical purposes it is important, however, to make some distinction between the benign and the malignant varieties, and between the simple dermoid cysts as differentiated from complex teratomas. The relevant data will therefore be roughly classified as follows:

TERATOID TUMORS

Benign	Malignant
Dermoid Cyst	Dermoid Carcinoma Dermoid Sarcoma
Teratoma (incl. Embryoma)	Malignant Teratoma

PATHOLOGIC ANATOMY

MACROSCOPIC CHARACTERISTICS: Ovarian dermoids are globular cystic tumors whose outer surface is usually smooth. They may be attached to the ovary by a pedicle which is subject to torsion and may undergo complete self-amputation (see Sect. IV, Vol. VI). In other instances, the dermoid is in close contact with the ovary, the latter forming part of the cyst wall. The center of the cyst usually contains sebaceous, fatty material, while the wall, which is made up of skin tissue, often bears hair, teeth or nails—structures derived from an epidermal primordium. Bone and cartilage may also form in the cyst wall and thus give it a hard consistency. From the wall a large protuberance or papilla protrudes into the fatty material contained in the center. Usually this pedicle contains a distinct "head" or "oral part" the skin of which bears most of the hair. In it there is frequently a stoma in whose surroundings teeth and brain tissue tend to develop. The papilla may also contain structures resembling the respiratory and intestinal tracts. In rare instances there may be two or more separate pedicles. The various tissues and organs which can develop in ovarian dermoids will be discussed in more detail in connection with their microscopic appearance. Suffice it here to re-emphasize that the less obvious the skin cyst formation and the greater the development of tissues arising from various germinal layers at the expense of simple skin and skin appendages, the more we approach the teratomatous type.

The *size* of teratoid tumors is extremely variable. There are dermoid cysts whose diameter does not exceed a few millimeters.[6] Some of these very small dermoids develop inside the ovarian tissue and are

[1]A76510/658. [2]B20934/24.

[3]*Nysten* A87637/803, *Josephi* A73850/803, *Phillipps* A76288/818.

[4]A76346/814.

[5]*de Lamzweerde* A73942/686, *De Maurice* A87630/698-00, A87631/755, *Haller* A69379/756, *Respinger* A87649/755, *Saviard* A87604/766, *Buddens* A69349/781, *Schmucker* A76484/782, *Blumenbach* A73314/785-6, *Cleghorn* A73431/787, *Baillie* A73232/789, *Lallize* A73938/792, *Braun* A73364/798, *Autenrieth* A73225/807, *Coley* A69360/810, *Fleischmann* A73593/815, *Meckel* A76100/815, *Abernathy* A69337/815, *Henderson* A87526/818, *Murat* A87634/819, *Bostock* A73341/819, *de Fremery* A87522/825, *Latham* A68728/826-7, *Scherb* A69757/828, *Denis* A73489/828, *Cruveilhier* A73454/829-35, *v. Jasinski* A73837/829, *Mayer* A68735/831-2, *Pelletier* A76263/833, *Kloss* A69763/838, *Negrier* A76197/840, *Stahlberg* A76558/842, *Guignard* A69376/842, *Larrey* A73950/842, A73951/846, *Kohlrausch* A73908/843, *Schabel* A76465/844, *Löbl* A76013/844, *Houston* A68717/844, A68718/849, *Chereau* A69356/845-6, A69355/845, A69357/845, A69358/848, *Blot* A73313/846, *Grivot Grandcourt* A73710/847, *Ward for Page* A76721/847-8, *Montgomery* A87633/849, *Delatremblaye* A69365/849, *Clapp* A69359/849, *v. Haartmann and Marcusen* A69378/849-53, *Steinlin* A76566/850, *Follin* A73599/850.

[6]*Haffter* A73726/875, *Wilms* A76752/897, A76755/899, A76756/00, *Hoffmann* A73797/898, *Emanuel* A73541/00, *Strassmann* A76580/01, *Falkner* A73554/06, *Novak* A76229/09, *Kermauner* A73881/09, A64880/32, *Dransfeld* A73513/18, *Rosenstein* A76420/28, A76421/28.

completely surrounded by the latter.[1] Conversely, dermoids and teratoma may reach an enormous size.[2] Dermoid cysts weighing as much as 24 lbs.,[3] or even about 30 lbs.[4] or more than 40 lbs.[5] have repeatedly been described. The largest dermoids on record weighed 100 lbs. or more.[6]

According to Miller's[7] survey of the literature, dermoids occur with approximately equal frequency in the right and the left ovary. Among 951 cases surveyed, 431 occurred on the right, 374 on the left, while in 146 cases *bilateral dermoids* were found. In addition to the cases mentioned above, numerous instances of bilateral dermoids have been reported in the literature.[8]

The exact incidence of bilaterality among dermoids is difficult to estimate, although there is agreement concerning the fact that a woman developing a dermoid in one ovary is rather likely to develop a similar tumor in the other ovary. Bilateral development is estimated at 8%,[9] 9.8%,[10] about 10%,[11] 18.4%[12] and 24%[13] of all cases of dermoids examined by various investigators. McClellan[14] who analyzed the Mayo Clinic's material, found dermoids to be bilateral in 14% of all cases.

Novak[15] defines as *multiple* dermoid cysts those in which two or more dermoids develop in the same ovary and are separated from each other by septa of normal ovarian tissue. Such formations are comparatively rare and probably even some of the purportedly multiple dermoids were actually multilocular.[16] In most cases, only two or three dermoids develop in the same ovary, although more may be present and in one particularly striking instance the right ovary contained 10 and the left 11 completely separate dermoid cysts in addition to some other cystic cavities.[17]

The so-called *multilocular* dermoid cysts are not to be confused with true multiple dermoids. In the former, septa of the blastoma tissue subdivide the cavity into distinct spaces but only a single tumor is formed.[18]

So-called *tubo-ovarian dermoids* which connect the ovary with the tube, are rare in comparison with the rather common serous and pseudomucinous tubo-ovarian cystomas.[19]

Upon incision of a typical ovarian dermoid, attention is first drawn to the *fatty or sebaceous cyst contents*, which are frequently described as greasy or vaseline-like and may be white or yellowish in color. Within this amorphous material free hair is often observed. The fatty substance is rarely solid at body temperature but usally solidifies upon

[1]*Emanuel* A73541/00, *Martzloff* A76081/22.
[2]*Langenbuch* A73947/891, *Ullmann* A47477/895, *Keith* A48273/895-6, *Roux* A76436/896, *Foster* A68916/01, *Roche* A68946/02, *Jewett* A91811/04, *Brownlee* A73380/07, *Humiston* A73812/07, A73813/07, *Lancial* A73943/13, *Unterberger* A80304/14, A80305/15, *Hörrmann* A73796/14, *Chastenet* and *Dariau* A73426/28, *Raisz* B1028/31, *Timpanaro* A62954/32, *Vanrell* A28183/35, *Sanchez* A97523/41.
[3]*Boerstler* A40669/885.
[4]*Le Jemtel* A66896/12, *Murray* A76188/32, *Murray and Jeffcoate* A62942/32.
[5]*Voigtel* A76700/895, *Byford* A47991/898, A47970/898.
[6]*Keith* A48273/895-6, *Cardaliaguet and Marquer* A73407/05.
[7]A18279/37.
[8]*Ruge* A76441/878, *Poole* A76317/883, *Löhlein* A76014/884, *Carter* A40826/885, *Thornton* A42140/886, *Neumann* A83077/886, *Orecchia* A41919/887, *Mundé* A76178/887, *Bantock* A73251/890, *Briquet* A68907/890, *Baer* A43518/890, *Dock* A83353/891, *Camelot* A83340/891, *Flaischlen* A73589/893, *Sims* A76530/895, *Reymone* A47321/895, *Vanverts* A49018/896, *Tocheport* A83509/896, *Taylor* A48398/896, *Love* A68934/896, *Janvrin* A42028/896, *Tschirmer* A76659/897, *Wikerhauser* A50653/898, *Pollock* A76306/898, *Masson* A49242/898, *Delaunay and Pilliet* A50567/898, *Pothérat* A76323/900, A83500/03, A82743/19, *Massen* A76083/01, *Löwenberg* A76017/01, *Loewy and Gueniot* A76018/01, A76019/02, *Castan* A83341/02, *Laurens* A83368/02, *Matzewscki* A76090/03, *Hyde* A83360/03, *Van der Linden* A76673/03-4, *Pollak* A76305/04, *Meredith* A76114/04, *Jacobson* A73831/04, *Lindquist* A68753/04, *Pfeifer* B12615/04, B6830/05, *Henrotay* A68746/04, *Adams* A83333/04, *Condamin* A73440/04, A73442/11, *Withrow* A68673/05, *Guibal* A73717/05, *Fischer* A73575/05, *Wahrer* A68641/06, *Smith* A68949/06, *Leopold* A73987/06, *Campbell* A73404/06-7, *Wiener* A76742/07, *Lackie* A73936/07-8, *Logothetopulos* A76020/08, *Ivens* A73825/08, *Delporte* A73486/08, *Vignard* A68582/09, *Petri* A76277/09, *Novak* A76229/09, *Maiss* A76055/09, *Vaccari* A76669/10, *Füth* A73643/10, *Ferran* A73571/10, *Menne* A76111/11, *Hörrmann* A73795/11 *Pollosson* A76308/12, *Rosenstein* A77079/12, *Ferré* A73572/13, *de Rouville* A76435/13, A81106/14, *Chalier* A73418/14, *Barkley and Herring* A68559/15, *Hines* A73789/16, *Hertz* A73775/20, *Viannay* B8721/20, *Gonzalez* A68566/20, *van Rooy* A76411/22, *Moxter* A76166/22, *Irland* B21016/23, *Estor and Sicard* A73550/23, *Wertheimer* A80308/23, *Josephson* A68568/24, *Harguindeguy* A73735/24, *Mathews* A76085/25, A76086/25, *Duncan* B7468/25 *McDowell* A76038/27, *Keiffer* A73873/27, B7231/27, *Cotte* A73445/27, *Poppen* A76318/28, *Bourg* A73346/28, A73347/28, *Lastra and Colillas* B6027/28, *Gheorghiu et al.* A73675/29, *Hammond* A65546/30, *Falsia and Viggiano* A65147/31, *Ducuing and Guilhem* A73515/31, *Andrews* A66138/32, *Miller* A76139/33, *Fitzgibbon* A73583/33, A73582/33, *Taddei* A61811/33, A76597/33, *Treutinger* A53075/34, *Newell* A95304/37, *Hollstein* A97175/38, *LeGac* A97695/39, *Southward* A35397/40, *Bowles* A37818/42.
[9]*Smith* A76538/07.
[10]*Kermauner* A64880/32.
[11]*Pfannenstiel* A76286/08, A49152/897.
[12]*Mayer* A78681/24-9, A64459/30.
[13]*Miller* A61885/33.
[14]A76037/21.
[15]A76229/09.
[16]*Lacroix* A73937/833, *Thomson* A76623/895, *Latham* A73953/898-9, *Gottschalk* A73696/899, *Wilms* A76755/899, *Dienst* A73493/899, *Hertz* A73776/899, *Winston* A68958/01, *Norris* A68675/06, A76227/06, *Shattock* A76523/06-7, *Ferré* A73572/13, *Bluysen* A68550/13, *Frankl* A73617/15, A73618/15, *Kaboth* A73885/24, A73857/25, *Koucky* A73916/25, *Frembgen* A73630/25, *Rosenstein* A76422/28, A76420/28, *Whitehouse* A64209/31, *Runeskog* A62947/32, A61892/32, *Miller* A61885/33.
[17]*Novak* A76229/09.
[18]*Alquie* A73187/857, A69338/857-8, *Negri* A29517/880, *Terrier* A80300/885, *Florschütz* A73597/888, *Bergengrün* A73288/891, *Krug* A73924/891, *Preisendanz* A76340/01, *Macnaughton-Jones* A76047/06-7, *Jones* A82667/06-7, *Wiener* A76744/07, A76745/09, *Brohl* A73376/07, *Morestin* A76158/11, *Muller* A76176/32.
[19]*Meyer* A76123/05.

cooling. The chemical composition of the dermoid contents will be discussed later in a separate subdivision of this section.

Perhaps the most striking inclusions within the cavaties of dermoid cysts are *solid concretions* variously described in the world literature as "erbsenartige Körper",[1] "rounded balls",[2] "epithelial balls",[3] "boules de graisse",[4] "caviar-like bodies",[5] "Dermoidkugeln",[6] "Butterkugeln",[7] "Fettkugeln",[8] "pill-like bodies",[9] etc.[10] Their number is often enormous. Thus Bonney[11] counted 4000 and Kusuda[12] as many as 300,000 small rounded bodies usually only a few millimeters in diameter and white or greyish in color. In other cases these balls are larger and brittle. They may assume the size and shape of a fowl's egg,[13] and their surface may be smooth or covered with numerous facets.[14] Not infrequently, hair is mixed with the fatty material which composes these balls.[15] In these cases distinct layers of the brittle material are often deposited around the hair-containing center. In other instances, the central portion is represented by a cavity containing dark oily material.[16] The color of these concretions is also subject to great variation depending upon the amount of pigment material in them. If the balls are dark, semisolid and large, they may resemble fecal material. The pea-sized, hard, dark stones examined by Fränkel[17] and Schröder[18] turned out to be true bilirubin-calcium gallstones. Gallstone formation in dermoids has also been observed by v. Szathmary[19] and v. Rokitansky.[20]

Microscopically the structure of these concretions is also extremely variable. In some cases the balls consist almost exclusively of cornified epithelial cells and fatty-acid needles.[21] In most cases, however, hair is mixed with these tissues and the hard stone-like formations often contain a good deal of calcium as well as other mineral constituents. It is evident that these concretions are formed partly by cast-off surface cells of the epidermis which covers the wall of the cysts and partly by the secretions of the skin glands. Their shape is probably determined by the grinding of individual concretions against each other, a process similar to that responsible for the shape of many ordinary gallstones, urinary bladder calculi etc

Many investigators studied the process of *fat absorption* which takes place in the walls of some dermoid cysts and may lead to infiltration of the wall (and—in the case of rupture—even of the broad ligament) by a giant-cell-containing fat granuloma tissue.[22]

Upon removal of the amorphous material and the concretions contained in the cyst, the *papilla* ("Wilms Zapfen" of the German literature)—which corresponds to the body of the malformed embryo—becomes visible in the majority of typical dermoid cysts.[23] This is a protuberance of variable size and irregular outline frequently covered by small wart-like epithelial excrescences. On its dorsal aspect, the skin of the so-called cranial pole of the papilla is often covered with hair, while on its ventral surface it possesses a mucosa lining which is macroscopically distinguishable by its glossy, hairless and reddish appearance. The variability of this papilla is enormous and it may be entirely missing or developed into an almost complete embryo.[24]

It is not within the scope of this Encyclopedia to discuss in detail the almost limitless variations of the papilla. Suffice it to call attention to the fact that many rudimentary organs, such as well developed fingers,[25] may develop on a rather irregular papilla, or large segments of a fairly well proportioned embryonic body may be distinguishable. In the latter case, three main types are recognized, namely, the embryomas with a free cranial pole, those with a free caudal or pelvic pole, and those in which both poles are free and sufficiently developed to imitate a complete small human body. Occasionally the embryoma is almost entirely delimited from the cyst wall and only a thin pedicle—similar to an umbilical cord—remains as an attachment or hilus.

The embryomas with a *free cranial pole* are the most frequent and the common dermoid with well developed hair, teeth and an imitation of an oral

[1] *Kehrer* A73870/11, A73871/11.
[2] *Wilson* A76757/12-3.
[3] *Bonney* A73333/02.
[4] *Cuendet* A73455/14.
[5] *Schockaert* A76486/23.
[6] *Schwalbe* A76505/12, *Ebergenyi* A95440/39.
[7] *Friedländer* A73637/20.
[8] *Schlank* A76476/12.
[9] *Butler-Smythe* A73394/895.
[10] *Wladimirsky* A76761/, *v. Swiecicki* A76592/895, *Savels* A76463/09, *Piltz* A76292/10, *Frankl* A73616/12, *Plenz* A76298/12, *Dietrich and Kellendonk* A73494/22, *Petrowa* A76280/32.
[11] A73333/02.
[12] A73058/25.
[13] *Jacobsen* A73830/889, *Strassmann* A76579/00.
[14] *Schröder* A76500/18, *Tedenat* A66216/31.
[15] *Thornton* A76626/875-6, *Fränkel* A41308/884, *Mundé* A76180/887, *Florschütz* A73597/898, *Plenz* A76298/12, *Dittrich* A61956/33.
[16] *McMeans* A76046/14.
[17] A41308/884.
[18] A76500/18.
[19] A27891/35.
[20] A76409/842.
[21] *Knauer* A48358/896, *Askanazy* A73220/05, A73221/07.
[22] *Ramsbotham* A76357/852-3, *Sutton* A46552/893, *Williamson* A76750/04, *Gentili* A73668/06, *v. Ulesko-Stroganowa* A76666/10, Stewart A76572/12-3, Wolff A76766/13, Hirschland A73790/14, *Wagner* A76707/18, *Kehrer* A73872/21, *Benda* A73284/22, A73285/22-3, *Schickele* A76474/23, *Otto* A76248/28, A76249/28, *Petrowa* A76280/32.
[23] *Meyer* B11327/09.
[24] *Miller* A18279/37.
[25] *Omori and Ikeda* A43374/890, A46343/892, *Klaussner* A43343/890, *Reverdin and Buscarlet* A44702/894.

cavity belong to this type;[1] indeed, the cranium may even be almost complete.[2]

A *free caudal pole* with more or less developed pelvic bones, external sex organs and lower extremities, is likewise not infrequently observed.[3]

The most complete embryomas have both *free cranial and caudal poles*, which are sufficiently well developed to imitate a fairly proportionately built human body. Thornton's[4] famous "homunculus" belongs to this group. He described the structure as follows: "The cyst contained a curious solid mass covered with skin, with long hair, very like a foetal head, with a projection of bone, from which grew several teeth of various kinds, while from another part of its surface a small projection like an abortive limb, with long nails at the extremity, could be seen. The central part of the mass was solid fat, like an ordinary fatty tumor".

The degree of differentiation which may be acquired by such teratoids is illustrated by a case described by Repin.[5] This embryoma had four extremities and a head-like structure. The latter consisted of rather irregular bone spicules with three teeth and salivary gland tissue. On its caudal pole there was a small penis-like structure which histologically proved to be a nipple. The extremities were malformed but clearly recognizable, although the skeletal musculature remained undeveloped, fat-tissue having taken its place. Both clavicles and several ribs could be distinguished though none of the thoracic organs were detectable. The sciatic nerve emerged on each side from a groove in the vertebral column which was open on its ventral aspect. On the side of the embryoma a typical loop of small intestine was found.

The individual organs found in embryomas will be discussed below in the passage on Microscopic Characteristics.

Statistical considerations concerning the characteristics of dermoid cysts have been published by several investigators.[6]

The numerous relevant *case reports* supply ample data concerning the structure of *dermoids*.[7]

[1]*Meyer* A76130/24, A76131/25.

[2]*Schmucker* A76484/782, *Mainzer* A79606/08, *Shattock* B21075/23.

[3]*Key* A73885/863, A73886/863-4, *Repin* A76379/892, A76380/892, *Wertheim* A76735/894, *Shattock* A76523/06-7, *Askanazy* A73221/07, *Ingier* A73824/08, *v. Moser* A76161/14, A76162/22, *Heijl* A73751/21, *Köhler* A73906/21, *Albrecht* A73184/23, *Staffel* A76557/23, *Burgkhardt* A73391/23, *Kaboth* A73854/24, *Meyer* B6673/25, *Rosenstein* A76422/28.

[4]A76629/882.

[5]A76379/892, A76380/892.

[6]*Koucky* A73916/25, *Rohdenburg* A76407/26, *Furlong* A64220/31, *Miller* A18279/37.

[7]*Olshausen* A76238/, *Goth* A73696/, *Markusen* A76071/850, *Mailly* A76051/851, *Adams* A73180/851-2, *Schnepff and Davaine* A76485/852, *Laboulbène* A73935/852, *Jarjavay* A73835/852, *Hare* A73734/852-3, *Davaine* A73467/852-3, *Lebert* A73960/852, A73959/852, A73961/857, A73962/858, *Mauriac* A76094/853, *Steudel* A76571/854, *Decès* A69364/854, *Richet* A87650/857, *Pesch* A76271/857, *Wagner* A76705/857, A76706/857, A76704/03, *Wieland* A76741/858, *Derocque* A73492/858, *Civiale* A73429/859, *Salter* A76449/860, *Lee* A73971/860, *Heschl* A73780/860, *Emery* A73544/860, *Pelikan* A76262/861, *Foot* A73600/863, *Pommier* A76310/864, *Humphrey* A73814/864, *Eichwald* A73535/864, *His* A73792/865, *Leroy* A68730/866, *Hervieux* A68715/867, *Hart* A68714/867, A73737/02, *Mollière* A68737/869, *Hicks* A68716/869, A73783/13, A73785/14, A73784/14, *Chantreuil* A73420/870, *Hutchinson* A68721/870-1, A68722/874, *Porter* A76320/871, *Martens* A76074/871, *Kreis* A68727/872, *Friedländer* A73636/872, *Ponfick* A76315/872, A76314/873, *Boéchat* A69345/873, *Flewellen* A69369/873-4, *Thornton* A76626/873-4, A76628/881, A76629/882, A41601/883, A41223/883, *Rendu* A76377/874, *Terrier* A83090/875, *Haffter* A73726/875, *Cabot* A69352/875, *Pauly* A76260/875, A76261/875-6, *Polaillon* A76301/875, A76300/875, *de Sinéty* and *Malassez* A76531/876, *Féré* A73569/876, *Foulis* A73605/876-7, *Griffiths* A73709/876-7, *Thomas* A76620/876, A83091/879, A76621/882, *Weber* A75273/878, *Byford* A73399/878, A73400/886, A73397/888, *Eames* A69952/878-9, *Marcy* A76067/879, *Helmuth* A83065/879, *Gussenbauer* A73719/879, *Delzell* A69366/879, *Baker* A75274/879, *Byrne* A29237/879, *Grant* A68922/879-80, *Tait* A76598/879, A76599/883, A76600/890, *Osler* A29547/880, *Lee* A29445/880, *Allen* A29557/880, *Smith* A68950/880-2, A76537/882, A76534/884, A40841/885, A76535/891, A76538/07, *Mann* A40022/881, *Bang* A24895/881, *Baskett* A40102/881, *Doran* A73502/881, A40532/882, A73506/07-8, *Flaischlen* A29762/881, A40044/882, A73587/890, A73588/893, *Schreiber* A40508/882, *Nicolaysen* A76216/882, *Houze de l'Aulnoit* A40501/882, *Elsner* A40565/882, *Duplay* A40535/882, *Sims* A40196/883, *Lange* A41264/883, *Johannovsky* A41213/883, *Heyder* A73782/883, *Henston* A73768/883, *Edis* A41605/883, *Delens* A40654/883, *Chambers* A40187/883, *Bantock* A73249/883, *Fränkel* A73611/883, A41308/884, *Hunter* A41336/883-4, A73819/884, A83067/885, A73821/887, A42167/887, *Schröder* A76498/883, A76499/05, *Rubeska* A68631/884, *Polk* A76304/884, *Engström* A40791/884, *Düvelius* A73519/884, *Berger* A41633/884, *Closs* A83052/884-5, *Goodell* A83061/884, A73687/884, A73688/888, A46393/892, *Macdonald* A41486/884-5, *v. Säxinger* A41469/885, *Prewitt* A40840/885, *Méhu* A40800/885, *Munk* A42014/885, *Monod* A41001/885, *Luys* A76034/885, *Elliot* A73542/885, *Cushier* A41018/885, *Neilson* A68940/885-7, *Terrillon* A76615/886, *Nilsen* A76218/886, *Neumann* A76203/886, *Löhlein* A76015/886, *Lefranc* A73974/886, *Guichard* A69375/886, *Limont* A68933/886-7, *Tuholske* A43004/887, *Redard* A76368/887, *Proske* A41981/887, *Küster* A73927/887, *Barrett* A41837/887, *Boyd* A73358/887, *Fenger* A73568/887, A41773/887, *Jackson* A41781/887, A73828/887, *Mundé* A76181/887, A76182/888, *Poupinel* A41867/887, A76335/888, *Vignard* A76691/888, *Tison* A76641/888, *Seeger* A76511/888, *Longaker* A76021/888, *Leopold* A73986/888, *Jacobi* A42396/888, *Homans* A73804/888, *Fuller* A42375/888, *Duret and Voituriez* A42519/888, *Briggs* A42222/888, *Beatson* A73274/888, *Boldt* A73323/888, *Sutton* A42496/888, A73304/892, *Price* A76342/888, A76341/888, A76343/888, *Princeteau* A76344/888-9, *Potherat* A76322/888, A73626/01, A76324/01, A76327/02, A76328/03, A76330/05, *Veit* A76684/888, A76685/893, A76686/899, *Tischendorf* A76640/889, *Parkes* A43317/889, *Mauny* A43475/889, *Jacobsen* A73830/889, *Grammatikati* A45167/889, *Bulius* A43454/889, A43363/889, *Frank* A73615/889, A73614/02, *Anonymous* A42680/889-90, *Stengel* A68636/889-90, *Tussenbroek* A45709/890, *Seyfert* A76519/890, *Sänger* A76446/890, *Meij* A76101/890, *Klaussner* A43343/890, *Hatherly* A73739/890, *Hildebrandt* A73786/890, *Drappier* A45627/890, *Decio* A73472/890, *Cushing* A43600/890-1, *Czempin* A73460/890,

Footnote cont'd.

While, as we said above, the distinction between clear-cut instances of dermoids and teratomas is indistinct, attention is drawn to the large number of case reports describing more or less typical *teratomas and embryomas*[1]

[7] cont'd *Mendes de Leon* A76107/890, A76109/896, *Petit* A45635/890, A76276/891, *Wolcott* A45715/891, *Stryk* A76586/891, *Spanton* A76548/891, *Mackenordt* A76044/891, *Grechen* A73707/891, *Freeborn* A43991/891, *Duncan* A46364/891, *Barette* A44047/891, *Barnes* A73257/891, *Martin* A76078/891, A68659/898, A68658/898, A76079/12, *Tripier* A68955/892, *Thévenard* A76618/892, *Schauta* A76468/892, *Galabin* A73649/892, *Goffe* A73684/892, *Kelley* A44175/892-3, *Stark* A76560/892, A46293/892-3, A68634/05, *Souligoux* A76544/892, *Sutton* A46552/893, *Saks* A44619/893, *Reynier* A46436/893, *Purslow* A76350/893, *Fusino* A73647/893, *Derien* A73491/893, *Croom* A46464/893, *Charrier* A46387/893, *Shoemaker* A44705/893-4, *Tavel and Lanz* A76607/893-4, *Wertheim* A76735/894, *Tissier* A68639/894, *Cooper* A44858/894, *Brindel* A68906/894, *Ratchinski* A76359/894, A76360/894, *Thomson* A76623/895, *Sargnon* A76458/895, *Laroyenne* A68625/895, *Liaras* A68626/895, *Julhiet* A73852/895, *Graves* A73703/895, *de la Combe* A47443/895, A47376/895, *Aschoff* A73219/895, *Keeling* A73868/895, A73869/895, *Reverdin* A47469/895, A76381/896, *Massen* A76082/895, *Wilms* A79682/895, A68642/898, A76756/00, *Simons* A48288/896, *Knauer* A48358/896, *Herbet* A73770/896, *Fraikin* A68918/896, *Chase* A48429b/896, *Braun* A73363/896, *Lejars* A48275/896, A68752/04, A73981/04, *Reed* A76371/896, A76372/03, *Schramm* A76494/896, A76495/01, *Wettergren* A76736/897, *Shimonek* A68948/897, *Recasena* A68612/897, *Reamy* A76364/897, *Oliver* A49149/897, *Means* A48388b/897, *Geyl* A49100/897, *Frantzen* A49045/897, *Eberhart* A73525/897, *Danel* A49168/897, *Dietz* A73495/897, *Brown* A48427b/897, *Bovée* A73351/897, A73352/899, A73353/00, A73354/02, *Cohn* A68616/897-8, *Tipjakoff* A68954/898, *Théophilides* A76617/898, *Szabo* A50480/898, *Sabbe* A50621/898, *Pierre* A50620/898, *Portioli* A50681/898, *Lovrich* A50977/898, *Hoffmann* A73797/898, *Doléris* A73499/898, *Bäcker* A73230/898, *Alexander* A73185/898, *André* A50492/898, *Fox* A50535/898, A68917/04, *Cumston* A50633/898-9, *Fritts* A68619/898-9, *Sobestianski* A68951/898-9, *Frank* A50996/898-9, *Verdelet* A76689/899, *Sarkewitsch* A76459/899, *Polienoff* A81487/899, *Gottschalk* A73696/899, *Polanow* A76303/899, *Kaarsberg* A73853/899, *Holtschmidt* A73803/899, *Gebhard* A73657/899, *Fairbairn* A73551/899, *Dubuchy* A68911/899, *Betagh* A68646/899, *Bétrix* A73293/899, *Aalbertsberg* A73175/899, *Arnsperger* A73212/899, *Giffard* A68919/899-00, *Witthauer* A76760/00, *Talbot* A76601/00, *Solowij* A76542/00, *Lewers* A73995/00, *Kerr* A68930/00, *Habs* A73725/00, *Gibson* A68621/00, *Flatau* A73591/00, *Funke* A73646/00, *Delatour* A68913/00, *Atlas* A75298/00, *Elder* A73539/00-1, *Opitz* A76241/00, A76243/06, *Steinert* A68635/00-1, *Strassmann* A68638/01, *Stewart* A68637/01, *Seitz* A76516/01, *Saniter* A76452/01, *Ricard* A76387/01, *Martinoff* A68937/01, *Münster* A76174/01, *Markwald* A76072/01, *Katsurada* A73865/01, *Ikeda* A73823/01, *Haggard* A73727/01, *Ernst* A73549/01, *Dennemark* A73490/01, *Castaing and Phillippe* A68741/01, A68742/01, *Baudler* A68759/01, *Bertelsmann* A73292/01, *Bosc* A73340/01, *Alexander* A73186/01, *Schachner* A68947/01-2, *Vrbanic* A68957/02, *Tannen* A76602/02, *Reinprecht* A76376/02, *McGinnis* A68935/02, *Neck and Nauwerck* A76195/02, *Kroemer* A75302/02, *Khautz* A73887/02, *Foster* A68915/02, *Delassus* A68912/02, *Chandler* A68908/02, *Blau* A73309/02, *Azéma* A68901/02, A68903/02, *Asch* A73216/02, A73217/08, A73218/09, *Merkel* A76116/02, *Bogdanovici* A68905/02-3, *Poncet* A68945/03, *Price* B8961/03, *Muller* A76175/03, *Ludwig* A76029/03, *Leriche* A73989/03, *Iwase* A68622/03, *Jelke* A73838/03, *Grandin* A73700/03, *Baldwin* A68902/03, *Balloch* A73237/03, *Ahrens* A73183/03, *Anderson* A68899/03-4, *Fordyce* A73602/03, A73603/09-10, *McMurtry* A68936/03-4, *Ward* A76719/03, A76720/19, *Hue* A73811/04, *Wood* B12984/04, *Bégouin* A73276/04, *Amann* A73193/04, *Ogata* A68627/04, A68764/04, *Villar* A68640/05, *Sutcliffe* A76589/05, *Kelly* A68929/05, *Edgar* A68617/05, *Sneguireff* A76539/05, *Stretton* A76584/05, *Scheffen* A76470/05, *Ricci* A76388/05, *Pollosson and Violet* A76309/05, *Kerntler* A73883/05, *Horand* A73807/05, *Gaimard* A68620/05, *Demons* A73488/05, *Casalis* A68614/05, *Brewis* A73368/05-6, A73372/07-8, *Jaboulay* A68925/05, *Metcalf* A83461/05-6, *Santi* A68665/06, *Reay* A76365/06, *Poroschin* A76319/06, *Garcia Roura* A80979/06, *Grawitz* A73704/06, *Falkner* A73554/06, *Fuchs* A73644/06, *Chénieux* A68615/06, *Czyzewicz* A73461/06, *Brünings* A73382/06, *Rosenstein* A76412/06, A76413/06, *Schottländer* A76492/06, A68633/06, *Stookes* A76578/07, *Lyons* A76035/07, *Girgensohn* A73678/07, *Ferguson* A73570/07-8, *Haim* A73728/07, A73729/08, *Mendels* A79613/07, A76106/08, *Schwarzenbach* A76508/08, *Ravano* A76362/08, *Monod and Roche* A82754/08, *McArthur* A76036/08, *Kauffmann* A73866/08, *Horne* A73808/08, *Daels* A73464/08, *Woltring* A76768/09, *Schick* A76473/09, *Kehr* A82735/09, *Kermauner* A73881/09, *Jolly* A73848/09, *Flinzer* A73596/09, *Riedinger* A76392/09, A76393/09, *Wieder* A76740/10, *Rabinowitsch* A76355/10, *Jewett* A73841/10, *Heijl* A73747/10, A73749/16, A73748/16, A73750/20, *Carmichael* A73410/10-1, *Gemmell* A73667/10-1, A73666/11, A73665/35, *Sellheim* A76517/11, *Rüder* A76440/11, *Neu* A76198/11, *Fraser* A73628/11; A63514/28, *Saltykow* A76450/12, *Förster* A73598/12, *Eccles* A73527/12, A73526/12, *Weibel* A76725/13, *Schwarzbach* A76507/13, *Phillips* A76289/13, *Péraire* A76266/13, *Henkel* A73767/13, *Grube* A73714/13, *Friedrich* A73639/13, *Chapuis* A73421/13, *Baudouin* A68560/13, *v. 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[1] *Keyser* A87468/867, *Thornton* A40001/881, *Marchand* A80252/881, *Bayer* A41197/883, *Mendes de Leon* A42457/888, *Coats* A80169/888, A46297/892, *Kramer* A43344/890, *Gorodetski* A68920/891, *Kundrat* A80242/892, A80241/892, *Emanuel* A46390/892-3, *Schreiber* A46508/893, *Sigwart*

Footnote cont'd.

Apart from the highly differentiated embryoma, the solid teratoma of the ovary is often extremely malignant particularly when it develops in young girls. Curiously, the microscopic appearance of the solid ovarian teratomas rarely suggests malignancy;[1] hence many cases which were not adequately followed over a long enough period were not recognized as malignant growths. There are, however, numerous case reports in which the tumor is definitely designated as a *teratoid carcinoma,* malignant teratoma or malignant embryoma.[2] (See also carcinomatous and sarcomatous transformation in passage on Microscopic Characteristics below.)

MICROSCOPIC CHARACTERISTICS AND ORGANOLOGY: Although many of the organs found in teratoid tumors are macroscopically visible, the entire organology (macro- and microscopic) of the embryomas will be discussed conjointly for the sake of simplicity.

The *skin* which lines the dermoid cysts usually varies in the different various portions of the tumor. Generally speaking it closely resembles the normal cutis. On the papilla it usually contains much hair, thus simulating the normal scalp;[3] the remaining parts of the cyst are lined with skin more reminiscent of that covering the rest of the body. In most cases all layers of the cutis are fully developed, the surface being covered with many layers of cornified cells. These accumulate because, unlike in the case of ordinary surface skin, in the protected interior of a dermoid, mechanical factors fail to aid their removal. Occasionally, the stratum granulosum and lucidum are missing just as in thin regions of the normal surface skin.[4] It must be emphasized, however, that only in very rare instances is the entire cyst lined by derma.[5] Commonly, certain portions are covered by a mucous cylindrical epithelium which may or may not contain ciliated cells. Such a covering is mostly found on the tip of the papilla although it may extend far over the wall.[6] This mucosa probably corresponds to misplaced gastrointestinal or respiratory epithelium.

Pigmented areas are sometimes seen in the skin of dermoids.[7] The fact that in colored races the pigmented portions of dermoids contain more melanin than in white patients will be discussed in the part devoted to the incidence of dermoids in negro women.

Pigmented warts can also develop within the skin of dermoids.[8] It is rather probable that the darkly pigmented melanomas and melanosarcomas[9] often found in dermoids, result from malignant transformation of such areas. Fischl[10] published a detailed study of skin pigmentation in dermoid cysts with special regard to its behavior during pregnancy. (See also chapter on Melanosarcomas of the Ovary).

Sometimes the entire papilla is transformed into a papillomatous structure.[11]

The *hair,* which is such a striking constituent of almost all dermoid cysts and even of some solid teratomas, has been the subject of considerable study.[12]

The color of the hair in dermoids is usually light, blond or reddish.[13] Frequently grey hair is mixed

[1]cont'd A80292/893, *Wernitz* A47479/895, *Chase* A48434/896, A48429b/897, *Wilms* A48379/896, A48380/896, A76752/897, A76753/899, *Weitzel* A80306/897, *Sirleo* A49156/897, *Wyss* A80311/899, *Kworostansky* A64782/899, *Keitler* A80230/00, *Jones* A80222/00, *Strassmann* A76579/00, A76580/01, *Wulkow* A76769/01, *Glockner* A80203/01, *Backhaus* A80154/01, *Bolzano* A73329/01, *Jung* A80224/01, A68514/05, *Sekiba* A68671/03, *Beard* A73273/03, *Rothe* A80277/04, *Puech* A68662/04, *Earl* A80184/04, *Goth* A80207/04, *Völker* A76697/05, *Schmidlechner* A68632/05, *Ribbert* A76384/05, *Offergeld* A76233/05, *Nechayeff* A68939/05, *Mühlenkamp* A76168/05, *Grawitz* A73705/06, *Neuhäuser* A76202/06, *Rosenstein* A80276/06, *Schiller* A80285/06, *Wanner* A76718/06, *Shattock* A76523/06-7, *Ruppert* A80278/07, *Kalischer* A80226/07, *Forselius* A80195/07-8, *Redlich* A80274/08, *Lissowskaja and Krimm* A76009/08, *Iwase* A73827/08, *Bukojemsky* A80166/08, A80167/08, *Nadossy* A80260/09, *Fuchs* A80199/10, A80200/10, *Didier and Rousseau* A80176/10, *Bovin* A80162/10, *Franco* A80196/11, *Landau* A73944/12, *Dörr* A68552/13, *White* A80309/13, *Strong* A80298/19, *Vautrin* A70426/21, *Shufflebotham* A80290/22, *Porter* A76321/22, *Blum* A80160/22, *Reverdin* A68577/24, *Neumann* A76204/25, *Meyer* A76131/25, *Leone* A73984/25, *Black* A80158/25, A80159/25, *Sutherland* A76590/26, *Stellakatu* A80296/26, *Momigliano* A80257/26, *Gaifami* A80201/26, *Fischmann* A73580/26, *Monjardino* B8050/26, A76151/26, A76152/28, *Kato* A80228/27, *Doyle* A80180/28, *Davidson* A80172/28, *Döring* A80177/28, *Bretschneider* A80163/28, *Gossard* A65609/30, *Carloni* A80168/30, *Hicks* A80216/30-1, *Melville* A80256/30-1, *Tédenat* A66216/31, *Froboese* A62928/31, *Lordy* A61930/32, *Jacobson* A62931/32, *Göcke* A80205/32, *Wakeley* A61947/33, *Sarma* A61630/33, *Nicholson* A28166/34, *Masterman* A53098/34, *Binkley* A53148/34, *v. Szathmary* A28071/35, *Sanderson* A28175/35, *Ortiz Perez* A61853/35, *Mennenga* A76112/35, *Marsalek* A28162/35, *Barco* A80155/35, *Atakam* A95377/37, *Witzberger and Agerty* A95127/37, *Hoeppner Dutra and Delascio* A97552/40, *Sakurai* A97522/41, *Pulskamp et al.* A97516/41, *McElhinney* A97493/41.

[1]*Smeltzer* A37338/41.

[2]*Jung* A80223/01, *Hicks and Targett* A80217/05, A80218/05, *Dudgeon* A80182/06, *Targett and Hicks* A80299/06, *Frank* A80197/07, *Kaulen* A80229/14, *Harris* A21505/17, B7480/25, *Björkenheim* A68159/29, A64415/30, *Ley* A97178/38, *Oda et al.* A96568/40.

[3]*Wilms* A79682/895.

[4]*Krömer* A70091/08, *Fischl* A73578/24, *Miller* A18279/37.

[5]*Draganic* A97269/39.

[6]*Friedreich* A73638/858, *Wilms* A79682/895, *Askanazy* A73220/05, *Schröder* A76500/18, *Miller* A18279/37.

[7]*Wang* B7255/27.

[8]*Kappeler* A73862/896, *Corsy* A73443/27, *Lubarsch* A76024/32, A62938/32.

[9]*Lorrain* A76022/05, *Amann* A77353/09, *v. Hoosen* A77867/22.

[10]A61752/33.

[11]*Baer* A45717/890-1, *Reed* A76370/891.

[12]*Bartlett* A69343/834-5, *Bouvier* A69346/838-9, *Jackson* A68724/848, A68725/854, *Bucquoy* A69348/853, *Browne* A69347/853-4, *Coward* A69362/856, *Hutchinson* A68719/865, A73822/865, A68720/867, *Aron* A69341/874.

[13]*Klob* A70086/864, *Olshausen* A41468/886, *Bond* A73330/06, B12883/06, *Bell* A73282/06, A73281/06, *Kermauner* A73881/09, A64880/32, *Dransfeld* A73513/18, *Miller* A18279/37.

in with the colored hair[1] and it may even be entirely white.[2] There is no close correlation, however, between the age of the patient and the greying of the hair within the dermoid or between the scalp hair and the cyst hair. Thus Shattock[3] described the case of a Jewess whose scalp hair was completely black, as was that of her husband, yet she bore a dermoid cyst with flax colored hair. Omori and Ikeda[4] reported blond hair in the dermoid of a Japanese woman and Yamasaki[5] emphasized that among 71 Japanese women with dermoids, only 17 had black hair within the cyst, while in the others the dermoid bore brownish hair in spite of the fact that all these orientals had jet-black scalp hair. The lack of correlation between the color of the scalp and the dermoid hair has also been emphasized by many other investigators.[6] In an interesting case of bilateral dermoids one cyst contained flaming red hair, the other blond hair.[7] In a white haired 82-year old woman[8] dark brown and black hair were found in one and red hair in the contralateral dermoid. Even within the same cyst brown and blond patches of hair may be seen side by side.[9]

The length of the hair is also subject to great variation. Generally it measures about 5-8 cm.[10] The exact average in 84 dermoids examined by one author[11] was 9.07 cm. It may become much longer, however, and many cases are on record in which dermoids contained hair several feet long.[12] In one dermoid[13] a five feet long switch of hair was encountered and (according to Miller)[14] Blandin observed hair three meters long in the dermoid of a seventy-five year old woman. The hair in dermoids is subject to frequent molting.[15]

The structure of the hair in dermoids is likewise very variable. It may be as fine as lanugo or as thick as beard hair.[16] Sometimes only beard-like hair is found.[17] The hair may be straight or curly, and both straight and curly hair may occur side by side in the same dermoid.[18] The extremely curly hair sometimes seen, is reminiscent of that normally observed in the pubic region and since such hair is often found at the caudal end of the embryoma-like dermoid papilla it has been regarded as a true equivalent of pubic hair.[19] Completely hairless dermoids are extremely rare.[20]

Histologically the hair in the dermoids also resembles normal human hair. Some hair shafts contain a marrow cavity and are comparatively thick, while others are thin and free of marrow.[21] Arrectores pilorum muscles are rarely found although in exceptional cases they may be particularly well developed.[22]

Nails—either loosely embedded in skin or on fingers —are comparatively common in dermoids.[23]

Skin glands, especially sebaceous glands, are usually well developed. Some of them are connected with the hair follicles, while others empty their secretion directly onto the skin surface.[10] Dermoids in which sebaceous glands are scarce have only rarely been observed.[24]

Kohlrausch[25] was the first to report the occurrence of sweat glands in dermoid skin. Such have also been noted by several subsequent investigators[26] although others missed them.[27] The peculiar dermoid observed by Macchi[28] contained neither sweat nor sebaceous glands and was also devoid of hair.

The sweat glands of dermoids are frequently subject to cystic dilation.[29]

Teeth are likewise common constituents of dermoid cysts, although they are not quite as regularly found

[1]*Schnepff and Davaine* A76485/852, *Askanazy* A73220/05, A73221/07.
[2]*Yamasaki* A76771/11.
[3]A76522/06.
[4]A43374/890, A46343/892.
[5]A76771/11.
[6]*Dienst* A73493/899, *Woltring* A76768/09, *Frembgen* A73630/25, *Neumann* A76204/25, *Bocock* A66105/32.
[7]*Lippert* A76005/13, A76006/13.
[8]*Féré* A73569/876.
[9]*Jackson* A73828/887, *Rendu* A76378/896, *Askanazy* A73220/05, A73221/07, *Yamasaki* A76771/11.
[10]*Miller* A18279/37.
[11]*Yamasaki* A76771/11.
[12]*Lebert* A73963/875, *Haffter* A73726/875, *v. Wahl* A41225/883, *Shattock* A76522/06, *Askanazy* A73221/07.
[13]*Mundé* A76183/891.
[14]A18279/37.
[15]*Steinlin* A76566/850.
[16]*Friedländer* A73636/872, *Baumgarten* A41799/887, *Florschütz* A73597/888, *Kappeler* A73862/896.
[17]*Seyfert* A76519/890.
[18]*Jackson* A73828/887, *v. Moser* A76162/22.
[19]*Key* A73885/863, A73886/863-4, *Repin* A76380/892, A76379/892, *Wilms* A76753/899, *Shattock* A76522/06, *Askanazy* A73221/07, *Heijl* A73751/21, *Albrecht* A73184/23, *Kaboth* A73854/24, A73856/25, *Meyer* A76131/25.
[20]*Macchi* A76039/24.
[21]*Klaussner* A43343/890, *Katsurada* A73865/01.
[22]*Baumgarten* A41799/887, *Wilms* A79682/895, *Askanazy* A73220/05, A73221/07, *Heijl* A73751/21, *Albrecht* A73184/23, *Meyer* A76131/25.
[23]*Thornton* A77856/883, *Klaussner* A43343/890, *Omori and Ikeda* A43374/890, A46343/892, *Goffe* A73684/892, *Ratschinsky* A76359/894, A76360/894, *Askanazy* A73221/07, *Ingier* A73824/08, *Köhler* A73906/21, *Heijl* A73751/21, *v. Moser* A76162/22, *Albrecht* A73184/23.
[24]*Klauhammer* A73891/12.
[25]A73908/843.
[26]*Heschl* A73779/852, *Wilms* A79682/895, *Klauhammer* A73891/12.
[27]*Friedreich* A73638/858, *Florschütz* A73597/888, *Rabinowitsch* A76355/10.
[28]A76039/24.
[29]*Friedländer* A73636/872, *Haffter* A73726/875, *Biermann* A40994/885, *Kappeler* A73862/896, *Merttens* A48983/897, *Wilms* A76753/899, *Preisendanz* A76340/01, *Askanazy* A73220/05, *Krömer* A70091/08, *Latteux and Thevenard* A73955/14, *Kaboth* A73854/24, A73855/24.

as hair.[1] The minute structure of such dermoid teeth was examined in special detail.[2]

Not infrequently the teeth are attached to bony plates which may be entirely irregular or may resemble a mandible or maxilla; indeed in some cases even a more or less complete rudimentary mouth may be formed.[3] Regular maxillae and mandibles may be visible in vivo on X-ray films.[4]

The number of teeth present in dermoid cysts is extremely variable. Sometimes they are completely absent, while in other instances only a few are present, but occasionally they are very numerous. In a single dermoid 44 teeth,[5] 36 molars and 10 incisors,[6] 58 teeth[7] or even more than 108 "blendend weisse" teeth[8] were observed; "manche wurden bei der Sektion verschleudert", hence the exact number is unknown. One case[9] was described as follows: "Die Zähne, welche mit den Knochenstücken vermischt gefunden wurden, und deren kaum die Hälfte, und ihrer doch ungefähr 300 herausgenommen und gezählt wurden, fanden sich, wie die natürlichen Zähne im Kiefer des neugeborenen Kindes, in geschlossenen, mit Gallerte oder Schleim gefüllten Beuteln, die aus einer festen, blutgefässreichen Membran bestanden". From these observations it is evident that the impulse for tooth formation, as for the formation of other ectodermal derivatives, is especially characteristic of dermoids and more pronounced in them than could be expected if such teratoids were only malformed single embryos.

The color of the teeth is generally white or slightly yellow. There are dermoids, however,[10] in which all the teeth are definitely brownish in color.

The shape of these teeth is often very irregular; it may, however, be a more or less exact copy of normal, oral teeth, imitating the shape and structure of incisors, canines, premolars or molars.[11] Among the abnormalities, concretion of two teeth may lead to the formation of so-called twin teeth.[12] Usually the teeth in dermoids are subnormal in size.[13]

The substitution of milk teeth by permanent teeth and the resorption of the former occurs in dermoids in essentially the same manner as in oral teeth, although irregularities are more common.[14] It was pointed out[15] that none of the teeth in a dermoid cyst of a 14-year old girl were completely mature as yet so that the development of permanent teeth in the cyst appears to be slower than that of oral teeth. Several other investigators confirmed that the differentiation of dermoid teeth does not generally correspond to the age of the patient.[16] The foramen apicale tends to remain wide open in most of the dermoid teeth, thus corresponding to the juvenile form. From this it was concluded that dermoids cannot be regarded as teratomas of an age equal to that of the bearer.[17] Although some dermoid teeth have well developed roots and are surrounded by normal gingival tissue, the lack of root formation is a common phenomenon.[18]

Development of caries in dermoid teeth has occasionally been demonstrated histologically.[19] This, if it can be confirmed, is of great interest in connection with some of the current theories concerning the etiology of dental caries as a consequence of locally acting exogenous agents.

The irregularities, which so frequently occur in connection with the absorption of the milk teeth and their substitution by permanent teeth, may explain the occasional occurrence of paradental epithelial debris in dermoids.[20] Occasionally *adamantinoma*,[21] *odontoma*[22] and *epulis*[23] formation has been reported within dermoids.

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[1] *Anderson* A69339/806, *Forget* A69370/848, *Conant* A69361/857, *Böttlin* A45085/889, *Benington* A68645/890-1, *Harres* A73736/892, *Kammerer* A46371/893, *Merttens* A48983/897, *Glazebrook* A50998/898-9, *Bar* A68644/01, *Trauner* A68667/03, *Broomell* A73378/05, *Miller* A76143/05, A76144/05, *Moser* A76161/14, A76162/22, *Marthaler* A76075/18, A76076/18, *Potherat* A68576/19, *Polano* A76302/20, *Freundlich* A73635/20, A73634/20, *Steinhoff* A76565/22, *Schubert* A76501/23, *Macchi* A76039/24, A82752/24-5, *Labry* A68570/25, *Sannai* A76453/25, *Weinmann* A76727/27, *Delevaud* A68551/27, *Kanamori* A73861/28, *Klemm* A73897/28, *Lübke* A76025/31, *King and McCallum* A73889/32, *Williams* A76749/34, *Churchill* A59925/36, *Kronfeld* A97388/40.

[2] *White and Sutton* A45652/890, A43494/890.

[3] *Greetham* A69374/834, *Raikern* A82515/841, *v. Haartmann and Marcusen* A69377/852, *Doran* A43457/889, *Baer* A45903/891-2, *Harres* A73736/892, *Fehling* A73564/03, *Müller* A76171/20, *Germann* A73671/23, *Labry* A68570/25, *Pélissier* B8154/28, *Heron* A97550/41.

[4] *Asch* A73217/08, A73218/09, *Pont* A76316/26, *Schmid* A76480/32.

[5] *Cleghorn* A73431/787.

[6] *Neunhöffer* A76207/892.

[7] *Cardaliaguet and Marquer* A73407/05.

[8] *Schabel* A76465/844.

[9] *Autenrieth* A73225/807.

[10] *Kappeler* A73862/896.

[11] *Meckel* A76100/815, *Steudel* A76571/854, *Doran* A43457/889, *Harres* A73736/892, *Rabe* A49191/897, *Römer* A76404/04, *Neugebauer* A76200/05, *Steinhoff* A76565/22.

[12] *Freundlich* A73634/20, A73635/20, *Steinhoff* A76565/22.

[13] *Harres* A73736/892, *Böttlin* A45085/889, *v. Moser* A76161/14, *Freundlich* A73634/20, A73635/20, *Steinhoff* A76565/22.

[14] *Meckel* A76100/815, *Wells* A76729/874, *Köberlé* A70087/878, *Harres* A73736/892, *Niemer* A76217/895, *Merttens* A48983/897, *Maystre* A76099/02, *Trauner* A76648/04, A76647/04, *Krömer* A70091/08, *Bluntschli* A73315/11, *Meissner* A76102/14, *Freundlich* A73634/20, A73635/20, *Steinhoff* A76565/22, *Schubert* A76501/23, *Sannai* A76453/25, *Klemm* A73897/28.

[15] *Kartuschanskaja* A80227/06.

[16] *Meissner* A76102/14, *v. Moser* A76162/22, *Schubert* A76501/23.

[17] *Schubert* A76501/23, *Godard and Bouland* A73682/25.

[18] *Trauner* A76648/04, *Müller* A76171/20, *v. Moser* A76162/22, *Macchi* A76039/24.

[19] *Miller* A76145/06, *Potherat* B8708/20.

[20] *Malassez* A68733/886.

[21] *Zajewloschin* A65197/31.

[22] *Condamin* A44081/892.

[23] *v. Szathmary* A28073/35, A28074/35.

In one peculiar case[1] a tooth was apparently embedded in normal ovarian substance without there being the slightest trace of tumor or cyst formation.

Bone formation in dermoids has already been mentioned in connection with the maxilla-like bony plates in which the teeth are frequently embedded. The histologic structure of these *ossified plates* and of the other, more or less *irregular bony formations* found in dermoids, has been subjected to much careful study.[2] Sometimes formations have been found in dermoids which resemble certain normal bones in their shape and structure. Thus plates simulating a *temporal bone*,[3] an *occipital bone*[4] and even more or less completely formed *crania*[5] have been observed, although *maxillae and mandibles* are most common;[6] *ribs*[7] are rare. Küster[8] described a rib which was preperitoneal and thus cannot be regarded with certainty as part of the ovarian dermoid.[9]

The development of a *vertebral column* has repeatedly been observed, both in that type of dermoid in which the cranial end of the papilla is free and in that which has an unattached pelvis.[10] Some investigators attribute special importance to the occurrence of vertebral columns since they represent definite proof of axiation and metameric segmentation in dermoids the existence of which had been denied.[11] Individual vertebrae,[12] and *notochordal tissue*[13] may also be encountered.

Individual *pelvic bones* or more or less completely formed infantile pelves occasionally develop on the caudal pole of the papilla.[14] *Sternum*-like formations have also been mentioned,[15] but their identification is subject to a great deal of doubt owing to the lack of characteristic features in the case of this bone.

Bones imitating the *extremities* or individual digits are not uncommon in the embryoma-like papillae and these hardly deserve special description.

A case has also been described in which dermoid tumors of both ovaries were complicated by a deposit of bone upon each side of the true pelvis, but these bones had no connection with the ovarian tumors.[16]

Cartilage is a fairly constant constituent of teratoid tumors. It is usually found in connection with the embryonic skeleton, the joint surfaces and the respiratory passages. In other instances its growth is quite irregular as in the "teratoma enchondromatosum".[17] Frequently, cartilage grows to the exclusion of other recognizable teratomatous tissues. In such instances it is difficult to differentiate between a purely cartilaginous teratoid and a true chondroma; in fact, it is somewhat doubtful whether there is any difference between the two. A chondroma of the ovary would most probably arise from heterotopic tissue remnants (unless it originates following metaplasia) and hence would represent a teratoid growth.

The cartilage in teratoid tumors may be fibrous or hyaline and in general resembles that of normal embryos (see also chapter on Chondromas).

The ordinary *connective tissue* of teratoids is likewise devoid of any special morphologic characteristics. It may contain plasma cells[18] or mast cells.[19]

Smooth muscle cells are quite common in the skin and the intestinal loops of embryomas. These require no special discussion here and the reader is referred to the passages on skin and on the gastro-intestinal tract.

Striated *muscle cells* are very rare in teratoid tumors. Usually the skeletal musculature is immature and undifferentiated so that cross striation is not distinguishable. In some cases the entire skeletal musculature appears to be replaced by fat, perhaps as a result of fatty degeneration.[20] The rarity of striated muscle cells in ovarian teratoids is all the more remarkable since teratomas of other organs (e.g., lung, kidney) frequently possess such inclusions; yet in a certain number of cases skeletal muscle cells were demonstrable.[21] The occurrence of striated muscle cells in the tongue and heart of embryomas (see corresponding passages of this chapter) will have to be kept in mind before making the diagnosis of skeletal muscle in severely malformed embryomas.

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[1] *Saxer* A76464/02.

[2] *Denny* A69367/850-2, *Helfft* A73759/852, *Atlee* A69342/870-1, *Boechat* A69345/873, *Schmidt* A43381/890, *Dombrowski* A73501/891, *Hellier* A73764/13, *Chueco* A66891/22, *Bühlmann* A73388/27.

[3] *Bourneville and Bourgeois* A73348/867, *Harres* A73736/892, *Wilms* A76753/899, *Mauny* A68573/11.

[4] *Milbradt* A76136/893, *Wilms* A79682/895.

[5] *Grechen* A73707/891, *Kalina* A73859/24.

[6] *Wilms* A76753/899, *Opitz* A76241/00, *Bolzano* A73329/01, *Wulkow* A76769/01. *Fehling* A73564/03, *Askanazy* A73220/05, *Asch* A73217/08, *Ludewig* A76027/20.

[7] *Repin* A76379/892, A76380/892, *Dietz* A73495/897, *Wilms* A76753/899, *Opitz* A76241/00, *Schramm* A76495/01, *Kaboth* A73854/24.

[8] A73927/887.

[9] *Miller* A18279/37.

[10] *Repin* A76379/892, A76380/892, *Shattock* A76523/06-7, *Riopelle* A96576/40, 80887/41.

[11] *Willis* A94816/37.

[12] *Seyfert* A76519/890, *Heijl* A73751/21, *Zschau* A76775/22.

[13] *Bertone* A80156/25, *Riopelle* A96576/40, 80887/41.

[14] *Dombrowski* A73500/890, *Wheaton* A76737/893, *Ratchinsky* A76359/894, A76360/894, *Heijl* A73751/21.

[15] *Schabel* A76465/844, *Tschirmer* A76659/897.

[16] *Noble and Tunis* A47412/895, A47503/896.

[17] *Keller* A45094/889.

[18] *Kappeler* A73862/896.

[19] *Arnsperger* A73212/899.

[20] *Anders* A73202/21, *Meyer* A76131/25.

[21] *v. Velits* A41829/887, *Répin* A76379/892, A76380/892, *Kappeler* A73862/896, *Merttens* A48983/897, *Yamagiva* A48461/897, *Askanazy* A73221/07, *Krömer* A70091/08, *Novak* A76229/09, *Rosenstein* A76418/13, A76422/28, *Kaboth* A73854/24, *Lanman* A68183/29.

Fat tissue is almost regularly present in the stroma of all dermoids. As emphasized above, the skeletal musculature of embryomas may be more or less completely replaced by adipose tissue.

Excessive development of fat within embryomas and dermoids may lead to formation of large fat cell accumulations resembling *lipomas*.[1] The distinction between a lipoma and an abnormal fat accumulation in a teratoid tumor is practically impossible, however (see also chapter on Lipomas). The pseudo-lipomas, which result from rupture of dermoids with extrusion of their contents into the broad ligament, have been discussed above (see dermoid contents).

The *blood vessels* of teratoids deserve no particular discussion, but it is well to emphasize clearly that they are branches of the ovarian vessels of the "mother".[2] Wilms[3] was the first to point out that the embryomas possess a "maternal" circulation. This fact is rather important in connection with the various theories which attach great importance to the role, in embryonic development, of a semi-permeable membrane between mother and fetus as well as to the endocrine and nutritive function of placental tissue. The embryomas teach us that none of these placental functions are indispensable for the formation of the organs found in such tumors, yet it is noteworthy that in no case was a normal embryo developed within these growths.

Lymphatic vessels are plentiful in embryomas.[4] Within these growths *lymphangiectases*[5] or *lymphangiomas*[6] may also develop.

The "*endotheliomas*" and "*peritheliomas*" of teratoids have been discussed in the chapters specifically devoted to these tumors.

Lymphnodes are quite commonly detectable in teratoid tumors, frequently in the proximity of portions of the gastro-intestinal or respiratory organs.[7]

Portions of the *gastro-intestinal tract* are often recognizable in embryomas by mere naked eye inspection. A more or less well developed *tongue*[8] is rare, but *salivary glands*[9] are extremely common. In some cases they were identified as a parotid,[10] salivary glands of the lips or oral cavity,[11] mixed salivary glands[12] or a distinct sublingual salivary gland.[13] *Pharynx*-like structures with well developed adenoids or *tonsil*-like formations,[14] an *esophagus*-like structure[15] and portions of *gastric mucosa*[16] have also been observed in dermoids. In many of these last mentioned cases, the histologic structure of the stomach (oxyntic and mucous cells) was so characteristic that it could be identified with absolute certainty. In some instances the structure of the intestinal tube resembled that of the *small intestine*.[17] Distinct Brunner glands helped to identify an intestinal segment of teratoid as a *duodenum*.[18] Portions of *large intestine*[19] and *appendix*[20] have likewise been seen. Several other teratoids with more or less clearly identifiable portions of intestinal tract, sometimes with mesentery, have been described.[21] Not infrequently these gastro-intestinal segments represent a curious mixture of various parts of the digestive tract; occasionally portions of respiratory epithelium may be mixed in with intestinal mucosa. These gastro-intestinal segments are usually supplied with sympathetic ganglion cells and plexuses.[22]

The intestinal segments may develop extramurally as in a case[23] in which a 28 cm. long intestinal loop was attached by a mesentery to the outer wall of a dermoid. A similar case was published by Michael.[24]

Occasionally *carcinoid argentaffine tumors* arise from the gastro-intestinal mucosa of teratoid tumors.[25]

The so-called *muco-dermoid cyst* may represent teratoids in which gastro-intestinal epithelium has undergone an atypical development (see Ovarian Remnant and Contralateral Ovary in chapter on Common Cysts).

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[1] *Potherat* A76324/01, A76325/01, A76326/01, *Ribbert* A76874/14, *Koucky* A73916/25, *Kermauner* A64880/32.
[2] *de Francesco* A68512/24.
[3] A79682/895.
[4] *Krömer* A70091/08.
[5] *Stübler* A76587/23, *Neumann* A76205/27.
[6] *Schottlaender* A68633/06, *Rössle* A70539/12, A70540/12.
[7] *Kappeler* A73862/896, *Jelke* A73838/03, *Meyer* A76131/25.
[8] *Johnstone* A73846/893, A73847/896, *Merttens* A48983/897.
[9] *Merttens* A48983/897, *Neck and Nauwerck* A76195/02, *Jelke* A73838/03, *Wagner* A76704/03, *Askanazy* A73220/05, *Offergeld* A76233/05, *Kermauner* A73881/09, A64880/32, *Stewart and Eglington* A70969/11, *Koucky* A73916/25, *Rohdenburg* A76407/26.
[10] *Simons* A48288/896.
[11] *Krömer* A70091/08.
[12] *Merttens* A48983/897, *Wilms* A76753/899, *Wulkow* A76769/01, *Novak* A76229/09.
[13] *Offergeld* A76233/05.
[14] *Askanazy* A73220/05, *Novak* A76229/09, *Kermauner* A73881/09, A64880/32, *Stewart and Eglington* A70969/11.
[15] *Kappeler* A73862/896.
[16] *Arnsperger* A73212/899, *Bandler* A73242/01, *Ernst* A73549/01, *Askanazy* A73220/05, *Novak* A76229/09, *Karsner* A73864/10, *Kaboth* A73854/24, *Schmid* A76480/32, *Gabrilove* A36665/41.
[17] *Arnsperger* A73212/899, *Stolz* A76576/00, *Wulkow* A76769/01, *Wagner* A76704/03, *Schottenfeld and Littauer* A96545/38.
[18] *Schröder* A76500/18.
[19] *Krömer* A70091/08, *Novak* A76229/09, *Kermauner* A73881/09, A64880/32.
[20] *Schottenfeld and Littauer* A96545/38.
[21] *Perls* A76268/876, *Koeberle* A70087/878, *Neumann* A76203/886, *Michael* A76133/886-7, *Flinzer* A73596/09, *Andrews* A73204/12-3, *Schönholz* A76487/23, *Roth* A76426/23, *Leibtschik* A73978/26.
[22] *v. Velits* A41829/887, *Askanazy* A73220/05, *Krömer* A70091/08.
[23] *Schönholz* A76487/23.
[24] A76133/886-7.
[25] *Stewart et al.* A31285/39, *Gabrilove* A36665/41.

Portions of the *respiratory tract* are also sometimes found in dermoids. Thus Wilms,[1] believed he saw a partially developed *lung* primordium, while others[2] described structures which resembled infantile *tracheae*. In some instances irregular portions of ciliated respiratory epithelium are found on cartilage plates.[3] A malformed *nose*, or at least structures resembling nasal conchae, may also develop[4] and in rare instances an entire *larynx* is found.[5]

The heart is usually not developed, although striated cardiac muscle fibers have been found in the vicinity of a thyroid nodule in a teratoid tumor[6] and a singular case[7] was described as follows: "This specimen had a well formed mitral valve, the columnae carneae, chordae tendineae, and all the muscular structures necessary to the formation of a heart, except that they were incorporated in the wall of a cyst and were lined with a perfect endocardium. The semi-cartilaginous ring that separates the ventricle and auricle was plainly marked, and there was quite a good attempt at the formation of the auricle as well as of the ventricle, so much so that any first-year student could have seen it for himself".

A macroscopically recognizable *kidney* is rarely found,[8] but portions of the *urinary bladder, ureter* or *urethra* are somewhat more common.[9] In some of these cases a *urachus-like structure* was distinguishable.

Mammary glands, with or without recognizable *nipples*, are not uncommon in dermoids cysts.[10] Some of these arise in close topographical relationship with the embryologically related sebaceous glands.

Malformed *ears* and portions of the internal auditory meatus including the labyrinth, are uncommon in dermoid cysts, though not unheard of.[11]

Eyes are rarely developed in dermoid cysts; if present they tend to be malformed single organs.[12] The pigment-epithelium of the retina is frequently detectable by naked eye inspection in the form of shiny dark black spots.[13] Some observers[14] described structures which apparently represented incompletely formed eyelids, while others[15] noted formations resembling the crystalline lens.

Nervous tissue is often found in embryomas. Structures resembling malformed portions of the central nervous system usually contain much glia tissue.[16] Occasionally nervous tissue is the major constituent of an embryoma.[17]

Cerebral tissue, if present, tends to occur near the cranial pole of the papilla within more or less irregular bony plates.[18] In some of these instances, differentiation of the cerebral cortex went so far that the specific structure of certain convolutions could be identified.

The presence of cerebellar tissue has only rarely been demonstrated,[19] but when present its macroscopic appearance, with the characteristic convolutions and its histologic structure, with the prominent Purkinje cells, made identification of cerebellar tissue very simple.

A spinal cord may also develop and in some instances its degree of differentiation may be such that typical spinal ganglion cells are seen. These are sometimes arranged in the characteristic butterfly pattern, recognizable macroscopically on cross sections.[20]

It is noteworthy that the central nervous system primordia found in teratoid tumors are usually enveloped in *leptomeninges* and *dura*.[21] The presence of tubes and cysts lined by typical ependyma is very common[22] and within these cavities papillary structures are found which resemble *chorioid* plexuses.[23]

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[1]A76753/899.

[2]*Baumgarten* A41799/887, *Ernst* A73549/01, *Askanazy* A73220/05, *Heijl* A73747/10.

[3]*Böttlin* A45085/889, *Arnsperger* A73212/899.

[4]*Arnsperger* A73212/899, *Offergeld* A76233/05, *Krömer* A70091/08.

[5]*Baumgarten* A41799/887, *Merttens* A48983/897, *Krömer* A70091/08.

[6]*Katsurada* A73865/01, *Askanazy* A73220/05.

[7]*Johnstone* A73846/893.

[8]*dos Santos* A76455/25, *Nicholson* A52288/34.

[9]*Ingier* A73824/08, *Albrecht* A73184/23, *Burgkhardt* A73391/23, *Staffel* A76557/23, *Meyer* A76130/24.

[10]*Haffter* A73726/875, *v. Velits* A41829/887, *Sutton* A45111/887-8, *Shattock* A45110/887-8, *Favell* A73561/05, *Norris* A68675/06, *Schottländer* A76492/06, A68633/06.

[11]*Born* A81009/868, *Shattock* A45110/887-8, *Askanazy* A73220/05, *Krömer* A70091/08, *Kaboth* A73854/24, *Timpanaro* A62954/32.

[12]*Baumgarten* A41799/887, *Van Duyse* A76674/895, *Hirst* A73791/03, *Amann* A73200/10, A73199/11, *Heijl* A73752/29.

[13]*Kappeler* A73862/896, *Katsurada* A73865/01, *Askanazy* A73220/05.

[14]*Habs* A73725/00, *Kartuschanskaja* A80227/06.

[15]*Magarinos Torres et al.* A96633/40.

[16]*Friedreich* A73638/858, *Wilms* A76753/899, *Katsurada* A73865/01, *Askanazy* A73221/07, *Heijl* A73751/21, *Rohdenburg* A76407/26, *Shaw* A61896/33, *Krafka* A97285/39, *Willis* A97834/42.

[17]*Feucht* A73574/16, *Cornil et al.* A59880/36.

[18]*Gray* A73706/853, *Van Duyse* A76674/895, *Kappeler* A73862/896, *Cleland* A68563/10, *Hajek* A73730/35, *Bettinger* A38039/41.

[19]*Askanazy* A73220/05, A73221/07, *Willis* A95457/39, *Bettinger* A38039/41.

[20]*Merttens* A48983/897, *Falkner* A73554/06, *Heijl* A73751/21, *Albrecht* A73184/23, *Staffel* A76557/23, *Burgkhardt* A73391/23, *McFarland* A61882/33.

[21]*Krömer* A50971/899, *Gebhard* A73657/899, *Askanazy* A73220/05.

[22]*Wilms* A79682/895, *Wolff* A25804/11, *Dransfeld* A73513/18.

[23]*Baumgarten* A41799/887, *Kappeler* A73862/896, *Krömer* A50971/899, *Limnell* A70119/01, *Rohdenburg* A76407/26, *Heijl* A73752/29, *Kermauner* A64880/32.

Corpora amylacea or *arenacea,* such as are normally found in the pineal gland, appear to be unusually common in the central nervous system tissue of embryomas.[1]

Peripheral nerves are often seen to leave the central nervous system and in their course ganglion cells may be found.[2] Some of these structures are clearly recognizable as spinal ganglia.[3] The proximity of these ganglionic structures to the vertebral column helps to identify them. Other ganglia appear to be peripheral autonomic or sympathetic ganglia.[4]

Among the *nervous end-organs* Vater Pacini corpuscles have been described,[5] but some[6] doubt this interpretation, at least as regards the corpuscles seen in one of these cases,[7] and state that judged by the illustration given by the author, the body was probably a "Renaut corpuscle".

Pathologic changes within the central nervous system of embryomas have also been observed and certain cystic dilations of cavities lined by ependyma have been interpreted as evidences of hydrocephalus,[8] although in some cases they may have resulted from liquefaction necrosis.[9]

The *accessory sex organs* are rarely sufficiently well developed to be clearly recognizable by naked eye inspection. As stated above, the pubic region is often richly supplied with hair; there may also be a more or less differentiated vulva, vagina and uterus. In one patient, the uterus of the dermoid was supplied with a histologically well differentiated endometrium.[10] An "incompletely closed" uterus has also been described[11] and more or less well developed labia and clitoris-like formations have repeatedly been seen.[12] Some authors speak of penis-like structures.[13]

Prostate-like formations have been reported both in apparently "male" and in "female" embryomas.[14]

It is interesting that our rather extensive review of relevant data failed to reveal a single instance of recognizable *gonads* in dermoid cysts or embryomas.

Thyroid tissue is frequently detectable in dermoids. Occasionally it is found in the form of small circumscribed nodules situated in the vicinity of the respiratory organs near the cranial pole of the papilla. In these cases the thyroid primordia appear to represent an integral and proportionate part of the embryoma.[11] More often thyroid tissue proliferates in a disproportionate manner at the expense of other constituents of the embryoma[15] and sometimes the entire tumor consists of thyroid tissue only; in this event the growth is referred to as a "struma ovarii". Such thyroid tumors may elaborate excessive amounts of thyroid hormone and hence they have been discussed separately in one of the chapters devoted to potentially endocrine tumors.

Hypophyseal tissue is rarely, if ever, found in dermoids. Yet in certain cases, small nodules of anterior lobe-like tissue have been detected in the proximity of thyroid nodules in the cranial pole of the papilla and these may have represented true hypophyseal primordia.[16]

Pancreas, with typical Langerhans islets,[17] *thymus* tissue,[18] an almost complete *adrenal*[19] and nodules resembling *parathyroids*[20] represent other endocrine glands occasionally present in teratoids.

The *placenta* is rarely well developed in embryomas. A thickening near the attachment of the embryoma papilla, has in one case[21] been described as a placenta. This patient was a 14-year old virgin in whom the "placental tissue" obviously developed in the absence of fertilization. It was pointed out, however,[22] that in most cases this attachment region merely contains a multitude of thin-walled blood vessels. Its resemblance to a true placenta—which would act as a barrier between the fetal and maternal blood—is at best very superficial.

In some instances, *chorionepithelioma* tissue is found within the embryoma,[23] while in other cases it contains elements closely simulating a *hydatidiform mole.*[24] These instances without being conclusive are highly suggestive of placenta formation within embryomas. In certain cases distinction between

[1] *Wilms* A79682/895, *Krömer* A50971/899, *Arnsperger* A73212/899, *Katsurada* A73865/01, *Askanazy* A73220/05, *Landau* A73944/12, *Heijl* A73751/21, *Rohdenburg* A76407/26, *Kermauner* A64880/32.
[2] *Krömer* A50971/899, *Askanazy* A73220/05, *Wolff* A25804/11, *Albrecht* A73184/23, *Meyer* A76131/25.
[3] *Kappeler* A73862/896, *Krömer* A50971/899, *Stolz* A76576/00, *Jelke* A73838/03, *Kartuschanskaja* A80227/06, *Heijl* A73747/10, *Staffel* A76557/23, *Burgkhardt* A73391/23, *Kaboth* A73854/24.
[4] *Katsurada* A73865/01, *Latteux and Thevenard* A73965/14.
[5] *Askanazy* A73220/05, *Novak* A76229/09, *Kaboth* A73854/24.
[6] *Rabinowitch* A76355/10.
[7] *Askanazy* A73220/05.
[8] *Kappeler* A73862/896, *Askanazy* A73220/05, *Meyer* A76131/25.
[9] *Katsurada* A73865/01.
[10] *Kaboth* A73854/24.
[11] *Krömer* A70091/08.
[12] *Askanazy* A73220/05, *Shattock* A76523/06-7, *Kaboth* A73854/24, *Adeodato* A73181/25.
[13] *Dransfeld* A73513/18.
[14] *Staffel* A76557/23, *Burgkhardt* A73391/23, *Kaboth* A73854/24, *Kermauner* A64880/32.
[15] *Rosenberger* B8963/02-3, *Ruiz* B7248/27, *Riebel and Riebel* B7092/27, *Gargano* B6017/28.
[16] *Wilms* A79682/895, A76753/899, *Krömer* A70081/08.
[17] *Alvarez-Calderon* A79545/34.
[18] *Gögl* A96606/40.
[19] *Rothe* A76429/03, *Bolt* A94817/23.
[20] *Moench* A77333/18, A68108/29.
[21] *Staffel* A76557/23.
[22] *Budde* A73386/26.
[23] *Steinert* A76563/03, *Sbarcea* A32100/39.
[24] *Stoney* A76577/870, *Pick* A76290/02.

ovarian pregnancy and ovarian teratoids is hardly possible on the basis of the published data[1] and some of the tumors mentioned above may have been misdiagnosed instances of ovarian pregnancy. (The reader is also referred to Ovarian Pregnancy, in Sect. IV, Vol. VI, his attention being called to the fact that conversely some cases—especially those of the early literature—listed as ovarian gestation may have been embryomatous dermoids). It should also be kept in mind that "placental tumors" may develop independently of embryomas in the gonads of both sexes. Although chorionepitheliomas unaccompanied by other teratoid formations are discussed in one of the chapters devoted to potentially endocrine tumors, their possible relationship to teratoids is recognized.

Membranes resembling the *amnion*,[2] as well as constituents of the *umbilical cord*, such as the ductus omphalo-entericus or portions of the yolk sac,[3] have also been found in embyromas.

SECONDARY CHANGES IN TERATOIDS AND IN THE REMAINING OVARIAN TISSUE: Adhesions are encountered in approximately one-third of the cases, as judged by the statistics of various surgeons.[4] The comparative frequency of dermoids not fixed in their position by adhesions, is responsible for their tendency to undergo torsion (see Sect. IV, Vol. VI). If adhesions develop they may connect the dermoid with the urinary bladder, various portions of the intestinal tract or the omentum.[5] Following such adhesions perforation may occur into various internal organs or to the outside; these will be discussed in the part on Complications (see below).

Among the *retrogressive changes* which may occur in teratoid tumors, necrosis and gangrene are of particular importance.[6] They usually arise as a result of circulatory disturbances caused by torsion of the pedicle. Hemorrhage, inflammatory changes, and calcification in dermoids will be discussed in Sect. IV, Vol. VI in conjunction with retrogressive changes in the ovary in general.

In embryomas atrophy of the brain substance[7] or its almost complete substitution by connective tissue and fat,[8] fatty degeneration of various tissues, especially muscles[9] and hyalinization of the connective tissue elements,[10] or of the chorium[11] may also occur.

Not infrequently, dermoids undergo malignant transformation. They may be the site of *carcinoma formation* either because the skin tissue in the dermoid is transformed into a squamous epithelioma or because some of the glandular structures in the teratoid types of tumors (e.g. mammary gland tissue) undergo a cancerous change. In many cases it is difficult to identify the exact point of origin of these so-called dermoid carcinomas or carcinomatous dermoids.[12]

Among the many published cases there undoubtedly are some in which the assumption of carcinomatous transformation in primarily benign dermoids was unjustified. It is known that dermoids tend to arise in ovaries bearing other cysts and that these latter growths can be the site of primary cancer formation. (Instances in which this was definitely established are discussed in the part on cancer in

[1] *Dougal* A73509/28.
[2] *Pfannenstiel* A49152/897, *Krömer* A70091/08.
[3] *Meyer* A76131/25, *Budde* A73383/26.
[4] *Miller* A18279/37.
[5] *Lauwers* A68932/01-2, *Lippert* A64789/05, *Lemarinien* A73983/26.
[6] *Boldt* A73324/00, *Price* A96724/28.
[7] *Krömer* A70091/08.
[8] *Wilms* A76753/899.
[9] *Johnstone* A73847/896.
[10] *Walthard* A76896/03, *Jelke* A73838/03, *Glockner* A70015/06, *Ulesko-Stroganowa* A76665/10, *Dingels* A76798/12, *Aisenstadt* A76779/13, *Sitzler* A76882/13, *Werth* A76897/28.
[11] *Kermauner* A64880/32.
[12] *Mauriac* A78680/853, *Grenser* A79581/875, *Schröder* A79651/882, *Flaischlen* A40044/882, *v. Wahl* A41224/883, *Babinski* A40669/884, *Thornton* A76633/885, *Biermann* A40994/885, *Pottien* A79638/887, *Pomorski* A76311/889, *Eberlin* A79566/899, *Purrucker* A43294/889, *Shoemaker* A45705/890, *Veit* A79672/890, *Pilliet* A79632/893, *Tauffer* A79662/895, *Morison and Rattray* A79618/895, *Wilms* A79682/895, *Dor and Bérard* A47437/896, *Masson* A68674/896, *Leblanc* A73964/896, *Mermet* A76118/896, *Genersich* A79577/897, *Thumin* A49040/897, *Chavannaz* A49226/898, A47993/898, *Lauro* A50974/898, *Bäcker* A50493/898, *Deanesly* A73470/898, *Clark* A50599/898, *Petersen and Völcker* A79628/898, A79627/00, *Cumston* A50922/899, *Lockhart and Anderson* A51003/899, *Debuchy* A73471/899, *Wolff* A68679/00, A25804/11, A79683/11, A76764/11, *Davis* A73469/00, *Kehrer* A79590/01, *Klokow* A79593/01, *Pompe van Meerdervoort* A79636/01, A79637/02, *Wood* A82174/01-2, *Zalenski* A79685/03, *Fliedner* A68754/03, *Nijhoff* A79622/03, *Pölzl* A79633/04, *Benjamin* A68755/04, *Jacquemaire* A79588/04, *Ludwig* A76030/05, *Landau* A68757/05, *Gorizontow* A79580/06, *Geipel* A79576/06, *Bab* A73226/06, *Mendels* A79613/07, *Mainzer* A79606/08, *Franck* A79572/09, *Shaw* A79653/09-10, *Boxer* A79554/10, *Pierre-Nadal and Lacouture* A79631/10, *Stewart* A79659/11, A79658/11, *Reppun* A79643/11, *Williamson and Barris* A79681/11, *Sievers* A76527/11, *Guggisberg* A79582/11-2, *Vacher de Lapouge* A79671/13, *Eylenburg* A79569/13, *Seitz* A76515/14, *Andrews* A79547/14-5, *Frank* A66880/15, A66881/15, *Wiener* A79680/15, *Pfeiffer* A75849/17, *Lauermann* A79599/18, *Hartmann and de Jong* A79583/18-9, *Spalding* A76547/19, *Frankl* A73620/20, *Eisenstädter* A79567/21, *Böttger* A79552/21, *MacCarty and Caylor* A70804/22, *Borrmann* A79553/24-5, *Rohdenburg* A76407/26, *Salacz* A79646/27, *Westermark* A79679/27, *Forster* B15655/27, *Schmuckler* A79648/28, *Tedenat* A65671/29, *Masson and Ochsenhirt* A79611/29, *Ascanio Suarez* A68095/29, *Marinucci* A78663/30, *Hoffmann* A79587/30, *Schneider* A79649/31, *Deaver* A64216/31, *Delaney* A79565/31, *Kleinknecht et al.* A62934/32, *Vos* A79674/32, *Schockaert* A79650/32, *Puhr* A52294/34, *Alvarez-Calderon* A79545/34, *Counseller and Wellbrock* A52258/34, *Millot and Hinard* A52274/34, *Caillot and Boulez* A27699/34, *Fein and Goldberg* A27701/34, *Petrowa and Karaewa* A28085/35, *Meriel and Dieulafe* A28008/35, *Villard and Caillot* A28088/35, *v. Szathmary* A28072/35, *Meeker* A79612/36, *Bride* A79556/36, *Kent* A59900/36, *Fein and Hobart* A95253/37, *Bowles* A95235/37, *Breipohl* A96003/37, *Cardwell and Pund* A97259/38, *Meiklejhohn and Stallworthy* A97179/38, *Brody* A36038/41.

combination with other tumors.) In other patients the possibility of carcinoma metastases in dermoid-bearing ovaries, or direct infiltration by carcinomas of adjacent organs, must be considered (e.g. Oliver's[1] case). It is obvious that in either of these events carcinoma tissue and dermoid tissue will be found in the same ovary. The dermoid and the invading blastoma may become so closely intermixed that it becomes impossible to distinguish such cases from carcinomas developed by malignant transformation of the dermoid. These sources of error are hardly sufficiently frequent, however, to justify the current belief that carcinoma formation in dermoids is a great rarity.

Brody[2] and Ewing[3] surveyed the relevant literature and came to the conclusion that only about 40 relevant cases have ever been described, an estimate which appears to be far too low.

In the case of bilateral dermoids, carcinomatous transformation may remain limited to one of the two tumors.[4] (See also Teratoid Carcinomas in passage on Macroscopic Characteristics.)

Sarcomatous transformation of dermoid cysts and teratomas is not uncommon. In these instances, it is apparently the stroma of the cyst that becomes malignant.[5] As a result of this transformation very complex malignant tumors arise which are designated by such names as for instance "rhabdo-leio-myo-neuro-carcino-sarcoma".[6] It is probable that many of the so-called chondrosarcomas, lymphosarcomas and especially the so-called primary melanosarcomas of the ovary arise from teratoid growths although the original structure of the tumor may be unrecognizable as a result of destruction by invading malignant cells. These sarcomas will be discussed in connection with the corresponding benign tumor in other chapters of this volume.

Even benign ovarian teratoids may *spread* into contiguous structures especially the broad ligament.[7] It will also be recalled that dermoids are particularly subject to self-amputation by torsion. This may lead to the formation of so-called pseudo-metastases due to re-implantation of amputated dermoids in various parts of the peritoneal cavity[8] (see also chapter on Self-amputation in Sect. IV, Vol. VI).

Because of the existence of transitional forms between benign and malignant teratoids[9] it is sometimes difficult to differentiate "pseudo-metastases" from the true *metastases* so characteristic of the malignant solid teratomas.[10] In some of these cases it is not the teratoid itself that metastasizes, but the originally benign tumor undergoes malignant transformation into a rather homogeneous carcinoma or sarcoma and it is this transformation product which forms the metastases. Since most solid teratomas are malignant, many additional cases may be found by perusing the case reports of teratomas cited above.

From Miller's [11] review of pertinent cases, it will be seen that solid teratomas may metastasize into the uterus, the vagina, the contralateral ovary, the stomach, intestines, pleura, lung, pelvic bones, retroperitoneal lymph nodes and almost any part of the peritoneum.

In addition to the teratomatous, carcinomatous and sarcomatous metastases mentioned above, the *structure of the metastases* may exhibit the characteristics of a chorionepithelioma[12] if the original tumor is of this type. Especially noteworthy are certain cases in which all the metastases consist of nervous or glia tissue.[13]

Metastatic ovarian teratoids may apparently also occur. In one case a "dysembrioma containing nephrogenic tissue", which originated in the lumbar region, was claimed to have metastasized into the ovary.[14]

The *remaining ovarian tissue* itself may be practically normal and healthy corpora lutea may develop in the vicinity of dermoids.[15] The frequent complications arising from pregnancy in dermoid-bearing women (see part on Incidence) bear witness to the fact that ability to conceive is not necessarily impaired by these tumors. In the case of large dermoids, the ovary is usually detectable in the region where the pedicle is attached and if the teratoid develops within the ovary, gonadal tissue is found in the cyst wall.[16]

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[1] A45846/891.
[2] A36038/41.
[3] A64873/42.
[4] *Himmelfarb* A73787/886.
[5] *Dow* A83054/878, *Unverricht* A76668/879, *Reclus* A44755/894, *Schwertassek* A47088/894, *Forbes and Reid* A48248/896, *Busse* A73393/896, *Krecke* A77608/897, A73917/898, *Kötzle* A73907/898, *Lorrain* A76022/05, *Müller* A76169/07, *Schmidlechner* A82394/08, *Nyström* A68855/11, *Kloss* A22230/13, *Dransfeld* A73513/18, *Geipel* A77507/22, *Spencer* A66889/22-3, *Preisecker* A77754/24, *Lochrane and Keatinge* A64232/31, *Bowles* A33302/40, *Menju* A34904/40.
[6] *Wallart and Scheidegger* A95338/36.
[7] *Janvrin* A42123/886, *Gsell* A80208/896, *Pestalozza* A76272/05, *Fairbairn and Taylor* A73552/24-5.
[8] *Lazarus* A42702/888, *Poupinel* A43483/889, *Orrillard* A76245/893, *Klein* A73895/899, *Fleischmann* A80193/05, *Melchior* A76103/08, *Duse* A80183/09, *Bonney* A73334/09-10, *Venot* A76688/12.
[9] *Miller* A18279/37.
[10] *Kolaczek* A73909/879, *v. Dittel* A83053/884, *Dembo* A46317/892, *Yamagiva* A48461/897, *Ewald* A48971/897, *Falk* A80188/898, A80189/00, A80190/05, *Backhaus* A80153/01, *Fleischmann* A80194/05, *Thorn* A80301/06, *Thies* A79668/07, *Falco* A80187/14, *Roth* A76427/15, A76428/16, *Kleinknecht et al.* A62934/32, *Schairer* A95106/37.
[11] A18279/37.
[12] *De Walsche* A80054/29-30.
[13] *Neuhäuser* A76202/06, *Büttner* A80165/09, *Nordmark* A66182/32, A62943/32, *Ruzicska* A52303b/34, A52304b/34, *Helmke* A97149/38.
[14] *Ionescu-Bujor* A95262/37.
[15] *Gottschalk* A73697/01.
[16] *Pfannenstiel* A49152/897, A76286/08, *Wilms* A76753/899, *Ulesko-Stroganowa* A76665/10.

TERATOIDS IN COMBINATION WITH OTHER OVARIAN TUMORS: Simultaneously with an ovarian teratoid there may be found:

A *fibroma* either in the same [1] or the contralateral ovary;[2] a *sarcoma* in the contralateral ovary;[3] an *adenofibroma* in the same ovary;[4] a "*perithelioma*" in the contralateral ovary.[5]

It should be emphasized that teratoids have a special tendency to develop in conjunction with other ovarian tumors—especially pseudo-mucinous cysts—but in agreement with the order of presentation used in this Encyclopedia, teratoids found in combination with growths other than those mentioned above, are listed in preceeding chapters.

In this connection it is also noteworthy that in several cases ovarian dermoids developed simultaneously with dermoids or other *para-ovarian* tumors in the broad ligament.[6]

CHEMICAL COMPOSITION

The chemical composition of teratoid tumors has been the subject of many investigations.[7] These studies showed that in most cases the main constituents of the dermoid contents are lipids, especially cholesterol; a variety of amino acids, oxalic acid, urea, silica magnesium, calcium, pseudo-mucine, bilirubin etc. may also be present in teratoids. In addition to cholesterol and several of its derivatives, Muck[8] was able to isolate from the unsaponifiable remnant of dermoid contents a monobasic acid having the empirical formule $C_{19}H_{34}O_4$. The unsaponifiable fraction of the dermoid fat was subjected to especially careful investigations.[9] In one Chinese patient the carotin content of the dermoid (and the blood) was surprisingly high.[10]

Strogaja[11] found that if dermoid contents are injected into the ovaries of rabbits or dogs, they cause a much more pronounced tissue reaction than if sterile fat is introduced in a similar manner. Eventually, however, the material is absorbed and removed through the lymph vessels. These observations indicate that some of the dermoid contents are particularly irritating to tissues and may be responsible for the, often so pronounced, inflammatory reaction to them.

INCIDENCE

The *general incidence* of teratoids is difficult to estimate since the various authors who give statistical data use widely different criteria; some consider under this heading only dermoids, others only solid teratomas and embryomas, others again all types of teratoids. It is undoubtedly true, however, that dermoids are among the most common ovarian tumors as judged by the number of case reports given in earlier paragraphs of this chapter. In one series of 1101 ovarian tumors (in which simple follicle and corpus luteum cysts were included among the neoplasms) the incidence of dermoid cysts was 16%, that of carcinomatous dermoids 0.2% and that of malignant teratomas 0.7%.[12] Ewing[13] estimates that dermoids alone account for about 10% of all ovarian tumors. A survey of several statistics concerning the incidence of solid teratomas, however, led to the conclusion that it is less than 1% of the dermoid incidence.[14]

More precise data are available concerning the *age incidence* of teratoids. A survey of 1,804 cases (dermoid cysts only) described by various authors revealed[15] that among these, 813 occurred in women between 30 and 50 years of age. The others were distributed among the various age group as follows: 30 during the first decade, 193 during the second, 586 during the third, 124 during the sixth, 42 during the seventh and 7 in women over 70 years old; in the remaining 9 cases the exact age of the patient was not given.

Our own survey of all types of teratoids revealed that although most cases were detected during the child-bearing period of life, a comparatively large number occurred in children less than one year old,[16] 1-5 years old,[17]

[1] *Boucaud* A65835/00, *Maiss* A70141/08, A76055/09, *Vautrin* A70426/21, *Manon* A76062/23.
[2] *Duroux* A65959/02, *Efler* A65961/16.
[3] *Rousseau* A77779/13.
[4] *Wolfe* A70450/27.
[5] *Whiteford* A68789/13-4.
[6] *Lusk* A76032/883, *Guizzardi* A73718/899, *Brewis* A73369/06-7, *Oliver* A91419/13, *Liegner* B20941/24, *Hamant et al.* A70748/29, *Vanverts* A28184/35.
[7] *Haffter* A73726/875, *Méhu* A40053/885, *Mundé* A76180/887, *Pfannenstiel* A76283/890, *Lieblein* A74000/895-6, *Ludwig* A48982/897, *Hoffmann* A73797/898, *Zeynek* A76773/897. *Neugebauer* A76201/12, *Schlank* A76476/12, *Plenz* A76298/12, *v. Zeynek and Ameseder* A76774/13, *McMeans* A76046/14, *Schröder* A76500/18, *Arnold* 11918/20, *Bergé et al.* A73287/20, *Dietrich and Kellendonk* A73494/22, *Behmel* A62830/32, *Dimter* B21686/32, *Bell and Datnow* A66142/32, *Otto* A76250/35, *v. Szathmary* A27891/35.
[8] 13566/22.
[9] *Dimter* A97790/41.
[10] *Chi et al.* A28098/35.
[11] 35507/11.
[12] *Bernstein* 81758/36.
[13] A64873/42.
[14] *Menju* A34904/40.
[15] *Miller* A18279/37.
[16] *Mears* A74879/871-2, *Kidd* A29396/880, *Neville* A76209/880, A76210/880, A76211/880, *de Sant'Anna* A69168/895, A48374/896, *Pujol y Brull* A66897/12.
[17] *Kidd* A29568/880, *Hooks* A73806/886, *Doranth* A44588/893, *Hue* A50968/899, *Cattermole* B21295/17, *Shattock* B21075/23, *Kincaid and Andrews* A73888/28, *Peters* A62534/32, *Delthil* A96015/37.

5-10 years old[1] and 10-15 years old.[2] Many additional case reports indicate the comparative frequency of dermoids in young girls.[3]

In elderly women teratoids have also frequently been seen.[4] Cases in women aged 65-80 are not uncommon;[5] probably the oldest patient on record was a woman aged 92 who suffered from bilateral dermoids.[6]

It must be remembered that all these data refer merely to the age at which the patient came to the attention of the physician. Since dermoids often develop very slowly or remain stationary, detection of such tumors in old women does not necessarily indicate initiation of the growth at an advanced age.

The incidence of dermoids in *pregnancy* is surprisingly high. In many cases, bilateral dermoids are detected during the period of gestation and even in spite of the often extensive destruction of ovarian tissue, pregnancy is rarely prevented or interrupted. The presence and increased growth of dermoids may, however, lead to various serious complications such as torsion, hemorrhage and abscess formation within the dermoid. The latter condition is particularly frequent in cases of septic puerperium. In some instances the dermoid interferes with delivery and has to be removed during labor. In other patients increased intra-abdominal pressure may lead to expulsion of a self-amputated dermoid at delivery. All these disturbances are discussed in the part on Complications; suffice it here to call attention to them and to the many published case reports on dermoids in pregnant women.[7]

The skin of dermoids appears to participate in the tendency of the host's skin to undergo increased pigmentation during gestation.[8]

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[1] *Alt* A73188/837, *Bouchacourt* A73343/850, *Thornton* A40032/881, *Black* A44225/892, A44224/892, *v. Muralt* A80259/899, *McKee* A69161/899-00, A69160/00, *Delassus* A69155/03, *Lurz* A80249/03, *Deletrez* A69156/04, A69157/04, *Waldo* A76713/08, *Cuff* A73457/10, A73456/10, *Lammers* A73941/23, *Payr* A80266/23, *Cahill* A73403/24, *Pozzo* A64441/30, *Lefebvre* A73973/30, *Notti et al.* A97500/41.

[2] *Gibert* A73676/856, *Darey* A45220/889, *Usiglio* A45648/890, *Ramaugé* A69165/891, *Davidson* A69154/892, *Swiecicki* A46314/892, *Alexander* A50623/898-9, *White* A76738/05, *Robinson* A76400/26, A76399/26, *Lassen* B7331/26, *Krieger-Lassen* A80238/26, *Nutter* A80264/28, *Delmas* A65607/29, *McElhinney* A97493/41.

[3] *Anonymous* A69164/894, *Routier* A69167/895, A69166/896, *Dandois* A47344/896, A69153/898, *Kalb* A49000/897, *Herzog* A73778/897, *Fusino* A26932/00, *Legueu* A73977/01, *Pissareff* A80269/02, *Lingen* A76003/03, *Nagel* A76191/04, *Kartuschanskaja* A80227/06, *Pinkuss* A80268/07, *Klaubammer* A73891/12, *Seyfarth* A76518/16, *German* A73670/22, *Zschau* A76775/22, *Conrad* A80170/25, *Froelich and Bohème* A73642/26, *Cannon* A73405/26, *Pendleton* A76264/26, *McDowell* A76038/27, *Lanman* A68183/29, *Siddall* A65573/30, *Manitz* A80251/30, *Baccarini* A52252/34, *Searby* A96546/37, *Witzberger and Agerty* A95127/37.

[4] *Key* A73885/863, A73886/863-4, *Vanverts* A49018/896, *Meagher* A80255/31.

[5] *Aron* A73213/873, *Petri* A76277/09, *Raum* A76361/10, *Behrend* A73279/11, *Fitzgerald* A73581/12, A73584/12.

[6] *Pollock* A76307/08-9.

[7] *Coley* A69360/810, *Merriman* A76119/819, *Cederschöld* A69354/870, *Ruge* A76442/878, *Wilson* A40269/882-3, *Thornton* A41873/886, *Bartlett* A73265/886, *Mundé* A41916/887, *MacKenzie* A42487/888, *Gelstrom* A73664/889, *Murray* A43312/890, *Tison* A76642/892, *Homans* A91661/892, *Ballantyne* A73234/892, *v. Rosthorn* A76425/893, *Eberhart* A73524/893, *Fischer* A73576/893, A73577/893, *Flaischlen* A73589/893, *Butler-Smythe* A46421/893, *Byford* A46488/893, *Abegg* A73177/894, *Rubeska* A76438/895, *Staude* A76562/895, *Blanc* A93511/895, *Mangin* A76061/896, *Kortright* A91673/896, *Denny* A93536/896, *Hohl* A73798/896, *Herrgott* A73773/896, *Kochurova* A73915/896, A91671/896, *Morse* A76159/896, A76160/04, *Ostermayer* A76247/897, *Späth* A76546/897, *Schwarz* A76506/897, *Levitski and Gogotski* A91684/897, A73997/897, *Treub* A76651/898, *Boxall* A73356/898, *Spencer* A76549/898, A76550/898, A76551/898, A76552/898, A76553/898, *Routh* A91740/899, *Kime* A91669/899, *Braun v. Fernwald* A73365/899, *Walls* A76716/00, *Quénu* A91733/00, *Siedentopf* A76526/00, *Friedrich* A73640/00, *Demons and Verdelet* A68760/00, *Backhaus* A73229/00, *Nippert and Moore* A91705/01, *Stratz* A76582/01, *Kerr* A73884/01, *Favell* A73558/01, A73559/03, *Flatau* A73592/01, *Dravet* A69632/01, *Marschner* A76073/02, *Loewenberg* A83522/02, *Jordan* A73849/02, *Haultain* A73743/02, *Bachmann* A73228/02, *Edge* A73532/02-3, *Condamin* B12756/03, *Hermann* A73772/03, *Jardine* A91663/03, A73834/05, A91664/05, *Werder* A76733/04, *Tate* A76605/04, *Gläser* A73680/04, *Cholodkowski* A73428/04, *Condamin* A73441/04, A73440/04, A73442/11, *Geisthövel* A91646/04, A73660/05, *Lepage* A91681/04, A73988/05, *Thompson* A76622/05, *Kelly* A91668/05, A73879/05, A73880/05, *Kosminski* A73914/05, *Heinsius* A73756/05, *Cadet* A73402/05, *Fuchs* A91642/06, *Dubar and Drucbert* A93540/06, *Chavannaz* A93526/06, *Cleveland* A73432/06, *Campbell* A73404/06-7, *Lea* A73958/07, *Cusmano* A73459/07, *Weinhold* A76726/08, *Scholl* A76489/08, *Delporte* A73486/08, *Ivens* A73825/08, *Purslow* A76351/08-9, *Wiener* A76745/09, *Petri* A76279/09, A76278/09, *Stern* A76570/10, *Barrows* A73260/10, *Boldt* A73328/10, *Amann* A73197/10, B11313/10, *Hörrmann* B11318/10, A73795/11, *Blacker* A73300/10-1, *Ribbius* A76386/11, *Saltzman* A76451/11, *Manton* A76065/11, A76064/11, *Beckmann* A73275/11, *Walker* A76714/12, *Oui* A76253/12, *Hellier* A73763/12, *Gallant* A73651/12, *Barjaktarovic* A73256/12, *Bondy* A73331/12, *Young* A76772/12-3, *Norris* A76228/13, *Kuschnir* A73930/13, *Foulkrod* A73606/13, *Bonney* A82723/13-4, *Oldfield* A76235/14, *v. Kubinyi* A80240/14, *Delétrez* A82727/14, *Lahmann* A73939/17, *Cassioli* A82724/17, *Block* A73312/17, *Hutchison* B11800/18, *Levi* A73991/18, *Turnesco and Bulliard* A76662/20, *Andérodias and Lacouture* A82770/21, *Vayssière* A76683/21, *Newell* B21215/21, *Davidson* A73468/22, *Baer* A73231/22, *Nagel* A76193/23, *Holmes* A73800/23, *Taylor* A76608/24, *Mesa* B16023/24, B7584/25, *Dougal* A73508/24, *Guyot and Delmas* A73721/24, *Armstrong* A82721/24, *Vallois and de Rouville* A76671/25, *Ricevuto* A76389/25, *Duboucher* A73514/25, *Commandeur and Patel* A73439/25, *Harwood and Gerin-Lajore* B7973/25, *Charbonnel and Costedost* A73422/25, *Peycelon* A76281/26, *Costantini and Ferrere* A73444/26, *Truffi* A76658/27, *Cotte* A73445/27, *Bourdon* A73345/27, *Wacher* B7254/27, *Chait* A73417/28, *Schmechel* A76477/29, *Zwirner* A76777/30, *Favreau et al.* A73562/31, *Trempe* A61699/32, *Fürst* A66158/32, *Cunningham* A62875/32, *Brault* A61367/32, *Abruzzese* A62827/32, *Levy-Solal et al.* A28160/34, *Campbell* A95385/38, *Hastings* A96501/38, *Notes* A96526/38, *Manzi* B21392/39, *Rocmans* B21398/39, *Guillot* A97683/39, *Ellis* A97792/39, *Andrews et al.* A32560/40, *King* A32341/40, *Goodwin* A56305/42, *Bowles* A97782/42, *Wanderley* A98186/42, *Doyle and Daversa* A98106/42, *Peralta Ramos and Wernicke* A97818/42, A96935/42, *Leon and Leon* A96925/43, A98162/43.

[8] *Fischl* A61752/33.

During the *puerperium* ovarian dermoids have also been observed.[1]

The *racial incidence* of teratoid tumors has not been subjected to any systematic statistical analysis. It has been claimed that they are especially common in the Erzgebirge in Germany.[2] The material of the Johns Hopkins Hospital collected over a period of 5 years, revealed 17 dermoids in white and 7 in Negro women; that is a proportion of 2.5—1.0, while during the same period the proportion of white to Negro hospital admissions was 6.75—1.0. This would indicate a considerably greater incidence in the colored race.[3] Additional instances in Negro women have frequently been described.[4] It has been claimed that the pigmentation of dermoids tends to be more pronounced in Negro than in white women.[5] Among other races teratoids have been described in the Chinese,[6] the "Hova" of Madagascar,[7] Batak,[8] Japanese[9]—where they are responsible for 32-35% of all ovariectomies—and Javanese.[10] It has also been claimed (without indicating the sources of information)[11] that dermoids are unknown in India and Ceylon, rare in Syria and Egypt, while in Australia they occur among the white, but not among the native population.

Data concerning hereditary predisposition to teratoid formation are discussed in the part of Pathogenesis.

PATHOGENESIS

The pathogenesis of ovarian teratoids and especially dermoids has been the subject of many investigations and innumerable theories have been put forward in an effort to elucidate their etiology.[12] The purely morphologic mechanism of their *histogenesis* has also received a great deal of attention.[13]

Many of the theories proposed to explain the origin of teratoids are so far fetched and fantastic that it does not appear profitable to review them here. Among other suggestions, internal twinning, developmental errors affecting the primitive streak, fertilization of polar bodies etc. have been held responsible for the development of these growths. The interested reader is referred to Miller's[14] pertinent surveys. Only three theories are seriously considered by contemporary pathologists: 1) the parthenogenetic theory, 2) the blastomere theory and 3) the embryonic organizer theory.

According to the *parthenogenetic theory*, the teratoids develop from unfertilized ova. There are two modification of this concept.

According to the first, the tumors originate from immature ovogonia[15] while the corresponding testicular teratomas develop from male gonoblasts.[16] This interpretation has not been generally accepted since most investigators consider it was held to be very unlikely that immature egg-precursors could form tridermal teratoids of a highly organized and complicated nature.[17]

The second modification of the parthenogenetic theory postulates that the teratoids arise as a result of cleavages in unfertilized, but mature, ova.[18] This would imply that the tumor is, in a sense, the child of the bearer created by immaculate conception. Bosaeus,[19] was a strong proponent of this concept because of his extensive experimental work on frogs and toads in which he showed that in unfertilized ova, cleavage can be initiated by chemical or mechanical means. He also noted that abnormal teratoma-like embryos develop from such ova if they are allowed to grow in the celomic cavity of a host animal. The malformations in these embryos, especially their tendency not to develop sex cells, was similar to the defects usually seen in teratomas. The author ascribed these malformations to the abnormal medium in which the embryos develop. It has also been mentioned, in favor of this interpre-

[1] *Hohl* A73798/896, *DaCosta* A73463/897, *Lane* A73945/03, *Maiss* A76052/07, A76053/07, *Barjaktarovic* A73256/12, *Bertolini* A82722/13, *Cotte and Trillat* A73446/22, *Johnston* B21591/30, *Abruzzese* B21679/32, A73179/32-3.
[2] *Burgkhardt* A73391/23.
[3] *Brown* A50990/899.
[4] *Balloch* A73237/03, *Lecène* A73967/08, *Porter* A76321/22, *Cahill* A73403/24.
[5] *Lecène* A73967/08.
[6] *Vos* A76702/32, *Chi et al.* A28098/35.
[7] *Cloitre* A95244/37.
[8] *Kouwenaar* A80235/32.
[9] *Omori and Ikeda* A43374/890, A46343/892, A93142/893, A93143/893, A46475/893, *Yamasaki* A89673/09, A76771/11.
[10] *Eerland* A61747/32.
[11] *Ludewig* A76027/20.
[12] *Pappa* A68660/841, *Bruch* A73381/849, *Répin* A76379/892, *Fuchino* A46467/893, *Geijl* A46527/893, A68654/897, A68655/03, *Johnstone* A73846/893, A73847/896, A48411/896, *Pestalozza* A68765/895, *De Rechter* A68649/895, *Kworostansky* A64782/899, *Emanuel* A73541/00, A73543/00, *Bonnet* A73336/01, A73332/01, *Armknecht* A73211/01, *Bandler* A73248/01, *Piantieri* A68661/01, *Geyl* B8856/03, *Fiorio* A68651/03, *Solovyeff* A76543/04, A68666/04, *Basso* A73266/05, *Meyer* A76126/05, A76127/10, *Grawitz* A73705/05, *Freund* A73632/06, *Ingier* A73824/08, *Baudouin* A73268/09, *Sjövall* A80294/11, *Sutton* A73307/12, *Termier* A82757/14, *Goodall* A73686/19-20, *Geller* A73663/21, *Kaboth* A73856/25, *Rehorn* A76375/26, *Bosfeus* B6041/28, *Heijl* A73753/30, *Peyron* A97430/40, *Holmdahl* B20681/42.
[13] *Pfannenstiel* A49152/897, A76286/08, *Kroemer* A50971/899, *Clark* A68647/899, *Giannettasio* A68656/00, *Ricci* A68663/01, A68664/01, *Meyer* A76123/05, A76125/05, *Kudoh* A73925/13, *Heinze* A73757/22, *Nicholson* A76214/29.
[14] A76140/24, A18279/37.
[15] *Peyron* A79520/22, *Lelièvre and Corsy* A73982/27.
[16] Peyron B21438/39.
[17] *Wilms* A76753/899, *Askanazy* A73221/07, *Ingier* A73824/08.
[18] *Répin* A76380/892, *De Rechter* A68650/895, *Pfannenstiel* A76286/08, *Bertels* A73291/12, *Loeb* 48973/12 *Goodall* A73686/19-20, *Bosaeus* A73339/26, *Sutton* B7196/27, B8184/28, *Schmid* A76480/32, *Bargmann and Scheffler* A71738/43.
[19] A73339/26, B21740/28.

tation, that cleavage of ovarian ova is not uncommon among vertebrates and has even been seen in women, although in them such cleavages rarely go further than the first few cell divisions.[1] For relevant data, see the chapters on the histology and Comparative Morphology of the ovary (Sect. IV, Vol. I). The concept that parthenogenetic development in mammals may go further under optimum conditions, received additional support through the experiments of Pincus,[2] who claims to have obtained phenotypically normal rabbits following implantation of unfertilized ova (cleavage started by chemical means) into the uterus of pseudo-pregnant does. The great frequency of ovarian (and even multiple ovarian), as compared with extra-ovarian teratoids, also speaks in favour of their origin from ova.

Gardner[3] described, within the cumulous oöphorus of a human ovary, what probably represents the smallest dermoid on record. Because of the position of this growth in the region where the ovum would be expected to be, he considers it likely that the tumor developed through parthenogenetic cleavage of the egg cell. The same author also emphasized the occurrence of squamous metaplasia of granulosa cells in human ovarian follicles, hinting that the granulosa may likewise participate in the formation of dermoids.

The production of teratoid tumors in the testes of cocks by local application of zinc or copper salts (see Sect. VIII) suggests that perhaps even male germ cells are capable of parthenogenetic development. Yet the parthenogenetic theory has many opponents[4] especially because of the occurrence of extra-ovarian dermoids even in males and even in the cranial part of the body (e.g. hypophysis, thyroid) where germ cell precursors are normally absent.

The second current interpretation is the *blastomere theory* of Bonnet[5] and Marchand.[6] This theory assumes that at least the primordium for the formation of teratoids is congenitally present and that these tumors are derived from blastomeres separated from the rest of the fetal body, their growth being delayed and abnormal. In the sense of this interpretation, there would be no essential difference between the so-called true fetal inclusions, and the teratoid tumors. It would be possible for the teratoids to arise from somatic blastomeres and it is claimed that this could explain the absence of gonadal cells in them.[7] The greatest objection to this theory is that it fails to explain the unusual frequency of gonadal teratoids. It was pointed out, however,[8] that during the first cleavages somatic and sexual blastomeres are not separated, and a partly somatic and partly sexual blastomere could easily reach the gonadal primordium before separation occurred.

For the sake of completeness let us mention the concept according to which teratoids are *formed from polar bodies*. This interpretation has been considered entirely untenable[9] because a greater number of separate dermoids may occur than could be accounted for by the polar bodies formed from a single ovum. This objection is perhaps not as serious as it appears, since multiple teratoids could arise from the polar bodies of several ova, especially considering that a hereditary predisposition for the formation of these tumors is clearly established (see below). The fact still remains that since there is no proof to support this theory it hardly deserves to be debated.

Bandler[10] derived the teratoid tumors *from the Wolffian body* but this concept is rather problematic and has not been seriously considered by others.

Needham[11] arrived at the assumption that teratoma formation is due to the failure of the individuation-field at an early period in development. To control the action of organizers thinking along similar lines, Krafka[12] proposed an interpretation based on Spemann's *organizer theory*. He believes that interference with the normal effect of the organizer may elicit the formation of secondary embryonic axes in the primitive shield. This could explain the formation of teratoids in any location, although the observed frequency of gonadal teratoids could be due to the proximity of the potential fields to Hensen's node, namely the sacrococcygeal, urogenital and branchiogenic regions. Since there is no limit to the degree of diffusion of the factor, the occasional occurrence of teratoids in other locations, however, would not be inexplicable.

Irrespective of the derivation of the tumors, it may be said that certain interventions can act as *eliciting factors* in pre-disposed individuals. Thus dermoid formation has been observed in an ovary following oophoropexy,[13] trauma[14] and after X-ray treatment.[15] There is no definite proof, however, of a casual connection between these interventions and the development of the tumors.

Experimental work shows that teratoid structures may arise from transplanted embryonic primordia,[16]

[1] *Gross* A73712/23, *Courrier* A73449/23, *Lelievre and Corsy* A73982/27.
[2] 76765/39.
[3] A92816/38.
[4] *Bard* A73254/893, *Miller* A18279/37.
[5] A73336/01.
[6] A76066/10.
[7] *Meyer* A76127/10, A76131/25.
[8] *Ingier* A73824/08.
[9] *Miller* A18279/37.
[10] A73240/00, A73239/00, A73238/00, A73242/01.
[11] A94807/36.
[12] 78927/36.
[13] *Jaboulay and Dor* A81137/893.
[14] *Van den Helm* B11819/18.
[15] *Granzow* A73701/34, A54163/34.
[16] *Traina* A81296/01, A81297/02. *Askanazy* A80150/08, *Jentzer* A80221/08.

but this sheds little light upon the mechanism of their formation in man.

In connection with the etiology of teratoid tumors, *heredity* appears to play an important role. Several investigators emphasized the tendency of these tumors—especially the dermoids—to appear in sisters, mother and daughter, or at least in various members of the same family.[1] The frequent occurrence of bilateral or multiple dermoids in the same patient may likewise be interpreted in this sense. The frequency of malformed offspring among dermoid-bearing women[2] has also been noted. It is claimed, furthermore, that twinning — whether measured by the percentage of families with twins or by the incidence of twin births—is unduly high in the families of teratoid bearing patients.[3] This gives additional support to the view that in twinning and in teratoid tumor formation some common hereditary factor may play a role.

In this connection it is important to emphasize that in many women who suffer from dermoids the accessory sex organs are congenitally malformed, showing atresia of the genital passages, aplasia of the Müllerian derivatives etc.[4] In one case,[5] dermoid cysts developed in a patient in whom one kidney was absent due to a congenital aplasia; in another case[6] there was severe renal ectopia and in a third case the appendix vermiformis was severely malformed due to cystic degeneration.[7]

CLINICAL COURSE

The general course and symptomatology of ovarian teratoids has repeatedly been reviewed[8] but is remarkably poor in specific characteristics.

In a large number of cases *local signs* call attention to the growth. A mass in the lower abdomen is frequently first noticed by the patient herself. It may be located on one side, in the midline, or—in the case of bilateral teratoids—on both sides. In many instances the patient's only complaint is the constant increase in the size and hardness of her abdomen.[9]

Ascites[10] is comparatively rare, although in one series[11] it was observed in 6 out of 66 cases. In one patient 54 litres of ascitic fluid had to be evacuated by repeated tappings in the course of time, while after removal of the bilateral dermoids further fluid accumulations were not formed.[12] In another patient[13] chronic pleural fluid accumulations developed simultaneously with an ovarian teratoid tumor. It has been stated[14] that ascites is much more frequent in teratoids consisting mainly of thyroid tissue (see chapter on Struma Ovarii).

Fertility is apparently not seriously affected even by large bilateral dermoids.[15] The comparatively common occurrence of dermoid cysts in pregnant women is evidenced by the many reports cited in the part dealing with the incidence of teratoids during gestation. In some cases, however, tubal pregnancies occur in dermoid bearing patients.[16]

The *uterus* of women suffering from teratoids is often malformed (see part on Pathogenesis, passage concerning hereditary predisposition). Not infrequently uterine fibroids develop simultaneously with ovarian teratoids.[17] Some workers[18] observed patients in whom ovarian dermoids and a uterine carcinoma developed simultaneously.

Anomalies of *menstruation* are quite common.[19] Two-thirds of the patients studied by one observer,[20] suffered from meno- or metrorrhagia a fact which the author ascribed to mechanical interference with the uterine blood supply. Among 100 cases of dermoids studied by another worker,[21] 28 showed disturbances of menstruation. In one patient,[22] who was past the menopause, bleeding re-occurred apparently as a result of a growing teratoid tumor. Conversely, in rare instances, bilateral dermoids may lead to extensive ovarian destruction with consequent amenorrhea.[23]

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[1] *Thornton* A83093/878. *Hue* A68750/04, A68751/04. *Luxenburger* A76033/06, *Butler-Smythe* A73395/08, *Kolłonski* A73911/19, 10511/20. *Wohllaib* A76762/22, *Sippel* A76533/24. *Lucksch and Ringelhan* B7334/26, *Riemann-Preuss* A76394/28. *Koller* A73910/28.
[2] *Töpfer* A76644/27.
[3] *Edmonds and Hawkins* A97542/41.
[4] *Iversen* A42382/888. *Robb* A76398/891. *Gläser* A73679/892. *Amico-Roxas* A49113/897, *Pazzi* A68668/899, *Mackenrodt* A76045/00, *Haultain* A73740/01, *Carles* A73409/05, *Dujon* A73521/07, *Crosti* A68564/21, *Adeodato* A73181/25. *Cotte and Vachey* A73447/28, *Holtmann* A73802/28, *Trempe* A61699/32.
[5] *Mey* A61884/32.
[6] *Macnaughton-Jones* A76048/08-9.
[7] *Michinard* B11907/16.
[8] *Lippert* A76008/05, *Novak* A63534/41.
[9] *Novak* A63534/41.
[10] *Guibal* A73717/05, *Dransfeld* A73513/18, *Luftspringer* A76031/18, *Bruns* A65858/24.
[11] *Lippert* A76008/05.
[12] *Guibal* A73717/05.
[13] *Hartmann* A40711/884.
[14] *Miller* A18279/37.
[15] *Blazejczyk* A73310/898, *Walther* A76717/01, *Brewis* A73371/06-7, *Franz* A73626/23.
[16] *Chambers* A73419/892, *Perkins* A76267/899, *Coe* A73434/10, *Bolboli* A95381/37.
[17] *Nisot* A68941/895, *Gibert* A68745/896, *Masson* A49242/898, *Mauclaire and Pilliet* A76091/898, *Amann* A73192/899, *Menge* A76110/01, *Simon* A76528/04, *Noble* A76222/06, A76223/06, A76224/06, A76221/06, *Bouchet* A73344/07, *Haultain* A70041/09-10, *Rosenstein* A76415/12, A76414/12, *Hertz* A73775/20, *Watson* A76723/24-5, *Commandeur and Patel* A73439/25, *Holstein* A97175/38, *Pastorini* A96932/42.
[18] *Dudley* A73516/888, *Hollstein* A97175/38.
[19] *Smith* A68121/29.
[20] *Strassmann* A76579/00.
[21] *Koucky* A73916/25.
[22] *Levy* A80246/35.
[23] *Wiener* A76746/13.

Swelling of the *vulva*[1] and *vaginal* prolaps[2] may occur owing to mechanical pressure of the tumor.

Enlargement of the *mammary glands* is very rare with dermoid cysts. In one case where it was present it did not vanish after ablation of the tumor, hence, it could hardly be ascribed to hormones produced by the latter.[3] In another instance lactation set in following ablation of an ovarian dermoid,[4] but since the ovary also contained a corpus luteum cyst it is likely that milk secretion was due to the "progesterone withdrawal phenomenon".

Genital infantilism of varying degrees is not uncommonly seen in combination with teratoids.[5] Some observers[6] report infantilism and amenorrhea in 4% of all their cases and even higher incidence rates are occasionally recorded.[7] In some of these cases, sexual development may have been retarded as a result of ovarian destruction by the dermoid, while in others it was probably due to a hereditary defect.

Conversely, in a few cases, *precocious puberty* was noted in young girls with ovarian teratoids.[8] Miller[9] denies any relationship between the precocious puberty and the ovarian teratoids because simultaneous occurrence of the two conditions is rare. I do not believe that these lesions should be regarded as necessarily coincidental since the proportion of sexual malformations in teratoid bearing patients is rather high, even though this particular type—namely premature development—represents only a small percentage of the total.

Virilism, sometimes to the extent of *pseudohermaphroditism,* has also repeatedly been observed in patients with ovarian teratoids.[10] As in the case of other genital malformations in dermoid bearing women, it is difficult to decide whether the ovarian tumor was the cause of the sexual anomaly or whether the same abnormal hereditary predisposition led to the development of both the tumor and the pseudohermaphroditic changes. Dermoids may develop slowly and remain unnoticed for a long time; hence, even in patients in whom the abnormality of the sexual organs is evident at an early age, much before the tumor, it may be caused by the latter. In view of the frequency of evidently congenital uterine malformations in teratoid bearing women, it appears more probable, however, that the tumor is not the cause of the pseudohermaphroditism but merely another manifestation of hereditary inadequacy. The occasional coincidence of ovarian teratoids and "*Cushing's disease*"[11] should also be noted in this connection.

Nervous disturbances such as ataxia,[12] catalepsy,[13] neurasthenia,[14] mania of persecution[15] or disturbances in the function of the sympathetic nervous system,[16] have also been noted in the presence of ovarian dermoids but their occasionally suspected causal relation to the latter is entirely unproven.

COMPLICATIONS

Many of the common complications of teratoids have been discussed in the sections devoted to other ovarian lesions such as hemorrhage, necrosis, torsion and abscess formation (see Sect. IV, Vol. VI).

A common complication is *rupture* of dermoid cysts which most frequently occurs into the *peritoneal cavity* itself.[17] Rupture may occur as a result of a direct trauma to the abdomen or under the influence of increased intra-abdominal pressure such as develops during pregnancy. In these cases, blood and the dermoid contents may cause pronounced peritoneal irritation with the formation of foreign body tubercles and symptoms resembling peritonitis. Rupture is particularly frequent in dermoid cysts whose wall has become brittle as a result of malignant transformation but it is noted even among benign dermoids especially if they are infected or partially necrotic. The same dermoid may even rupture repeatedly.[18]

[1] *Luftspringer* A76031/18.
[2] *Miller* A18279/37.
[3] *Lepper et al.* A96507/38.
[4] *Walter* A95339/37.
[5] *Baillie* A73232/789, *Schabel* A76465/844, *Wells* A76729/874, A40376/882, *Pauly* A76260/875, *Leopold* A40429/882, *Freund* A44201/892, *Simons* A48288/896, *Hoffmann* A73797/898, *Armknecht* A73221/01, *Tribukait* A76656/02, *Schauta* A76469/03, *Lippert* A64789/05, *Demons* A73488/05, *Bab* A73226/06, *Benda* A73283/22, *Moxter* A76166/22, *Frembgen* A73630/25, *Neumann* A76204/25.
[6] *Stübler and Brandess* A76588/24, *Mayer* A78681/24-9.
[7] *Nördlinger* A76225/887, *Luftspringer* A76031/18.
[8] *Fusino* A73647/893, *Harris* A21505/17, B7480/25, *Orel* A76244/28, *Neurath* A76208/31, *Wakeley* A61947/33, *Schiller* A62173/35.
[9] A18279/37.
[10] *Litten and Virchow* A80247/879, *Audain* A44580/893, A73223/893, *Apert* A68557/14, *Harris* A21505/17, *Uhlrich* A76664/23, *Dreyfus* A80181/36.
[11] *Krönke and Parade* A97153/38.
[12] *Variot* A29974/881, A40122/881.
[13] *Picqué* A76291/01.
[14] *Vincent* A76695/07.
[15] *Voisin* A48420b/897, A48460/897.
[16] *Miller* A68736/876.
[17] *Herapath* A73769/849, *Koeberlé* A83069/870, *Hue* A73809/883, *Powne and Morris* A76338/884, *Engström* A73548/887, *White and Walter* A45713/891, *Tison* A76642/892, *Stirling* A48456/896, *Phocas* A68944/896, *Sgourdéos* A50595/898, *Bégouin* A49222/898, *Dirner and Wenhardt* A73497/899, *Le Conte* A73969/00, *Jewett* A68927/03, *Billington* A66966/04, *Brewis* A73370/06-7, *Potherat* A76332/08, *Lucy* A66882/10, *Carter* A82762/10, *Fraser* A73627/11, *Herzog* B11283/11, A82768/12. *Engelhorn* A73546/17, *Roedelius* A66887/18, *Bull* B8756/19-20, *Roth* A76426/23, *Meyer* A76121/24, *Lecène and Béclère* A73968/29, *Coulson* A66288/29, *Althabe and di Paola* A65599/29, A73190/31, *Buzoianu and Dimitriu* A73396/33, *Seibile* A28177/34, *James* A97177/38, *Montanari* A96635/38, *Velten* A97445/39, *de Castro Barbosa* A96674/41, *Piper* B81139/41.
[18] *Haultain* A73741/01.

In some cases, dermoids evacuate their contents into the *broad ligament* causing infiltration of the latter with fatty material (see part on Pathologic Anatomy).

Another frequent complication is rupture into the *bladder*. If teeth enter the bladder, this may lead to symptoms such as are caused by urinary calculi. In some instances a tooth may act as a nucleus around which a true urinary calculus is formed. Sebaceous material and hair may also be emptied into the bladder. The excretion of hair through the urine has been referred to as "pilimiction" or "trichiasis of the urinary passages".[1]

Perforation into the *intestinal tract*—usually the rectum, colon or sigmoid, rarely the small intestine or appendix—is less frequent.[2] In one rather unusual case a dermoid tooth, protruding on the outer surface of the teratoid, perforated the adjacent bowel.[3]

Rupture into the *oviduct*,[4] or *uterus*[5] or *vagina* may lead to evacuation of the cyst contents through the genital passages.[6] In Martin's[7] patient the entire cyst prolapsed through the vagina.

In some instances the dermoid breaks *through the skin to the outside* and a fistula is established, frequently through the naval.[8] Occasionally *complicated perforations* occur which may establish communciations between various internal organs such as the bladder, intestine, genital passages etc. and these may even become connected with the outside by means of skin fistulae.[9]

A comparatively frequent complication is *obstruction of the ureters* with subsequent hydronephrosis due to the mechanical pressure of expanding dermoids.[10] In many cases the dermoid itself, or adhesions in its vicinity, lead to *ileus* due to intestinal obstruction.[11] Complication of dermoids with *appendicitis* has also been reported[12] but this is rare.

Perhaps one of the most important complications is *pregnancy* since the growing uterus may cause impaction or rupture of the dermoid, the latter being most frequent during labor when intra-abdominal pressure is at its maximum.[13] (For additional cases of dermoids complicated by gestation see passage on pregnancy in part on Incidence). Complication by *tubal pregnancy* is mentioned above in connection with the fertility of dermoid bearing women.

Impaction in the pelvis[14] or *migration*[15] of ovarian dermoids may also lead to serious complications, and during labor *rupture of the uterus* may ensue owing to mechanical interference with delivery.[16] Occasionally an ovarian dermoid is complicated by *pyosalpinx*,[17] *peritoneal tuberculosis*[18] *or cancer of the stomach*,[19] but these complications are exceptional and almost certainly coincidental.

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[1] *Wallace* B8/700, *de la Rivière* A76397/759, *Josephi* A73850/803, *Beling* A73280/823, *Larrey* A83072/842-3, A73951/846, *Montgomery* A76155/846, A68738/849, *Heinrich* A73754/846, *Rayer* A76363/850, *Ulrich* A82557/859, A82558/860, *Hall* A73732/860, *Broca* A73375/868, *Blackman* A73301/869, *Fuller* A73645/869-70, *Blich* A73311/870, *Ruge* A76441/878, A76442/878, *Walle* A76703/881, *Taylor* A76609/883, *Pincus* A81310/883, A76295/884, *Doran* A70475/884, *Feleki* A73565/889, A73566/889, *Duncan* A43525/890, *Sänger* A76447/890, *Bardenheuer* A73255/894, *Hare* A44808/894, *Clado* B9/895, *Le Gendre* A73975/896, A73976/896, *Treub* A76649/897, *Carrel* A73412/00, *Solowij* A76542/00, *Roy* A76437/00, *Barsukow* A73263/00, *Gerszun* A73673/01, *Schmit* A76482/01, *Saniter* A76452/01, *Münch* A76172/01, A76173/02, *Kynoch* A73933/07, *Delore and Alamartine* A73485/09, A73484/09, *Germain* A73669/09, *Woltring* A76768/09, *Himmelfarb* A73788/10, *Ekehorn* A73538/11, *Heller* A73760/13, *Kellner* A73877/17, *Guinby* A76353/19, *Carl* A73408/23, *Ankelen* A82761/24, *Santy* A76456/28, *Thomas and Exley* A65673/30, *Kalo* A64429/30, *Tonello* A66218/32, *Ewell* A61749/33, *Dittrich* A61956/33, *Shih and Char* A95107/37, *Townsend* A95456/39, *Carter et al.* A31391/39.

[2] *Garland* A69371/866, *Gentilhomme* A69372/876, *Fränkel* A40282/883, *Herman* A73771/885, *Munk* A42014/885, *Atlee* A73222/885, *Janvrin* A42028/886, *Langenbuch* A73947/891, *Colle* A44586/893, *Sieveking* A46601/893, *Baylac* A46440/893, *Frédéricq* A73629/893, *Lesourd* A73990/894, *Malcolm* A47121/895, *Tauffer* A68677/895, *Richardson* A47506/895, *Grosse* A51000/898, *Hoffmann* A73797/898, *Lindquist* A76002/02, *Schauta* A76469/03, *Lippert* A64789/05, *Kroph* A73923/07, *Lissowskaja and Krimm* A76009/08, *Schmidt* A80286/10, *Barth* A73264/10, *Sellheim* A76517/11, *Tédenat* A70984/13, A66216/31, *Dransfeld* A73513/18, *Ohrenstein* A76234/22, *Stübler and Brandess* A76588/24, *Monjardino* A76152/28, *Mayer* A64459/30, *Ottow* A76252/30, *Moulonguet* A64805/32, *Kermauner* A64880/32, *Mavrodin* A28163/35, *v. Szathmary* A97159/37, A95330/37, *Murdoch* A97570/38, *Carter et al.* A31391/39.

[3] *Mason* B7241/27.

[4] *Meyer* A76123/05, *Krömer* A70091/08.

[5] *Mundé* A76184/897, *Lippert* A64789/05, *Monod* A76154/27.

[6] *Mundé* A76177/878, *Mantel* A46318/892, *Bauereisen* A73269/28, *Jarocinski and Szenwic* A73836/28, *Counseller* A65606/30, *Pruis* A80271/31, *Spirea* A66211/32, A76556/32, *Soimaru and Spirea* A76541/33-4, *Kamniker* A96505/38.

[7] A76079/12.

[8] *Archer* A69340/809, *Heinrich* A73754/846, *Köhler* A73905/825, *Moore* A76156/866, A68739/866-7, *Krogmann* A73921/878, *Powne and Morris* A76338/884, *Morris* A68740/884, *Polenow* A76303/899, *Menzel* A76113/02, *Gayet* A73656/08, *Sage* A76448/13, *Binet* A73295/22, *Leibtschik* A73978/26, *Bocock* A66105/32.

[9] *Schmucker* A76484/782, *Larrey* A73950/842, *Heslop* A73781/850, *Blackman* A73301/869, *Stoney* A76577/870, *Robb* A76398/891, *Strassmann* A76579/00, *Amann* A73195/05, *Himmelfarb* A73788/10, *Mayeda and Shinagawa* A76097/31, *Carter et al.* A31391/39.

[10] *Butler-Smythe* A43629/890, *Routier* A69167/895, A69166/896, *Barbour* A47481/895, *Viannay* A66890/08, *Ervin and Oehlbeck* A97543/41.

[11] *Hardy* A69380/845, *Conant* A69361/857, *Klebs* A73893/872, *Lücke* A76026/872, *Routier* A45703/890, *Ricard* A45641/891, *Arrou* A73215/891, *Schalit* A76466/897, *Mouchet* A76163/01, *Machard* A76040/01, A76041/01, *Parry* A76258/04, *Karczewski* A73863/04, *Cholodkowski* A73428/04, *Woodmann* A76767/22, *Danzis and Parsonnet* A76465/26.

[12] *Jessett* A68926/03-4, *Lichtenauer* A73999/09, *Doyle* A73510/16, *Romeo* A97587/39.

[13] *Morse* A76159/896, A76160/04, *Spencer* A76553/898, *Cusmano* A76459/07, *Walker* A76714/12, *Oldfield* A76235/14, *Davidson* A73468/22.

[14] *Klyachkina* A68931/894.

[15] *Shoemaker* A45773/890-1.

[16] *Söderberg* A76540/10.

[17] *Ucros* B8968/03.

[18] *Bertino* B12640/05.

[19] *Van Gieson* B40203/883.

DIAGNOSIS

The clinical criteria which facilitate the recognition of dermoid cysts have been reviewed by a number of authors.[1] In many cases preoperative diagnosis is impossible because of the indefinite symptoms produced by these growths.[2] The identification of the cyst itself is based on the same *local signs* as are characteristic of other cysts; bimanual palpation will help to establish the position, size, shape and mobility of the tumor.

Diagnostic puncture was advocated by some[3] and may help to identify the specific nature of the cyst by its characteristic contents; the danger inherent in this intervention is too great, however, to justify it, especially since in most cases surgical removal of the cyst would be indicated irrespective of its specific structure.

Küster[4] called attention to the frequent position of dermoid cysts in front of the uterus between the latter and the urinary bladder. He also emphasized that after manual dislocation these cysts tend to return to this position. Since other cysts usually sink into Douglas' space behind the uterus, he felt that this characteristic anterior position might facilitate the diagnosis of dermoids. Many subsequent investigators discussed the value of "Küster's sign" and found that although it is by no means infallible, it is positive in a large number of cases.[5] Undoubtedly, some dermoids may develop in Douglas' space[6] and conversely cysts other than dermoids may be situated in the typical anterior position and return there after dislocation just as if they were dermoids.[7] Perusal of many relevant case reports indicates, however, that while not pathognomonic, Küster's sign is more frequently positive with dermoids than with other tumors.

The most valuable diagnostic means capable of identifying dermoid cysts as such is the *X-ray examination.* If the tumor contains no calcified material this diagnostic means frequently yields inconclusive results. On the other hand, extensive calcification of an ovarian cyst may always be taken as suggestive evidence in favor of its teratoid nature, especially if the X-ray shadows imitate the outlines of bones or teeth. The latter are particularly characteristic of dermoids and permit their preoperative diagnosis in many cases.[8] The incidence of calcification in dermoids is reported in two series of patients as 18%[9] and 49%[10] respectively. Some radiologists claim that roentgen diagnosis of dermoids is possible even in the absence of calcification. The mass is usually rounded or ovoid, of diminished density and of mottled appearance. It is encircled by a distinct ring of increased density, which delineates it sharply from the surrounding tissues. These features permit the differentiation of dermoids from other growths even if the latter exhibit calcified shadows due to phleboliths, ureteral or vesical calculi, or calcified non-dermoid tumors.[11]

In connection with the differential diagnosis of ovarian dermoids, the most frequent mistake made is confusion with *ectopic gestation,* especially tubal or ovarian pregnancy.[12] A positive Ascheim-Zondek reaction and the sexual history of the patient may help in arriving at the correct conclusion. These indications will also be of use in the rare instances in which the dermoid is difficult to differentiate from *normal gestation.*[13]

Among the less common diagnostic errors, confusion of dermoid cysts with *salpingitis,*[14] *renal colic,*[15] *kidney tumor,*[16] *floating kidney,*[17] *appendicitis,*[18] *uterine fibroids,*[19] or *tuberculous peritonitis*[20] are noteworthy, but in most cases of this type, correct identification of the condition is not too difficult. Small calcified concretions or teeth in dermoids may be difficult to distinguish from *urinary calculi*[21] with which they have often been confused in X-ray pictures.

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[1] *Lesourd* A73990/894, *Guinard* A47102/894, A68761/894-5, A47116/895, *Reed* A48422/896, *Mieczkowski* A76135/14, *Penkert* A76265/22, *Mailer* A76050/29, *Micholitsch* A76134/30.

[2] *Linn and Ragins* A35879/41.

[3] *Zweifel* A76776/883.

[4] A40601/882.

[5] *Freund* A44201/892, *Ahlfeld* A73182/892, *Gottschalk* A73695/892, *Cohn* A73437/893, *Mandelstam* A46566/893, A76059/893, A48314/896, *Scheunemann* A76472/895, A76471/895, *Latzko* A46304/895, A73957/895, *Burgmann* A73392/896, *Breuer* A73367/01, *Shoemaker* A76524/01, *Favell* A73560/04, *Thienhaus* A68678/05, *Vautrin* A76681/13.

[6] *Gradenwitz* A73699/04, A73698/04, *Engelhorn* A73545/08.

[7] *Latzko* A46304/895.

[8] *Gosset and Sicard* A73692/13, *Sonntag* A68580/19-20, *Dunet* A68565/22, *Edeiken* A82731/22, *Alexander* A68558/23, *Pless* B7667/23, *Aimé* A68554/25, *Fried* B16107/27, *Seidler and Lenartowski* A76512/28, *Benassi* A94503/28, *Spillman* A94505/29, *Marion* A68106/29, *Villard and Labry* A76693/29, *Kleine* A73896/32, *Schultze* A62949/32, *Oppenheimer and Hofer* A61627/32, *Allende* A61952/33, *Rusconi* A52299/34, *Galifi* A27869/35, A94502/37, *Heffernan* A59894/36, *Saupe* A62172/36, *Mazzola and Ryan* A96517/38, *Tedesco* A97186/38, *Burthiault* A97257/39, *Danelius* A97578/39, *King* A32341/40, *Good* A97375/40, *Ahumada and Sardi* A96902/42, *Leon and Leon* A98162/43.

[9] *Glass and Rosenthal* A94506/37.

[10] *Marshall* A94504/28.

[11] *Robins and White* A33056/40.

[12] *Garrigues* A73653/882, *Garrigues and Mitchell* A40592/882, *Hudson* A46333/892-3, *Muratow* A76187/895, *Reyenga* A76382/898, *Vineberg* A50954/899, *Metcalf* A68763/05-6, *Nagel* A76192/20, *Romant* A66197/31.

[13] *Lörincz* A76016/23.

[14] *Pinaud* A43480/889, *Morel and Hubert* A76157/04.

[15] *Fagge* A82766/18-9.

[16] *Morris* A47465/895.

[17] *Isaacs* A68762/05, *Siciliano* A95322/36.

[18] *Niot* A76219/01, *d'Andrade* A68758/04, *Loeb and Levy* A62936/32, *Siciliano* A95322/36, *Delthil* A96015/37.

[19] *Edgar* A73530/899, *Weisswange* A76728/11.

[20] *Shaw* A80289/23.

[21] *Sonntag* A68580/19-20, *Alexander* A68558/23, *Siciliano* A95322/36, *Stolz* A97443/39.

PROGNOSIS

The prognosis of teratoid tumors depends mainly on their benign or malignant nature. The highly malignant, usually solid teratomas which occur most often in children have a very unfavorable prognosis. Out of a total of 32 cases reviewed by one investigator,[1] 21 were known to have died while the rest survived from 1 to 10 years following surgical removal of the growth. According to the same author, X-ray treatment does not give encouraging results. Even in teratoids, which have undergone secondary sarcomatous transformation, radical surgery may, however, sometimes yield satisfactory results.[2]

On the other hand, benign dermoids have a very good prognosis, especially if they are treated by complete removal of the affected ovary. It must always be kept in mind that these tumors tend to be multiple and hence the contralateral ovary, as well as the entire pelvic peritoneum, should be examined for possible additional growths. In benign dermoids the rate of development is very variable.[3] In some cases growth is exceedingly rapid,[4] while in others it is very slow. Thus in one patient[5] a colossal dermoid was known to have developed over a period of 50 years. It will be remembered that these tumors may grow for many years without producing detectable symptoms and hence in most cases the age of the tumor is unknown. According to some theories concerning their pathogenesis (e.g. the blastomere theory) these growths develop on the basis of a congenital malformation and in this event their age would necessarily be the same as that of the bearer.

Following surgical removal the prognosis of dermoids is very good and if sufficient ovarian tissue is left behind normal pregnancies may ensue.[6]

If secondary malignant changes set in and a carcinoma or sarcoma develops from a dermoid, the prognosis becomes very unfavorable unless all malignant tissue can be removed. Because of these possibilities and the ever present danger of hemorrhage, torsion, secondary infection, rupture and perforation into other organs, surgical removal of dermoids is indicated—the general condition of the patient permitting—as soon as the growths are recognized.

THERAPY

The usual therapy in the case of teratoid tumors is their surgical removal through *ovariectomy*. In the case of very small dermoids, enucleation of the growth or partial ovariectomy may be attempted, but in most cases the entire gonad has to be removed.[7]

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[1] *Smeltzer* A37338/41.

[2] *Menju* A34904/40.

[3] *Pfeilsticker* A76287/26.

[4] *Mallett* A76058/12.

[5] *Brownlee* A73380/07.

[6] *Martin* A64458/30.

[7] *Lee* A83073/851, *Bradford and Dunlap* A87190/854, *Brown* A83046/859, *Briggs* A87094/861, *Koeberlé* A83068/864-5, A83069/870, *Marsack* A83076/866, *Keith* A73875/866, A48273/895-6, *Helber* A73758/867, *Bourneville and Bourgeois* A73348/867, A83042/867, A83041/869, *Schroeder* A83086/868, A76497/878, *Sklifasovski* A83088/868, *Harms* A75272/868, *Giraldès* A83058/868, *Thompson* A83092/869, *Brandt* A83044/869, *Boysen* A83043/871, *Mears* A74879/871-2, *Peruzzi* A83080/872, *Battey* A75276/872, A75275/872, A75277/874-5, *Nottingham* A87145/872, *Cheever* A83049/873, *Cabot* A83048/875, *Terrier* A76613/875, A42108/886, A42000/887, *Veit* A70428/876, *Boinet* A73322/877, *Kocher* A73904/877, *Eder* A83055/877, A83056/877, *Thornton* A75188/878, *Rendu* A83082/878, A83083/879, *Torres* A76646/878, A40595/882, A29483/880, *Péan* A83078/878, *Taylor* A83089/879, *Bennett* A75278/879, *Berthold* A75279/879, *Bozeman* A86331/879, *Müller* A76170/879, *Byford* A83047/879, *Miller* A29516/880, *Chiari* A83050/880, *Ruggi* A29889/881, *Murphy* A40573/882, *Leopold* A40429/882, *Houzé de L'Aulnoit* A83066/882, *Queirel* A83081/882, *v. Wahl* A41224/883, A41225/883, *Gusserow* A73720/883, *Stelzner* A76568/883-4, *Wettergren* A83095/884, *Fränkel* A83057/884, A41308/884, *Jacobi* A41614/884, *Muralt* A76186/884, *Burton* A40824/885, *Elliot* A40913/885, *Sievers* A83087/885, *Boerstler* A40699/885, *Braun von Fernwald* A75068/885, A42670/888-9, *Janvrin* A42123/886, A42028/896, *Bantock* A42192/887, *Pölchen* A76299/887, *Stevenson* A41723/887, *Bieljaeff* A75280/887, *Michael* A76132/887, *Casuso* A42251/887-8, *Fasola* A73557/888, *MacKenzie* A42487/888, *Takaki* A42497/888, *Menocal* A42270/888, *Tirifahy* A45264/889, *Groves* A45175/889, *Henao et al.* A91806/889-90, *Jessett* A43278/889-90, *Potter and Krauss* A43286/889-90, *McMurtry* A43543/890, *Omori and Ikeda* A43374/890, A46343/892, *Parvin* A43438/890, *Parkes* A43318/890, *Jacobs* A43424/890, *Braun* A43408/890, *Goodell* A43633/890, *Ludlam* A43429/890, A48277/896, *Stamm* A45931/890-1, *White and Walter* A45713/891, *Jaume and Matas* A45793/891, *Frank* A44198/892, *Camelot* A44052/892, A44190/892, *Page* A46498/893, *Costa* A46555/893, A44587/893, *v. Neugebauer* A76199/894, *Cortiguera* A47094/894, *Cittadini* A68910/894, *Morison* A47080/894-5, A47078/894-5, *Witte* A47515/895, *Malcolm* A47121/895, *Farrell* A47448/895, *Bueno* A47131/895, *Matthaei* A47425/895, *Hecht* A47435/895, *Martin* A48280/896, A76077/12, A64458/30, *Williams* A91853/896, *Treub* A76649/897, *Potieyenko* A49107/897, *Hofmokl* A49089/897, *Curti* A91778/897, *Mundé* A76184/897, *Bishop* A73296/897, A73297/897, *Annandale* A73206/897, *Potherat* A50980/897-8, *Tipyakoff* A68954/898, *Werder* A50687/898, A50686/898-9, *Stretton* A76583/898, *Routh* A91740/898, A76434/02, *v. Patten* A49220/898, *Hültl* A93075/898, *Elischer* A47997/898, *Dubar* A49228/898, *Lauro* A50974/898, *Gersuny* A50997/899, *Baldy* A73233/899, *Minkiewicz* A76147/899, A76148/00, *Aranda and Ruiz y Garcia* A68900/00, *Boldt* A73325/00, A73326/03, *de Boucaud* A83174/00, *Chavannaz and Hobbs* A68909/00, *Bücheler* A73387/01, *Foster* A68916/01, *Anufriew* A93240/02, *Cripps* A73451/02, *Krabbel* A80236/02, *Strominger* A68952/02, *Morkovitin* A68938/02-3, *Jewett* A68927/03, *Hamonic* A68923/03, *Dillard* A91784/04, *Johnson* A68928/04-5, *Flaischlen* A68914/05, *Pfannenstiel* A80267/05, *Reford* A76373/05, A76374/05, *Stiénon* A83503/05, *Thienhaus* A91847/05, *Déveze* A66893/08, A66892/08, *Barth* A73264/10, *Williamson* A80310/12, *Lancial* A66895/13, *Ferrari* A66894/14, *Heurlin* A82384/16, *Chueco* A81635/21, A66891/22, *Patel* A76259/28, *Vanverts* A76677/28, *Keller* A80231/29, A73876/29, *Smith* A68121/29, *Ducuing and Guilhem* A73515/31, *Falkiner* A73553/31, *Levi* A97289/39.

PLATE XXXIII
TERATOIDS

Fig. 1. DERMOID CYST WITH AN ALMOST COMPLETELY FORMED FETUS (after Kaboth A73854/24). (A) "Enterocystoma" (B) dermoid cyst open (C) embryoma with female genital organs and long and abundant scalp hair. The embryoma is connected with the wall of the dermoid by means of a stalk (D) but in addition to this an umbilical cord (E) connected it with the enterocystoma. Hence, the latter was interpreted as a yolk sac. The arrows (E) point to the stumps of the umbilical cord, since the latter was transcised.

Fig. 2. GROSS APPEARANCE OF CROSS-SECTION THROUGH COMPLEX DERMOID CYST OF OVARY (after Novak B109 44). Note coarse hair in some of the cystic cavities and abnormally formed teeth (the latter marked by arrow).

Fig. 3. X-RAY APPEARANCE OF DERMOID CYST (after Robins and White A33056/40). Note marked degree of mottling. The small calcified shadow, just above the midpoint of the tubes probably represents an incomplete tooth. The sharp demarkating ring adds to the contrast between the dermoid and the surrounding soft tissue.

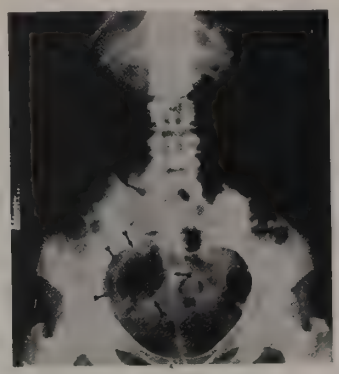

Fig. 4. X-RAY APPEARANCE OF DERMOID CYST (after Robins and White A33056/40). The ovoid area of increased radiance is well outlined. The dense wall surrounding the area is sharply defined as is characteristic of dermoid cysts.

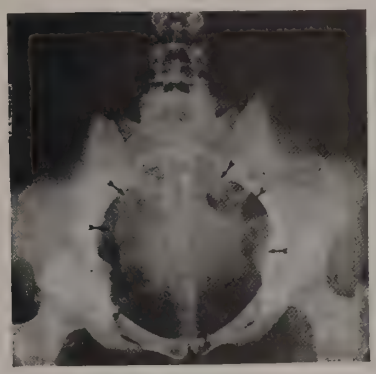

Fig. 5. X-RAY APPEARANCE OF DERMOID CYST (after Robins and White A33056/40). The encircling ring of the cyst is clearly defined at caudal and lateral borders of the mass. This cyst measured 14 x 11.5 x 9.5 cm and contained hair and sebaceous material.

Fig. 6. X-RAY APPEARANCE OF DERMOID CYST (after Robins and White A33056/40). The calcified area is poorly differentiated, but the cyst is readily identified as a teratoid because of the presence of a tooth (identified on pathologic examination).

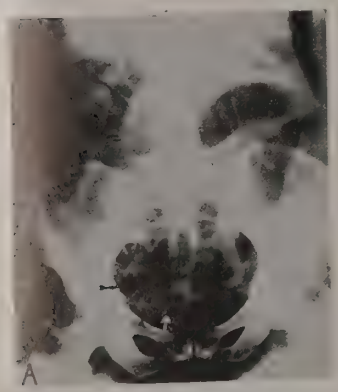

Fig. 7. X-RAY APPEARANCE OF DERMOID CYST (after Robins and White A33056/40). An irregular, calcified plaque is present in the cranial portion of the cyst wall; a ureteral calculus (white arrow) is about the same size as the calcified bodies within the cyst.

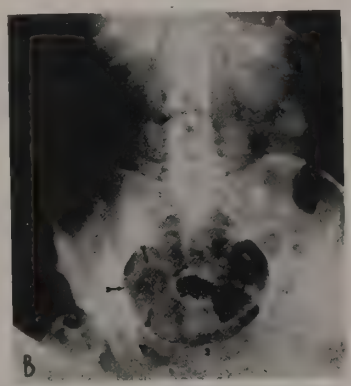

Fig. 8. X-RAY APPEARANCE OF DERMOID CYST. Same patient after the calculus has been passed. Note the contrast to the intestinal shadows on the other side of the pelvis.

Fig. 9. X-RAY APPEARANCE OF DERMOID TEETH (courtesy of Department of Radiology, Royal Victoria Hospital). X-ray taken especially to illustrate structure of dermoid teeth. Note cluster of teeth, with well-defined root canals, in the vicinity of an ossified plaque on one side, and two less regularly formed teeth on the other side of the pelvis.

PLATE XXXIV

TERATOIDS

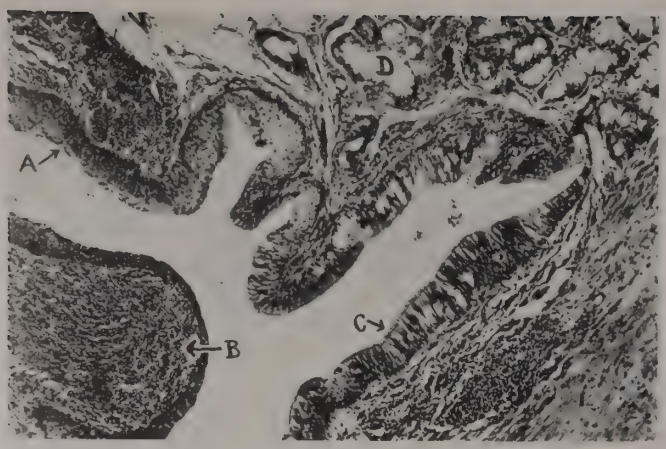

Fig. 1. TYPICAL FIELD IN A DERMOID CYST (courtesy of Dr. H. T. Karsner). In this field, we see stratified squamous epithelium (A), subepithelial, tonsil-like lymphatic tissue accumulations (B), ciliated respiratory epithelium (C), and subepithelial mucous salivary glands (D).

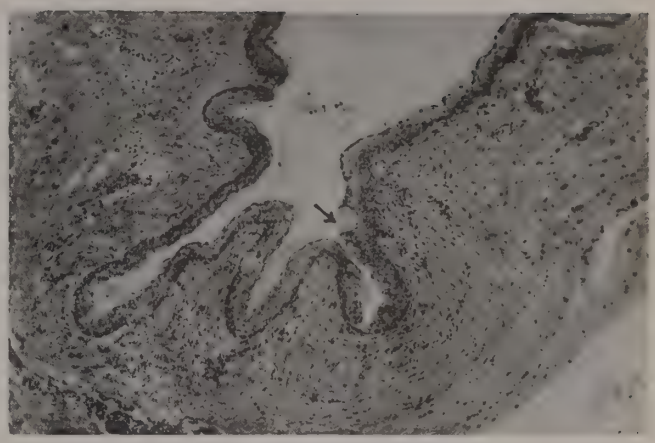

Fig. 2. DYSEMBRYOMA (courtesy of Dr. L. Berger). This was a polycystic teratoid which contained a large number of highly differentiated structures without any effort toward actual organ formation. The present section shows a cyst cavity lined by stratified but not cornified epithelium. Within it there are several small intra-epithelial mucous glands, consisting of a few cells only (marked by arrows).

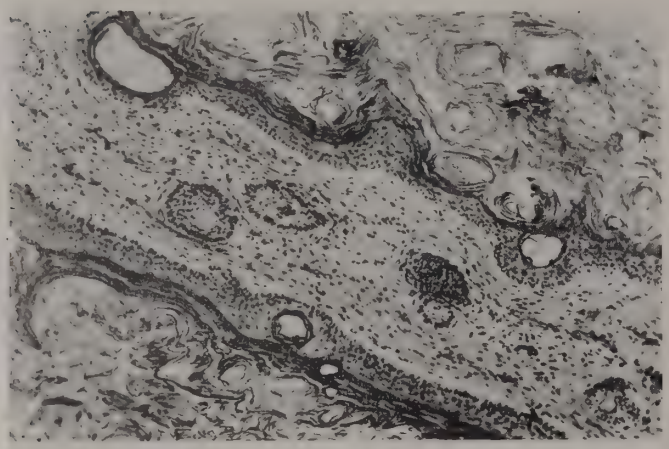

Fig. 3. DYSEMBRYOMA. Another field of the tumor illustrated in Fig. 2. Here we see a septum between two cystic cavities, both of which are lined by stratified and heavily cornified squamous epithelium similar to that seen in normal skin. Note several hair roots in the stroma of the septum.

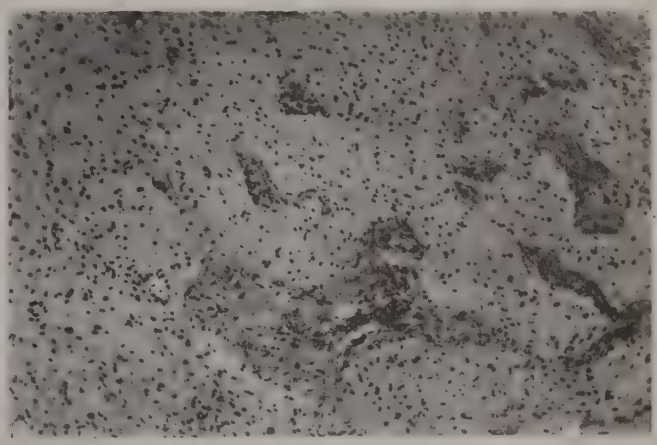

Fig. 4. DYSEMBRYOMA. Yet another field of the tumor illustrated in Figs. 2 and 3. Note that this entire region consists of brain tissue.

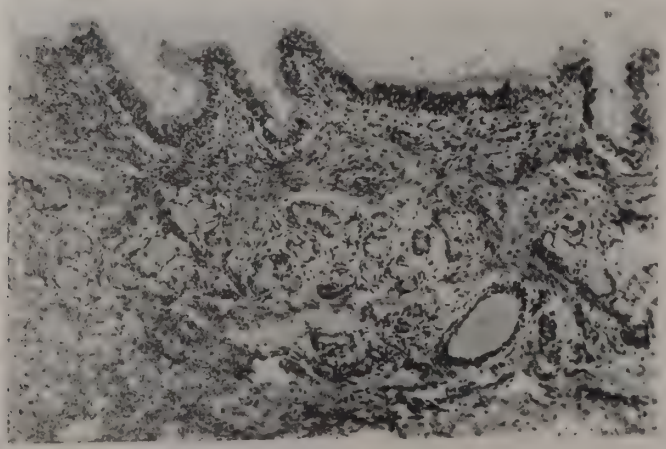

Fig. 5. DYSEMBRYOMA. Yet another field of the tumor illustrated in Figs. 2—4. Cyst cavity lined by ciliated, respiratory epithelium; underneath it, the stroma contains several mucous glands.

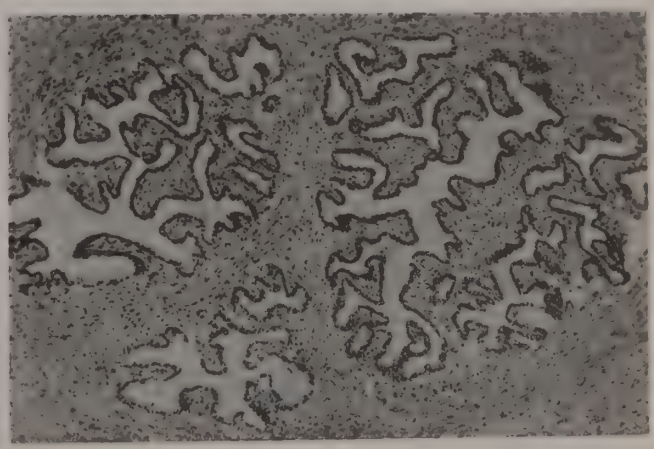

Fig. 6. DYSEMBRYOMA. Yet another area of the tumor illustrated in Figs. 2—5. Three small cystic cavities lined by a mucosa reminiscent of the Fallopian tube.

PLATE XXXV

TERATOIDS

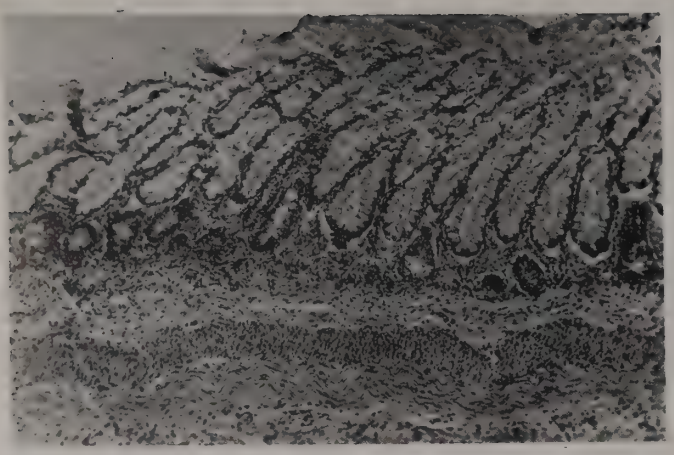

Fig. 1. DYSEMBRYOMA. Portion of a particularly polymorph, microcystic teratoid. In this field a well-differentiated and regular intestinal wall is clearly distinguishable. Note numerous mucus-producing cells in intestinal crypts, lamina propria mucosae and two layers of smooth muscle cells, the latter constituting the muscular wall of the intestinal segment. The region is highly reminiscent of large intestine.

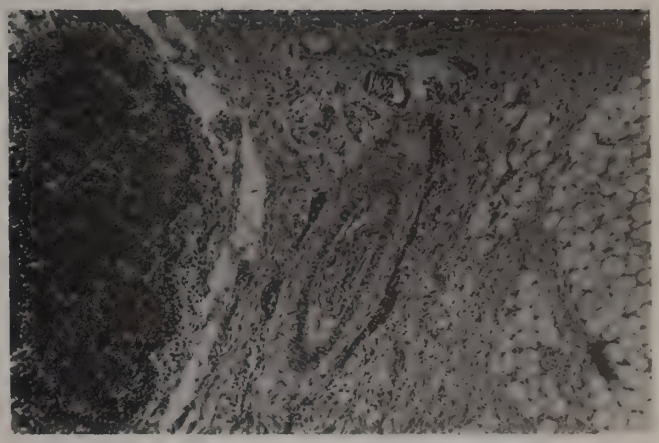

Fig. 2. DYSEMBRYOMA. Another field of the tumor represented in Fig. 1. Note large lymph tissue accumulation in the left half of the field and infiltration of lymphatic elements in periarterial spaces surrounding the vessel in the center of the field. On the right, normal fat tissue is visible.

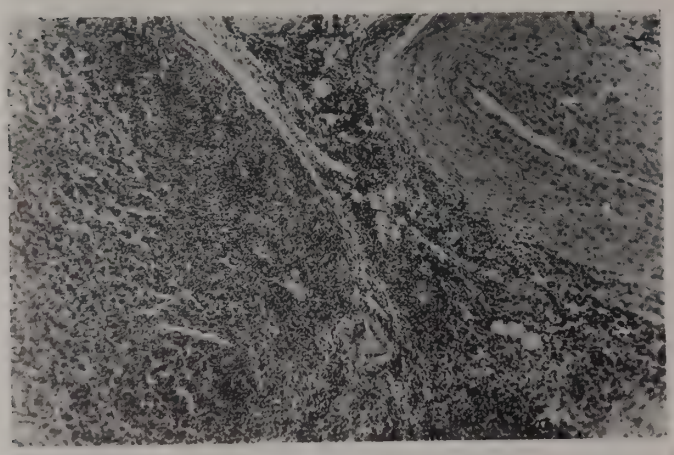

Fig. 3. DYSEMBRYOMA. Yet another field of the tumor represented in Figs. 1 and 2. Note extensive lymphatic tissue fields on the left with infiltration of the connective tissue toward the artery on upper right corner of the field. Lymphatic elements were very strongly represented throughout this neoplasm.

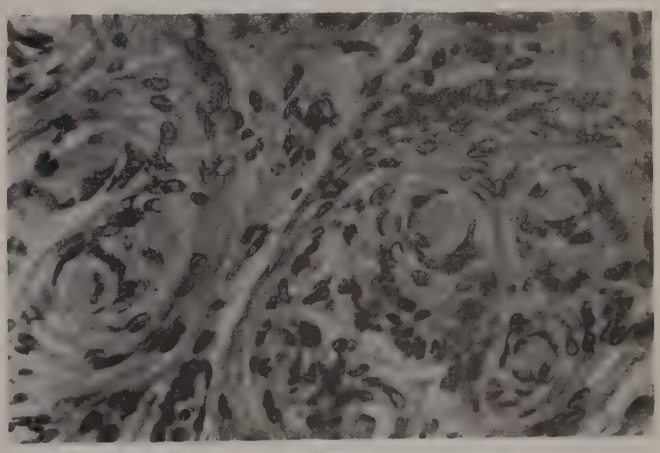

Fig. 4. DYSEMBRYOMA. Yet another field of the neoplasm illustrated in Figs. 1—3. Note the presence of several structures reminiscent of Hassall's corpuscles.

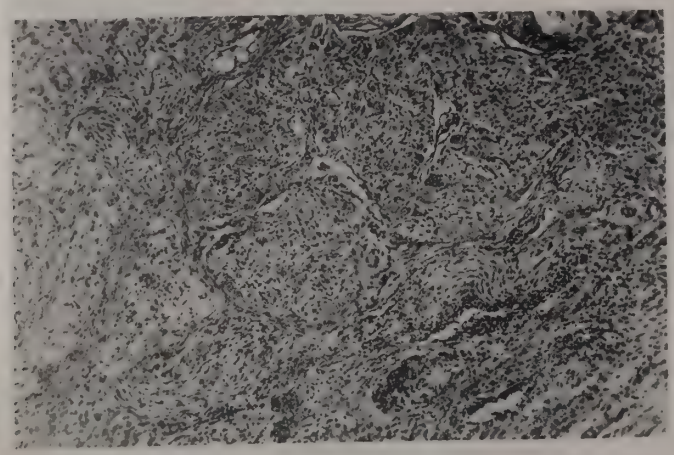

Fig. 5. DYSEMBRYOMA. Yet another field of the tumor illustrated in the Fig. 1—4. Large ganglion cell accumulation with fat tissue in the left and slight lymphatic infiltration in lower, right part of this field.

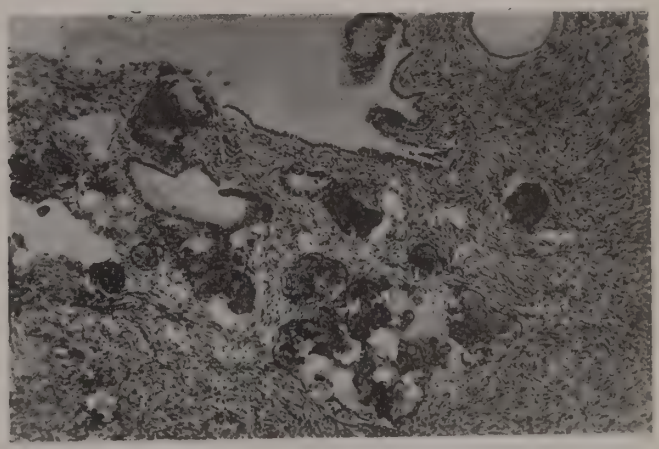

Fig. 6. DERMOID CYSTS. Part of a dermoid in which the epithelium lining the cyst cavity is serous and definite calcified psammoma bodies are visible within the stroma. This region is very reminiscent of serous, psammomatous cystomas. The remainder of the cyst was lined by stratified, squamous epithelium, characteristic of dermoids.

PLATE XXXVI

TERATOIDS

Fig. 1. **DERMOID CYST** (courtesy of Dr. H. T. Karsner). Typical skin-like area in the wall of a dermoid cyst. Note stratified, squamous epithelium lining the cyst cavity on the left and numerous sebaceous glands around hair follicles in the right part of the field.

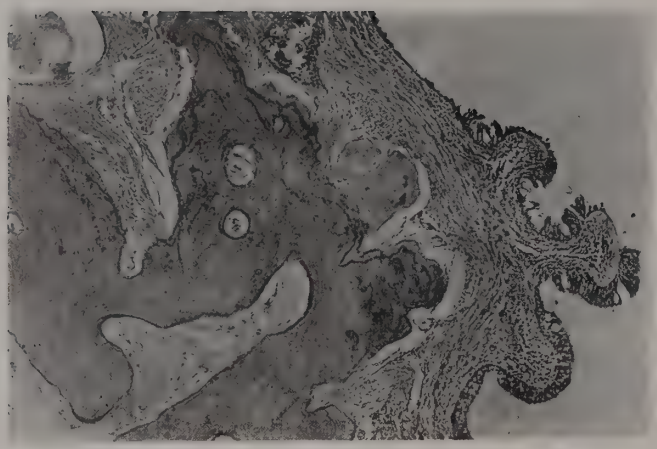

Fig. 2. **DERMOID CYST.** Note presence of irregular bone spicules within the cyst wall. The lining (on the right) is a typical ciliated respiratory epithelium.

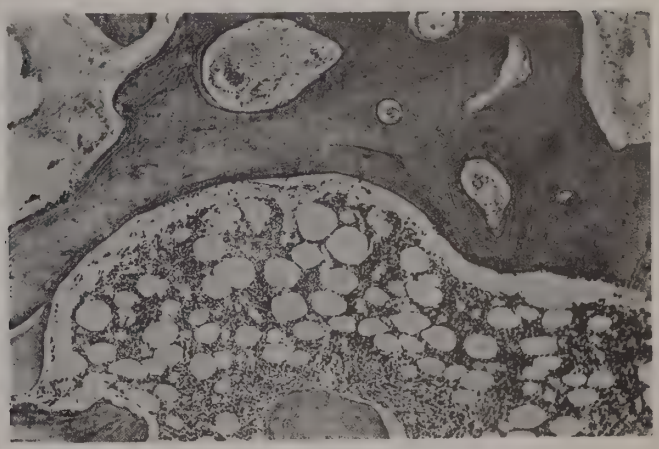

Fig. 3. **DERMOID CYST.** Another region of the neoplasm shown in Fig. 2. Apparently normal bone tissue with bone marrow are visible here within the cyst wall.

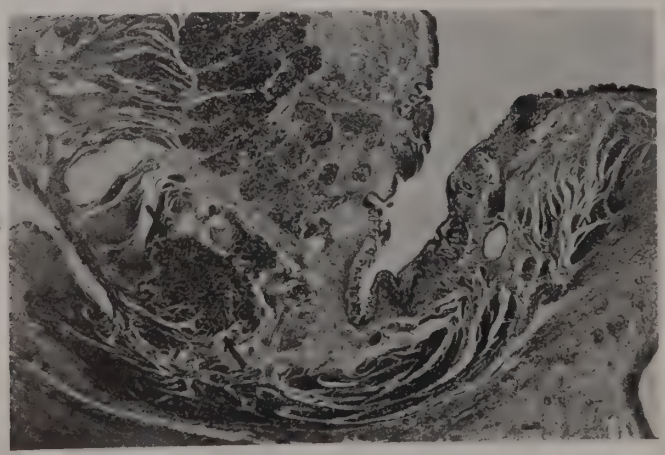

Fig. 4. **DYSEMBRYOMA WITH A CARCINOID TUMOR** (courtesy of Dr. L. Berger). Typical carcinoid cell group (between arrows) underneath the lining epithelium of a teratoid cyst.

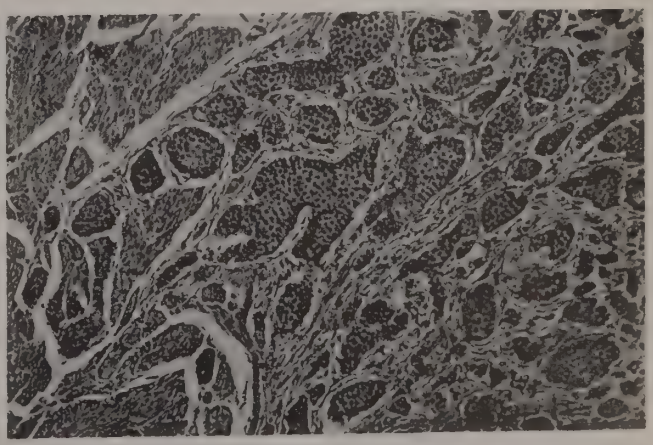

Fig. 5. **DYSEMBRYOMA WITH A CARCINOID TUMOR.** High magnification of the carcinoid shown in Fig. 4.

PLATE XXXVII

TERATOIDS AND FIBROMAS

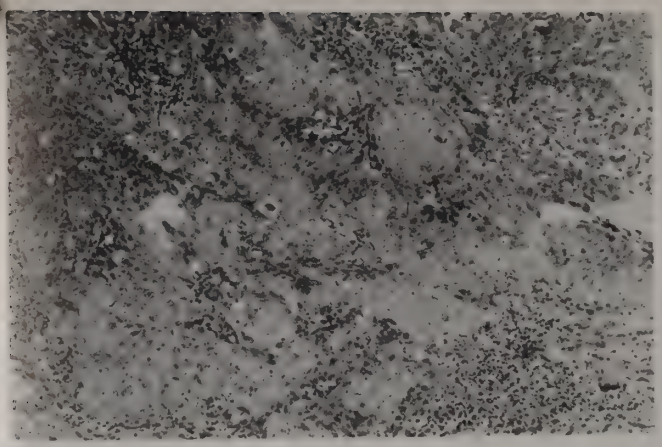

Fig. 1. CARCINOMATOUS TRANSFORMATION IN A DERMOID CYST. Squamous cell carcinoma developing on the basis of a dermoid cyst. Note irregular nuclei in the epithelial cells and polymorphonuclear leucocytes in stroma.

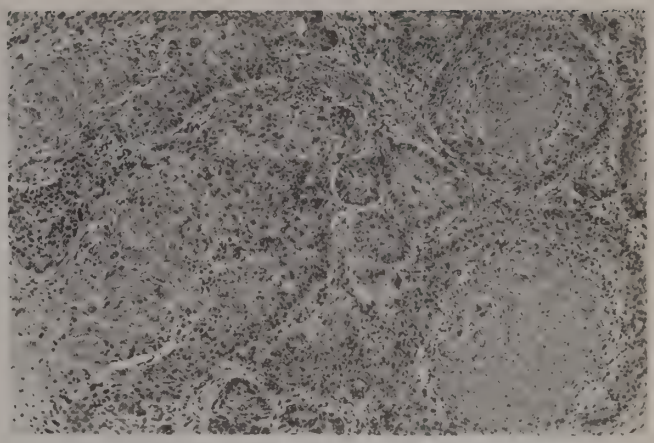

Fig. 2. CARCINOMATOUS TRANSFORMATION OF A DERMOID CYST. Note marked cornification and carcinoma pearl formation in this tumor.

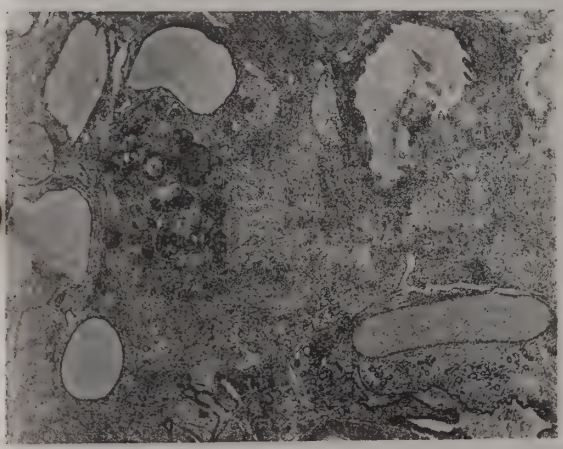

Fig. 3. SOLID, MICROCYSTIC EMBRYOMA (courtesy of Dr. L. C. Simard). This highly malignant, primary, solid teratoma weighed 460 gm. and produced extensive peritoneal metastases weighing 13,500 gm. at death, ten months after removal of the primary neoplasm. At this low magnification, elements of the central and peripheral nervous system, bronchial tissue, intestinal tissue, ectodermal cysts, fat and cartilage are visible.

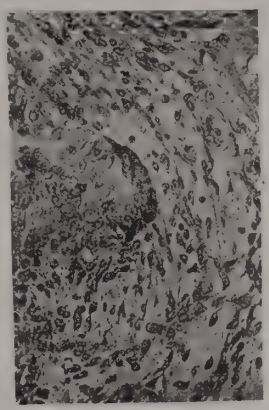

Fig. 4. SOLID, MICROCYSTIC EMBRYOMA. Argentaffin cells (heavily laden with black granules) in the intestinal epithelium of the solid embryoma shown in Fig. 3.

Fig. 5. SOLID, MICROCYSTIC EMBRYOMA. A fully differentiated ganglion, surrounded by neuroglia in the solid teratoma, represented in Figs. 3 and 4.

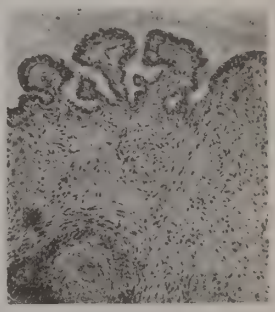

Fig. 6. SOLID, MICROCYSTIC EMBRYOMA. Brain tissue lined by a choroid plexus within the solid teratoma shown in Figs. 3—5. This tumor illustrates the degree of maturity which can be reached by organoid formations within these highly malignant tumors.

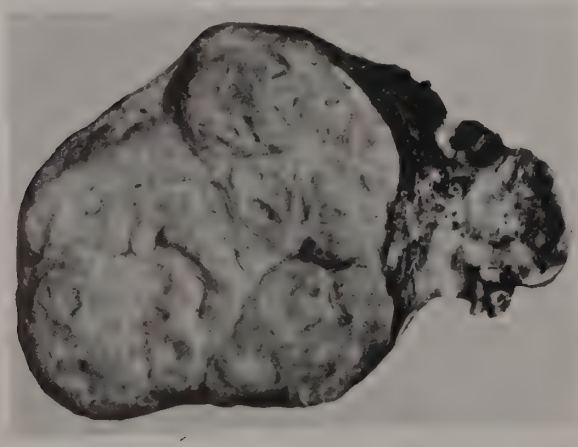

Fig. 7. FIBROMYOMA (courtesy of Dr. H. T. Karsner). Gross appearance of a solid, nodular fibromyoma of the ovary.

Fig. 8. FIBROMA (courtesy of Dr. H. T. Karsner). General appearance of a solid fibroma under low magnification. Note elongated nuclei and spindle-shaped cells similar to those seen in dense connective tissue.

During *pregnancy,* ovariectomy may face the surgeon with special problems inasmuch as in the course of labor, the tumor may have to be removed by the vaginal route, or its ablation may have to be performed simultaneously with a cesarean section; yet in view of the complications which tend to arise during pregnancy in women with large dermoid cysts, surgical interventions frequently become necessary at this time. The technical considerations which are of importance in such cases have been reviewed by various surgeons.[1]

In *children,* the therapy of choice is surgical as it is in adult women; in the majority of cases, complete removal of the tumor is necessary since the growth is rarely recognized before most of the normal ovarian tissue is destroyed. Especially radical operations are necessary in the case of solid malignant teratomas which are comparatively common in children.[2]

Mere *incision* or *puncture,* with or without aspiration of the dermoid contents, was used as a therapeutic measure in the last century and in a limited number of cases this intervention itself, or the granulation process resulting from a secondary infection, led to permanent obliteration of the cyst cavity.[3] Even *injection of iodine* into the cyst cavity was tried to accelerate the obliteration of dermoids[4] but all these antiquated procedures are now merely of historic interest.

X-ray therapy of teratoid tumors has been attempted,[5] especially in the case of solid malignant teratomas which became inoperable or in which prophylactic postoperative treatment appeared advisable. The results have not been encouraging.[6]

[1]*Merriman* A76119/819, *Wilson* A40269/882-3, *Backhaus* A73229/00, *Favell* A73558/01, A73559/03, *Bachmann* A73228/02, *Treub* A76653/07, *Weinhold* A76726/08, *Blacker* A73300/10-1, *Manton* A76065/11, *Favreau et al.* A73562/31.
[2]*Mears* A74879/871-2, *Thornton* A40032/881, *Darey* A45220/889, *Usiglio* A45648/890, *Black* A44225/892, A44224/892, *de Sant'Anna* A69168/895, *Pujol y Brull* A66897/12.
[3]*Chereau* A69357/845, A69355/845, A69356/845-6, *Mahot* A68732/867, *Jacobi* A73829/883, *Markis* A76070/887.
[4]*Lhonneur* A73998/856.
[5]*Walthard* A79676/20, A79677/21.
[6]*Frank* 58775/32, *Smeltzer* A37338/41.

PARA-OVARIAN TERATOID TUMORS

The great majority of the para-ovarian teratoid tumors are dermoids, derived from the ovary itself, but exhibiting the so-called intraligamentous type of development. In some cases, the connection with the ovary proper may become rather indistinct while in other instances, a primary dermoid of the ovary re-implants itself in the para-ovarian region, following self-amputation, subsequent to torsion of the pedicle. There are some cases, however, in which the dermoids appear to have developed primarily in the broad ligament[1] or pelvic mesenchyme.[2]

Little is known concerning the *pathogenesis* of the truly primary teratoid tumors of the para-ovarian region but the data concerning the corresponding ovarian tumors, discussed in the preceding chapter, are equally applicable to para-ovarian teratoids. Their possible development from an accessory ovary[3] or a self-amputated primarily ovarian neoplasm must also be kept in mind.

A few cases are listed in the literature as *dermoids of the parovarium,*[4] the round ligament[5] or the *Fallopian tubes.*[6]

The *incidence* of para-ovarian teratoids is certainly very low but cases have been described in children[7] as well as in senile women.[8] In one case, an extraperitoneal intraligamentous dermoid cyst was discovered in a pregnant woman.[9]

As regards the *prognosis, clinical course and therapy* of these neoplasms, the statements made concerning the corresponding ovarian growths are generally applicable.

In one curious instance an apparently teratoid tumor was found in the vicinity of the ovary in a pseudohermaphroditic individual, but unfortunately the growth was only incompletely described so that its exact nature cannot be determined.[10]

[1]*Rendu* A76378/896, A91456/897, *de Quervain* A74210/898, *Bertholet* A91446/898, *Mauclaire* A91454/898, *Switalski* A91457/899, *Latteux* A51002/899, A91459/899, *Dünnwald* A73518/01, *Gottschalk* A91450/01, *Meyer* A91455/02, *Coen* A73435/03, *Goffe* A73685/04, *Potherat* A76329/05, *Jaboulay* A73832/06, *Vellemin* A91458/09, *Aimes and Puech* A68556/21-2, Colombet A91508/27, Gucci A91558/36.
[2]*Kampschulte* B11680/22, *Perkins* B20946/24.
[3]*Strong* B11830/18.
[4]*Clay* A83051/879, *Czyzewicz* A73462/07, *Muller* B8240/28, *Matthieu* B12177/30, *Nordlander* B21783/41.
[5]*Kamann* A73860/04.
[6]*Orthmann* B13054/04, *Ronsisvalle* B12303/29.
[7]*Marshall* A91453/899, *McKay* A76043/899.
[8]*Lunn* A91452/01.
[9]*Kreutzmann* A82728/14.
[10]*Tschirdewahn* B8559/20.

OVARIAN TERATOIDS IN ANIMALS

Some of the celomic teratoids which occur in the *fowl* may be of ovarian origin. It is amusing to note that the ovarian equivalent of a dermoid contains feathers instead of hair.[1]

In an old *dog* a malignant ovarian teratoma[2] and in a pregnant bitch a complex dysembryoma[3] have been described.

A spontaneous teratoma has been observed in the ovary of a pregnant guinea pig.[4]

In the *horse* typical dermoids and teratomas of the ovary have repeatedly been seen and were found to have essentially the same structure as the corresponding tumors of women. In many instances, teeth and hair were the most prominent constituents of such cysts.[5]

In the *mouse* (C_3H) a spontaneous ovarian embryoma was successfully transplanted through 11 serial transplants; it retained its pleomorphic nature both in vivo and in tissue culture. It was interpreted as a true tumor which grows from foci of rapidly dividing embryonal cells, "throwing up some cells which mature into diverse specialized tissues and others which retain the ability to grow indefinitely". An analogy was seen between this "divided responsibility of daughter cells and polar body formation in ova".[6]

[1]*Mashar* B21717/32.
[2]*Feldman* B8138/27.
[3]*Diss and Fontaine* B8376/24.
[4]*Giordano* A95441/39.
[5]*Joest* B6551/17, *Schlegel* B6554/22, *Scott* B6543/24.
[6]*Jackson and Brues* A97553/41.

OVARIAN NERVE TUMORS

Among the apparently primary nerve tumors of the ovary the *ganglioneuromas* or *gangliocytoneuromas* are of some interest in spite of their great rarity. In one instance such a growth appeared as a small hamartoma in the ovarian hilus region and was almost entirely composed of proliferating ganglion cells, while the nerve fibers or neurofibrils were less conspicuous.[1] In another instance a much larger mass, weighing 200 gm. was found. On section, the tissue of the tumor was translucent, very vascular, of soft consistency and yellowish-pink color. Microscopic examination showed but a thin layer of ovarian tissue around the periphery, while the rest of the organ was replaced by the tumor. The stroma of the latter was very loose and edematous. The cells varied in size and shape, but the most common type was a large multipolar cell whose cytoplasm contained fine basophilic granules. The nucleus was large, round or oval, and contained a prominent, densely staining nucleolous. The processes of the typical cells extended far into the stroma. Thus the cellular elements of the growth strikingly resembled typical ganglion cells. A large portion of them was multinucleated and the presence of numerous plasma cells and mature polymorphonuclear cells in the stroma was also conspicuous. Following preparatory X-ray treatment, the growth was removed and recovery was uneventful.[2]

The relationship between these tumors, the sympathicotropic cells and the paraganglionic tissue of the ovarian hilus has not been completely clarified as yet. Rather similar neoplasms have been described as *paragangliomas* or *paraganglioneuromas* of the ovary.[3]

Ovarian *neurofibromas* are likewise very rare and generally associated with v. Recklinghausen's disease of which they merely represent an ovarian manifestation.[4] In one case, a neurogenic sarcoma developed in the ovary of a woman suffering from v. Recklinghausen's disease. Probably this sarcoma arose from an originally benign neurofibroma which appears to have developed within the wall of an ovarian papillary cystadenoma in this patient.[5] One tumor described as "névraxo-épithéliome de l'ovaire"[6] is also noteworthy in this connection.

Metastatic nerve tissue tumors of the ovary may also occur. Thus in the case of a retinal glioma which caused generalized metastases, one tumor deposit was found in the ovary.[7] In another instance a "metastatic glioma (neuro-epithelioma)" of the ovary was found in a child aged 3. Here again the primary tumor appears to have been in the eye and multiple metastases were observed in various other organs as well.[8]

In a patient with a neuroblastoma sympathicum of the adrenal, both ovaries contained metastases which exhibited the structure characteristic of the primary tumor.[9]

[1]*Meyer* A65111/31, A71382/43.
[2]*Schmeisser and Anderson* A97156/38.
[3]*Joachimovits* A64225/31, *Moulonguet* A64805/32.
[4]*Smith* A65179/31, *Meyer* A71382/43.
[5]*Stewart and Copeland* B99/31.
[6]*Gosset and Masson* A77943/13.
[7]*Heymann and Fiedler* A77944/869.
[8]*Lockyer* A77945/16-7.
[9]*Barnewitz* 39125/21-2.

PARA-OVARIAN NERVE TUMORS

A *para-ovarian ganglioneuroma*[1] and a *neurinoma of the broad ligament*[2] have also been described.

[1]*Stoeckel* A91574/23.
[2]*Zagarese* A91578/33.

FIBROMAS

SYNONYMS: Keloid of ovary, ovarian fibroid.

REVIEWS

DUTCH: Nijhoff A70185/899.

ENGLISH: Peterson A69419/02, A69420/03, *Briggs and Walker* A65853/08, *Lockyer* A70121/18, *Sutton* A65825/22, *Hoon* A70052/23, *Geist* A70004/24, *McIlrath* A96510/37, *Bomze and Kirshbaum* A34639/40, *Brody* A56304/42.

FRENCH: Koberle A70087/878, *Amon* A65792/881, *Castelnau* A65898/890, *Lallemand* A70097/896, *Dartigues* A65928/899, A65927/899, *Cascheau* A70001/03, *Meriel* A66913/10, *Cabanes* A65886/14, *Martinaud* A70155/31.

GERMAN: Orthmann A96831/899, *Geibel* A70002/02, *Kromer* A70091/08, *Adler* A66898/15, *Efler* A65961/16, *Hamsa* A70034/21, *Bickenbach* A97533/41, *v. Lam* A96866/42.

ITALIAN: Massazza A66912/24, *Picciolo* A65173/30.

POLISH: Klein A70084/29.

PORTUGUESE: Souza Rudge et al. A97827/42.

RUSSIAN: Tikinads A70418/11.

SPANISH: Gandolfo Herrera A97277/39, *Pisano Blanco* A98130/41, *Avaro* A98140/42, *Bassan and Caccia* B10131/43.

SWEDISH: Alin A65786/10, *Forssner* A65987/10.

DEFINITION

Fibromas of the ovary are benign neoplasms of the ovarian connective tissue. They may be diffuse and affect the entire ovarian stroma or circumscribed and limited to one part of the gonad. Histologically, the pure fibromas consist of connective tissue cells only; there is, however, a gradual transition between these neoplasms and the pure leiomyomas of the ovary which consist of smooth muscle cells. Because of the many intermediate types, it is impossible to demarcate sharply fibromas from leiomyomas. In agreement with common usage, the pure fibromas and the so-called "myo-fibromas" will be discussed conjointly in this section since they consist exclusively, or at least predominantly, of neoplastic connective tissue.

Additional borderline cases will be found in the section on leiomyomas which also includes the "fibromyomas". The latter are tumors consisting of both connective tissue and smooth muscle cells with the latter prevailing.

HISTORY

Fibromas of the ovary have been known to gynecologists for a very long time as indicated by the numerous relevant case reports in the old literature[1]

It is difficult to identify many of these cases with certainty, since histologic examination was often superficial, and sometimes completely omitted. In many cases apparently pertinent neoplasms were merely described as "fibrous tumors of the ovary" and their separation from other solid growths, especially Krukenberg tumors, thecomas, sarcomas and microcystic fibroadenomas is necessarily based on debatable evidence. There is no doubt, however, that the ovarian fibroma was known to physicians as early as the middle of the 19th century.

The publications cited in the clinical section of this review indicate that the simultaneous occurrence of ovarian fibromas and ascites was also often mentioned in the old literature. More recently Owen[2] and Hoon[3] independently mentioned the presence of hydrothorax, as well as ascites, in patients with ovarian fibromas. They noticed, furthermore, that the water accumulations disappear after ablation of the ovarian neoplasms. It was undoubtedly to the merit of Meigs and Cass[4] to have called attention to the clinical significance of the association between ovarian fibromas and transudates in the large body cavities. The syndrome was subsequently studied in great detail[5] and is now generally known as "Meigs' syndrome".

CLASSIFICATION

According to their histologic structure the ovarian fibromas may be subdivided into pure *fibromas* and *myofibromas*. As outlined above, the transition between these groups is very gradual and hence their sharp demarcation is impossible.

Another possible basis for a classification is the purely anatomic development of the neoplasms. In this sense it is customary to distinguish between *diffuse* fibromas which are comparatively rare[6] and the more common *circumscribed* fibromas[7]. The former appear to affect the entire ovarian stroma more or less uniformly, while the latter are limited to a specific area. The circumscribed fibromas may, in turn, be subdivided into those having no capsule, those which have a capsule but remain embedded in the ovary, and those which are attached to the gonad by a distinct pedicle.[8]

[1]*Herrmann* A80315/799-800, *Haase* A70032/839, *Baron* A69741/842, *Lee* A70107/848, *Leudet* A70114/851, *Kiwisch* A70081/852, *Dufour* A65958/852, *Ashwell* A65796/853, *Cruveilhier* A65918/856, *Wilks* A70445/857-8, *Wells* A69761/858-9, *Rokitansky* A70247/861, *Forster* A65983/863, *Klob* A70086/864, *Scanzoni* A70261/867, *Lücke and Klebs* A70130/867, *Gripat* A70025/870, *Lecourtois* A70105/870, *Waldeyer* A70435/871, *Roberts* A70240/872, A70242/05, *Fioupe* A65974/873, *Tait* A70402/873-4, *Goodhart* A70020/873-4, *Ziembicki* A70453/874, *Leopold* A70111/874, *Grenser* A70024/875, *Walsham* A70436/875-6, *Klebs* A70082/876, *Crisp* A65915/876-7.

[2]A70198/23.

[3]A70052/23.

[4]A74976/37.

[5]*Meigs* A96565/40.

[6]*Barbosa* A65174/31.

[7]*Miller* A18279/37.

[8]*Miller* A18279/37.

In some instances, small surface fibromas may be covered by papillary excrescences and thus assume the shape of the so-called "*superficial papillary fibroma*".[1] It is rather improbable that all of these structures are true neoplasms and at least some of them should perhaps be interpreted as irregular accessory ovaries incompletely separated from the main gonad.[2] In this connection it is noteworthy that true fibromas have also been observed in completely separate accessory ovaries.[3]

The so-called "*fibromas of the corpus luteum*", frequently mentioned in the old literature,[4] have never been observed in recent years and their very existence is rather doubtful.

PATHOLOGIC ANATOMY

MACROSCOPIC CHARACTERISTICS: The *size* reached by these neoplasms, at the time of observation, is variable. Some typical fibromas measure only a few millimeters in diameter and represent small nodules attached to the ovarian surface by an almost microscopic pedicle.[5] In other instances the tumors become very large and may weigh several pounds.[6] The weight of some ovarian fibromas ranged from 20-30 lbs.[7] or even 30-40 lbs.[8] Still larger fibromas are rarely encountered nowadays since surgical treatment is sought before the neoplasm reaches such an enormous size. In the old literature, however, we find instances of fibromas weighing 46 lbs.,[9] 56 lbs.[10] or even more than 60 lbs.[11] Undoubtedly the largest fibroma on record was one, erroneously described as a "solid hard medullary sarcoma",[12] which weighed 80 lbs.; since it persisted for 10 years it could hardly have been a sarcoma.

The *shape* of ovarian fibromas—though extremely variable—is usually round, oval, pear- or kidney-shaped[13]. In exceptional instances their surface may be highly convoluted and reminiscent of a cerebral cortex.[14] The small, so-called "diffuse fibromas" tend to imitate the normal shape of the ovary, but this is only exceptionally true of large fibromas.[15]

The *consistency* of these neoplasms is usually hard, sometimes cartilage-like, and the frequent occurrence of calcification within fibromas may even give them an almost wood-like texture.[16]

The *color* of typical ovarian fibromas is shiny white on the surface, somewhat reminiscent of the white matter of the brain, Occasionally, they have a more greyish, yellowish or reddish tinge, but bright yellow fibromas which, upon histologic examination prove to contain many fat granules, should always be suspected of being thecomas. A reddish tinge is occasionally due to the presence of comparatively numerous or large blood vessels in this usually not very well vascularized neoplasm. Bright red spots are only seen in the case of hemorrhagic infarction. On the cut surface, the pure fibromas are white, thus differing from the pure myomas which have a distinctly red tinge.[13]

The *position* of small fibromas is likewise variable, but they are usually found in the pelvis where they do not displace the ovary. As their size increases they either become impacted in the pelvis or have to shift craniad in the abdominal cavity. In this respect they do not differ significantly from other ovarian tumors.[13] Since fibromas usually possess a well developed pedicle, intraligamentous development is rare.[17] The descent of a fibromatous ovary into an inguinal hernia pocket[18] is certainly exceptional.

The so-called *cystic fibromas* result from secondary degenerative changes within the neoplastic tissue, with eventual liquefaction necrosis of certain areas. Some purportedly relevant cases appear to have been cystic fibroadenomas in which the lining epithelium had undergone severe degenerative changes so that it became indistinguishable. In other cases, there may be some doubt concerning the benign nature of the tumor. Secondary cyst formation is undoubtedly quite common, however, especially in the large fibromas in which nutritional disturbances are likely to arise.[19]

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[1] *Pfannenstiel* A80267/05, *Kromer* A70091/08.
[2] *Beigel* A74212/877, *Miller* A18279/37.
[3] *Latzko* A70101/16.
[4] *Klob* A70086/864, *Jenks* A70065/873, *Rokitansky* A70247/861.
[5] *Dienst* A65945/05, *Neumann* 42643/25.
[6] *Cailliot* A65887/824, *Nunn* A70188/856-7, *Spiegelberg* A70287/866, *Ingham* A70057/873, *Mundé* A45102/889, *Andrews* A44162/892, A46319/892, *Bailey* A74644/896, *Ikeda and Oshima* A74656/02, *Stone* A69429/03, *Mauclaire* A70162/04, *Doran* A65952/05, *Hannes* A70036/08, *Fordyce* A65984/08-9, A65985/09-10, *Ferguson* A65972/09-10, *Friedman* A65992/11, *Briggs* A65851/11, *Levi* A66910/12, *Gminder* A70016/13, *Le Filliatre* A70108/13, *Calmann* A65888/17, *Fleischer* A65979/22, *Martini* A70156/25, *Grynfeltt* A70026/27, *Guillemin* A70029/29, *Pessano* A64442/30.
[7] *Homans* A40865/885, *Mauclaire* A83459/03, *Darling* A65926/04, A65925/04, *Le Moniet* A66908/12.
[8] *Nagel* A70183/06, *Titus* A70419/13, *Caro* A65892/14.
[9] *Cruveilhier* A65918/856.
[10] *Ashwell* A65796/853, *Cailliot* A65887/824.
[11] *Spiegelberg* A70287/866.
[12] *Clemens* A65903/873.
[13] *Miller* A18279/37.
[14] *Basso* A65810/05.
[15] *Geibel* A70002/02, *Merttens* A70170/03, *Miller* A18279/37.
[16] *Massazza* A66912/24.
[17] *de Boucaud* A65835/00, *Graham* A70023/03, *Cuff* A65919/06, *Kromer* A70091/08, *Derbaremdiker-Zarchi* A65942/10, *Backofen* A65801/13, *Calmann* A65888/17, *Bruns* A65858/24, *Papin* A70199/25, *Holtermann* A70051/32.
[18] *Amon* A65792/881.
[19] *Wells* A70440/865-6, *Cayley* A68398/869-70, *Stiegele* A82063/872, *Carter* A68395/872-3, *Dave* A65930/874, *Wylie* A40207/883, *Emmet* A65962/885, *Cohn* A65909/885, *Mendes de Leon* A42454/888, *Byford* A65863/889, *Péraire* A70210/890, *Goelet* A70017/891, *Boldt* A65828/892, A65831/16, *Bock* A44739/894, *Norris* A70187/896, *Glockner* A83040/04, *Briggs* A65849/05, *Heil* A70043/06, A70044/07, *Bell* A65815/08, *Haultain* A70040/08-9, *Kynoch* A70093/10-1, *Giles* A70012/12-3, *Aubert* A65799/13-4, A66899/15, *Schmincke* A70267/14, *Orthmann* A70197/15, *Darnall* B21198/21, *Cotte* A66900/23, *Cotte and Policard* A65913/23, *Croft* A65916/25.

Bilateral development of ovarian fibromas is not infrequent.[1] The incidence of bilateral development is variously estimated as corresponding to 10-25%,[2] 20%[3] or 5%[4] of all ovarian fibromas.

Numerous *case reports* describe the characteristics of the various fibromas and myofibromas of the ovary. Although some tumors diagnosed as fibromas may have been Krukenberg tumors, thecomas, or even sarcomas, it is evident from the large number of relevant observations that the ovarian fibroma is by no means as rare as has often been claimed.[5]

MICROSCOPIC CHARACTERISTICS: The histologic structure of ovarian fibromas is rather similar to that of the fibromas seen in other organs. In typical cases, the neoplasm resembles the cellular stroma of the normal ovary. Its cells contain spindle-shaped nuclei which appear to lie freely between the connective tissue *fibrils*. *Cytoplasm* is generally not

[1]*Lee* A70107/848, *Marshall* A70148/871, *de Boyer* A65841/873, *Cullingworth* A29479/879-80, *Amon* A65792/881, *v. Winckel* A70448/881, A70449/890, *Polk* A69753/885, A69752/885, A70222/885, *Baudouin* A65812/888, *Orthmann* A70193/888, *Terrier* A42410/888, *Williams* A46484/893, *Bantock* A65806/894-5, *Amann* A65787/00, *Gemmell* A70009/02, *Bauby* A74645/02, *Bovée* A65837/02, *Dobratvorsky* A75304/03, *Bender and Heitz* A65817/03, *Pinzani* A69421/05, A70219/05, *Penkert* A70209/07, *Maiss* A70141/08, *Bushnell and Kerrawalla* A65860/08, *Haultain* A70041/09-10, *Robertson* A70243/12, *Meigs* A70164/22, *Laurentie* A70102/24, *Geist* A70004/24, *Bride* A65844/26, A65845/26, *Ivens* A70058/27, *Vachey* A70424/28, *de Mora* A79507/31, *Haumeder* A34822/40, *Borg* A55873/41.

[2]*Krömer* A70091/08, [3]*Geist* A70004/24, [4]*Miller* A18279/37.

[5]*Patenko* A70202/880, A70203/881, *Oettinger and Tissier* A70189/881, *Lecoq* A70104/881, *Thomas* A40349/881, A70415/896, *Goodell* A40075/882, A74654/882, *Coe* A40588/882, *Carter* A41199/883, A65895/887, *Williams* A41228/883, *Ruge* A70257/884, *Martin* A70149/884, A70150/894-5, A70153/02, *Sims* A41660/886, *Dagron* A65922/887, *Rueder* A45084/888, *Doran* A65947/888, A48995/896, A65950/897, A65951/02, A65953/23, *Landau* A70098/888, *Lanelongue* A42485/888, *Montgomery* A70177/888, *Griffith* A45121/889, *Gibbes* A43632/890, A43531/890, *Bagot* A65802/890, *Winckel* A70449/890, *Cushing* A43602/890-1, *Wylie* A70451/891, *Baudrimont* A74667/891, *Lihotzky* A70116/891, A70118/00, *Rutherford* A70258/892, *Bantock* A46320/892-3, *Delegrange* A44610/893, A46389/893, A74647/893, *Yoshida* A69434/893, *Dubar* A46360/893, *Hees* A70042/893, *Jacobs* A70059/893, *Schonheimer* A70268/894, *Bourgoin* A47126/894, *Chambers* A65901/894, *Horrocks* A70053/894, *Stratz* A70395/894, A70396/03, *Feis* A44656/894, *Postempski* A44853/894, *Rogée* A47086/894, *Lohlein* A70125/894, *Sanger* A70259/895, *Grafe* A47115/895, *Crawford* A47445/895, *Kynoch* A70092/895, *Rendu* A70236/895, *Michael* A70174/895, *Braun* A65842/895, *Zumbusch* A70454/896, *Malcolm* A70143/896, *Purslow* A70228/896, A49008/897, *Morely* A50901/896, *Hall* A70033/896, *Borreman* A48336b/896, *Macnaughton-Jones* A70135/896-7, A70136/05-6, *Schauta* A70265/897, *Pozzi* A70225/897, *Kessler* A70079/897, *Fletcher* A65982/897-8, *Harris* A70037/897, *Tofuji and Imisho* A69430/897, *Gaiser* A65998/897, *Strübe* A70397/898, *Chamayou and Gally* A47971/898, *Cullingworth* A50529/898, *Solé* A69427/899, *Orthmann* A64820/899, *Nagai and Kurimoto* A69417/899, *Testé* A70413/00, *Piering* A70218/00, *Menge* A70167/00, *Fleischmann* A65980/00, *Shober* A70274/00, *Weir* A70439/00, *Brothers* A65856/00, A65857/04, *Laidley* A70095/00, A74660/01, *Ikeda and Oshima* A74657/00-1, *Gemmell* A70008/01, *Bissell* A65822/01, A65823/03, *Obizvestvlennaya* A80316/01, *Routier* A70251/01, *Degorce* A65933/01, *Lauwers* A74662/00-1, *Sendtner* A70272/01, *Limnell* A70119/01, *Andrews* A65793/01, *Potherat* A69422/02, *Kotschau* A70089/02, *Fairbairn* A65967/02, A65968/02, *Giles* A70011/02, *Demons* A65939/02, *Sticher* A70391/02, *Shober* A70275/02, *Peterson* A70212/02, *Maiss* A70138/02, *Hunner* A70054/02, *White* A70443/02, *Boyd* A65838/03, *Flaischlen* A65976/03, A65977/28, *Kablukow* A70070/03, A70071/04, *Royster* A69426/03, A70255/03, *Walter* A70437/03, A70438/04, *Graham* A70023/03, *Graves* A74655/03, *Merttens* A70170/03, *MacLean* A70133/03, *Stone* A70393/03, *Sturmer* A70398/03, *Tchakmakoff* A70409/03, *Begouin* A65814/04, *Taylor* A70407/04, *Le Fort* A70109/04, *Recasens* A69423/04, *Bongrand and Bernex* A65834/04, *Reichhold* A70232/04, A70233/04, *Vignard* A69433/04, *Goffe* A70018/04, *McGuire* A69415/04-5, *Zaborsky* A70452/04, *Glockner* A70014/05, *Heinricius* A70045/05, *Puech* A70226/05, *Campbell* A65889/05, *Basso* A65810/05, *Jones* A74710/05, A74658/05-6, *Soli* A69428/06, *Routh* A70250/06, *Opitz* A70191/06, *Campbell and Lewis* A65890/06, *Rindfleisch* A70238/06, *Mallett* A70144/06, *Spencer* A70285/06, *Adler* A65784/06, *Cestan* A74646/06, *Jordan* A70067/06-7, A70068/07, *Graupner* A70022/07, *Kachel* A70072/07, *Lorrain and Chaton* A70128/07, *Westermann* A70441/08, *Bushnell and Kerrawalla* A65860/08, *Favell* A65969/08, *Baldowsky* A65804/08, *Scharlieb* A70263/08-9, *Haultain* A70040/08-9, *Vautrin and Hoche* A70427/09, *Taddei* A70401/09, A70403/09, *Mapes* A70147/09, *Teissonière* A70410/09, *Sloan* A66917/09, *Wiener* A70444/10, *Leckie* A70103/10, *Westermark* A70442/10, *Jeannel and Dambrin* B11219/10, *Derbaremdiker-Zarchi* A65942/10, *Boldt* A65830/10, A65832/16, *Mériel* A70169/10, *M'Lellan* A70134/11, *Demons and Charbonnel* A65940/12, *Keil* A70075/12, *Mandl* A70145/12, *Backofen* A65801/13, *Fullerton* A65995/14, *Johnson* A66906/15, *Gustafsson* A70031/15, *Deutsch* A65943/15, *Hellmann* A70046/15, *Metzger and de Kervily* A70172/15, *Douglas* A65956/16, *Reel* A70231/17, *Pedrazzini* A70208/18, *Fleming* A65981/19, *Richardson* A70237/19-20, *Becker* A65813/20, *Delmas and Cohen* A66902/20, *Bussa-Lay* A65862/20, *Vautrin* A70426/21, *Clark and Gabe* A65902/21, *Jacquin* A70061/21, *Mauthner* A70163/21, *Ashhurst and Walkling* A65795/21, *Lory* A66909/22, *Meigs* A70164/22, *Rouve* A70253/22, *Davidson* A65931/22, *Solomons* A70283/22, *Lediard* A70106/23, *Hoon* A70052/23, *Owen* A70198/23, *Smythe* A70280/23, *Dennis* A65941/23, *Cassidy* A65897/23, *Vila* A70431/24, *Fordyce* A65986/24-5, *Dartiques and Gresset* A66901/25, *Searight* B16086/25, *Lait* A70096/26, *Patti* A70205/26, *Bride* A65845/26, A65844/26, *Francesco* B8049/26, *Kleemann* A70083/26, *Delfourd and Lucien* A65934/26, *Mathias* A70161/26, *Infantozzi* B20717/26, *Bermann* A65818/27, A65819/27, A65820/28, *Eriksen* A65964/27, *Moretti and Arrigoni* A70180/27, *Laffont et al.* A70094/27, *D'Erchia* A65963/28, *Stacey* A70388/28, *de Rouville et al* A70254/28, *Clement* A65904/29, *Delmas* A65938/29, *Geisler* A70003/29, *Herbst* A68228/29, *Levit* A65556/29, *Capecchi* B6006/29, *Kraul* A70090/29, *Mestitz* A70171/29, *Piccioli* A70217/30, *Martzloff* A65616/30, *Molin and Sassard* A70176/31, *Ducuing and Rieunaud* A65957/31, *Clare* A65146/31, *Palacios Costa and Falsia* A65912/31, A66170/32, *Rodrigues Barbosa* A65174/31, *Gabrielianz* A65997/32, *Koenig* A70088/32, *Alsobrook* A61741/33, *Soto Longoria* A61808/33, *Pereira* A53104/33, *Duncan* A61925/33, *Marshall and Swanton* A52272/34, *Paucot and Tison* A70207/34, *Likes* A53177/34, *Cannon* A65891/35, *Mascia* A61848/35, *Arenas* A59921/36, *Castagna* A59924/36, *Coletti* A59915/36, *Aguilar Pavez* A95276/36, *Stadiem* A95326/37, *Peltier de Queiroz* A95090/37, *Curran et al.* A97141/38, *Nobre* A97299/39, *Freire* A97367/39, *Ramirez and Telleria* A97585/39, *Palacios Costa and Pastorini* A95449/39, *Bellomo* A97574/39, *Cabrera and Pardo* A96597/40, *Avaro* A96593/40, *Cue and Romanos* A97538/41, A97537/41, *Romero et al.* A97519/41, *Scipiades* A39518/42, *Pividori* A97820/42, *Urrutia and Longo* A97831/42.

detectable around the nucleus, even if the section is examined under oil immersion.[1] The fibrils and nuclei are often arranged in parallel bundles, which form an interlacing but solidly woven connective tissue network. *Elastic fibers* are also plentiful in some ovarian fibromas,[2] but this is not commonly the case.

The *nuclei* are quite variable in their shape and although they generally assume a rod-like or spindle-like appearance, they may be curved, pear-shaped, indented, or more or less irregularly branched. Mitotic figures, however, are rarely seen in ovarian fibromas.[3] The density and multiformity of the nuclei in certain fibromas led to the description of the "fibroma ovarii multicellulare" as a special neoplasm.[4]

The common occurrence of *smooth muscle cells* within ovarian fibromas has been mentioned previously. These may originate from the media of ovarian vessels, the muscle cells normally found at the attachment of the ligamentum ovarii proprium or from those cells present in the ovarian hilus.[5]

The differentiation of fibromas from myomas is sometimes difficult on the basis of purely morphologic criteria and hence in doubtful instances special stains, such as van Gieson's picric acid-acid fuchsin mixture, should always be used to check the diagnosis.

In some fibromas, the arrangement of the neoplastic cells around the blood vessels assumes a "*perithelioma-like*" aspect.[6]

Occasionally fibromas appear to be permeated by *epithelioid cells* which bear some resemblance to infiltrating carcinoma cells but are sometimes interpreted as equivalents of ovarian *Leydig* cells.[7] Such cases suggest a possible close relationship between the endocrinologically "silent" fibromas and the hormone-producing lipid-cell tumors of the ovary.

In this connection, the so-called *lipid-storing fibroma* deserves special attention. Certain fibromas are conspicuous because of the bright yellow color of their cut surface and the presence of histologically detectable lipid granules both within and between their cells. This tumor type is frequently regarded as a mere subgroup of the common ovarian fibromas, the lipid granules being interpreted as due to fatty degeneration.[8] In many of these cases, however, the condition of the endo- and myometrium, as well as other clinical minifestations, clearly indicate an excessive folliculoid hormone production. Perusal of relevant case reports fails to show any feature which would allow us to separate these "lipid-storing fibromas" from the thecomas described in the chapter on Folliculomas. Common fibromas do not contain significant amounts of tingible fat granules.[9]

Perhaps the most important practical point in connection with the histology of the ovarian fibromas is their *differentiation from fibroblastic sarcomas*. In the fibromas, the nuclei are often closely packed and hence the neoplasm may be very "cellular", yet, this should not lead to the diagnosis of sarcoma. Although the nuclei may be densely packed and polymorph they are more regular than in the fibrosarcomas. The absence of orderly strands of fibrils is characteristic of sarcomas, but the presence of such strands does not necessarily eliminate the possibility of malignancy. Perhaps one of the most characteristic features of the sarcomas is the presence in them of mitotic figures in comparatively large numbers. As stated above, these are almost invariably absent in fibromas. The density and distribution of the chromatin granules within the nuclei and the size of the nuclei, is extremely variable in the sarcomas and much more uniform in the fibromas.[1]

SECONDARY CHANGES IN TUMOR AND REMAINING OVARIAN TISSUE: Adhesions are estimated to occur in about one-third of all the ovarian fibromas but are generally not very extensive.[10]

Among the secondary changes which may occur in older fibromas *edema* is particularly common especially in the central portions of the neoplasms.[11] If this process progresses further, small cysts may develop within the fibroma and many of the so-called cystic fibromas (quoted above) may originate through this mechanism.

Interstitial edema is often difficult to differentiate from *lymphangiectases* which may also occur in these neoplasms, giving rise to the so-called "fibroma lymphangiectaticum".[12] The presence of a definite endothelial lining, if detectable around the fluid deposits is, of course, a good indication of their vascular nature.

The formation of *mucoid connective tissue* within the fibromas leads to the development of the so-called "fibroma myxomatosum" or "myxoma" of the ovary. It is readily recognizable by the positive mucicarmin reaction of the interstitial substance.

[1]*Miller* A18279/37.
[2]*Gusserow* A70030/892.
[3]*Miller* A18279/37, *Brody* A56304/42.
[4]*Schwarz* A70270/899, A70269/899.
[5]*Kromer* A70091/08, *Miller* A18279/37.
[6]*Castro* A62061/35.
[7]*Lordy* A65615/29, A63400/29, *Fleming* A65541/29.
[8]*Kellert* A70077/34, *Miller* A18279/37.
[9]*Brody* A56304/42.
[10]*Fuster* A65996/13, *Stübler and Brandess* A76588/24, *Miller* A18279/37.
[11]*Pichevin* A49131/897, *Orthmann* A70196/899, *Pestalozza* A69418/02, *Briggs* A65850/08, *Frankl* A65990/29, *Hellman* A70046/15, *de Mora* A79507/31.
[12]*Orthmann* A96831/899.

Several supposedly relevant cases may be found in the literature.[1] Unfortunately in many instances, special stains were not used and a diagnosis was made merely on the basis of the macroscopic aspect of the tumor and its appearance on histologic slides stained with the common dyes. The tendency of ovarian fibromas to undergo mucoid transformation suggests that perhaps even in Krukenberg tumors this change is not entirely dependent upon the potentialities of the invading primary carcinoma cells, but may depend, at least partly, upon the ovarian stroma itself.

In connection with these "myxomas" which appear to result from mucoid degeneration of ovarian connective tissue, the so-called "pseudomyxoma ovarii", which is sometimes also designated as an ovarian myxoma, comes to mind (see chapter on Common Cysts). In this latter neoplasm, the secretion of a pseudomucinous cyst appears to invade the stroma, but transitional types have been noted in which most of the mucoid material appears to originate in the stroma, some adenoid formations with pseudomucinous epithelium also being detectable.[2] The myxosarcomas are treated in a separate chapter.

Hyalinization is frequently seen in certain portions of fibromas and is usually accompanied by disappearance of the nuclei in the affected region.[3] This change is of no clinical significance and probably merely represents a process of ageing within the neoplasm.

The most severe retrogressive change which may occur in fibromas is, of course, actual *necrosis*.[4] The necrosis may be limited—usually to the central portions—or it may comprise the entire neoplasm. In some cases the liquefaction necrosis is conducive to the formation of cysts within the fibroma. In other cases, secondary infection and *suppuration* occur.[5] There is a gradual transition between these latter instances and the more diffuse inflammation of the fibroma tissue which has been described under the name of "fibromitis".[6]

Hemorrhagic infarction and especially massive *hemorrhages* are rarely seen in fibromas since these neoplasms are comparatively poor in blood vessels.[7]

Calcification and ossification is a very frequent degenerative change in fibromas (see Sect. IV, Vol. VI) and is of some clinical importance, especially in connection with their diagnosis by X-rays.

It must be kept in mind, however, that fibromas may secondarily undergo "sarcomatous degeneration", a process which may occur simultaneously in different parts of the neoplasm.[8] In a series of 280 fibromas obtained by operation this sarcomatous change was noted in about 1.5%[9] and instances of malignant transformation have been reported frequently in the literature.[10]

The *ovarian remnant* usually represents a small appendage on one pole of the much larger fibroma. Fibromas which originate in the center of the ovary tend to destroy the gonadal tissue by distension. Histologically, sclerotic or mild chronic inflammatory changes are sometimes detectable in the gonadal rest.[8] It may also be affected by endometriosis.[11]

The *stalk* of ovarian fibromas is usually well defined but its length is subject to great variation. Sometimes, of course, there is no stalk because the fibroma is directly attached to the ovary or develops more or less diffusely within its substance. In other instances, however, the stalk may be several inches long.[12] In one case it was so long that the fibroma itself lay in the lumbar region at a great distance from the ovary and was diagnosed as a floating kidney.[13] Occasionally, the fallopian tube and the mesosalpinx participate in the stalk formation.[14]

The *contralateral ovary* shows no constant changes and in most cases is unaffected by the unilateral ovarian fibroma.[8] Occasionally, however, as we shall see later, it is the site of another neoplasm.

OVARIAN FIBROMAS IN COMBINATION WITH OTHER OVARIAN TUMORS: Simultaneously with an ovarian fibroma there may be found a *sarcoma*[9] but in such cases it is difficult, of course, to differentiate between simultaneous occurrence of fibroma and sarcoma or malignant transformation of a fibroma (a phenomenon described in a previous paragraph).

The simultaneous occurrence of an ovarian fibroma and neoplasms of the *ovarian ligaments* has also been reported. In these instances the extraovarian growth

[1] *Galabin* A70512/878, *Thomas* A70416/879, *Slavjansky* A40509/881-2, *Popoff* A40293/881-2, *Martin* A70517/884, *Buzzi* A70509/885, *Netzel* A74591/886, *Doléris* A70510/888, A43336/889, *Petit* A70213/888, *Kickhefel* A70514/892, *Sabbe* A50555/898, *Potherat and Lenoble* A74592/898, A47982/898, *Jones* A74589/899, *Orthmann* A70196/899, *Kotschau* A70515/02, *Hennig* A70513/02, *Cordaro* A74587/03, *Basso* A65810/05, *Briggs* A65850/08, *Tate* A70406/09-10, Morosowski A70518/12, *Nagel* A70520/12, A70519/12, *Flaischlen* A70511/12, *Kornfeld* A70516/15, *Micotte* A68477/22, *Pastiels* A52291/34, *Anagnostidis* A59871/36.

[2] *Hjelt* A69748/870, *Martin* A70517/884, *Buzzi* A70509/885, *Kotschau* A70515/02.

[3] *Kromer* A70091/08, *Laidley* A70095/00, *Spencer* A70963/23.

[4] *Lihotzky* A70117/892, *Macnaughten-Jones* A70137/11-2, *Amann* A65791/15, *Massazza* A66912/24, *Bardon and Darrasse* A65809/28.

[5] *Dannien* A65924/878.

[6] *Guelliot* A70027/06.

[7] *Paramore* 70200/01, *FitzGibbon* A65975/25.

[8] *Miller* A18279/37.

[9] *Caylor* A65899/25.

[10] *Bourgoin* A47126/894, *Freund* A65991/899, *Geibel* A70002/02, *Alexandrov* A77344/03, *Gemmell* A77511/06, *Beuzart* A77387/07, *Bushnell and Kerrawalla* A65860/08, *Jayle* A77572/08, *Vautrin and Hoche* A70427/09, *Flatau* A65978/10, *Hartz* A70039/12, *Martin* A70152/14, *Büchler* A77413/19, *Rohdenbourg* A76407/26, *Caylor* A68163/29, *Caylor and Masson* A65604/30, *Mahfouz Bey* A64189/31, *Johnson and Wills* A53169/34.

[11] *Tasch* A96643/40.

[12] *Goodell* A43461/890, *Miller* A18279/37, *Tronci* A97317/39.

[13] *Brothers* A65857/04.

[14] *Veit* A70428/876, *Massabuau* A70158/07.

may also be a *fibroma* or *fibromyoma*,[1] a *parovarian cyst*[2] or a *lipoma* of the broad ligament.[3]

INCIDENCE

The ovarian fibromas are often claimed to be extremely rare neoplasms.[4] A review of 19 statistical surveys, covering a total of 13,473 ovarian tumors, revealed 392 cases of fibromas; that is, an average *general incidence* of 2.9%. The incidence in the different series varied between 0.6% and 12.6%. This great variation may be due, at least partly, to the fact that myofibromas were included only by some of the authors. As examples of the incidence in a few large series the following figures may be mentioned: 1.3%,[5] 2%,[6] 3.5%[7] or 7.6%[8] of all ovarian tumors. In one series in which the fibroma incidence was expressed as a percentage of the benign group, it was found to be 9.9%.[8] These figures clearly indicate that the fibromas are by no means exceptional ovarian neoplasms.

The *age incidence* of ovarian fibromas in a series of 429 cases selected from the literature was as follows: 0-15 years 1; 16-20 years 16; 21-25 years 42; 26-30 years 54; 31-35 years 36; 36-40 years 54; 41-45 years 37; 46-50 years 55; 51-55 years 38; 56-60 years 38; 61-65 years 33; 66-70 years 12; 71-75 years 9; 76-80 years 2; 81-85 years 1 and 86-90 years 1 case.[9] It has been stated "that very young women were subject to ovarian fibroma and not to uterine myoma, whilst women over thirty were subject to uterine myoma and not to ovarian fibroma".[10] Others believe, however, that the ovarian fibromas have a special tendency to develop in older women.[11] A marked predisposition of any particular age group is not evident from the above mentioned large statistical series and Geist[12] emphasizes that fibromas have been seen between 8-83 years of age although he claims them to be most common between 40-50 years. Among 30 relevant cases observed at St. Mary's Hospital in Manchester 19 were 40-60 years old.[13]

Our own survey of the case reports mentioned earlier in this review indicates that the lack of predisposition of any particular age group is rather characteristic of the ovarian fibromas.

Additional cases in children of 13-14 years[14] and old women aged 70 years or more[15] are frequently reported in the literature.

Accurate statistical data concerning the *pregnancy incidence* of ovarian fibromas are not available, although numerous case reports show their comparative frequency during gestation.[16] There is no evidence indicating that pregnancy actually enhances the development of fibromas, but since these tumors are likely to cause complications owing to pressure of the gravid uterus and interference with delivery, it is not surprising that many relevant cases come to the physician's attention during the gestation period.

The *puerperal incidence* is comparatively low since women bearing ovarian fibromas which are sufficiently large to cause clinical manifestations, would generally seek medical advice before or at delivery. The occasional fibroma, has however, been detected during the post-partum period.[17]

Very few data are available concerning the *racial incidence* of ovarian fibromas although it is known that they occur not only in the white, but also in the negro race.[18]

PATHOGENESIS

With regard to the *histogenesis* of ovarian fibromas, there appears to be little doubt that they originate from the connective tissue stroma of the gonad.[19] In the older literature, the view was occasionally expressed that hemorrhages into the ovarian parenchyme might be of pathogenic importance or that the epithelial elements of the ovary might play some part in stimulating the neoplastic growth of the connective tissue, without actually participating in it. These theories are not based on any convincing data and it has been emphasized that fibromas can also develop in other organs in the absence of hemorrhage or epithelial elements.[9]

Concerning the *functional pathogenesis* of the ovarian fibromas very little is known. Some authors think that *hereditary* influences may be of

[1] *Briggs* A65846/896, A65847/896, *Jacobs* A70060/00.
[2] *Maiss* A70141/08, *Purslow* A70230/12-3.
[3] *Balaschoff* A65803/13.
[4] *Ashwell* A65796/853, *Pozzi* A78855/07, *Sutton* A65825/22.
[5] *Geist* A70004/24.
[6] *Bernstein* 81758/36.
[7] *Hoon* A70052/23.
[8] *Bomze and Kirshbaum* A34639/40.
[9] *Miller* A18279/37.
[10] *Doran* A65950/897.
[11] *Ravano* A76362/08, *Sutton* A65825/22, *Crile* A57535/42.
[12] A70004/24.
[13] *McIlrath* A96510/37.
[14] *Griswold* A69779/871, *Macdonald* A70132/22, *Fekete* A96845/42.
[15] *Baudouin* A65812/888, *Terrier* A42410/888, *McCann* A70131/03, *Peterson* A82391/08, *Brewis* A65843/12-3.
[16] *Rokitansky* A70247/861, *Wells* A70440/865-6, *Kleinwächter* A70085/872, *Carstens* A43364/889, *Swan* A70400/898, *Lomer* A70126/899, *Doganoff* A88142/03, *Leaueux* A70113/04, *Fehling* A65970/04, *Philipps* A70216/04, *Glockner* A70014/05, *Lepage and Mouchotte* A70112/06, *Conway* A65911/07, *Gemmell* A70010/07, *Kerr* A70078/08, *Stewart* A70390/08, *Rossier* A70249/08-9, *Spencer* A70286/08-9, *Link* A70120/10, *Souttar* A70284/12-3, *de Snoo* A70281/14, *Frankl* A76805/14, *Danforth* A65923/15, *Rongy* A70248/22, *Gamel and Bourde* A66000/22, *Faguet* A65966/24, *Martini* A70156/25, *Cetroni* A65900/30, *Pugliatti* A95315/37, *Leon and Lascano Gonzalez* A96924/43.
[17] *Bompiani* A61919/33.
[18] *Alsobrook* A61741/33, *Dickinson* A74649/01, *Smythe* A70280/23, *Brody* A56304/42.
[19] *Frankl* A76805/14, *Stübler and Brandess* A76588/24.

importance as judged by the comparative frequency with which fibromas occur in the ovaries of women exhibiting certain congenital malformations, most frequently in the urogenital system.[1]

Whether *previous pregnancies* predispose women to ovarian fibroma formation is very debatable.[2]

(Concerning the pathogenesis of the clinical manifestations see part on Clinical Course).

CLINICAL COURSE

One of the most striking clinical manifestations of ovarian fibromas is their tendency to cause *fluid retention*, especially in the large body cavities. The frequent association of even small ovarian fibromas with *ascites* has been recognized for a considerable length of time.[3] This peritoneal fluid accumulation is often accompanied by unilateral or bilateral *hydrothorax*.[4] The association of ovarian fibroma, ascites and hydrothorax is commonly described as "Meigs' syndrome".

The tendency towards water retention does not appear to be entirely limited to the large body cavities, since *edema of the subcutaneous tissue* in the region of the abdominal wall,[5] *edema of the legs*[6] and the *labia majora*[7] may also occur in such cases. The incidence of ascites is variously estimated to be 40%[8] or 50%[9] of all the ovarian fibroma cases, while hydrothorax and tissue edema are less common.

Dyspnea has frequently been noticed[10] and is usually most pronounced in cases with marked hydrothorax. Since the correlation between the degree of pleural fluid accumulation and the severity of the dyspnea is not very close, some investigators do not regard the latter as consequent upon the former.

The *pathogenesis of the fluid accumulations* has been the subject of much debate. It has long been known that they are not merely coincident with, but actually the consequence of, the ovarian fibromas, since they disappear after ablation of the neoplasms.[11] Many physicians think that local irritation by the tumor, as well as the accompanying hyperemia of the pelvic region, suffice to explain the development of ascites in these cases.[12] It has been stated that the transudate is probably formed within the fibroma itself. These tumors frequently tend to become edematous and possess engorged lymphatic vessels from which fluid could transude directly into the peritoneal cavity. Thus, one fibroma which originally weighed 3,200 gm, lost so much water after having been placed in a dry dish for 24 hours that at the end of this period its weight was only 2,050 gm.[13] The view that the peritoneal fluid originates in the tumor itself is shared by several other investigators.[14]

This interpretation fails to explain, however, the formation of pleural fluid accumulations. It has been found that the characteristics of the pleural and peritoneal fluid are identical with respect to all aspects measured, and that in patients with Meigs' syndrome carbon particles placed in the abdominal cavity pass quickly and easily into the pleural fluid.[15] It is, therefore, not impossible that the ascites develops first, and that pleural fluid accumulations occur only if and when the conditions for the transudation from the peritoneal into the pleural cavity are favorable. Yet none of these theories can explain the tendency for the formation of subcutaneous water accumulations. In an effort to interpret these, it has been postulated that the fibroma produces toxic substances or metabolites which increase edema tendency.[16] Along somewhat similar lines it has been suggested that peritoneal irritation caused by the fibroma may elicit an "alarm reaction" and increase edema tendency in all tissues by virtue of this effect.[17]

Some investigators believe that the ascites and pleural effusions may be the result of a mild cardiac decompensation in a patient who has an otherwise compensated cardiac weakness and is just able to withstand the strain of normal activities. The added

[1] *Boyd* A65840/841, *Buss* A65861/899, *Stinson* A70392/00, *Deutsch* A65943/15, *Spencer* A70963/23, *Snowden et al.* A70282/25.

[2] *McIlrath* A96510/37, *Miller* A18279/37.

[3] *Herrmann* A80315/799-800, *Blin* A65827/852, *Marshall* A70148/871, *Hartmann* A70038/884, *Mann* A41815/887, *Baudouin* A65812/888, *Terrier* A42410/888, *Coe* A65908/890, *Gusserow* A70030/892, *Doran* A65949/897, *Potel* A50552/898, *Deligny* A50655/898, *Eden* A65960/02, *Helme* A70047/02, *Erck* A74651/03, A74650/03-4, *Croom* A65917/07-8, *Peterson* A68546/10, *Amann* A65790/10, A65789/10, A65791/15, *Sichal* A70277/12, *Ortbauer* A70192/16, *Saint* A70260/19, *Geist* A70004/24, *Tasch* A96643/40.

[4] *Marshall* A70148/871, *Nicaise* A40319/881, *Ferguson* A65972/09-10, *M'Lellan* A70134/11, *Hoon* A70052/23, *Rhoads and Terrell* A95100/37, *Weld* A96583/38, *Bomze and Kirshbaum* A34639/40, *Harris and Meyer* A96689/41, *Lock and Collins* A96632/41, *Borg* A55873/41, *Ritvo* A56272/42, *Glass and Goldsmith* A98121/42, *Brody* A56304/42, *Herrick et al.* A98157/42, A98156/43, *Gild* A71759/43, *Jones* A98160/43, *Thompson* A99024/43, *Canessa* A96912/43, *Salerno* B10143/43, *Kelemen* B10137/44.

[5] *Marshall* A70148/871, *Lallemand* A70097/896, *Thomas* A70415/896, *Nagel* A70183/06, *Brody* A56304/42.

[6] *Marshall* A70148/871, *Rogée* A47086/894, A47322/895, *Papin* A70199/25.

[7] *Deligny* A50655/898.

[8] *Peterson* A70212/02.

[9] *Strübe* A70397/898, *Titus* A70419/13.

[10] *Dagron* A65922/887, *Baudouin* A65812/888, *Rogée* A47086/894, A47322/895, *Morely* A50901/898, *Demons* A65939/02, *Begouin* A65814/04, *Codet-Boisse* A65905/04, *Ortbauer* A70192/16, *Owen* A70198/23, *Papin* A70199/25.

[11] *Hartmann* A70038/884, *Baudouin* A65812/888.

[12] *Olshausen* A41468/886, *Grafe* A47115/895, *Thomas* A70415/896, *Shober* A70275/02.

[13] *Geibel* A70002/02.

[14] *Spencer* A70285/06, *Miller* A18279/37, *Rubin et al.* B6263/44.

[15] *Meigs et al.* A59855/43.

[16] *Pfannenstiel* A7554/898, A80267/05, *Kermauner* A64880/32.

[17] *Meigs* A31603/39.

stress to which the heart is exposed as a result of pressure by voluminous fibromas, perhaps combined with interference with circulation in the lower abdomen, may be sufficient to produce some decompensation and consequent transudate formation.[1] It has been pointed out, however, that this view does not account for the fact that fluid accumulations may also occur with small fibromas, hardly large enough to interfere with circulation by virtue of their weight or size.[2]

The pathogenesis of the tendency to retain water in the presence of ovarian fibromas is far from completely elucidated, but it appears fairly well established that in addition to local factors some general systemic change must also be operative.

The *menstrual cycle* is usually *normal*,[3] and may remain unchanged even in the case of bilateral ovarian fibroids.[4] In other cases more or less pronounced *menorrhagias and metrorrhagias* occur.[5] Ovarian fibromas may even cause *postmenopausal uterine bleeding*[6] but this is rather rare. In some patients more or less regular periodic monthly uterine bleeding is re-established after the menopause under the influence of an ovarian fibroma.[7] In other instances, however, the fibroma produces *amenorrhea*.[8] Occasionally normal menstrual cycles re-appeared in previously amenorrheic women following surgical removal of ovarian fibromas.[9]

In some patients the ovarian fibromas were accompanied by histologic uterine lesions of the *metropathia hemorrhagica* type,[10] glandular *polyps of the endometrium* [11] or *uterine fibroids*.[12] Several statistical surveys indicate that about 1/4—1/3 of all women with ovarian fibromas also possess uterine fibroids.[13] These and similar observations led to the view that fibromas may be the source of folliculoid hormones,[14] but the differentiation between a folliculoid producing ovarian fibroma and a true thecoma would hardly be possible.

The fact that the ovarian fibroid may be only one manifestation of a general tendency to develop fibromas or fibromyomas is shown by cases described as "fibromatosis of the genital organs". In these, fibromas develop simultaneously in the uterus, ovary and broad ligament.[15] In other cases, in addition to the ovarian fibroma, there was a fibroma in the vagina[16] or fibroids both in the uterus and in the anus.[17] In this connection animal experiments come to mind which showed that, at least in certain species (e.g. guinea pig), folliculoid hormones can cause generalized fibromatosis (see Sect. IV, Vol. III).

Hypoplasia of the uterus is exceptional in cases of ovarian fibromas although it has been seen.[18]

Displacement of the uterus is a frequent consequence of fibroma development, but not specific for this tumor type. As is the case with other ovarian neoplasms, the fibromas may elicit ante- or retroversion of the uterus[19] or cause its upward displacement and elongation.[20] There may also be uterine prolapse, especially if the ovarian fibroma led to a great deal of ascites and thus increased intra-abdominal pressure.[21] In other instances the prolapse of the uterus appears to have been a co-incidental accompaniment of the fibroma formation.[22] The fact that ovarian fibromas are pre-eminently subject to torsion will be discussed elsewhere (see Sect. IV, Vol. VI). Suffice it to mention here that the uterus may participate in this torsion.[23]

Not infrequently, *uterine carcinomas* are found in patients having ovarian fibromas.[24]

Vaginal prolapse may be seen in women with ovarian fibromas. As with uterine prolapse it usually appears to result from the increased intra-abdominal pressure caused by the accompanying ascites.[25]

In one case, bilateral ovarian fibromas were associated with a large *carcinoma of the vulva*.[26]

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[1] *Bomze and Kirschbaum* A34639/40.
[2] *Brody* A56304/42.
[3] *Hoon* A70052/23, *Geist* A70004/24, *Massazza* A66912/24.
[4] *Cullingworth* A29479/879-80.
[5] *Doléris* A43336/889, *Treymann* A45265/889, *Bourgouin* A47126/894, *Massabuau* A70159/12, *Cotte and Policard* A65913/23, *Cotte* A66900/23, *Moulonguet-Doléris* A70181/24, *Frankl* A65990/29, *de Mora* A79507/31, *McIlrath* A96510/37.
[6] *Royster* A70255/03, *Frankl* A65990/29, *Kraul* A70090/29, *de Mora* A79507/31, *Shaw* A61532/32, *Tenconi* A53109/33.
[7] *Amann* A65791/15, *de Mora* A79507/31.
[8] *Spiegelberg* A70287/866, *Roberts* A70240/872, *Castelnau* A65898/890, *Bourgouin* A47126/894, *Graham* A70023/03, *Graupner* A70022/07, *Ivens* A70058/27.
[9] *Martin* A70154/870, A96835/899, *Routier* A70251/01, A70252/09, *Doran* A65951/02.
[10] *Meyer* 4508/25, *Brody* A56304/42.
[11] *Leopold* A70110/06, A70111/874, *Moulonguet-Doléris* A70181/24, *Delmas* A65938/29, *de Mora* A79507/31, *Smith* A65179/31.
[12] *Leudet* A70114/851, *Lallemand* A70097/896, *Fletcher* A65982/897-8, *Deligny* A50655/898, *Freund* A65991/899, *Lomer* A70126/899, *Abadie* A65782/899, *Seyerlen* A70273/00, *Degorce* A65933/01, *Amann* 65788/01, *Eden* A65960/02, *Graham* A70023/03, *Maiss* A70140/06, A70139/06, *Leopold* A70110/06, *Haultain* A70041/09-10, *Fuster* A65996/13, *de Snoo* A70281/14, *Lockyer* A70121/18, *Meyer* A70173/21, *Delle Chiaje* A65937/22, *Sutton* A65825/22, *Meigs* A70164/22, *Hoon* A70052/23, *Laurentie* A70102/24, *Casper* A83397/24, *de Mora* A79507/31, *Alfredo* A97532/41.
[13] *Miller* A18279/37.
[14] *Luisi* A97566/39.
[15] *Jacobs* A70060/00.
[16] *Virchow* 7060/863.
[17] *Moore* A52285/34.
[18] *Snowden and Campbell* A70282/25.
[19] *Guelliot* A70027/06, *Fulconis and Xicluna* A65994/33.
[20] *Cruveilhier* A65918/856, *Spiegelberg* A70287/866, *Dennis* A65941/23.
[21] *Lallemand* A70097/896, *Sendtner* A70272/01, *Latronche and Charrier* A70100/05, *de Mora* A79507/31.
[22] *Atlee* A65798/849.
[23] *Seyerlen* A70273/00, *Keitler* A70076/03, *Kachel* A70072/07.
[24] *Hartmann* A70038/884, *Tate* A70404/04, *Macnaughten-Jones* A70137/11-2, *Hofstatter* A70049/18-9, *Kusuda* A73058/25.
[25] *Spiegelberg* A70287/866, *Gusserow* A70030/892, *Jacobs* A70059/893, *Efler* A65961/16, *King* A70080/34.
[26] *Winckel* A70448/881.

Malformations of the *oviduct*, such as accessory infundibula[1] or complete accessory tubes,[2] may also occur in combination with ovarian fibromas. Usually, however, the oviduct is intact or merely elongated due to traction or torsion by the tumor.[3] Since fibromas have no great tendency to form adhesions, it is comparatively rare to find these neoplasms strongly adherent to the oviduct.[4]

The combination of bilateral ovarian fibromas with an adenoma of the *breast*[5] is certainly very exceptional.

Pain is a comparatively frequent accompaniment of ovarian fibromas, perhaps because they are very subject to torsion and even temporary, partial rotation of the tumor may cause severe ovaralgia.[6] Observations on a large series of ovarian fibromas indicate that the pain is most frequently felt in the side, but in some cases there may be more or less generalized pelvic or abdominal pain, sometimes with acute symptoms characteristic of torsion. Less frequently the pain is felt in the back or in the leg and thigh. In this series, pain is mentioned as the most common clinical symptom.[7]

Severe *emaciation* is not uncommon in women having ovarian fibromas which have led to a good deal of ascites. The German authors actually speak of a "Fibromkachexie"[8] as a characteristic clinical entity. This cachexia adds to the difficulty of the differential diagnosis between Meigs' syndrome and peritoneal carcinomatosis.

COMPLICATIONS

The most common complication of ovarian fibromas is *torsion* around the frequently narrow and long pedicle. In some cases an ovarian fibroma is noted simultaneously with a more or less isolated torsion of the fallopian tube.[9] The clinical manifestations of this complication are the same as those elicited by torsion of the ovary and adnexa resulting from other causes (see Sect. IV, Vol. VI).

As a result of their continued growth, ovarian fibromas may become *impacted* within the pelvic cavity and cause complications due to pressure upon the neighboring organs.[10]

The *prolapse* of the vagina and uterus which may result from increased intra-abdominal pressure due either to the neoplasm itself or to the resulting ascites, has been discussed above. Suffice it to add here that in an exceptional case a fibroma of the ovary fixed in the pelvis led to severe complications due to complete extrusion of the uterus.[11] Retro-uterine prolapse of an ovarian fibroid may also lead to complications.[12]

Intestinal occlusion resulting from an ovarian fibroma may lead to fatal ileus unless the neoplasm is rapidly removed.[13]

The rare complications of ovarian fibromas, such as thrombophlebitis of the utero-ovarian veins,[14] intraperitoneal *rupture* of the cystic variety[15] or coincidental development of *appendicitis and gall stones*,[16] deserve only cursory mention.

DIAGNOSIS

The clinical diagnosis of ovarian fibromas forms the subject of several review articles.[17] Perhaps the most important consideration is the differentiation of the benign fibroma from *malignant ovarian tumors*. This is frequently difficult, because fibromas often become twisted on their pedicles, in which case a hard fixed mass is formed in the pelvis; this simulates an infiltrating and metastasizing ovarian cancer, especially if peritoneal and thoracic fluid accumulations are also manifest.[18] In many of these cases a certain clinical diagnosis is impossible and sometimes even naked eye inspection of the tumor, at operation, does not suffice to distinguish it with certainty from malignant, primary or metastatic, solid ovarian neoplasms. Histologic control is therefore always necessary. If this is not feasible during the operation, the surgeon should keep in mind the possibility that a fibroma may be confused among other things with a Krukenberg tumor and if there is any suspicion of the latter a careful search for the primary site is obligatory.

Not infrequently, ovarian fibromas are difficult to differentiate from *uterine fibroids* especially if they are adherent to the uterus or closely pressed against it.[19] Confusion with a pedunculated ovarian fibroid is possible even if the ovarian neoplasm is not contiguous with the uterus.[20]

The extensive peritoneal transudate which accompanies a large percentage of the ovarian fibromas may

[1] *Spencer* A70963/23.
[2] *Deutsch* A65943/15.
[3] *Cruveilhier* A65918/856, *Orthmann* A64820/899, *Sendtner* A70272/01.
[4] *Deligny* A50655/898, *Andrews* A65793/01, *Bovée* A65837/02.
[5] *Haumeder* A34822/40.
[6] *Rendu* A41657/886, A70234/886, A69424/887, *Rocher* A69425/00, *Chi* A28083/35.
[7] McIlrath A96510/37.
[8] *Miller* A18279/37.
[9] *Vila and Viriot* A65190/31, *Barrett and Lash* A58620/43.
[10] *Doran* A65949/897, *Fehling* A65970/04, *Dauber* A65929/07.
[11] *Dauber* A65929/07.
[12] *Ludlam* A44777/894.
[13] *de Boyer* A65841/873, *Zumbusch* A70455/896, *McDowell* A50900/898.
[14] Infantozzi B15668/26.
[15] *Condamin and Brunat* A65910/29.
[16] *Sichel* A70277/12.
[17] *Roberts* A70241/03, *McIlrath* A96510/37, *Rieper and Nogueira* A98176/43.
[18] *Hoon* A70052/23, *Papin* A70199/25, *McIlrath* A96510/37, *Crile* A57535/42, *Ritvo* A56272/42.
[19] *Homans* A42559/889, *Barbour* A65808/06-7, *de Rouville* A66916/22.
[20] *Debiasi* A65932/28.

give rise to the suspicion of *tuberculous peritonitis*.[1] In the case of torsion, the differentiation from *twisted ovarian cysts*[2] or acute *appendicitis*[3] was occasionally a problem. In one rather unusual case *urinary incontinence* was simulated by an ovarian fibroma in which large quantities of ascites escaped periodically through the widely patent oviducts and the vagina.[4] Another extraordinary fibroma was attached to the ovary through a very long pedicle which permitted the tumor to ascend into the lumbar region and led to the erroneous diagnosis of a *floating kidney*.[5]

As the above discussion indicates, ovarian fibromas may simulate a variety of clinical conditions. The reverse is also true, however, and it is readily understandable that diverse diseases accompanied by fluid retention in the large body cavities may elicit what has been termed a "false Meigs' syndrome".[6]

PROGNOSIS

The prognosis of ovarian fibromas is generally good. Even without any therapeutic measures these tumors usually do not tend to proliferate rapidly. In one case, for instance, a fibroma weighing 17 lbs. was under observation for 10 years during which time it grew very slowly.[7] Conversely, in some cases they grow so rapidly that the presence of a malignant tumor may be suspected.[8] It should also be kept in mind that an originally benign fibroma may undergo malignant transformation[9] owing to a transition into a sarcoma (see part on Pathologic Anatomy). In very rare instances, sudden death may result from an ovarian fibroma, perhaps owing to pressure on the mediastinum by a one-sided hydrothorax.[10]

Following operation, the prognosis is excellent since ovarian fibromas do not recur.[11] The comparatively simple operation of the conservative removal of ovarian fibromas was well tolerated even under the surgical conditions prevailing during the second half of the last century and even by elderly women past 75 years.[12] Patients from whom ovarian fibromas have been removed during the child-bearing age may subsequently become pregnant.[13]

THERAPY

The treatment of ovarian fibromas must always be surgical and *operative removal* of the growth is indicated as soon as it is diagnosed. Even with the comparatively crude surgical technics used during the last century the simple conservative removal of the ovary bearing the fibroma, yielded very satisfactory results in the vast majority of cases.[14] With the operative procedures customarily employed for laparotomies at the present time, ablation of ovarian fibromas is a simple and safe intervention.[15]

In the case of small circumscribed fibromas it is possible merely to excise the tumor, saving even part of the affected ovary.[16] Since in general, these tumors do not form any important adhesions, technical difficulties are not likely to arise in connection with their removal. It is not impossible to remove small fibromas by posterior colpotomy, although the approach through the anterior abdominal wall is generally preferred.[17]

In the rare instances in which the ovarian neoplasm is strongly adherent to the uterus, simultaneous hysterectomy may become necessary.[18]

During *pregnancy*, and especially at the time of delivery, mechanical complications may arise due to the presence of large ovarian fibromas. Surgical removal of these neoplasms is generally not difficult even in pregnant women, but during the last stage of gestation it may be advisable to combine this intervention with a caesarean section.[19]

The only important *operative complication* which is recorded in some cases is generalized peritonitis due to a faulty sterile technic.[20]

The *X-ray* sensitivity of ovarian fibromas is very low and radiation therapy is not indicated either in lieu of, or as an adjunct to surgical therapy.[21] This is especially true since these neoplasms may so readily be removed and have no tendency to recur.

The antiquated procedure of placing an *elastic ligature* around the ovarian pedicle[22] is mentioned merely because of its historic interest.

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[1]*McIlrath* A96510/37.
[2]*Chi* A28083/35.
[3]*Massabuau* A70158/07.
[4]*King* A70080/34.
[5]*Brothers* A65857/04, *Manon* A76062/23.
[6]*Rieper and Nogueira* A98176/43.
[7]*Doran* A65952/05.
[8]*Crile* A57535/42.
[9]*Codet-Boisse* A65905/04.
[10]*Borg* A55873/42.
[11]*Jungmann* A70069/05, *Hohne* A70050/05, *Pflaum* A70215/10, *Crile* A57535/42.
[12]*Terrier* A42410/888.
[13]*Hoon* A70052/23.
[14]*Scott* A70271/, *Atlee* A65798/849, *Van Buren* A87169/850, *Toland* A87168/860-1, *Martin* A70154/870, *Gripat* A87120/874, *Battey* A87090/874-5, *Veit* A70428/876, *Hunter* A70055/876, A87127/879, A70056/885, *Geissel* A87117/877, *Goodell* A70019/878, A74653/877-8, *Williams* A41632/884, *Hamilton* A40470/885-6, *Rendu* A70234/886, A69424/887, *Terrier* A42410/888, *Homans* A42559/889, *Summers* A43444/890-1, *Bianchi* A45684/891, *Wettergren* A45900/891, *Andrews* A46319/892, *Keiffer* A70073/893, A70074/894, *Schachner* A70262/894, *Doran* A48389/896, A65949/897.
[15]*Bürger* A65859/00, *Addinsell* A65783/00, *Seyerlen* A70273/00, *Teufel* A70414/01, *Helme* A70048/02, *Kelly* A74659/02, *Mauclaire* A70162/04, *Fritsch* A65993/05, *Hohne* A70050/05, *Jungmann* A70069/05, *Glockner* A70015/06, *Pflaum* A70215/10, *Lop* A70127/11, *Titus* A70419/13, *Caro* A65892/14, *Estor and Aimes* A65965/21, *Hoon* A70052/23, *Bruns* A65858/24, *Crile* A57535/42.
[16]*de Rouville* A66915/11.
[17]*Philipps* A70216/04.
[18]*Boldt* A65829/03.
[19]*Kleinwachter* A70085/872, *Carstens* A43364/889, *Kerr* A70078/08, *Rossier* A70249/08-9, *Link* A70120/10, *Martini* A70156/25.
[20]*Millot-Carpentier* A43434/890, *Ledoux* A74663/00.
[21]*Frankl* A65990/29, *Ritvo* A56272/42.
[22]*Hofmokl* A40220/882.

PARA-OVARIAN FIBROMAS

DEFINITION

As in the corresponding chapter on ovarian fibromas, the pure fibromas of the para-ovarian region as well as the "myo-fibromas" will be discussed conjointly in this chapter, since they consist exclusively, or at least mainly, of neoplastic connective tissue. Additional borderline cases will be found in the chapter on leiomyomas of the para-ovarium which includes the "fibro-myomas". These are mixed tumors consisting of both connective tissue and smooth muscle cells, with the latter prevailing.

PATHOLOGIC ANATOMY

MACROSCOPIC CHARACTERISTICS: Although the fibromas of the para-ovarian region are usually of moderate *size,* they may sometimes reach unusually large dimensions;[1] several case reports describe para-ovarian fibromas and myo-fibromas which weighed 15-50 pounds.[2]

Concerning their *shape* and *consistency,* it may be said that these tumors are generally rounded although their surface is sometimes irregular and nodular. If they are soft and cystic, however, (a rather common occurrence in para-ovarian fibromas) they tend to adapt themselves to the shape of other pelvic organs. The innominate line, muscles, and even the ureters or other pelvic organs may leave definite imprints upon the surface of such fibromas.[3]

Bilateral para-ovarian fibromas and myo-fibromas have also been described,[4] although in most cases the tumor develops on one side only. *Multiple* myo-fibromas are quite exceptional.[5]

The *position* of the para-ovarian fibromas and myo-fibromas is somewhat variable. Most of them develop within the broad ligament but, unlike the uterine fibroids with intraligamentous development, they have no connection with the body of the uterus and are entirely free within the ligaments. Rarely the uterus itself is the site of additional fibroids and its general outline and size are not considerably changed by the presence of para-ovarian fibromas.

It has been emphasized that the displacement of the uterine artery and the ureter are entirely different in para-ovarian fibromas and in uterine fibroids with intraligamentous development.[6] In the former instance, the uterine artery is compressed between the tumor and the uterus, while the ureter is pressed downward. In the latter instance, the neoplasms which originate in the uterus push the artery laterad and upwards (craniad), consequently, the uterine artery comes to lie closer to the ovarian artery and the two vessels tend to run parallel with each other above the neoplasm. The ureter is displaced towards the pelvic wall and generally lies below the tumor, except in rare cases of cervical lateral myomas situated deep in the pelvis.[7] These topographic differences are, of course, of the greatest interest to the surgeon, especially since it is rarely possible to distinguish intraligamentous uterine fibroids from primarily para-ovarian fibromas on the basis of clinical symptoms and signs alone.

From the surgical point of view, it is also important that certain para-ovarian fibromas may grow forward and adhere to the bladder, interfering with its function, or the tumors may extend processes towards the crural or inguinal canal.[8]

Conversely, certain para-ovarian fibroids tend to grow dorsad into the retroperitoneal space. It is these neoplasms which most frequently cause signs due to compression of the rectum or sigmoid, with consequent intestinal obstruction.[9]

Finally, certain para-ovarian fibromas tend to grow caudad (downwards) towards the pelvic floor, vagina, vulva and inguinal canal.[10]

Although most para-ovarian fibromas tend to spread into the broad ligament, some are connected with the latter merely by means of a comparatively thin pedicle.[11]

The vast majority of the *case reports* concerning para-ovarian fibromas describe such growths in the

[1] *Douvrin* A91307/898, *Doran* A91304/00, *Bustillo Lirola* A91375/06, *Bégouin* A91282/07, *Albertin* A91279/09, *Delaunay* A91298/11, *Brewis* A91289/12-3, *Mori* A91337/15.

[2] *Doran* A42601/889, A91303/899, *Spencer* A91363/05, *Bustillo Lirola* A91377/16.

[3] *Lauwers* B6482/843, *Buschman* B6483/880, *Terrillon* B6481/890, *Rouffart* A44216/892, *Roberts* B6480/899, *Doran* A91304/00, *Forgue and Crousse* A91555/25.

[4] *Abbott* A45781/891, *Duncan and Daly* A46329/892, *Pearse* A91343/10, *Eising* A91312/11.

[5] *Abbott* A45781/891, *McNeile* A91334/19.

[6] *Forgue and Crousse* A91555/25.

[7] *Berkeley and Bonney* B6469/13.

[8] *Thorn* A77855/00, *Forgue and Crousse* A91555/25.

[9] *Keith* B6500/883, *Lauwers* B6497/893, *Schwartz* B6496/894, *Guermonprez* B6495/895, *Mangin* A49129/897, *Gartner* B6498/898, *Guillioud* B6501/899, *Wertheim* B6499/00.

[10] *Vierow* B6503/892, *Brin* A91290/10.

[11] *Mikulicz* B6486/879, *Bilfinger* B6487/887, *Duncan and Daly* A46329/892, *Briand* B6491/893, *Guerard* B6492/893, *Binaud* B6493/893, *Cullingworth* A48301/896, *Sibut* A48418b/897, *Da Costa* A91297/898, *Delétrez* A91299/01-2, *Martin* B6494/05, *Bevers* A91284/09, *Gross* B6488/12.

broad ligament[1] a smaller number has been found in the *round ligament* of the ovary.[2]

MICROSCOPIC CHARACTERISTICS: Histologically, the structure of para-ovarian fibromas and myofibromas is almost identical with that of the corresponding ovarian tumors and, indeed, may even be difficult to distinguish from that of uterine fibroids. The entire growth consists of more or less normally developed fibroblasts, connective tissue fibers and smooth muscle cells, the latter representing an inconstant admixture seen only in the so-called myofibromas, not in the pure fibromas. As with the corresponding ovarian tumors, the fibromas of the para-ovarian region tend to undergo degenerative changes, especially *edema*[3] or *myxomatous transformation.*[4] It is unnecessary, however, to distinguish the para-ovarian "myxoma" as a separate neoplastic entity.

INCIDENCE

No accurate statistical data are available concerning the *general incidence* of para-ovarian fibromas. It may be stated, however, that even at the turn of the century Stroheker[5] collected as many as 204 purportedly relevant cases but only about 50 of these appear to have been primary para-ovarian growths, the others being intraligamentous uterine fibroids. The present survey indicates, however, that many more instances have been seen since that time, so that while fibromas of the para-ovarian region are by no means among the common pelvic tumors, they cannot be regarded as great rarities.

These neoplasms may occur at any *age*[6] and in rare instances, they even develop during *pregnancy*[7] at which time they may interfere mechanically with delivery.

PATHOGENESIS

Most investigators believe that the para-ovarian fibromas and myo-fibromas (as well as the pure myomas and fibro-myomas which will be discussed in a subsequent chapter) originate from fibroblasts and smooth muscle cells of the ovarian ligaments.[8] While it is true that smooth muscle and connective tissue cells are plentiful in the broad ligament, some investigators[6] wondered why the broad ligament is an exception and why similar tumors are so rare in other locations where smooth muscle and connective tissue cells are also plentiful (e.g. scrotum, labia majora, esophagus, stomach, wall of the bladder, prostate, epididymis, ductus deferens).[6] Similar considerations as well as histologic studies led others[9] to express the view that para-ovarian fibromas and myo-fibromas may develop from embryonic vestiges of the Wolffian body. While we have no explanation for the comparative frequency of occurrence of fibromas and myo-fibromas in the para-ovarian region, it must be kept in mind that similar tumors do arise even more frequently in the uterus and it is well known that different tissues vary in their tendency to undergo neoplastic transformation. Perhaps the greater tumor incidence of para-ovarian mesodermal structures could be ascribed to their sharing with the myometrium a specific sensitivity to the growth stimulating actions of sex hormones, especially folliculoids. It would be very difficult to implicate the Wolffian body in the formation of the para-ovarian fibromas or myo-fibromas which arise from the round ligament (see above). In our opinion, the theory which derives these neoplasms from pre-existent connective tissue and smooth muscle cells within the ovarian ligaments is more likely to be correct, at least in the vast majority of the relevant instances.

CLINICAL COURSE

The para-ovarian fibromas and myo-fibromas have no specific symptomatology which would characterize them and permit their clinical differentiation from

[1] *Vautrin* B6475/, *Lasalle* B6476/891, *Desguin* A46298/892, *Lang* B6474/892, *Kletzsch* A44635/894, *Pryor* A44868/894, *Cullingworth* A48301/896, *Krekels* A91276/896, *Mallet* A47391/896, *Duncan* A91308/897, *Smith* A49219/897, *Pauchet* A91342/897, *Hodgson* A91326/897-8, *Da Costa* A91297/898, *Doran* A91303/899, A91306/07, *Griffon* A91322/899, *Hansen* A91448/899, *Walton* A91368/899, *Fuchs* A91449/00, *v. Mars* A91335/00, *Castaing and Phillippe* A91293/01, *Monod* A91336/01, *Pasteau* A91341/01, *Delétrez* A91299/01-2, *Borée* A91287/02, *Galabin* A91315/02, *Goldspohn* A91320/02, *Lewers* A91330/02, *Shaw* A91360/02, *Stroheker* A91278/02, *Demons* A65939/02, A91300/03, *Boursier and Venot* A91286/03, *Lewis* A91331/03, *Boyd* A65839/04, *Duroux* A91309/04, *Roulland* A91350/04, *Pollosson* A91345/04, A91346/04, *Parsons* A91340/04, A91339/04-5, *Burkard* A91291/05, *Desmoulins and Roulland* A91302/06, *Guicciardi* B6479/06, *Martin* B6477/06, *Gerbier* A91275/06, *Thiery* A91365/06, *Kravehenko* A91328/07, *Vance* A91366/07, *Freund* B6478/10, *Deniker* A91273/10, *Pollosson and Martin* A91347/11, *Delaunay* A91298/11, *Bender* A91283/12, *Rendu* B6471/12, *Radomski* A91348/12, *Alfieri* A91280/13, *Castano* A91294/14, *Haller* A91323/14, *Salvador* A91354/14, *Mori* A91337/15, *Füth* A91314/17, *Schiffman* A91356/17, *Hamilton* A91324/17, *Descomps and Hue* A91301/20, *Wilkinson* A91577/20, *Bégouin* A91543/21, *Delépine* A91550/21, *Estor et al.* A91553/21, *Pousson and Blanchot* A91568/21, *Turco* A91575/22, *Vernejoul* A91576/22, *Michel and Nicolleau* A91566/23, *Seaver* A91573/24, *Crousse* B6473/24, *Doren* A91552/25, *Buendia and Luque* A91547/26-7, *Liebmann* A91563/27, *Zarnitzky* A91579/27, *Brugeas* B8187/28, *Vanverts* B12315/29, *Gutiérrez* B21585/29, *Dambrin and Thomas* B21582/29, *Lapeyre and Estor* A91562/33, *Brea* A91546/35.

[2] *Doran* A42255/887, A41805/887, A48995/896, *Ludlam* A44845/894, *Pilliet and Gosset* A49190/897, *Amann* A70567/04, *Manton* A66911/10, *Nisot-Wuyts* A66914/10-1, *Hellman* A66905/15, *Engelhard* A66903/18-9, *Fatyol* B7700/37.

[3] *Oliver* A91338/10, *Roy* A91352/14.

[4] *Brin* A91290/10.

[5] A91278/02.

[6] *Forgue and Crousse* A91555/25.

[7] *Vincent and Ferrari* A91367/12.

[8] *Gross* A46395/892, *Vautrin* B6470/893, *Sacchi* A91353/07.

[9] *Lang* B6474/892, *Gallo* B12327/33.

other similar pelvic neoplasms. They produce no hormonal disturbances and manifest themselves almost exclusively as a result of their mechanical presence in the pelvis (e.g. compression of adjacent organs, torsion, inflammation etc.).

Interference with the *uterus* is uncommon, although occasionally metrorrhagia may ensue as a result of the pelvic congestion occasioned by these neoplasms.[1] The *fallopian tubes* are displaced and elongated if the fibromas develop within the mesosalpinx, but with broad ligament fibromas and myo-fibromas, there is no tendency to cause any derangement of the oviduct even if the tumors reach a considerable size.[2]

Occasionally there may be *ascites*[1] or *cardiac insufficiency*[3] but not as frequently as with ovarian fibromas.

COMPLICATIONS

The para-ovarian fibromas and myo-fibromas may elicit the usual complications seen in the case of other para-ovarian or ovarian neoplasms; that is, they may be subject to *torsion* (especially if they have a long and thin pedicle), *hemorrhage,* secondary infection and *inflammation* and even herniation (see Sect. IV, Vol. VI where the corresponding ovarian and para-ovarian lesions are discussed conjointly).

Mechanical *compression of the ureter* may lead to severe urinary retention;[4] in one case, such a retention of urine was periodic and coincident with menstruation.[5] In rare instances, para-ovarian fibromas may cause *intestinal obstruction,*[6] *edema of the lower extremities*[1] or *prolapse* of the genital organs.[1]

DIAGNOSIS

The symptoms and signs of para-ovarian fibromas and fibromyomas are almost exclusively the result of mechanical complications and have already been discussed above. From the viewpoint of differential diagnosis, the most common source of error is the confusion of primarily para-ovarian neoplasms with *fibroids of the uterus,* especially the pedunculated subserous variety which tends to exhibit pronounced intraligamentous development.[7] If a uterine fibroid develops into the broad ligament and is connected with the body of the uterus only through the intermediary of a comparatively narrow pedicle, it may be impossible to palpate any connection between the pelvic growth and the uterus itself. In fact, this distinction may be difficult even when the abdomen is open and the surgeon can directly inspect the pelvic organs. In the latter case, the course of the uterine artery and the ureter are of some diagnostic value (see data on Macroscopic Characteristics, in the part on Pathologic Anatomy).

If the para-ovarian fibroma has undergone extensive degenerative changes with softening or edema and cyst formation, it is often confused with an *ovarian cyst,* a *hydrosalpinx*[1] or *salpingitis.*[8] The more common firm variety of this neoplasm, however, shows no fluctuation and in the event of a hard, resistant para-ovarian tumor, the true nature of the neoplasm may, at least occasionally, be suspected.[1]

THERAPY

The only effective therapy of para-ovarian fibromas and myo-fibromas is their surgical removal. This may be technically difficult if the growths have reached a considerable size or formed extensive adhesions with other pelvic organs. Under such circumstances their blood vessels are usually extremely well developed and there is constant danger of severe hemorrhage during the intervention.[9]

[1] *Forgue and Crousse* A91555/25.
[2] *Doran* A91303/899.
[3] *Chavannaz* A91296/07.
[4] *Stroheker* A91278/02, *Bouvier* B6507/10, *Bonnet* B6512/24.
[5] *Furniss* B6508/13.
[6] *Barette* B6509/04.
[7] *Pilcher* A44597/893, *Ludlam* A44846/894, *Forgue and Crousse* A91555/25.
[8] *Sibut* A48418b/897.
[9] *Vautrin* B6504/895, *Forgue and Crousse* A91555/25.

OVARIAN COMMON SARCOMAS

REVIEWS

ENGLISH: Geist B6672/42.

FRENCH: Dubois A50688/898, *Ladouce* A45619/890.

GERMAN: Virchow A77876/864-5, *Lobeck* A77638/874, *Teichmann* A77847/888, *Oppenheim* A77716/894, *Heinrichs* A96832/899, *Stauder* A77830/02, A77829/02, *Baumfelder* A77381/02, *Argutinski-Dolgorukow* A77366/06, *Wermuth* A77897/10, *Kaufmann* 39132/31.

DEFINITION

Sarcomas of the ovary are highly malignant, mesenchymal growths. All malignant mesenchymal tumors of the female gonad are listed in this Encyclopedia as ovarian sarcomas. It should be kept in mind that, in addition to the primary ovarian sarcomas, this definition includes originally benign neoplasms, (e.g. fibromas) which have undergone malignant transformation, ovarian metastases of extragonadal sarcomas and even cases in which a sarcoma of an adjacent organ invades the ovary directly.

The present chapter deals only with the "common sarcomas", a term under which we include (primary and secondary) spindle and round cell sarcomas which possess no specific hormone-producing ability. It is assumed that most of the "sarcomas" of the literature not adequately characterized histologically, belong to one of these two types since the vast majority of all the ovarian sarcomas consist of spindle or round cells. Hence, for didactic reasons, the "common sarcomas" will be discussed separately from the histologically or endocrinologically more specialized malignant mesenchymal growths in this chapter, which will also serve as a basis for a general discussion of characteristics common to all types of sarcomas.

The comparatively highly differentiated malignant mesenchymal growths (chondro-, osteo-, leiomyo-, rhabdomyo-, lipo-, teratoid sarcomas etc.) will be treated in separate chapters conjointly with the corresponding benign neoplasms. Obviously, this procedure can only be followed if the cells of the malignant tumor are sufficiently mature to be recognized as atypical varieties of cartilage, bone, muscle, fat, etc., cells. It is perhaps illogical to deviate from this procedure in the case of the spindle cell sarcomas which could have been discussed conjointly with the fibromas. Because of their great frequency, however, these are also listed as common sarcomas and only the sarcomatous degeneration of typical fibromas is discussed in the chapter dealing with the corresponding benign neoplasm.

In conclusion, attention is drawn to the frequent confusion, especially in the old literature, of sarcomas and carcinomas and the impossibility of differentiating primary and metastatic sarcomas if the primary nodule is not detectable. Furthermore, many of the cases previously described as primary sarcomas undoubtedly belong to the group now known as Krukenberg tumors, which are metastatic carcinomas. Wherever the published evidence suffices to draw definite conclusions, such misdiagnosed cases are listed in the group to which they actually appear to belong rather than in that to which the author ascribed them.

HISTORY

The historic development of the sarcoma concept in general had its repercussions in the views expressed concerning the sarcomas of the ovary. Supposedly relevant cases were described as early as the first part of the nineteenth century,[1] but it was not until much later that the distinguishing characteristics of malignant epithelial and mesodermal tumors of the ovary were clearly formulated.[2] Even in the recent literature, many case reports will be found in which there is considerable doubt concerning the accurate classification of supposedly sarcomatous ovarian neoplasms.

Much of this confusion was due to the fact that as prominent an authority as Virchow[3] claimed that sarcomas of the ovary are great rarities, a view which led many subsequent investigators to doubt the mesodermal origin of almost any malignant ovarian tumor they observed.

CLASSIFICATION

The ovarian sarcomas are generally classified according to two main points of view; a) their histogenesis, or b) their histologic appearance. From a histogenetic stand point the following groups may be distinguished:

1. *Primary,* originally solid sarcomas which may, however, contain a variable number of more or less extensive secondary liquefaction cysts.

2. *Secondary sarcomas* which arise from the malignant transformation of originally benign mesodermal neoplasms (fibromas, leiomyomas, chondromas, lipomas, hemangiomas etc.) or from the stroma of epithelial tumors (serous or pseudomucinous cysts and cystadenomas, teratoid cysts etc.). These secondary sarcomas are discussed conjointly with the benign neoplasms from which they arose. It will be noted that the word "secondary" in the sense in which it is used here is not synonymous with "metastatic".

[1] *Macfarlane* A69750/832, *Robbs* A69756/838.
[2] *Waldeyer* A73013/870.
[3] A77876/864-5.

3. *Metastatic* sarcomas.

4. *Sarcomatous invasion from adjacent organs* ("fortgeleitete Sarkoma" of the German investigators).

According to their histologic appearance, the pure sarcomas of the ovary may be classified in the following manner:

1. *Spindle cell sarcomas*
2. *Round cell sarcomas*
3. *"Alveolar sarcomas"*
4. *"Giant cell sarcomas or mixed cell sarcomas"*
5. *"Adenosarcomas"*
6. *"Myxosarcomas"*
7. *Melanosarcomas*
8. *Lymphosarcomas*
9. *Myelomas and Chloromas*
10. *Liposarcomas*
11. *Chondrosarcomas*
12. *Osteosarcomas*
13. *Leiomyosarcomas*
14. *Rhabdomyosarcomas*
15. *Angiosarcomas* (including the so-called hemangio- and lymphangio-sarcomas as well as the "endotheliomatous" and "peritheliomatous" sarcomas).

It should be kept in mind that different cases of the same group in this histologic classification may belong to different categories of the histogenetic classification. It should also be remembered that according to our definition only the first five groups of this classification are "common sarcomas". The fourth group (giant or mixed cell sarcomas) is included mainly because it is difficult to separate it strictly from the first three. The terms listed in quotation marks refer to tumors whose fundamental difference from the spindle and round cell sarcomas is in doubt. They are treated separately for purely didactic reasons, not because of any desire to distinguish them as independent blastoma entities.

The *sarcomatoid theca cell tumor* probably also belongs to the pure sarcomas, but is discussed separately with the potentially hormone-producing neoplasms, while the *partly sarcomatous and partly epithelial blastomas* are treated in conjunction with the corresponding epithelial tumors.

PATHOLOGIC ANATOMY

The structure of the common ovarian sarcomas is rather variable since a great many probably heterogeneous growths are at present listed under this title. The following outline is designed merely to sketch the general morphologic characteristics of ovarian sarcomas and to furnish an opportunity for the registration of those case reports of the ancient or purely clinical literature in which the tumors were not accurately characterized as regards histologic structure. At first sight it may appear rather wasteful to assign space to the discussion of sarcomas which have not been adequately identified by histologic study but it must be borne in mind that important facts concerning the course, possible complications, prognosis etc., can be learned from even these sarcomas, characterized only on the basis of their gross features.

Numerous reviews deal with the *statistics* of ovarian sarcomas.[1] In these surveys, data will be found concerning the incidence, frequency of bilateral development, formation of metastases, prognosis and therapy of ovarian sarcomas. All these data will be discussed in more detail in the corresponding paragraphs of this chapter.

MACROSCOPIC CHARACTERISTICS: In general, the malignant tumors of the ovary, whether sarcomas or carcinomas, do not become as voluminous as do the benign neoplasms since the death of the patient generally occurs before the tumor can reach a very great *size*. Several reports of unusually large ovarian sarcomas can be found in the literature, however.[2] Many of these tumors weighed 10 lbs. or more.[3] Some of the still larger ovarian sarcomas of the literature, which weighed 30 lbs. or more[4] may have been epithelial neoplasms; the largest instance on record described as a medullary sarcoma weighing 80 lbs.[5] was almost certainly a fibroma.

The *shape, position and color* of the ovarian sarcomas are subject to such enormous variations that it does not appear profitable to discuss these points here. These characteristics have been reviewed in great detail in other monographs to which the interested reader is referred.[6]

The *consistency* of ovarian sarcomas is likewise rather variable, but most cases are described as brittle, mushy, soft or brain-like;[7] for the latter the terms "medullary sarcoma"[8] or "encephaloid sarcoma"[9] are commonly in use. It is important to realize, however, that these terms refer merely to the consistency of the neoplasm, not to any of its fundamental characteristics.

Many sarcomas are *cystic*. These are variously referred to as cysto-sarcomas, cystic sarcomas and sarcomatous cysts. They may originate as a result

[1] *Krasting* A77606/06, *Steinhardt* A77833/24, *Schamoni* A77788/25, Miller A18279/37.

[2] *Wenning* A42739/888, *Horrocks* A47458/895, *Treub* A77860/899, *Seeligmann* A77818/14, *Schröder* A77805/20, *Rouville et al.* A77780/26, *Mattos* A97295/37.

[3] *Zangemeister* A48381/896, A77916/896, *Tate* A77841/899, *Bruandet and Lefas* A77410/00, *Stauder* A77829/02, A77830/02, *Nabitz* A77710/17, *Spinelli* A77826/23, A77827/23, *Massazza* A77674/25.

[4] *Krug* A77611/891, *Engström* A77473/897.

[5] *Clemens* A65903/873.

[6] *Kaufmann* 39132/31, *Miller* A18279/37.

[7] *Miller* A18279/37.

[8] *Mackmurdo* A88347/853.

[9] *Mo* A88351/878, *Assaky* A88266/879, *Braquehaye* A43452/889-90, *Pepin* A69508/891.

of sarcomatous degeneration within the wall of a common cyst or cystic carcinoma. More frequently, their cavities are due to necrosis and liquefaction of cer... in areas within a primarily solid sarcoma. In some cases, differentiation between these two types is impossible, since the epithelial components may be completely destroyed by the invading sarcoma cells. Some investigators clearly distinguish between unilocular and multilocular varieties of the cystosarcomas.[1]

The data concerning the frequency with which ovarian sarcomas develop *bilaterally* are very contradictory. In a review of 21 different series of cases with a total of 921 patients who bore ovarian sarcomas, bilateral occurrence was listed in 229 instances, that is 24.9%.[2] It is noteworthy, however, that in the individual groups the percentual incidence of bilateral occurrence varied between 0 and 57.1%. In any case, the large number of case reports which describe bilateral sarcomas clearly indicates that this neoplasm frequently occurs in both ovaries simultaneously.[3]

The many ovarian tumors described as ovarian sarcomas, furnish abundant statistical data concerning these tumors, but as mentioned above, the case *reports* of the old literature must be viewed critically, since the tumors described in many of them do not qualify as sarcomas on the basis of present day criteria.[4]

MICROSCOPIC CHARACTERISTICS: Upon histologic examination, the majority of the ovarian sarcomas prove to consist of neoplastic, malignant, oval or spindle-shaped cells. These are known as

[1]*Schultz* A82050/854, *Smith* A82539/863, A82540/867, *Stiegele* A82063/872, *Rémy* A77762/874, *Tresfort* A77858/874, *Butruille* A77417/876, *Engelmann* A68456/878-9, A77472/879, *Blackwell* A81281/879, *Gillette* A29442/880, *Chiarleoni* A40443/882, *Criado* A41528/883-4, *Ludlam* A40835/885, A43994/891, *Terrillon* A77849/886, *Winckel* A45083/887, *Bergesio* A42707/888, *Polaillon* A42462/888, *Rueder* A45084/888, *Fjodorento* A77484/889, *Kelly* A43608/890, A45695/890-1, *Krug* A77610/891, *Robb* A77769/891, *Eden* A77465/893, *Davis* A47447/895, *Noto* A49051/897, *Veelken* A77868/898, *Lovrich* A50507/898, A77645/898, A77644/898, *Thorn* A77855/00, *Knott* A83365/00, *Macnaughton-Jones* A77655/00-1, *Alcock* A77343/03, *Taylor* A77842/04, *Abadie and Bender* A77338/05, *Füth* A77502/06, *Perkins* A66928/12, *Outerbridge* A77725/14, *Händly* A77540/15, *Bell* A77385/24.

[2]*Miller* A18279/37.

[3]*Weinlechner* A86635/875, A77895/889, A42626/889, *Winckel* A45083/887, *Jacobs* A74751/891, *Baker* A45720/891, *Casuso* A44053/892, *Shaw-Mackenzie* A46547/892, *Theilhaber* A46511/893, A83506/894, *Gruzdeff* A74731/894, *Eustache and Duret* A74742/894, *Wiggin* A44646/894, *Brindel* A74736/894, *Freeborn* A74745/894, A74746/895, *Kötschau* A77598/897, *Doran* A77461/898, *Knott* A83365/00, *Kidd* A77587/00, *Cealac* A74737/04, *Löwit* A77641/11, *Smith and Motley* A77822/14, A77823/15, *Johansson* A66953/17, *Goldschmied* A77524/22, *Schumann* A66946/24, *Schockaert* A77799/24, *Manzi* A77663/27, *Maggi* A77658/35.

[4]*Villard* A77874/870, *Atthill* A74733/873-5, *Hildebrandt* A81211/876, *Atlee* A77367/877, A87089/878, *Haynes* A77545/878, *Leopold* A77633/878, A77634/886-7, A77635/887, *Emmet* A77469/879, *Wingate* A77904/881, *Thornton* A77856/881, *Musso* A77709/882, *Schröder* A77803/882, *Haas* A77539/882, *Elder* A41606/884, *Lang* A77626/884, *Cushier* A41019/885, *Gallozzi* A40861/885, *Polaillon* A40839/885, A40849/885, *Bradbury* A77402/885, *Underhill* A42011/886, *Cohn* A42018/886, *Meinert* A77678/886-7, *d'Antona* A41804/887, *Cavazzani* A41908/887, *Byford* A77418/888, *Taylor* A77846/888, *Purcell* A42730/888, A42565/888-9, *Murphy* A69472/888-9, A77705/888-9, *Chrobak* A77428/889, *Rieder* A42566/889, *Meredith* A77683/889, *Lamarque* A77623/889, *Guttmann* A77538/889, *Fresenius* A74730/889, *Ashton* A42581/889, *Johnson* A42610/889-90, *Ladouce* A45619/890, *Kelly* A77584/890, *Braquehaye* A74735/890, *Renz* A43981/891, *Neale* A44128/891-2, *Jacobs* A74752/892, *Hulke* A46369/892 *Unkraut* A77863/893, *Adam* A77339/893, *Martin* A77669/893, *Landau* A77625/893, *Amann* A77345/893, A44761/894, A77354/08, A77353/09, A77356/10, *Smith* A46509/893-4, *McLean* A77653/894, *Cordier* A47069/894, A47444/895, A47093/895, *Heine* A77546/894, *Dirner* A77454/894, *Bourgouin* A47126/894, *Dakin* A47446/895, *Langer* A77627/895, *Lipinski* A47462/895, *Mjkerttschjanz* A69470/896, *Davis* A74740/896, *Zangemeister* A48381/896, A77916/896, *Vonnegut* A77879/896, *Cameron* A77420/896, A77421/25, *Muret* A77704/896, *Gruzdeff* A77533/897, *Donald* A77456/897, *Brosin* A77407/897, *Lovrich* A77646/898, A77647/03, *Rossi* A50905/898, *Jessett et al.* A47976/898, A50541/898, *Schmorl* A77796/898, *Miller* A50549/898, *Dubois* A50688/898, *Tumanoff* A74768/898-9, *Tate* A77841/899, *Chamayou and Gally* A47971/898, *Contin* A74738/899, *Roxburgh* A77782/899, A77781/899, *Orthmann* A77721/899, A77720/10, *Boyd* A50961/899, *Adenot* A77340/899, *Napier* A51009/899, *Fossard* A77493/899, *Knauer* A77594/899, A77595/02, *Schramm* A77802/00, *Gibson* A77516/00, *Menge* A77680/00, *Bacaloglu and Herrenschmidt* A77370/00, *Hitschmann* A77556/00, *v. Ott* A77724/00, *Boudin* A77399/00, *Moser* A69471/01, *Schlosser* A77793/01, *Schenk* A74773/01, *Santi* A74764/01, *Theilhaber* A77852/01, *Dörner* A77455/01, *Baccus* A77371/01-3, *Westenhofer* A77898/02, *Walter* A77882/02, *Yamada* A74772/02, *Savage* A77787/02, *Horrocks* A77561/02, *Patricelli* A69474/02, *Parsons* A77728/03, *Goldenberg* A70728/03, *Watkins* A77886/03, *Rae* A74762/03, *Bluhm* A77390/03, *Blau* A77389/03, *Matzewscki* A77675/04, *Pollak* A77748/04, *Maes* A77657/04, *Sato* A74641/04, *Kouwer* A77602/04, A77603/11, *Mond* A77695/05, A77696/11, *Wilson* A74771/05, A77902/05, *Poli* A77747/05, *Pinto* A69510/05, *Gemmell* A77510/05, *Georgescu* A77512/05, *Gibbon* A74748/05, A74747/05, *Dambrin and Clermont* A74739/05, *Walther* A77883/06, A77884/21, *Zacharias* A77913/06, *Stewart* A77834/06, *Michaux* A77688/06, *Ferroni* A74744/06, *Albertin* A74732/06, *Dambrin* A77446/06, *Barth* A77375/07, *Andrews and Bransons* A77416/07, *Meyer* A77684/08, *Ehrendorfer* A77466/08, *Greggio* A77527/08, *Greenyer* A77526/09, *Lockhart* A77640/09, *Weichelt* A77893/10, *Jeannel and Dambrin* B11219/10, *Grube* A77532/10, *Weibel* A77890/11, A77891/13, *Verdelli* A77870/11, *Dauwe* A66939/11, *Daniels and Lankhout* A66938/11, *Philipsborn* A77736/12, *Gross* A77529/12, A77530/12, *Reichmann* A77761/12, *Seeligmann* A77814/13, *Stürzinger* A77840/13, *Jones* A77578/13, *Kubinyi* A77614/14, *Polak* A77744/15, *Porter* A77750/15, *Wolfson* A66951/15, *Engelhorn* A77471/15, *Jung* A77580/16, *Schwartz* A77809/17, *Nabitz* A77710/17, *Büchler* A77413/19, *Casper* B5528/19, *Shewman* B8719/20-1, *Judd* A77579/21, *Brown* A77408/21, *Murray* A77706/22, A77707/22, *Meigs* A70164/22, *Wolff* A77907/22, *Cova* A77439/22, *Hoon* A77559/22-3, *Petzold* A77735/23, *van Rooy* B20959/23, *Massazza* A77673/24, A77674/25, *Watson* A77887/24-5, *Pribram* A77755/25, *Gal* A77503/26, *Frank* A77497/26, *Møller* A77694/27, *Lahm* A77620/27, *v. Gusnar* A77537/27, *Ivens* A77566/27, *Atzerodt* A77368/27, *Jivatoff* B7228/27, *Bonnet* A77396/30, *London* A77642/31, *Orlova* A77717/32, *Grigorescu* A61874/32, *Thomas* A53074/33, *Proto* A28169/35.

spindle cell sarcomas (Synonyms: sarcoma fusicellulare, fibrosarcoma, fibroblastic sarcoma). Sometimes their cells are very anaplastic with many (typical and atypical) mitotic figures and occasional giant cells, while in other instances, the spindle cells are closely packed and apparently more mature. The size of the individual cells is variable even within a single tumor and it is customary to distinguish small and large cellular varieties. In some cases, intercellular fibrils can be demonstrated, especially if connective tissue stains are used. These are the growths frequently designated as "fibroblastic sarcomas" in order to distinguish them from the less mature varieties. It is striking that in early instances of spindle cell sarcomas, the malignant transformation appears to occur diffusely throughout the ovarian parenchyme rather than from any one specific focus. Numerous case reports describe the different histologic varieties of the ovarian spindle cell sarcomas.[1] The differential diagnosis between spindle cell sarcomas and fibromas is discussed in the chapter dealing with the latter. Among the manifestly sarcomatous growths the size of the nucleolus, in proportion to that of the nucleus, usually rises parallel with the degree of malignancy so that large or multiple nucleoli are an index of malignancy.[2]

The so-called *myxosarcomas* or myxoblastic sarcomas have been considered in a separate chapter (see Myxosarcomas). It appears probable, however, that they do not represent a special neoplastic entity, but arise merely as a result of mucoid degeneration within a common fibrosarcoma.

The *round cell sarcomas* are very immature neoplasms which are extremely malignant, often bilateral, and appear to occur more frequently in young children than in adults. They often have a brain-like (encephaloid) color and consistency and frequently contain necrotic and hemorrhagic areas. These tumors may consist of small cells in which the cytoplasm is hardly visible, or of larger cells with a definite cytoplasmic border surrounding the round nucleus. Some investigators sharply distinguish two varieties on this basis, namely, the small cellular, and large cellular, round cell sarcomas, but most of the neoplasms listed under this latter heading were probably seminomas. The resemblance of the round cells of these tumors to lymphocytes is rather striking in many cases.[3]

The tendency to surround blood and lymph vessels and to form "pseudo-alveolar" cell arrangements is common to all sarcomas but is particularly pronounced in the case of the round celled type. The growths in which these structures are prominent have often been referred to as "*alveolar sarcomas*".[4] It is probable, however, that many of the so-called alveolar sarcomas of the literature were carcinomas, especially seminomas or carcino-sarcomas.

The so-called *giant cell* sarcomas or mixed cellular sarcomas, contain polynuclear and polymorphonuclear giant cells which are rather reminiscent of the megakaryocytes of bone marrow. Spindle cells, as well as cellular elements of very irregular shape, may also be found in these tumors so that their structure tends to be extremely polymorph.[5] It should be kept in mind, however, that occasional giant cells occur in most fibrosarcomas, so that the difference between the latter and the typical giant cell sarcoma is merely quantitative.

The so-called "*adenosarcomas*" or "tubular sarcomas" of the ovary are somewhat reminiscent of the embryonal adenosarcomas or Wilms' embryonal tumor of the kidney. They are characterized by spindle shaped or polyhedral, sometimes myxomatous, cells which, in certain areas, tend to arrange themselves in a gland-like or tubular manner.[6] The occasional neoplasm specifically designated as "Wilms' tumor of the ovary"[7] probably also belongs to this group.

[1]*Baer* A41646/886, A43449/890, *Fraipont* A41941/887, *Price* A41997/887, A77756/887, *Wilson* A42740/888-9, *Handfield-Jones* A43462/889, *Pascale* A45193/889, *Monod* A77697/889, *Takaki* A45200/889, *De Renzi* A43572/890, *Baker* A45720/891, *Casuso* A44053/892, *Cragin* A46359/893, *Tansini* A44676/893, A44644/894, *Wiggin* A44646/894, *McLean* A77654/895, *Ivashtshenko* A74750/895, *Texier* A74767/895, *Riehm* A69466/896, *Goffe* A48381b/897, *Heuberger* A77553/897, *MacEwan* A77651/897, *Vineberg* A49160/897, *McFarland and Babcock* A50672/898, *Schwarz* A77811/899, A77810/899, *Garner* A77505/01. *Wimmer* A77903/01, *Vasiliu* A74769/01, A74770/02-3, *Clément* A77430/02, *Flatau* A77485/02, *Schmidt* A69467/03, *Rendenbach* A77763/03, *Boldt* A77393/04, *Hamonic* A74749/04, *Michelmann* A69469/04, *Galabin* A65999/06, *Beguerestain* A74734/06, *Jesset* A74753/06, A74754/06, *Czyzewicz* A77445/07, *Péraire* A77732/07, A77733/08, *Albertin* A77341/08, *Hellendall* A77547/08, *Jayle* A77572/08, *Orthmann* A77719/08, *Patel* A77730/08, *Vincent* A77875/09, *Rosenstein* A77771/09, A77772/09, A77774/28, A77773/28, A77775/29, *Gross* A77531/12, A77530/12, *Keil* A70075/12, *Fitzgibbon* A77483/13, *Foerster* A77492/14, *Souligoux and Marchak* A66949/14, *Pierre-Nadal and Bouzons* A77739/17, *Barbier* A66935/22, *Schockaert* A77799/24, *Bauereisen* A77380/25, *Zampa* B7259/27, *Krafft* A77605/27, *Kocherginsky* A96783/27, *Chueco* A61831/33.

[2]*Page and MacCarty* A95087/37.

[3]*Ranneft* A87084/878, *Mann* A41815/887, *Mallett* A44639/894, *Eckardt* A77464/895, *Meinert* A77679/897, *Fränkel* A77494/897, *Kidd* A74755/899-00, A77587/00, A77588/00, *Siedentopf* A77821/00, *Weinbrenner* A77894/02, *Flatau* A77488/03, *Kelly* A77586/06, *Coe and Coley* A77433/07, *Mariotti* A77665/10, *Young* A77911/22, *Anspach and Scheffey* A77365/22-3, *Masieri* A77671/27, *Neumann* 42642/27.

[4]*Mo* A69788/876, *Doran* A70475/884, *Vvedenski* A40810/885, *Renz* A43981/891, *Zangemeister* A48381/896, *Kötzle* A73907/898, *Schwarz* A77810/899, *Unterberger* A77864/01, A77865/07, *Erlikh* A74741/04, *Amann* A77354/08, A77353/09, *Wolff* A77906/10. *Thalrose* A77850/13. *Horvath* A77562/14, *Spinelli* A77826/23, A77827/23, *Stübler and Brandess* A76588/24.

[5]*Pilliet and Souligoux* A49035/897, *Coignerai* A77437/02, *Glockner* A70014/05, *v. Velits* A73010/06, *Amann* A77353/09, *Pucher* A77757/09, *Bell* A77385/24, *Gal* A77503/26, *Jaisohn* A64457/30, *Taylor* A77845/31.

[6]*Thomas* A77854/875-6, *Fischel* A77481/876, *Elischer* A77468/898, A50503/898, *Glockner* A70014/05, *Stefancsik* A77831/28, *Wenger* A67370/30.

[7]*Baravalle* B10813/43.

It is not impossible that some of the supposedly relevant cases were merely common sarcomas with a prevailingly perivascular or alveolar arrangement (see round cell sarcomas of the "alveolar" type), while others were carcinosarcomas. Their derivation from embryonic kidney remnants or teratoid tumors may be suspected, but too little is known about these exceedingly rare growths to justify far-reaching speculations concerning their origin. They do not appear to elicit any characteristic specific clinical manifestations.

SECONDARY CHANGES IN SARCOMAS AND IN THE REMAINING OVARIAN TISSUE: Adhesions are perhaps not as frequent in the case of sarcomas as in carcinomas, yet a review of 186 ovarian sarcomas taken at random from case reports found in the literature, indicates that in 72 of these, significant adhesions between the tumor and its surroundings were detectable; this represents an incidence of 38.7%.[1] The secondary invasion of adjacent organs is discussed below. In some instances ovarian sarcomas may extend between the laminae of the broad ligament without producing important adhesions.[2]

The frequent occurrence of *mucoid degeneration*, especially in the spindle celled sarcomas, led to the concept of the so-called myxosarcoma which is treated in a separate chapter as a special neoplastic entity. Suffice it to mention briefly that other retrogressive changes may occur with these neoplasms e.g. *necrosis* with *hemorrhage* into the tissue, *fatty degeneration, calcification* and even secondary *infection*. In this respect, however, ovarian sarcomas behave as do most other rapidly growing malignant tumors.[1]

The *ovarian remnant* is usually atrophic if at all distinguishable; generally the sarcoma cells destroy it completely.[1] The *stalk* of ovarian sarcomas, if present, connects them with the broad ligament and only in exceptional cases with the ovary itself since the latter is usually completely replaced by tumor tissue. This attachment is subject to such great individual variations and is so frequently absent that a detailed discussion of it does not appear profitable. The interested reader is referred to the relevent section in Miller's[1] monograph.

The *contralateral ovary* may be the site of endometriosis, common cysts and other neoplasms but usually it shows no characteristic changes unless the sarcoma is bilateral.[1]

OVARIAN SARCOMAS IN COMBINATION WITH OTHER OVARIAN TUMORS: If a sarcoma develops in an ovary which simultaneously bears another tumor, then as a rule it is practically impossible to distinguish between the coincidental development of two different tumors in the same ovary and the sarcomatous degeneration of the other neoplasm. Such cases are therefore discussed under the heading of sarcomatous degeneration in the articles dealing specifically with the corresponding non-sarcomatous tumors (e.g. for sarcoma and fibroma in the same ovary see Fibromas; for sarcoma and dermoid see Dermoids etc.).

OVARIAN SARCOMAS IN COMBINATION WITH EXTRAOVARIAN SARCOMAS (including metastatic ovarian sarcomas and metastases of ovarian sarcomas): The combination of ovarian sarcomas with extraovarian tumors of a similar type is extremely common and a voluminous literature has developed concerning the pathology of *ovarian metastases of extragonadal sarcomas and the metastases of primary ovarian sarcomas.*[3] Hematogenous metastases are much more common than lymphatic deposits.[1] In a series of 265 ovarian sarcomas metastases were found in 48 instances (18.1%) most frequently among the round cell sarcomas.[4] In other series the incidence of metastases is given as 24.5%,[5] 31.8%[6] and 43.6%[7] respectively, not counting the bilateral sarcomas in which the neoplasm in one ovary may have been metastatic.

Since the etiologic relationship between the tumors is freqeuntly not evident from the published data, all cases in which ovarian sarcomas develop simultaneously with extragonadal sarcomas are discussed conjointly in this chapter. By consulting the original papers, however, the reader will find at least suggestive evidence concerning the relationship between these growths in many instances. It is evident that the ovarian sarcoma may be primary and the extragonadal tumor secondary or vice versa. Furthermore, both the ovarian and the extraovarian sarcoma may be primary independent growths, or they may both be secondary to a third (sometimes not detectable) primary tumor. Finally, a primary ovarian sarcoma may spread to other organs by direct invasion, and conversely, a primary extragonadal sarcoma may directly invade the ovary.

Peritoneal sarcomatosis, when seen in conjunction with ovarian sarcomas, may be due to direct propagation of a primary ovarian growth or to simultaneous involvement of the ovary and the peritoneum secondary to a primary sarcoma of another organ.[8]

Sarcoma deposits in *lymph nodes* rarely cause any difficulty of interpretation since they are almost invariably secondary to the ovarian sarcoma. Such sarcoma deposits may be found in the mesenteric,

[1]*Miller* A18279/37.
[2]*Monprofit* A77698/887.
[3]*Müller* A77702/892, *Muratow* A77703/895, *Chiari* A77426/05, *Strassmann* A77837/06, *Kohlmann* A77600/17, *Crawford and Hebert* A68167/29.
[4]*Temesvary* A47325/895.
[5]*Baumfelder* A77381/02.
[6]*Stübler and Brandess* A76588/24.
[7]*Zangemeister* A48381/896, A77916/896.
[8]*Vonnegut* A77879/896, *Madden* A77656/899, *Stauder* A77829/02, A77830/02, *Michel and Gy* A77689/06, *Higgins* A77554/15.

retroperitoneal, inguinal, mediastinal, supraclavicular etc. lymph-nodes.[1] In these cases the spread apparently occurs along the lymphatic vessels. In one case, an ovarian sarcoma even produced a thrombosis of the *thoracic duct*.[2]

Simultaneous development of sarcomas in the ovaries and the *Fallopian tubes* is not uncommon and almost invariably due to the direct invasion of a sarcoma of one of these organs into the other.[3] The same is true of those cases in which the ovaries and the *parametria* are simultaneously affected.[4]

The association of ovarian sarcomas with sarcomas of the *uterus* is especially common.[5] All the pathogenic possibilities, outlined above for the explanation of coexistent ovarian and extragonadal sarcomas in general, must be considered in these cases.

Less commonly, ovarian sarcomas are combined with similar neoplasms in the *vagina and vulva;* in these cases the same pathogenic possibilities exist as in those in which the uterus and the ovary are simultaneously affected.[6]

The simultaneous occurrence of ovarian and *mammary* sarcomas is rare. Here it may be difficult to determine which of the two tumors is primary.[7]

Various parts of the gastrointestinal tract may show sarcomatous growths in the presence of ovarian sarcomas. Thus the *oral cavity,*[8] the *stomach,*[9] more frequently the *small and large intestine*[10] and occasionally even the *appendix*[11] can be affected.

Sarcomatosis of the *skin* is a rare accompaniment of ovarian sarcomas.[12] The occurrence of secondary ovarian melanosarcomas in patients with similar sarcomas of the skin is discussed in the article dealing with melanosarcomas.

Implantation metastases of ovarian sarcomas can occur in the *abdominal scar* following operative removal of the primary neoplasm[13] and the *abdominal wall* is sometimes involved even in the absence of any operative intervention.[14]

Skeletal sarcomas, especially neoplastic deposits in the vertebral column,[15] various long bones[16] or the clavicle[14] have repeatedly been noted in the presence of ovarian sarcomas and in such cases the identification of the primary tumor may be difficult.

The respiratory organs, especially the *pleura and lung,* may be affected simultaneously with the ovary in cases of generalized sarcomatosis[17] as may the *nasopharynx,*[18] *mediastinum,*[19] *liver,*[20] *kidney,*[21] *urinary bladder,*[22] *retroperitoneal tissue,*[23] *thigh,*[16] *pancreas,*[24] *thyroid*[25] *and adrenal.*[26]

INCIDENCE

The *general incidence* of ovarian sarcomas corresponds to 2.84% of all ovarian neoplasms as judged by a statistical study of 12,092 ovarian tumors removed surgically.[27] In a series of 1,101 ovarian tumors observed at the Mount Sinai Hospital in New York only 0.8% were sarcomas,[28] but a review of ten independent statistics published by different observers shows that the incidence of sarcomas is anywhere between 1.6-7.5% of all ovarian tumors.[29] The data of workers who surveyed smaller series are obviously more variable, but all accurate statistical surveys clearly indicate that the commonly expressed view, according to which ovarian sarcomas are great rarities, is entirely erroneous. It is probable however that, as our knowledge concerning ovarian neoplasms becomes more precise, it will be possible to differentiate an increasing number of tumors from the all too comprehensive group of "common sar-

[1]*Haas* A77539/882, *Adam* A77339/893, *Resinelli* A49192/897, *Lesieur et al.* A74756/06, A74757/06, *Meyer* A77685/31.
[2]*Bruandet and Lefas* A77410/00.
[3]*Adam* A77339/893, *Pick* A77737/894, *Heinrichs* A96832/899, *Zangemeister* A77916/896, A48381/896, *Bacaloglu and Herrenschmidt* A77370/00, *Piwowarski* A77741/05, *Bircher* A77388/07, *Grieger* A77528/12, *Manzi* A77663/27, *Jaisohn* A64457/30.
[4]*Adam* A77339/893, *Zangemeister* A77916/896, A48381/896, *Heinrichs* A96832/899, *Piwowarski* A77741/05, *v. Velits* A73010/06.
[5]*Olshausen* A41468/886, *Gardner* A41777/886-7, *Cullen* A47095/894, *Pick* A77737/894, *Vonnegut* A77879/896, *Bastianelli* A70582/896, *Dubar* A49172/897, *v. Franqué* A77499/899, *Heinrichs* A96832/899, *Krukenberg* A77613/899, *Borrmann* A77397/00, *Cohn* A70630/00, *Fränkel* A77495/01, *Polano* A64823/04, *Piwowarski* A77741/05, *Knierim* A77596/05, *Krömer* A70091/08, *Amann* A77358/11, A77357/11, *Peine* A77731/11, *Lochrane* A77639/22, *Sampson* A78939/24, *Schmid* A76478/26, *Manzi* A77663/27, *Kovacs* A64100/31.
[6]*Fischel* A77481/876, *Rossbach* A77776/888, *Frank* A73615/889, *Viering* A77871/891, *Pick* A77737/894, *Zangemeister* A77916/896, A48381/896, *Freund* A65991/899, *Bacaloglu and Herrenschmidt* A77370/00, *Piwowarski* A77741/05, *Michel and Gy* A77689/06, *Horney* A78451/13, *Erler* A77474/14, *Büchler* A77413/19, *Schröder* A77805/20, *Bruns* A65858/24, *Cameron* A77421/25.
[7]*Delbarre* A77452/870, *Fränkel* A77495/01, *Zalelsohn* A77914/11, *Schottländer* A78998/13.
[8]*Brown and O'Keefe* A77409/28.
[9]*Wingate* A29997/881, *Fränkel* A77495/01, *Schottländer* A78998/13.
[10]*Marchand* A77664/894, *Bastianelli* A70582/896, *Zangemeister* A48381/896, A77916/896, *Heinrichs* A96832/899, *Higgins* A77554/15, *Petzold* A77735/23, *Loyer and Espieux* A61881/32.
[11]*Friedländer* A77501/891.
[12]*Bruusgaard* A77412/28, *Schulz* A77806/34.
[13]*Muratow* A77703/895.
[14]*Müller* A77702/892.
[15]*Scholz* A74765/899, *Seeligmann* A82395/14, A77815/13.
[16]*Driessen* A77462/03.
[17]*Hertz* A77550/866.
[18]*Cameron* A77421/25.
[19]*Theilhaber* A77852/01, *Huguenin* A77564/09.
[20]*Higgins* A77554/15.
[21]*Schottländer* A78998/13.
[22]*Grieger* A77528/12.
[23]*Kermauner* A64880/32.
[24]*Orthmann* A77720/10.
[25]*Müller* A77702/892, *Chiari* A77426/05, *Schottländer* A78998/13.
[26]*Cohn* A77435/894.
[27]*Miller* A18279/37.
[28]*Bernstein* 81758/36.
[29]*Geist* B6672/42.

comas" and to classify them under more specific headings.

With regard to the *age incidence* of ovarian sarcomas, the most striking fact is that they frequently occur in children.[1] Many case reports describe sarcomas in newborn infants and children under 5 years;[2] 5-10 years;[3] or 10-15 years old.[4] Conversely, however, ovarian sarcomas may also occur in women aged 65 years or more[5] and the average age incidence of patients suffering from this type of neoplasm is estimated to be 32.2 years[6] or 42.7 years[7] according to the calculations of different investigators. In one statistical survey it was pointed out that 40% of the sarcoma bearers were less than 25 years old,[8] yet it would be erroneous to assume that a young age in a bearer is more characteristic of sarcomatous than of carcinomatous ovarian neoplasms[9] since even in the young, carcinomas are more common than sarcomas[10].

A statistical survey of 725 cases of ovarian sarcomas gathered at random from the literature indicates the following incidence in the various age groups: between 1 and 10 years 28; 11-20 years 108; 21-30 years 153; 31-40 years 113; 41-50 years 165; 51-60 years 103; 61-70 years 53 and 71-80 years 2 cases.[9]

There are no reliable statistical data concerning the *pregnancy incidence* of ovarian sarcomas, but a noteworthy number of case reports describe such tumors during gestation.[11]

The *puerperal incidence* appears to be very low, since only few ovarian sarcomas have been found to complicate the postpartum period.[12]

PATHOGENESIS

Little can be said concerning the *histogenesis* of the common ovarian sarcomas, except that they appear to develop from the connective tissue stroma of the gonad as a result of the same process of anaplasia and atypical growth which is the basis of sarcoma formation in general.

The occurrence of ovarian sarcomas in children with precocious puberty and in pseudohermaphroditic individuals (see part on Clinical Course) has induced some workers to regard all ovarian sarcomas as derivatives of the theca or interstitial elements, that is, cells capable of testoid hormone production;[13] this view was definitely rejected by others, however.[9] It must be admitted that there is little, if any, evidence to support such an interpretation in the case of the common sarcomas which do not produce sex hormones. On the other hand, it is highly probable that many of the so-called ordinary sarcomas in pseudohermaphroditic individuals were malignant varieties of thecomas, sarcomatous granulosa cell tumors, arrhenoblastomas or Leydig cell tumors; that is, neoplasms which, according to our classification, should not be listed among the "common sarcomas". The seminomas, which tend to develop in congenitally pseudohermaphroditic and hermaphroditic individuals, were frequently described in the old literature as large cellular sarcomas as stated above; we need not discuss these neoplasms here, however, since they are not known to be carcinomas.

In connection with the *functional pathogenesis* great emphasis has been laid upon the possible role of hereditary factors. The comparatively frequent occurrence of ovarian sarcomas in children and sterile women led to the concept that the gonads of these patients may have been congenitally abnormal and predisposed to sarcoma development even before the neoplasm became manifest in them.[14] In support of this view it was also pointed out that

[1] *Mo* A69788/876, *Malins* A43474/890, *Viering* A77871/891, *Foerster* A77491/895, *Page* A47363/895, *Baldy* A49201/898, *Jochmann* A77575/898, *Helme* A77548/00, A77549/00, *Hawkes* A75831/01, *Hubert* A77563/01, *Piwowarski* A77741/05, *Ritzmann* A77768/06, *Bazy* A77382/11, *Klemperer* A77590/13, *Horvath* A77562/14, *Higgins* A77554/15, *Outerbridge* A77726/22-3, *Polano* A64824/23, *Scheffey* A77790/25, *Southam* A64841/28, *Meyer* A77686/31, *Gittins and Hawksley* A61871/32, *Kikuti and Minakawa* A36802/40.

[2] *Geinitz* A66351/. *Revern* A66311/802, *Doran* A43416/888-9, *Viering* A77871/891, *Byford* A44013/891-2, A44049/892, *Marchand* A77664/894, *Foerster* A77491/895, *Hoffman* A49085/897, *Flatau* A77486/03, A77487/03, *Gibb* A77515/03, *Riedl* A10701/04, *Savariaud* A66957/11, *Guibal* A77534/11, *Lesage and Girault* A66954/13, *Pawlik and Lenz* A66424/13, *Smith and Motley* A77822/14, A77823/15, *Higgins* A77554/15, *Matthews* A66955/16, *Johansson* A66953/17, A77576/18, *Hayd* A77544/18, *Jantschewa* A77571/24, *Wenger* A67370/30, *Bates and Sincerbeaux* A65143/31, *Copello et al.* A62874/32.

[3] *Schröder* A77804/883, *Cohn* A42018/886, *Lucas* A10538/888, *Stolypinski* A43443/890, *Turner* A44677/892-3, *Croom* A46327/893, *McBurney* A77650/895, *Pollak* A77749/07, *Rousseau* A77779/13, *Wilkinson* A66958/15, *Presno y Bastiony* A66956/17, *Jaisohn* A64457/30, *Björkenkeim* A62056/35, A62057/36, *Gragert and Wiesener* A96032/37.

[4] *Bailey* A75826/896, *Flatau* A65978/10, *Atakam* A59873/36, *Magnin and Canepa* A97567/39.

[5] *Fasbender* A77478/880, *Gough* A77525/28.

[6] *Temesvary* A47325/895.

[7] *Stübler and Brandess* A76588/24.

[8] *Temesvary* A47325/895, *Bircher* A77388/07.

[9] *Miller* A18279/37.

[10] *Temesvary* A47325/895.

[11] *Lahs* A77621/878, *Casati* A41253/883, *Murphy* A77705/888-9, *Schwarz* A77812/891. *Temesvary* A47325/895, *Zangemeister* A77916/896, A48381/896. *Borrmann* A77397/00, *Treub* A76649/897, *Wagner* A77880/897-9, A77881/03, *Orthmann* A64820/899, *Andrews* A77362/01, *Kropeit* A77609/01, *Watkins* A77886/03, *Jacobson* A77567/04, *Boissard and Coudert* A77392/04, *Lippert* A64789/05, A76008/05, *v. Velits* A73010/06, *Bircher* A77388/07, *Wiesinger* A77901/08, *Krömer* A70091/08, *Amann* A77353/09, *v. Kubinyi* A77614/14, *Brodhead* A77406/16, *Schwartz* A77809/17, *Herzog* A77551/18, *Potvin* A77753/20, *Schockaert* A77799/24, *Stübler and Brandess* A76588/24, *Young* A77912/30, *Goecke* A64453/30, *Holtermann* A77558/32, *Barnes and Konzelmann* A28142/35.

[12] *Brodhead* A77406/16, A66937/16, *Trillat and Puthod* A52309b/34.

[13] *Klemperer* A77590/13, *Frankl* A76805/14.

[14] *Temesvary* A47325/895.

sarcomas frequently develop in women exhibiting signs of infantilism[1] or at least of deficient and abnormal menstruation[2] long before the appearance of the ovarian neoplasm. It must be admitted, however, that several investigators specifically emphasized the absence of any genital anomaly in the past history of their patients, many of whom were the mothers of numerous children[3] (see also part on Clinical Course).

CLINICAL COURSE

The clinical course of ovarian sarcomas is generally not very characteristic and is essentially the same as that of any other highly malignant ovarian neoplasm. It is noteworthy, however, that *ascites*—sometimes intermixed with blood—is rather more frequent with ovarian sarcomas than with most other malignant neoplasms of the ovary. Significant fluid accumulations in the abdomen are mentioned in many relevant case reports.[4] A review of 194 ovarian sarcomas collected from the literature showed that the incidence of ascites is 46.4%.[5] *Pleural fluid accumulations* are likewise not infrequent; they may develop with or without accompanying ascites, even in the absence of metastatic pleural sarcomatosis.[6] This tendency to cause fluid retention in the large serous cavities of the body is reminiscent of Meigs' syndrome which develops in patients bearing ovarian fibromas (see chapter on Fibromas).

Important changes may also occur in the accessory sex organs. Thus the *Fallopian tubes* may be elongated, distended or deformed due to mechanical reasons;[7] they may be deeply involved in the adhesions[8] and their mucosa may become edematous and hyperplastic.[9] In one case, an accessory tube was observed.[10] Not infrequently, hemorrhage into the tube or gangrene of this organ may result from the torsion of ovarian sarcomas.[11] The occasional simultaneous occurrence of nonspecific salpingitis[12] or tuberculosis of the tube[13] should probably be considered as incidental. The comparatively common sarcomatosis of the oviduct has already been mentioned in the paragraph dealing with ovarian sarcomas combined with extraovarian sarcomas.

Menstrual anomalies, in the form of amenorrhea, excessive uterine bleeding, post-menopausal bleeding etc. are frequently noted in the bearers of ovarian sarcomas, but their nature varies so much in the individual cases that no typical pattern can be regarded as characteristic of this neoplasm.[14] These anomalies may be due to hormonal influences emanating from the tumor, but generally they are merely the result of uterine malformations or displacements or invasion of the womb by the malignant cells (for uterine metastases of ovarian sarcomas and primary uterine sarcomas occurring in combination with ovarian metastases see Ovarian Sarcomas Combined with Extraovarian Sarcomas in part on Pathologic Anatomy). It is evident, furthermore, that important *changes in the position of the uterus* may be caused by rapidly growing ovarian sarcomas.[15]

Fibroids of the uterus are comparatively common in women with ovarian sarcomas.[16] In one series of observations, 12.5% of all ovarian sarcomas were accompanied by uterine fibroids.[17]

Endometrial polyps in the cervix or body of the uterus,[18] *endometriosis interna of the uterus*[19] and *uterine cancers*[20] may also occur in combination with ovarian sarcomas, although these are not particularly common accompaniments of such gonadal neoplasms.

In a comparatively large number of instances, signs of *precocious puberty* were noted in children

[1] *Mauthner* A70163/21.
[2] *Zangemeister* A77916/896, A48381/896.
[3] *Stübler and Brandess* A76588/24, *Kovacs* A64100/31.
[4] *Weinlechner* A86635/875, *Kiemann* A29840/880, *Harsha* A40973/885, *Coe* A77432/887, *Péan* A42617/888, *Frank* A73615/889, *Casuso* A44053/892, *Adam* A77339/893, *Pick* A44852/894, A77737/894, *Bradley* A47091/895, *Zangemeister* A48381/896, *Orthmann* A64820/899, *Stouffs* A74766/00-1, *Kropeit* A77609/01, *Pestalozza* A69509/02, *Potvin* A77753/20, *Nowak* A77714/20, *Massazza* A77673/24, A77674/25, *Brown and O'Keefe* A77409/28, *Warren* A65191/31.
[5] *Miller* A18279/37.
[6] *Fischel* A77481/876, *Kelly* A43608/890, *Ladouce* A45619/890, *Shaw-Mackenzie* A46547/892, *Zangemeister* A48381/896, *Resinelli* A49192/897, *Freund* A65991/899, *Cova* A77439/22, *Warren* A65191/31.
[7] *Robb* A77769/891, *Romiti* A77770/891, *Oppenheim* A77716/894, *Zangemeister* A48381/896, A77916/896, *Kelly* A77586/06.
[8] *Seeger* A76511/888.
[9] *Oppenheim* A77716/894, *Zangemeister* A77916/896, A48381/896.
[10] *Krukenberg* A77613/899.
[11] *Zangemeister* A77916/896, A48381/896, *Thorn* A77855/00, *Judd* A77579/21.
[12] *Ravano* A76362/08.
[13] *Ivens* A77566/27.
[14] *Malins* A29905/881, *Cohn* A42018/886, *Adam* A77339/893, *Oppenheim* A77716/894, *Temesvary* A47325/895, *Zangemeister* A77916/896, A48381/896, *Stauder* A77829/02, A77830/02, *Baumfelder* A77381/02, *Krebser* A77607/03, *Schmidt* A69467/03, *Glockner* A70014/05, *Lippert* A64789/05, A76008/05, *Mauthner* A70163/21, *Wehse* A77889/24, *Stübler and Brandess* A76588/24, *Gough* A77525/28, *Kleefisch* A65552/30, *Bonnet* A77396/30, *Taylor* A77845/31, *Geist and Matus* A64760/33, *Chavannaz and Roche* A64745/36.
[15] *Adam* A77339/893, *Zangemeister* A48381/896, A77916/896, *Dubois* A50688/898, *Freund* A65991/899, *Baumfelder* A77381/02, *Gascheau* A70001/03, *Piwowarski* A77741/05, *Glockner* A70014/05, *Wehse* A77889/24, *Ivens* A77566/27.
[16] *Viguier* A77872/872, *Lang* A77626/884, *Desbonnets* A47136/895, A47484/895, *Schuster* A77807/898, *Heinrichs* A96832/899, *Freund* A65991/899, *Schlosser* A77793/01, *Knauer* A77595/02, *Poli* A77747/05, *Glockner* A70014/05, *McGlinn* A75322/06, *Wiener* A77900/06, *Löwit* A77641/11, *Rouffart* A77778/13, *Jones* A77578/13, *Erler* A77474/14.
[17] *Lippert* A64789/05, A76008/05.
[18] *Zangemeister* A48381/896, A77916/896, *Schuster* A77807/898, *Erler* A77474/14, *Bruns* A65858/24.
[19] *Cova* A77439/22, *Fitzgerald* A77482/26, *Gough* A77525/28.
[20] *Schmorl* A77796/898, *Hessel* A77552/05, *Schauta* A77789/07, *Brewis* A73372/07-8, *Horney* A78451/13, *Weibel* A76725/13, *Kaufmann* 39132/22, *Ferguson* A77480/23-4, *v. Gusnar* A77537/27.

with ovarian sarcomas.[1] In these cases, premature menstruation and breast development, precocious growth of pubic hair and other signs of abnormally early sexual maturation were seen in newborn infants or very young children.

In other instances, signs of *pseudohermaphroditism* were observed,[2] occasionally in combination with precocious puberty.[3]

In the light of present day concepts concerning the hormonal activity of ovarian tumors, it is extremely doubtful whether ovarian sarcomas, which elicit metrorrhagias, uterine fibroids, endometriosis, precocious puberty or signs of virilization, should be listed among the common ovarian sarcomas. Their classification depends upon the question whether these changes are due to hormones produced by the sarcoma or merely represent accidental accompaniments of the neoplasm. In all such cases the observer must consider the possibility of malignant thecomas, sarcomatoid granulosa cell tumors or arrhenoblastomas with a sarcomatoid stroma, since these are the tumors capable of sex hormone production. On the basis of purely histologic evidence a differential diagnosis between these various types is frequently impossible, hence it appears more logical to classify sarcomas with clinical manifestations of this type among the hormone-producing ovarian neoplasms of the folliculoma and arrhenoblastoma type. It should be kept in mind, furthermore, that—as mentioned above—there is a great similarity between certain round cell sarcomas and the ovarian seminomas. This led to a good deal of confusion in the old literature since seminomas are known to occur frequently in congenitally pseudohermaphroditic or hermaphroditic patients. The presence of cartilage in several of the so-called virilizing sarcomas[4] raises the suspicion that in some instances, sarcomatous teratomas were the underlying neoplasms associated with the development of pseudohermaphroditic traits.

Milk secretion by the mammary gland has also repeatedly been noted in women with ovarian sarcomas;[5] in such cases the underlying hormonal mechanism has not been clarified as yet.

None of the demonstrably hormone-producing sarcomas should be listed among the "common sarcomas" in the sense in which these neoplasms are here defined.

COMPLICATIONS

Circulatory disturbances, often elicited especially by large and metastasizing sarcomas, may lead to edema of the abdominal wall[6] or the legs,[7] a typical caput medusae[8] or varicose veins in the lower extremities.[9] One ovarian sarcoma even caused an obstruction of the superior vena cava through metastases in its vicinity.[10]

Increased intra-abdominal pressure is probably at least a predisposing factor in the formation of the inguinal, crural or umbilical *herniae* which have repeatedly been observed in women with ovarian sarcomas.[11]

A chronic type of *peritonitis* with peritoneal hyperemia, proliferative changes and occasional hemorrhages is not uncommon in patients with rapidly growing sarcomas of the ovary; it may play a part in the development of peritoneal fluid accumulations.[12] The frequently occurring peritoneal sarcomatosis has been discussed in the part on pathologic anatomy.

In many instances ovarian sarcomas cause complications due to *obstruction of the intestinal tract*[13] by invasion or compression of its walls. In such cases resection of intestinal segments may become necessary.

Obstruction of the ureter or renal pelvis[14] may result from direct invasion by the malignant cells, or from pressure exerted by the growing tumor mass. This complication may necessitate the resection of parts of the ureter and frequently results in pyelitis, pyelonephritis or at least hydronephrosis. *Interference with the urinary bladder* itself in the form of simple displacement[15] or actual invasion[16] by ovarian sarcomas has also been noted.

Rupture of cystic sarcomas into the abdominal

[1]*Geinitz* A66351/, *Revern* A66311/802, *Lucas* A10538/888, *Croom* A46327/893, *Riedl* A10701/04, *Guibal* A77534/11, *Savariaud* A66957/11, *Pawlik and Lenz* A66424/13, *Polano* A64824/23, *Jantschewa* A77571/24, *Halban* 26394/25, *Southam* A64841/28, *Jaisohn* A64457/30, *Frank* 58775/32, *Gragert and Wiesener* A96032/37.

[2]*Krug* A77612/891, *Unterberger* A77864/01, A77865/07, *Chauvel* A77425/07, *Bégouin* A77384/09, A77383/09, *Wolff* A77906/10, *Magnan and Pozzi* A94732/11, *Miloslavich* A77692/11, *Halban* 26394/25, *Brown* A80126/31.

[3]*Revern* A66311/802, *Brown* A80126/31.

[4]*Goldberg* A80131/28, *Frank* 58775/32, *Krock* A80136/33.

[5]*Unkraut* A77863/893, *Zangemeister* A48381/896, A77916/896, *Schmidt* A69467/03. *Donati* A77457/04, *Glockner* A70014/05.

[6]*Szurminski* A70542/872. *Frank* A73615/889, *Adam* A77339/893, *Cealâc* A74737/04, *Piwowarski* A77741/05.

[7]*Fischel* A77481/876. *Unkraut* A77863/893, *Zangemeister* A48381/896, A77916/896, *Dubois* A50688/898, *Elischer* A77468/898, *Kropeit* A77609/01, *Piwowarski* A77741/05, *Glockner* A70014/05, *Erler* A77474/14, *Higgins* A77554/15, *Bonnet* A77396/30.

[8]*Haas* A77539/882, *Ladouce* A45619/890, *Zangemeister* A48381/896, A77916/896, *Elischer* A77468/898, *Roxburgh* A77781/899. A77782/899, *Napier* A51009/899.

[9]*Michel and Gy* A77689/06.

[10]*Revilliod* A77766/07.

[11]*Zangemeister* A48381/896, A77916/896, *Piwowarski* A77741/05.

[12]*Haas* A77539/882, *Zangemeister* A48381/896, A77916/896, *Heinrichs* A96832/899. *Kropeit* A77609/01.

[13]*Stratz* A77838/893, *Bastianelli* A70582/896, *Zangemeister* A48381/896, A77916/896, *Petzold* A77735/23.

[14]*Viering* A77871/891, *Adam* A77339/893, *Vonnegut* A77879/896, *Bastianelli* A70582/896, *Wolff* A77906/10.

[15]*Baumfelder* A77381/02, *Wolff* A77907/22.

[16]*Viering* A77871/891.

cavity[1] or the Fallopian tubes[2] may help to spread the malignant cells. *Hemorrhage, torsion and suppuration* of ovarian sarcomas may also lead to severe complications (see Sect. IV, Vol. VI).

DIAGNOSIS

The clinical diagnosis of ovarian sarcomas has been the subject of several *reviews*.[3] It must generally be based on presumptive evidence only, since these neoplasms do not produce any pathognomonic symptoms. The development of a rapidly growing, often solid, ovarian neoplasm should always raise the suspicion of a sarcoma, but final identification of the tumor must be made dependent upon the histologic study of a tissue specimen.

In view of this great lack of characteristic symptoms it is not surprising that few ovarian sarcomas have been diagnosed on the basis of clinical evidence alone, and confusion with other ovarian tumors, such as *common cysts or carcinomas*,[4] and even normal *pregnancy*[5] has repeatedly occurred. Positive urinary hormone findings will help to distinguish the hormone-producing tumors from the common sarcomas.

PROGNOSIS

It is evident from several pertinent statistical surveys[6] that untreated ovarian sarcomas always terminate fatally. Even in the event of extensive surgical or radiation therapy, the prognosis is generally bad and recurrences are very common.[7] Complete recoveries or at least prolonged survivals may occur, however, if radical surgical interventions remove all malignant cells before metastases have formed.

In early cases even comparatively conservative interventions, in which the uterus and one ovary are saved, may effect a cure and such patients may subsequently go through a normal pregnancy.[8]

If the diagnosis of an ovarian sarcoma is definitely confirmed by histologic evidence, radical interventions are always to be recommended, however, since the danger of malignant recurrences far outweighs the possible advantages of conservative operations.

THERAPY

As stated in the part on the prognosis of common ovarian sarcomas, the only recommended therapy is the complete surgical removal of the neoplasm together with the contralateral ovary, the uterus and the tubes. In spite of the highly malignant nature of these sarcomas, surgical therapy has yielded satisfactory results in many cases, especially if the operation was performed at an early stage.[9] For the extensive radical operations which have to be performed in the case of ovarian sarcomas, suprapubic laparotomies are necessary, although occasionally ovariectomies through the vaginal route have been attempted.[10]

Complicating factors in the surgical treatment of ovarian sarcomas may be incidental adhesions to a ureter[11] or other organs in the vicinity of the neoplasm. If important adhesions connect the tumor with the intestine, parts of the digestive tube may have to be resected simultaneously with the ovarian neoplasm.[12]

X-ray therapy is advisable only in the case of inoperable ovarian sarcomas or as a postoperative prophylactic measure to prevent recurrences.[13]

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[1]*Fourmeaux* A47440/896, *Perkins* A66928/12, *Koster* A77601/25.

[2]*Fabricius* A77476/896.

[3]*Richmond* A45672/891, *Pagenstecher* A77727/11, *Anspach* A77364/30, *Novak* A63534/41, B109/44.

[4]*Pierre-Nadal and Bouzons* A77739/17.

[5]*Laws* A77628/14.

[6]*Pick* A44852/894, *Erler* A77474/14, *Postel* A77751/21, *Goldschmidt and Körner* A77523/27.

[7]*Beigel* A86790/869, *Alexander* A45683/891, *Göcke* A77519/32.

[8]*Routier* A44071/891, *Schockaert* A77800/28, A77801/28.

[9]*Grube* A87121/864, *Macfarlan* A87136/872, *Dow* A75470/877, *Atlee* A86327/877, *Creus* A87103/878, A41348/883, *Thomas* A87165/879-80, *Bottini* A29534/880, *Chiarleoni* A40234/882, *Patterson* A40551/882, *Omboni* A41268/882, *Oliver and Page* A77715/883, *Cauchois* A77422/886, *Sacré* A41789/887, *Zemann* A77917/888, *Rossbach* A77776/888, *Lucas* A10538/888, *Osterloh* A77722/888-9, *Reed* A45257/889, *Raymond* A74763/889, *Pascale* A45193/889, *Matlakowski* A43580/890, *Morton* A45599/890, *Ludlam* A45796/891, *Romiti* A77770/891, *Porter* A45871/891, A74758/891, *Routier* A44071/891, *Byford* A44013/891-2, *Casuso* A44053/892, *Laroyenne* A46430/893, *Repelin* A77765/893, *Tansini* A44676/893, A44644/894, *Brindel* A74736/894, *Lipinski* A47462/895, *Mason* A77672/895, *Desbonnets* A47484/895, A47136/895, *Mann* A77662/895, *Meek* A77676/896-7, *Jessett* A50542/898-9, *Nunez* A69473/899, *Rayner* A77760/01, *Vasiliu* A74769/01, *Purcell* A74761/01-2, *Krebser* A77607/03, *Jacobson* A77568/05, *v. Velits* A73010/06, *McKay* A77652/06, *Menge* A77681/07, *Chauvel* A77425/07, *Janczewski* A77570/08, *Stone* A77836/10, *Erler* A77474/14, *Murphy* A66944/15, *Schneider* A77798/27.

[10]*Chueco* A61831/33.

[11]*Osterloh* A77723/10.

[12]*Jessett* A45179/889, *Michaux* A77687/06.

[13]*Seeligmann* A77816/13, A77817/13, *Spinelli* A77826/23, A77827/23, A77828/23, *Frank* 58775/32, *Wintz* A95126/37.

PARA-OVARIAN COMMON SARCOMAS

Primary para-ovarian sarcomas are extremely rare neoplasms which represent the malignant variety of the corresponding para-ovarian fibromas. Histologically, most of them prove to be fibrosarcomas of the broad ligament.[1]

It is very probable that the vast majority of these tumors develop from pre-existing connective tissue cells in the para-ovarian region, although the occasional case is described as a "sarcoma of the parovarium"[2] or an "adenosarcoma of the parovarium".[3] As regards their histogenesis, it is assumed that these sarcomas generally arise owing to malignant transformation of para-ovarian fibromas and, in some cases, this derivation appeared extremely probable.[4]

Secondary sarcomas of the para-ovarian region may develop as a result of the implantation in the pelvic ligaments of metastases derived from sarcomas of other organs.[5] Primary sarcomas of the sacral vertebrae may directly invade the broad ligament and thus give rise to sarcomatous neoplasms in the para-ovarian region.[6]

[1]*Wathen* A49094/897, *Baron* A91461/898, *Limnell* A91471/899, A91472/00, *Bucco* A91463/01, *Wack* A91460/08, *Jacub* A91468/13, *Lauwers* A91469/13, *Rosenfeld* B6510/13, *Venot and Coiquaud* A91476/14, *Davies* A91464/14-5, *May* A91564/25.

[2]*Cortiguera* A48246/896.
[3]*Werth* A73082/895.
[4]*Rouville* A91571/24, *Forgue and Crousse* A91555/25.
[5]*Lauwers* A91469/13.
[6]*Bonifield* A91462/03, *Witherow* A91478/03.

OVARIAN COMMON SARCOMAS IN ANIMALS

Ovarian sarcomas are exceptional among animals, as judged by the available data. Two so-called ovarian sarcomas in the bird[1] are not described in sufficient detail to permit their exact classification. In another series of 8 cases[2] ovarian tumors of the Rous sarcoma types were found which probably arose from the interstitial cells and macrophages of the ovarian stroma.

[1]*Bulliard and Champy* A64213/31.

[2]*McGowan* A67342/30.

OVARIAN MYXOSARCOMAS

Synonyms: Myxoblastic sarcoma, malignant myxoma.

Sarcomatous transformation of ovarian fibromas which have undergone mucoid degeneration appears to account for most of the so-called myxosarcomas and myxofibrosarcomas of the literature; some of them may have been primarily malignant myxomatous growths. They contain atypical spindle- or star-shaped cells in a mucoid intercellular substance which gives a positive mucicarmine reaction.[1] One such myxosarcoma weighed as much as 17.2 kg.[2]

In some instances the presence of chondromatous[3] or angiomatous[4] admixtures suggests a teratoid origin, but too little is known about these exceedingly rare neoplasms to justify a more detailed discussion.

A *myxosarcoma of the parovarium* has also been claimed to occur.[5]

[1]*Monprofit* A77699/887, *Kluge* A77593/894, *Krecke* A77608/897, *Hanley* A74588/03-4, *Piwowarski* A77741/05, *Olshausen* A70876/05, *Pfannenstiel* A64886/08, *Boni* A77395/08, *Erler* A77474/14, *Pribram* A77755/25, *Van Tine* A66950/25, *White and Brunton* B16176/27, *Bozzolo* A77401/31, *Hixson* A64768/36.

[2]*Rouville et al.* A77780/26.

[3]*Jacobs* A53043/34.

[4]*Bozzolo* A77401/31

[5]*De Pena and Aguirre* A90239/05.

PLATE XXXVIII

VARIOUS MESENCHYMAL TUMORS

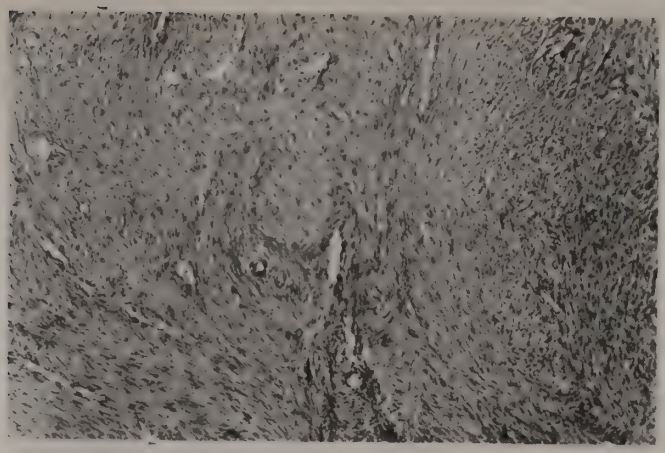


Fig. 1. FIBROMYOMA OF THE OVARY (courtesy of Dr. H. T. Karsner). Note that the entire tumor consists of interlacing strands of connective tissue and smooth muscle fibers.

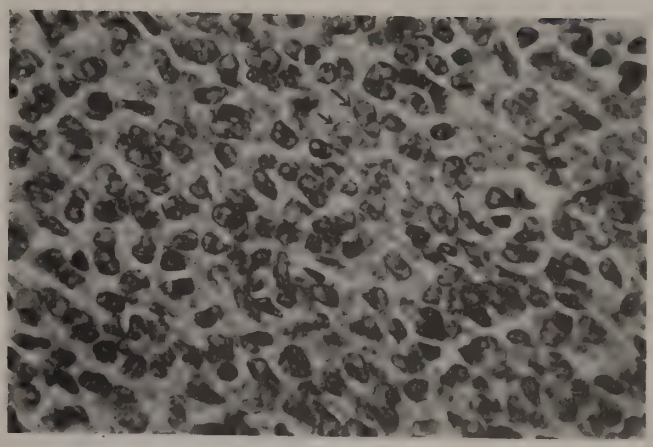


Fig. 2. SPINDLE-CELL SARCOMA OF THE OVARY. Part of this tumor consisted of entirely typical, benign fibroma tissue, while other parts were highly atypical and showed a direct transition of the benign fibroma into the malignant, spindle-cell sarcoma. Note polymorph appearance of nuclei which contain unusually large nucleoli. In some cells a marked indentation of the nucleus is seen in the vicinity of the nucleolus (some such cells are marked by arrows). These indented nuclei are very different from those illustrated in the plate on Brenner tumors.

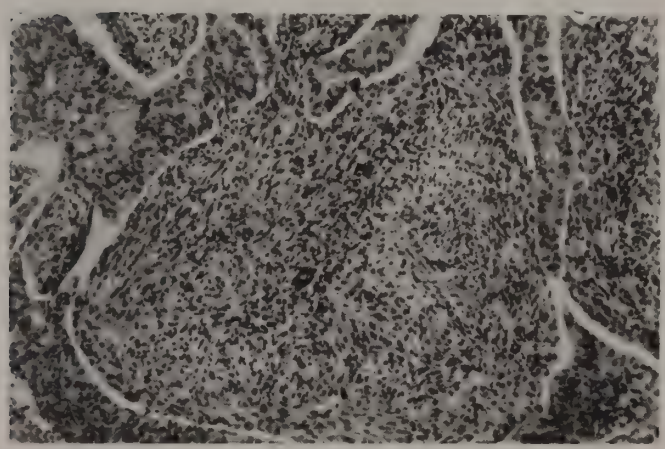
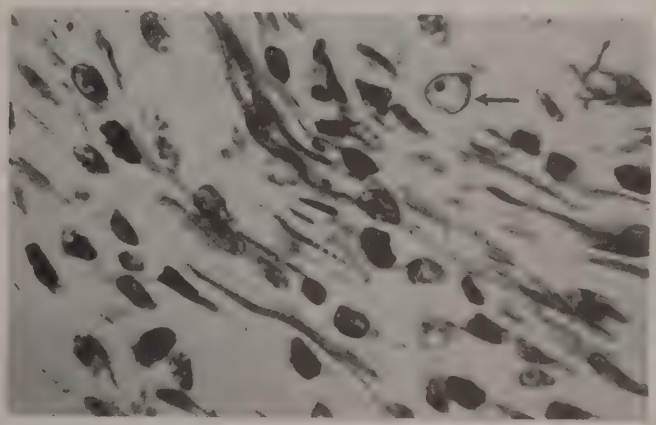


Fig. 3. CARCINO-SARCOMA OF THE OVARY (courtesy of Dr. L. Berger). Carcino-sarcoma interpreted as a malignant, solid teratoid tumor. Note carcinomatous, obviously epithelial tubules in the periphery of the field and a solid, sarcomatous formation in the center; the latter contains several giant cells. The remainder of this neoplasm consisted throughout of closely interwoven carcinomatous and sarcomatous elements.



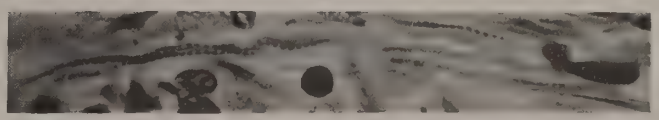


Fig. 4a and 4b. RHABDOMYOSARCOMA OF THE OVARY. (courtesy of Dr. L. Berger). Two fields in a typical rhabdomyosarcoma of the ovary showing bundles which consist of striated muscle fibrils. Note also polymorph nuclei, containing unusually large nucleoli. One such nucleus is marked by an arrow.

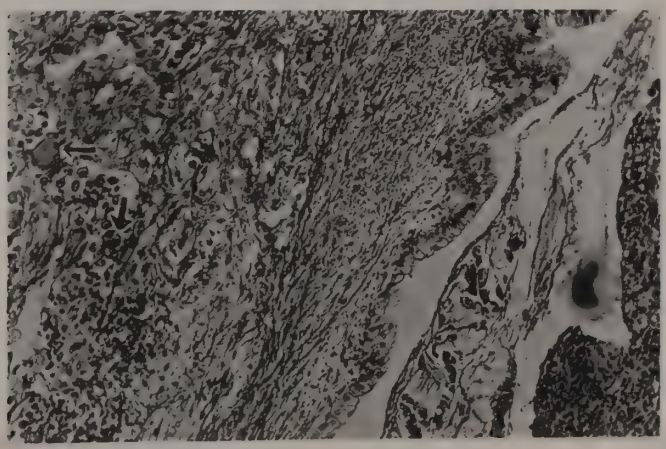


Fig. 5. ATYPICAL AREA OF A RHABDOMYOSARCOMA. Another field in the neoplasm illustrated in Figs. 4a and b. Note a cyst lined by an irregular epithelium in the right part of the field and several giant cells (marked by arrows) in the left part of the field. In this region, no differentiation into striated muscle cells has occurred; the presence of the epithelium suggests the teratoid origin of such tumors.

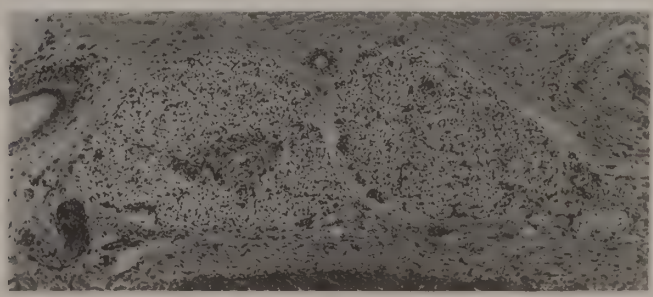


Fig. 6. PHEOCHROMOCYTOMA? OF THE BROAD LIGAMENT (courtesy of Dr. L. Berger). Two accumulations of chromaffin cells within the broad ligament in the vicinity of the ovary. The cells are entirely typical and differentiated; it is very doubtful whether such small ectopic tissue accumulations should be regarded as adenomas.

OVARIAN MELANOSARCOMAS

Synonyms: Malignant melanomas, sarcomatous melanoblastomas.

Melanosarcomas of the ovary have been described in several case reports[1] and, although they are very rare tumors, in some instances they even develop bilaterally.[2]

Their structure resembles that of similar tumors found in other organs. *Macroscopically* they are conspicuous because of their dark, bluish or black color and *histologically* they are characterized by the presence of pigmented mesenchymal chromatophores. Their cells may be round, spindle shaped or more or less irregular; generally they contain numerous melanin-like pigment granules. Mitotic figures are usually prominent and frequently atypical. Some infiltration with round cells and occasional areas of liquefaction necrosis as well as hemorrhages into the neoplastic tissue may also be detected.[3] These tumors tend to be very malignant and to produce widespread *metastases* in various organs.[4] In several cases the melanosarcoma tissue appears to have developed within common cysts.[5]

The *incidence* of melanosarcomas is difficult to estimate but it is obvious that they are among the rarest ovarian neoplasms. Several cases have been observed during pregnancy.[6]

With regard to their *pathogenesis* it is generally assumed that most of the ovarian melanosarcomas are secondary metastases of primary tumors originating in tissues which normally contain mesenchymal melanophores such as the choroid, iris or ciliary body of the eye, the pia arachnoid, the adrenals, the colon, pigmented moles and naevi of the skin etc.[7] Sometimes the ovarian metastases develop years after ablation of a primary pigmented tumor of the skin or eye.[8] Another possible source is the sarcomatous transformation of pigmented areas in teratoid ovarian tumors, especially dermoids (see also chapter on Teratoids).

Some investigators definitely deny the existence of *primary ovarian melanosarcomas*[9] although several cases have been described in which there was every reason to believe that the tumor originated in the gonad.[10] In many of these, the pathogenesis of the neoplasm could not be explained, since other teratoid elements were not detectable. It is quite possible, however, that they could be derived from teratoid tumors in which the melanosarcoma tissue destroyed all other elements.

Clinically these tumors have no typical manifestations other than those characteristic of melanosarcomas in other organs, combined with the physical signs of a rapidly growing neoplasm in the ovarian region. In rare instances an ovarian melanosarcoma may cause diffuse discoloration of the skin or may elicit complications due to torsion and hemorrhage.[11] In one peculiar case a black ovarian cyst was found with multiple black nodules in the peritoneum. The growth was considered to be an inoperable melanosarcoma. Three years later a normal pregnancy ensued although both urine and milk were black. A laparotomy 20 years later revealed a cystadenocarcinoma in a constantly growing cyst but the melanosis of the tumor and the peritoneum vanished.[12]

The preoperative *diagnosis* is next to impossible although it may be suspected in the case of metastatic neoplasms in which the presence of a detectable melanosarcoma, for instance, of the eye or skin, is noted simultaneously with an ovarian growth. At operation, however, the dark bluish-black color of these tumors is of some diagnostic significance.

If no tumor masses are found outside of the ovary, bilateral oöphorectomy and hysterectomy are the only logical *therapeutic procedures* which may give satisfactory results.[11]

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[1] *Hayne* A88323/862-3, *Basso* A66936/08, A77376/08, *Geraudel* A77513/09, *Markus* A77666/10, A77667/11, *Mauclaire* A66941/11, *Bondi* A77394/13, *Labhardt* A77615/14, *Herzog* A77551/18, *van Hoosen* A77867/22, *Frank* A77497/26, *Wiemer* A77899/28, *Valdman-Gurevitch* A65675/28, *Ranck* A77759/30, *Lambillon and Naulaerta* A97184/38, *Mauclaire* A66941/41.

[2] *Ranck* A77759/30, *Otken* A56056/42.

[3] *Miller* A18279/37, *Otken* A56056/42.

[4] *Marshall* A77668/05, *Markus* A77667/11, *Vogt* A77877/12, A77878/13, *Labhardt* A77615/14, *Strumia* A77839/34, *Ruffel* A77785/35.

[5] *Marshall* A77668/05, *Bab* A77369/06.

[6] *Markus* A77666/10, A77667/11, *Labhardt* A77615/14.

[7] *Mangelsdorf* A77661/05, *Dawson* A77451/22, *Schwab* A77808/25.

[8] *Nowak* A77714/20, *Schwab* A77808/25, *Wiemer* A77899/28, *Ranck* A77759/30.

[9] *Miller* A18279/37

[10] *Andrews* A77362/01, *Westenhöfer* A77898/02, *Amann* A73194/03, A77348/03, A77349/03, A77350/03, *Bab* A77369/06, *Winternitz* A77905/09, *Soubeyran and Rives* A66948/11, A77824/11, *Lahm* A77618/14, *Nowak* A77714/20, *Otken* A56056/42.

[11] *Otken* A56056/42.

[12] *Stewart* A82398/13.

OVARIAN LYMPHOSARCOMAS

In the case of generalized lymphosarcomatosis, deposits in the ovaries are only occasionally observed[1] and primary ovarian lymphosarcomas are great rarities.[2] A microphotograph of a "leucosarcoma of the ovary" in a woman with generalized leucosarcomatosis has been published without further comment.[3]

In all the purportedly relevant cases special attention must be given to the differential diagnosis between small common round cell sarcomas and true lymphosarcomas. The demonstration of a net-like argentaffine reticulum between the neoplastic lymphocytes is of diagnostic significance.

Ovarian lymphosarcomas have been seen in children.[4]

The point of origin of primary ovarian lymphosarcomas is highly debatable but their development from teratoid tumors or from the small lymphatic accumulations occasionally seen within the ovarian stroma must be considered.

[1]*Hugueuin* A77564/09, *Ghon and Roman* 46712/16, *Brown* A77408/21, *Brown and O'Keefe* A77409/28, *Kaufmann* 39132/31, *Wegelin* A77888/32, *Muscatello* A61887/33, *Walther* A77885/34, *Vasconcellos and Finocchiaro* A97322/38.

[2]*Petta* A77734/24, *Durfee et al.* A95248/37.

[3]*Geist* B6672/42.

[4]*Van Horne* A63476/32, *Wright* A77910/35.

OVARIAN MYELOMAS AND CHLOROMAS

A myeloma of the ovary which consisted mainly of typical plasma cells was found in the ovaries of a patient who subsequently developed a fracture of the femur due to another myeloma in this bone.[1] An additional case was described as a "tumoral myelosis" which developed simultaneously in both ovaries[2] and yet another as "sarcome à myeloplaxes de l'ovaire".[3] In patients with myeloid or lymphatic leukemia, greenish chloromas of the ovaries have occasionally been observed[4] but these tumors are exceedingly rare and deserve no special attention since they merely represent ovarian manifestations of a general disease.

Two instances of ovarian tumors in the fowl are apparently relevant since the growth consisted predominantly of myelocytes and premyelocytes.[5]

[1]*Kermauner* A64880/32.
[2]*Sammartino and Herrara* A97436/39.
[3]*Pilliet and Souliquoux* A49035/897.

[4]*Butler* A77415/07, *Schlagenhaufer* A77792/12, *Derman and Lifschitz* A77453/32.
[5]*McCowan* A67342/30.

OVARIAN LIPOMAS AND LIPOSARCOMAS

Several reports have appeared in the literature purporting to describe *lipomas* of the ovary.[1] In some cases the neoplasm was designated as "teratolipoma"[2] or "adenolipoma",[3] suggesting that the tumor was a one-sidedly developed teratoma or an adenoma with lipomatous stroma.

Some of the "lipomas" appear to have been self-amputated epiploic appendages which became adherent to the ovary, but did not represent true ovarian neoplasms.[4] In other instances, however, the possibility of a true benign, primary fat tissue tumor of the ovary must be considered seriously, although in our opinion the existence of these neoplasms has still not been proven beyond the possibility of doubt.

Simple lipomas of the ovary are of no clinical significance beyond the fact that they may elicit symptoms due to their physical presence in the gonad.

The so-called *liposarcomas* of the literature[5] were probably ovarian metastases of extragonadal liposarcomas and deserve only cursory mention here.

[1]*Parona* A45736/891, *Magnani* A70527/26-7, *v. Szathmary* A70530/29, *Herrmann* A62880/32, *Fahr* A98111/41.
[2]*Marré* A70528/15.
[3]*Hamilton* A91968/02, A91969/03.

[4]*v. Szathmary* A70530/29.
[5]*Tison* A77857/889, *Daniel et al.* A77448/33-4, *Daniel and Babes* A28148/35.

PARA-OVARIAN LIPOMAS

Para-ovarian lipomas are rare neoplasms the majority of which is probably secondary. Some may arise from the fat cells of the para-ovarian region, but in many instances it appears more likely that the neoplasms originate in the retroperitoneal fat tissue and expand secondarily into the broad ligament.[1] In rare instances lipomas arise from the oviduct.[2]

As regards their *size,* they vary from small lipomatous nodules, to an occasional very large tumor. One so-called "fibrolipoma" of the right broad ligament weighed 13 lbs.[3] In fact, the real danger of these endocrinologically "silent" neoplasms, which have no great tendency to become malignant, is their size, which may cause them to compress the pelvic organs and make their surgical removal extremely difficult.[4]

Bilateral symmetrical lipomas of the broad ligament have also been observed.[5]

As regards their *clinical course,* the para-ovarian lipomas are very similar to those of the retroperitoneal space. Their main characteristics are the above mentioned tendency to become very large, their benign nature, and the fact that they usually produce symptoms only by virtue of their volume.[6]

The *prognosis* of para-ovarian lipomas is excellent, except for the technical difficulty of removing the larger ones. Spontaneous regressions are not seen, but after surgical extirpation only few cases show recurrences, since malignant transformation is rare.[6]

The only effective *therapy* of para-ovarian lipomas is the surgical removal of the entire growth.[6]

[1]*Pollock* B6514/832, *Peyrot* B6513/875, *Treves* A46603/892-3, *König* B6515/00, *Friese* A91274/07, *Borrmann* A91285/07, *Proust and Trebes* B6472/08, *Lockyer* A91332/18-9, *Schickele* A91572/23, *Rawls* A91569/25-8, *Kanter* A91560/35.
[2]*Sampoerno* B12304/29.
[3]*Griffith* A91321/18-9.
[4]*Proust and Trebes* B6472/08.
[5]*Emrya-Roberts* A91313/09.
[6]*Forgue and Crousse* A91555/25.

OVARIAN CHONDROMAS AND CHONDROSARCOMAS

Pure ovarian *chondromas* are certainly extremely rare and indeed their very existence is still somewhat doubtful. Under the name of chondroma, enchondroma or chondroblastoma of the ovary a number of tumors have been described, some of which were diagnosed merely on the basis of the cartilaginous appearance of the structure on naked eye inspection.[1] This is obviously not permissable, since fibromas, and even fibrous connective tissue scars around old abcesses, may have a cartilage-like appearance and consistency. In other instances, it appears justifiable to suspect that the tumor was a fibroma or scirrhous carcinoma with myxomatous and perhaps partly cartilaginous metaplasia of connective tissue elements.[2] In some of the remaining purportedly relevant cases it is rather probable that the tumor was a teratoma with especially prominent development of cartilaginous tissue.[3]

The so-called *chondrosarcomas,* are also exceedingly rare and likewise appear to be either teratoid in nature or to result from the sarcomatous degeneration of mesodermal tumors in which cartilaginous metaplasia has taken place.[4]

Apparently primary *para-ovarian chondrosarcomas* have been observed in the broad ligament.[5] They may have been of teratoid origin.

[1]*Dlauhy* A70544/846, *Kiwisch* A70081/852, *Virchow* A77876/863, *Klob* A70086/864, *Scanzoni* A70261/867.
[2]*Reiss* A70553/882, *Schröder* A70555/883, *Brieger* A78098/883.
[3]*Oliver* A49149/897, *Solomons and Dockeray* A35157/40.
[4]*Jung* A70546/04, *Emanuel* A70545/04, *Meyer* A70551/04, *Kehrer* A70547/06, *Goldberg* A77520/22, *Pistolese* B7087/26.
[5]*Durck* A91465/897, *Desoll* A91292/899.

OVARIAN OSTEOMAS AND OSTEOSARCOMAS

While ossification is not uncommon in a variety of ovarian tumors (see Sect. IV, Vol. VI) and bone formation is very characteristic of ovarian teratoids (see chapter on Teratoids), it is questionable whether true primary osteomas and osteosarcomas can originate in the female gonad. So few supposedly relevant cases of ovarian *osteomas,*[1] *osteosarcomas*[2] and *osteochondrosarcomas*[3] have been reported in the literature that it would be impossible to present a critical discussion of this tumor group.

A purportedly *para-ovarian osteoma* has been seen in the broad ligament.[4]

[1]*Binet* A70543/30.
[2]*Donati* A77457/04.
[3]*Donati* A80314/04.
[4]*Routier* A91351/05.

OVARIAN LEIOMYOMAS

Synonyms: Myoma, ovarian fibroid. The latter term is ambiguous, being loosely used to designate pure fibromas or leiomyomas as well as fibromyomas.

REVIEWS

ENGLISH: Baldy A75307/02, A75308/02, *Watson* A70506/07, *Geist* B6672/42.

FINNISH: Basilier A70464/19.

FRENCH: Estor et al. A66904/20.

GERMAN: Miller A18279/37.

HUNGARIAN: Steiner A70504/34.

ITALIAN: Giannettasio and Lombardi A75320/02.

POLISH: Cohn A70474/899.

PORTUGUESE: Brito A95237/37.

RUSSIAN: Cholmogorow A70473/09.

SPANISH: Benzadon A97140/38.

SWEDISH: Franzen A70482/12.

DEFINITION

Leiomyomas of the ovary are benign neoplasms of smooth muscle tissue. As stated in the chapter on fibromas, there are many intermediate types between the latter and the pure leiomyomas. Hence it is impossible to demarcate these two tumor entities sharply. In agreement with common usage the pure leiomyomas and the "fibromyomas" will be discussed conjointly in this section since they consist exclusively, or at least predominantly, of neoplastic smooth muscle tissue.

Additional borderline cases will be found in the chapter on fibromas which also includes the "myofibromas". These are mixed tumors consisting of both connective tissue and smooth muscle cells with the former prevailing.

HISTORY

The leiomyomas of the ovary have been known to pathologists for a long time as indicated by relevant reports in the older literature.[1] Since at least the pure leiomyomas rarely produce important clinical manifestations, it is understandable that these neoplasms attracted more attention from pathologists than from gynecologists. It is noteworthy, furthermore, that even as late as 1932 certain pathologists denied the very existence of pure ovarian leiomyomas.[2]

PATHOLOGIC ANATOMY

MACROSCOPIC CHARACTERISTICS: The *shape* of the ovarian leiomyomas is generally round and their surface smooth or slightly nodular.[3] Their *size* varies from a few millimeters[4] to several inches in diameter.[5] The largest leiomyomas on record weighed 11 and 15 kg. respectively[6] and one was described as being the size of a football.[7]

Generally these neoplasms are encapsulated.[8]

On the cut surface, the *color* of the leiomyomas is usually more reddish than that of the fibromas.[9] Occasionally, however, it may be yellowish.[10] Another rather characteristic feature of the leiomyomas is the formation of "whirls" which is quite striking upon inspection of the cut surface.[11] Connective tissue septa from the capsule, which invade the reddish tumor tissue, tend to subdivide it into smaller nodules detectable by the naked eye.[12]

The *pedicle* of leiomyomas is similar to that of the fibromas.[3]

Bilateral ovarian leiomyomas have been noted repeatedly.[13]

Numerous *case reports* describe the characteristics of the ovarian leiomyomas,[14] although the identity of some purportedly relevant neoplasms is somewhat doubtful. Thus one tumor which had first been identified as a leiomyoma,[10] was later—perhaps incorrectly[3]—held to be a muscle cell-containing mixed-cellular myxosarcoma.[15] Two other supposedly pertinent neoplasms[16] were probably metastases of pylorus and gallbladder cancers respectively.[3]

MICROSCOPIC CHARACTERISTICS: Leiomyomas consisting only of smooth muscle cells are extremely rare, since some degree of fibrous tissue proliferation is almost invariably noticeable. In addition to the more or less typical smooth muscle fibers which constitute the major portion of the tumor tissue, blood and especially lymph vessels

[1] *Hayem* A70485/870, *Doran* A70475/884, A47996/898, A70478/02, *Brewis* A70467/888, *Bagot* A70461/890, A45747/890, *Feis* A44656/894, *Wiener* A70507/899, *Orthmann* A70499/899, *Henrotin and Herzog* A70486/899.
[2] *Kermauner* A64880/32.
[3] *Miller* A18279/37.
[4] *Küstre* A70491/870, *Krömer* A70091/08, *Miller* A18279/37.
[5] *Henrotin and Herzog* A70486/899, *Frankl* A70481/20.
[6] *Caillot* A28146/35.
[7] *Campbell and Lewis* A65890/06.
[8] *Baldy* A70463/02, *Krömer* A70091/08.
[9] *Doran* A65947/888, A70478/02, *Wiener* A70507/899.
[10] *Basso* A65810/05.
[11] *Doran* A70478/02, *Campbell and Lewis* A65890/06.
[12] *Doran* A47996/898, *Wiener* A70507/899, *Frankl* A70481/20.
[13] *Jacoby* A45618/890, *Schopf* A75333/893, *Tesauro* A62953/32.
[14] *Giannettasio and Lombardi* A75319/01, *Baldy* A70463/02, *Maiss* A70494/02, *Strumer* A75334/04, *Lanphear* A74661/06, *Jordan* A70488/07, *McGregor* A70493/07, *Atanasescu* A70459/90, *Frankl* A70481/20, *Gough* A70484/27, *Bär* A70460/29, *Godlewski* A70483/31, *Färber* A70479/34, *Steiner* A53107/34, *de Cunha Junior and Pirese Alberququerque* B10815/42.
[15] *Krömer* A70091/08.
[16] *Jacoby* A45618/890.

may be very prominent;[1] at least in one instance a large number of thin, partly medullated, nerve fibers were evident in a leiomyoma of probably ligamentous rather than ovarian origin.[2]

Among the *secondary changes* which may affect ovarian leiomyomas, *adhesions* are comparatively rarely of any importance.[3] In one case a leiomyoma underwent complete *suppuration*[2] but since the ovaries themselves appeared to have no connection with the tumor, it is doubtful whether this was a correctly diagnosed case.

Edema, sometimes described as mucification,[4] may be very prominent and lead to the formation of fluctuating small cavities within the tumor, so that the neoplasm assumes a cystic appearance.[5] *Fatty degeneration*[6] or *hyalinization* has only rarely been seen.[7] The exceptional *sarcomatous transformation* of ovarian leiomyomas[8] will be discussed in the chapter on leiomyosarcomas.

The *ovarian remnant* may disappear completely following substitution by the tumor mass,[9] but sometimes considerable portions remain detectable.[10]

Generally the *contralateral ovary* remains intact, although it may occasionally be the site of cyst formation[11] or may contain an adenomyoma[12] or a carcinomatous cyst.[13]

INCIDENCE

The general incidence of leiomyomas is so low that this must be regarded as one of the rarest ovarian neoplasms. No data are available, therefore, concerning such details as its age incidence, except that most of the cases described in the literature occurred in adult women between 20 and 53 years of age.[14] Cases have been noted in pregnant women.[15]

PATHOGENESIS

It is somewhat doubtful whether ovarian leiomyomas are derived from the smooth muscle fibers of the ovarian ligaments which enter the gonad,[16] or whether they originate from the vascular musculature.[17] It has been stated in favor of the latter interpretation that even in serial sections it is impossible to show any continuity between the ovarian smooth muscle fibers and those of the neoplasm, since the former do not enter the tumor stalk. (The possibility that a degeneration of the muscle fibers in the much exposed stalk may lead to their secondary disappearance does not appear to have been considered.) Conversely, the muscle fibers of the media appear to continue directly into those of the blastoma and at some places the vessels in the tumor have no muscle tissue of their own.[18]

CLINICAL COURSE

In a comparatively large number of cases, smooth muscle tumors of the ovary are accompanied by the development of *uterine fibroids.*[19] In one instance, the uterus was greatly dilated due to traction by the ovarian growth.[18]

Although this has never been specifically emphasized, there appears to be a counterpart to Meigs' syndrome among the ovarian leiomyomas and fibromyomas. Many of these neoplasms are accompanied by more or less pronounced *ascites*[20] and there may also be marked edema of the legs[21] although cases with pleural fluid accumulations have not come to our attention as yet.

Otherwise, the clinical course of the ovarian myomas is generally uneventful and its manifestations are not sufficiently characteristic to permit a clinical *diagnosis.*

Complications rarely occur although in one case there was a serious hemorrhage.[22] Another case occurred in a patient suffering from Pringle's disease and was somewhat complicated by hypertrophy and hyperplasia of sebaceous glands, neurofibromas of the skin, tuberous sclerosis, congenital cystic disease of the lungs, mesenchymal rests in the kidneys and retroperitoneal tissues, and recent hemorrhages into renal calyces.[23]

The only recommended *therapy* of ovarian leiomyomas is the conservative surgical removal of these growths.[24]

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[1] *Basso* A65810/05, *Lahm* A70492/14, *Bär* A70460/29.
[2] *Veyssière* A70505/870.
[3] *Campbell and Lewis* A65890/06, *Bär* A70460/29.
[4] *Baldowsky* A65804/08.
[5] *Wiener* A70507/899.
[6] *Pomorski* A70223/889.
[7] *Wiener* A70507/899, *Basso* A65810/05, *Lahm* A70492/14, *Bär* A70460/29.
[8] *Bortkewitsch* A70466/13.
[9] *Henrotin and Herzog* A70486/899, *Bär* A70460/29.
[10] *Orthmann* A70499/899, *Münchmeyer* A70497/02.
[11] *Wiener* A70507/899, *Adeodato Filho* A97573/39.
[12] *Cholmogorow* A70473/09.
[13] *Färber* A70479/34.
[14] *Miller* A18279/37.
[15] *Münchmeyer* A70497/02, *Luxardo* A82419/08.
[16] *Doran* A70478/02, *Krömer* A70091/08.
[17] *Henrotin and Herzog* A70486/889.
[18] *Basso* A65810/05.
[19] *Küster* A70491/870, *Kelly* A70489/894, *Schultze* A70501/898, *Baldy* A70463/02, *Seeligmann* A70502/08, *Amann* A70458/08, *Basilier* A70464/19, *Albrecht* A70457/23, *Bär* A70460/29, *Tessauro* A62953/32.
[20] *Cholmogorow* A70473/09, *Franzen* A70482/12, *Basilier* A70464/19, *Frankl* A70481/20.
[21] *Bär* A70460/29.
[22] *Dobranski* A62876/32.
[23] *Warren and Wesley* 84524/43.
[24] *Mazzoni* A87140/877, A87141/878, *Peruzzi* A29320/879, *Carter* A75312/888, *Doran* A93040/892, *Schopf* A75333/893, *Ema et al.* A46426/893, *Calderini* A70469/893, *Kelly* A70489/894.

PARA-OVARIAN LEIOMYOMAS

The pure leiomyomas and so-called fibromyomas of the para-ovarian region are rare neoplasms. In their histologic characteristics, they resemble the corresponding ovarian neoplasms. These growths probably develop from smooth muscle cells, pre-existent in the broad ligament,[1] round ligament[2] or Fallopian tube.[3]

Although many para-ovarian myomas are merely small, firm, roundish nodules, others may reach a considerable *size*.[4] Sometimes, they enclose *cystic* cavities. Upon closer investigation, however, these usually prove to be pedunculated intraligamentous uterine fibroids.[5]

The most important point in connection with the differential diagnosis of para-ovarian myomas and fibromyomas is their separation from uterine fibroids or uterine myomas which grow into the broad ligament. This differentiation is particularly difficult in the case of subserous cervical myomas of the uterus which may only be connected by a small pedicle with the body of the womb.[6]

As judged by the comparatively few relevant case reports, these neoplasms have little if any tendency to become malignant and they only produce symptoms owing to their expansion, with the resultant compression of other pelvic organs. In the event of surgical removal the prognosis is good. In a singular case galactorrhea ensued following surgical ablation of a fibromyoma of the round ligament.[7]

The only advisable therapeutic measure is the conservative ablation of the neoplasm.

[1]*Gardner* A91316/898, *Godart* A91319/898-9, *Harpel* A91325/02, *Edge* A91311/04, A91310/04-5, *Schiffman* A91356/17, *Hasselrot* A91559/23, *Goldschmidt* B12274/29, *Pokrovsky and Baisheva* B12298/29, *Vidrine and D'Aunoy* B1038/30, *Arrillaga and Courtis* B21527/37, *Masi and Marini* B7729/38, *Catone* B21405/39, *Counseller and Stalker* B21417/39, *de Campos* B15731/42.

[2]*Kleff* B12236/29, *Aman-Jean* B12152/30, *Mayo and Schunke* B15756/40, *Correa da Costa* B7846/43.

[3]*Hibbitt* B11674/22, *Meyer* B16152/27, *Hochloff* B12279/29, *Percival* B12295/29.

[4]*Hirst* A47455/895, *Küster* A91329/02.

[5]*Langley* A91561/29, *Witherspoon* A62959/32.

[6]*Giles* A91318/898.

[7]*Peltier de Quieroz* B7743/38.

OVARIAN LEIOMYOSARCOMAS

Under the name of leiomyosarcoma, malignant leiomyoblastoma, fibromyosarcoma, or myofibrosarcoma, a variety of ovarian tumors have been described, all of which are characterized by the presence of malignant smooth muscle cells.[1] They may be primarily malignant ovarian neoplasms or the result of sarcomatous transformation in an originally benign leiomyoma.

One such case was seen in a 71-year old woman with "persistent menstruation",[2] but in a postscript to his presentation the author states that "since this specimen was shown it has been suggested privately by Professor Newcomb and Mr. Wilfred Shaw that this tumour may be a xanthofibroma thecacellulare."

[1]*Wolff* A77908/895, *Steele* A74643/898-9, *Geraudel* A77513/09, *Bartkewitsch* A70466/13, *Stein and Bloom* A70967/29, *Perez et al.* A98087/41.

[2]*Peel* A34549/39.

OVARIAN LEIOMYOMAS AND LEIOMYOSARCOMAS IN ANIMALS

In a *fish* (*Macropodus opercularis L.*) the development of a large ovarian leiomyoma was accompanied by cystic degeneration of the ovarian remnant and great distention of the abdomen. At the same time the anterior parts of the body became completely depigmented, although there is no definite proof that the depigmentation was causally related to the development of the ovarian blastoma.[1]

In the ovary of a *mule* a "leiomyoma cavernosum malignum" was found and from the description given it is very probable that this neoplasm belonged to the hemangiosarcomas.[2]

A sarcomatous leiomyoma of the ovary in a *pig*[3] was found to metastasize into the uterus.

[1]*Klemm and Freund* 6523/30.

[2]*Serra* B6556/29.

[3]*Lutgens* B6581/33.

OVARIAN RHABDOMYOSARCOMAS

A number of ovarian neoplasms containing striated muscle fibers were described as rhabdomyosarcomas or rhabdomyomas.[1] Not all of them appear to have been definitely malignant but some were evidently sarcomas, exhibiting all the characteristics of highly anaplastic growths. These neoplasms are also extremely rare and do not deserve a detailed discussion.

A *para-ovarian rhabdomyosarcoma* of the round ligament[2] has also been described and apparently in *birds* infectious *metastatic rhabdomyosarcomas* may develop in the ovaries.[3]

[1]*Virchow* A77941/850, *Vignard* A43493/889, *Grieger* A77528/12, *Himwich* A77937/20, *Leopold* A77939/28, *Barris and Shaw* A77936/28-9, *Kuhn and Gaudemet* A77938/29, *Lanza* A95447/39.
[2]*Figurelli* B12357/33.
[3]*Peyron* B8653/21.

OVARIAN HEMANGIOMAS AND HEMANGIOSARCOMAS

Hemangiomas of the ovary are extremely rare neoplasms and only a few cases have been described. Generally, they consist of numerous intercommunicating blood vessels and do not differ essentially from corresponding neoplasms found in other organs.[1]

Not infrequently these neoplasms contain large vascular spaces, separated only by thin, sometimes edematous, connective tissue septa and then they are termed "cavernous hemangiomas" or "cavernomas" of the ovary.[2] Sometimes the ovarian hemangioma is merely one manifestation of a generalized tendency to form similar tumors in various organs.[3] Related neoplasms have been described under such names as "hemangio-endothelioma intravasculare of the ovary"[4] and "tumeur angio-myomateuse de l'ovaire".[5] It does not appear profitable to discuss the structure of these rare neoplasms in great detail, especially since their essential characteristics are expressed by the designations chosen for them.

The clinical characteristics of ovarian hemangiomas cannot be clearly outlined on the basis of the few available case reports. Suffice it to say that the presenting symptoms were repeatedly those of torsion (see Sect. IV, Vol. VI) and in one case there was a good deal of ascites reminiscent of that seen in Meigs' syndrome.[6]

The *hemangiosarcoma* or angiosarcoma represents the malignant variety of the hemangioma and is also exceedingly rare.[7] In a series of 1,101 ovarian tumors which required operative interventions, 3 instances of angiosarcomas occurred.[8] In some of these instances differentiation from lymphangiosarcomas is impossible and it is very doubtful whether "endotheliomatous",[9] or "peritheliomatous"[10] angiosarcomas should be recognized as distinct tumor entites (see chapters on Endotheliomas and Peritheliomas).

[1]*Szurminski* A70542/872, *Jones* A42687/889, *Stamm* A70541/891, *Braithwaite* A70532/894, *Ricketts* A83489/05, *Keller* B8205/27, *Presno Bastiony and Puente Duany* B6059/29, *Shearer* A28068/35.
[2]*Payne* A70538/868-9, *Gottschalk* A70535/888, A70534/888, *Marckwald* A44809/894, *Schaeffer and Cancelmo* A33602/39, *Ackermann* A98131/42.
[3]*Payne* A70538/868-9, *Stamm* A70541/891.
[4]*Fujii* A59926/36.
[5]*Albot and Choquart* A64411/30.
[6]*Keller* A70536/27.
[7]*Rheinstaedter* A69755/878, *Cullen* A47095/894, *Worthington* A77909/897, *Meyer* A77685/31.
[8]*Bernstein* 81758/36.
[9]*Federlin* A69696/03, A79882/04.
[10]*Steinhaus* A83490/00, *Uffreduzzi* A83491/05.

OVARIAN LYMPHANGIOMAS AND LYMPHANGIOSARCOMAS

Lymphangiomas are among the rarest ovarian tumors. They generally consist of closely packed lymphatic vessels varying in size and shape. These vessels are lined by the usual flat endothelial cells and possess very thin vascular walls. Occasionally, secondary changes such as necrosis, hemorrhage and edema, may occur in the tumor tissue.[1] In two instances lymphangiomas developed within dermoid cysts.[2]

The clinical symptomatology of ovarian lymphangiomas is not characteristic, and pre-operatively only the presence of an ovarian growth can be diagnosed at best. It is important to remember, however, that even if the histologic appearance of the neoplasm is benign at the time of the operation, recurrences with malignant transformation and fatal lymphangiosarcomatosis may ensue.[3] Hence, should the neoplasm be recognized during the operation, radical procedures appear to be justified. Since only a few cases have been reported, however, it is impossible to make any generalizations concerning this growth.

[1]*Krömer* A70091/08, *Fleischer* A70533/22, B21003/23, *Siddal and Clinton* A95108/37, *Rice et al.* A58773/43.

[2]*Schottlaender* A68633/06, *Rössle* A70539/12, A70540/12.

[3]*Rice et al.* A58773/43.

PARA-OVARIAN LYMPHANGIOMAS

It has been claimed that some para-ovarian cysts which arose following complete ovariectomy were of lymphatic origin.[1]

[1]*Hamant and Cornil* A94023/27.

OVARIAN ENDOTHELIOMAS

Synonyms: Mesothelioma, sarco-endothelioma, hemangio-endothelioma, capillary-angiosarcoma.

It is of *historic* interest that Leopold,[1] and Marchand[2] were first to describe a special group of ovarian tumors which they derived from the vascular endothelium and considered to be identical with the endotheliomas observed in other organs. Subsequently, a voluminous literature developed in connection, with supposedly relevant *case reports*.[3] Subdivision into specific sub-groups has even been attempted and some investigators speak of "endothelioma cysticum myxomatodes ovarii",[4] "hemangioendothelioma intravasculare ovarii",[5] "endothelioma ovarii lymphaticum",[6] "sarco-endothelioma",[7] "pseudochorionepitheliomatous ovarian hemangioendothelioma",[8] or "endothelioma ovarii lymphaticum cysticum".[9] Several so-called endotheliomas have been observed within dermoids.[10]

The resemblance of the so-called ovarian endotheliomas to various types of alveolar carcinomas

[1]A68346/878, A77633/878.

[2]A70821/880.

[3]*Jones* A42687/889, A44259/892-3, *Eckardt* A42602/889, *Pomorski* A69409/890, A43376/890, *v. Rosthorn* A44100/891, *Kime* A69703/891-2, A90205/892, *Müller* A44210/892, *Voigt* A47089/894, *Pick* A47084/894, *Bellati* A79864/895, *Bode* A77391/896, *Kötschau* A79904/896, *Rosinski* A48328b/896 *Guffroy* A69697/897, *Burckhard* A79872/898, A50991/899, *Trovati* A47987/898, A50559/898, *Fränkel* A79885/898, A79886/12, *Heinrichs* A96832/899, *Wiedersheim* A79937/00, Buday A79871/00, *Brouha* A79868/00, *Haacke* A79893/01, *Apelt* A69695/01, A79860/02, *Bruckner* A79869/01, *Garrigues* A69700/02, *Soubeuran* A69411/02, *Kadigroboff* A69702/03, *Lange* A79910/03, *Godart* A83358/03, *Lincoln* A69704/03, *Heinricius* A69701/04, *Landsberg* A70785/04, *Papaioannou* A78806/04, *Barbour* A69698/05, *Freeland* A79887/05, *Procopio* A74760/05, A68524/08, *Cigheri* A79876/06, *Kayser* A79903/06, *Brewis* A79866/06-7, A79867/07-8, *Espelet* A79880/07, *Kworostansky* A79907/08, *Carl* A79874/09, *Cosentino* A79877/09, A68508/10, *Schottländer* A79928/09, A79929/13, *Ferguson* A79883/09-10, *Ligabue* A79912/10, A68518/10, *Outerbridge* A79918/11, *Illner* A79900/12, A79901/12, *Giltscher* A79888/12, A79889/13, *Benthin* A79865/13, *Steinharter* A68526/13, *Oldfield* A79917/14, *Fothergill* A79884/14, *Hoffman* A79898/17, *Ashe* A79861/19, *Hamant* A77541/20, A66952/20, *Cappellani* A68463/21, *McCullagh* A79915/25-6, *Sunada* A79932/27, *Barnard* A79862/27-8, *Cattaneo* A78144/29.

[4]*Velits* A79934/888, A43384/890.

[5]*Sovak and Carabba* A65180/31.

[6]*Heinricius* A79894/04, *Eymer* A79881/09, *Spiro* A79931/12.

[7]*Hamant* B8706/20.

[8]*Horalek* A61876/32.

[9] *Herz* A79896/899, A79897/899, *Linck* A79914/00, *Schürmann* A69410/03, *Kubo* A79906/09.

[10]*Faguet* A47488/895, A47138/895, A75299/895, A75300/895, *Lanelongue and Faguet* A73946/896, *Spencer* A76554/17-8.

and sarcomas is so striking that it is highly probable that most, if not all, the supposedly relevant tumors were not true endothelial growths. This is certainly true of the numerous instances of Krukenberg tumors which were originally described as endotheliomas, but later recognized to be metastatic carcinomas.[1] A careful study of the relevant literature induced several prominent pathologists to doubt the existence of true ovarian endotheliomas[2] and Miller[3] goes so far as to state specifically that "the endothelioma of the gonad is a fiction: there is no endothelioma of the gonad", yet even in comparatively recent years instances of supposedly endotheliomatous ovarian tumors continue to be published.[4]

[1]*Sternberg* A79059/06.
[2]*Polano* A64823/04, *Ewing* A64873/42.
[3]A18279/37.
[4]*Holtermann* A79899/32, *Gittins and Hawksley* A61872/33, *Dougal* A79878/34.

OVARIAN PERITHELIOMAS

The literature contains many descriptions of ovarian tumors which were believed to be peritheliomas.[1] One of these occurred within a dermoid cyst[2] and another in the gonad of a woman whose other ovary contained a dermoid cyst.[3]

Miller [4] pointed out, however, that there is no reason to differentiate such tumors from common ovarian sarcomas which exhibit a tendency towards perivascular infiltration. He emphasized that perithelia do not occur within the ovary and hence should not be considered a possible source of tumor formation.

[1]*Voigt* A77934/895, *Pollak* A77933/898, *Krukenberg* A77930/899, *Mirabeau* A77932/899, *Amann* A77919/01, *Böhm* A77922/01, *Gräfe* A77928/04, *Lewers* A77636/07-8, *Goth* A77927/08, *Doran and Lockyer* A65954/08-9, *Bender and Proust* A77921/09, *Zinsser* A77935/11, *Lenzi* A77931/11-2, *Brettauer* A77923/13, *Hendry* A77929/23, *Donald* A77925/24, *Schmitz* A79927/25, *Babes and Rapile* A77920/26.
[2]*Neumann* A76206/899.
[3]*Whiteford* A68789/13-4.
[4]A18279/37.

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LIST OF PERIODICALS

A. Eder, Aerztl. Ber. - See: Aerztl. Ber. d. Priv.-Heilanst Wien, d. Dr. A. Eder.
A. M. J. (London) - Association Medical Journal (London).
A. Research Nerv. & Ment. Dis., Proc. - Association for Research in Nervous and Mental Disease, Proceedings.
A. for the Study of Int. Secr., - Association for the study of Internal Secretions.
A. Scient. & Tech. Soc. South Africa - Association of the Scientific and Technical Society of South Africa.
Abeille méd. - Abeille médicale.
Abhandl. d. Gerichtsarzneyk. -
Abhandl. d. naturwiss. Vereins (Hamburg) -
Abst. Doct. Diss. - Abstracts of Doctoral Dissertations.
Abst. Tr. Hunterian Soc. -
Acad. argent. de cir., Bol. y trab. - See: Bol. y trab., Acad. argent. de cir.
Acad. nat. curios. - Academia naturae curiosorum.
Acad. roy. de Belg., Bull. de la cl. d. sc. - Académie royale de Belgique, bulletin de la classe des sciences.
Accad. med. (Genova) - Accademia medica (Genova).
Accion méd. (La Paz) - Accion médica, (La Paz).
Acta Acad. nat. curios. - Acta, Academia naturae curiosorum.
Acta biol. belg. - Acta biologica belgica.
Acta biol. exper.(Warszawa) - Acta biologiae experimentalis (Warszawa).
Acta brev. Neerland. - Acta brevia Neerlandica.
Acta chir. Scandinav. - Acta chirurgica Scandinavica.
Acta Convent. tertii de trop. atque malariae morbis. - Acta conventus tertii de tropicis atque malariae morbis.
Acta dermat. - Acta dermatologica (dermatologia, syphilidologia et urologia).
Acta dermat. -venereol. - Acta dermato-venereologica.
Acta Gynec. Scandinav. - Acta gynecologica scandinavica.
Acta Helvet. Basilae - Acta Helvetica Basilae.
Acta leidensia scholae med. trop. - Acta leidensia scholae medicinae tropicae.
Acta med. Fac. Vytauti Magni Univ. Kaunas - Acta medicinae Facultatis Vytauti Magni Universitatis Kaunas.
Acta med. in Keijo - Continued as Keijo J. Med.
Acta med. Orient. - Acta Medica Orientalia, The Palestine and Near East Medical Journal.
Acta med. (Patavina) - Acta medica (Patavina).
Acta med.(Philippina) - Acta medica (Philippina).
Acta med.,(Rio de Janeiro) - Acta medica (Rio de Janeiro).
Acta med.Scandinav. - Acta medica Scandinavica.
Acta med. URSS. - Acta medica URSS.
Acta neerl. morph. - Acta neerlandica morphologiae normalis et pathologicae.
Acta obst. et gynec. Scandinav. - Acta obstetricia et gynecologica Scandinavica.
Acta odont. Scandinav. - Acta odontologica Scandinavica.
Acta ophth. - Acta ophthalmologica.
Acta ophth. orient. - Acta ophthalmologica orientalia.
Acta orthop. Scandinav. - Acta orthopaedica Scandinavica.
Acta oto-laryng. - Acta oto-laryngologica.
Acta paediat. - Acta paediatrica.
Acta path. et microbiol. Scandinav. - Acta pathologica et microbiologica Scandinavica.
Acta physiol. Scandinav.-Acta physiologica Scandinavica.
Acta psychiat. et neurol.- Acta psychiatrica et neurologica.
Acta radiol. - Acta radiologica, (Stockholm).
Acta radiol. et cancerol. bohem. et morav. - Acta radiologica et cancerologica bohemiae et moraviae.
Acta rheumatol. - Acta rheumatologica.
Acta scholae med. univ. imp. in Kioto - Acta scholae medicinalis universitatis imperialis in Kioto.
Acta Soc. med. fenn. duodecim. - Acta Societatis medicorum fennicae duodecim.
Acta Soc. med. Havn. -
Acta tuberc. Scandinav. - Acta tuberculosea Scandinavica.
Acta Union internat. contre cancer - Acta de l'Union internationale contre le cancer.
Actas dermo-sif. - Actas dermo-sifiliograficas.
Actas de las ses. d. Cong. region. d. cien med., (Cadiz). -
Actinoter. - Actinoterapia.
Actual. méd.-chir. - Actualités médico-chirurgicales.
Actual méd. (Granada). - Actualidad médica. (Granada).
Actual. méd. mund. - Actualidad médica mundial.
Actual. méd. peruana - Actualidad médica peruana.
Adv. mod. Biol. (russ). -
Advances Enzymol. - Advances in Enzymology and Related Subjects.
Aerobiology - Aerobiology.
Aerztl. Ber. d. k. k. allg. Krankenh. zu Wien -
Aerztl. Ber. d. Privat-Heilanst Wien, d. Dr. A. Eder. -
Aerztl. Int.-Bl., (München).-
Aerztl. Mitte. a. Baden - Aerztliche mitteilungen aus und für Baden.
Aerztl. Monatschr. - Aerztliche monatschrift.
Aerztl. Praxis - Aerztliche praxis.
Aerztl. Rundschau - Aerztliche rundschau.
Aerztl. Sachverst.-Ztg. - Aerztliche sachverstandigen-zeitung.
Aesculape - Aesculape.
Afrique franç. chir. - Afrique française chirurgicale.
Air Surgeon's Bull.- The air Surgeon's Bulletin.
Akad. Anz. (Wien.) - Akademischer Anzeiger.
Akus. i Ginek. - Akusherstvo i ginekologica.
Akusherka - Akusherka, obshchedostupnyĭ meditsinskii zhurnal.
Alabama M. J. - Alabama Medical Journal. (Vols. 1-12 publ. as Alabama M. & S. J.)
Alabama M. & S. J. - Alabama Medical & Surgical Journal. (Formely Alabama Medical Journal).
Albany M. Ann. - Albany Medical Annals.
Alcmeone - Alcmeone.
Algérie méd. - Algérie médicale.
Alienist & Neurol. - Alienist and Neurologist.
Alkaloid. Clin.(Chicago)- Alkaloidal clinic (Chicago).
Állatorv. Lap. - Állatorvosi Lapok.
Allg. med. Central.-Ztg. - Allgemeine medizinische central-zeitung.
Allg. Wien. med. Ztg. - Allgemeine Wiener medizinische zeitung.
Allg. Zellforsch. u. mikr. Anat. - Allgemeine zellforschung und mikroskopische anatomie. See: Ztschr. f. Zelforsch. u. mikr. Anat.
Allg. Ztschr. f. Psychiat. - Allgemeine Zeitschrift für Psychiatrie und ihre Grenzgebiete mit Beilage Zeitschrift für psychische Hygiene.
Am. A. on Ment. Deficiency - American Association on Mental Deficiency.
Am. Biol. Teacher - American Biology Teacher.
Am. Diabetes A. Proc. - American Diabetes Association. See: Proceedings of the American Diabetes Association.
Am. Gynec. - American Gynecology.
Am. Gynec. J. - American gynecological journal.
Am. Gynec. & Obst. J. - American gynaecological and obstetrical journal.
Am. Heart J. - American Heart Journal.
Am. J. Anat. - American Journal of Anatomy.
Am. J. Botany - American Journal of Botany.
Am. J. Cancer - American Journal of cancer. (Ceased publication)..
Am. J. Clin. Med. - American Journal of Clinical Medicine.
Am. J. Clin. Path. - American Journal of Clinical Pathology.
Am. J. Dent. Sc. - American Journal of Dental Science.
Am. J. Dermat. & Genito-Urin. - American journal of dermatology and genito-urinary diseases.
Am. J. Digest. Dis. - The American Journal of Digestive Diseases.

Am. J. Dis. Child. - American Journal of Diseases of Children.
Am. J. Hyg. - American Journal of Hygiene.
Am. J. Hyg., Monographic Series - American journal of hygiene. Monographic series.
Am. J. Insan. - American Journal of Insanity.
Am. J. M. Jurisp. - The American Journal of Medical Jurisprudence. (Ceased publication).
Am. J. M. Sc. - American Journal of the Medical Sciences.
Am. J. M. Technol. - The American Journal of Medical Technology.
Am. J. Med. - American journal of medicine. (is vol. 2, 1-6 of Am. M. & S. J.).
Am J. Ment. Deficiency - American Journal of Mental Deficiency.
Am. J. Nursing American Journal of Nursing.
Am. J. Obst. - American Journal of Obstetrics & Diseases of Women & Children.
Am. J. Obst. & Gynec. - American Journal of Obstetrics and Gynecology.
Am. J. Ophth. - American Journal of Ophthalmology.
Am. J. Orthodontics - American Journal of Orthodontics and Oral Surgery.
Am. J. Orthopsychiat. - American Journal of Orthopsychiatry.
Am. J. Path. - American Journal of Pathology.
Am. J. Pharm. - The American Journal of Pharmacy and the Sciences Supporting Public Health.
Am. J. Phys. Anthropol. - American Journal of Physical Anthropology.
Am. J. Physiol. - American Journal of Physiology.
Am. J. Psychiat. - The American Journal of Psychiatry.
Am. J. Psychol. - The American Journal of Psychology.
Am. J. Pub. Health - American Journal of Public Health and the Nation's Health.
Am. J. Roentgenol. - American Journal of Roentgenology and Radium Therapy.
Am. J. Surg. - American Journal of Surgery.
Am. J. Surg. & Gynec. - American Journal of surgery and gynecology.
Am. J. Syph., Gonor. & Ven. Dis. - American Journal of Syphilis, Gonorrhea and Venereal Diseases.
Am. J. Trop. Med. - American Journal of Tropical Medicine.
Am. J. Vet. Research. - American Journal of Veterinary Research.
Am. Lancet - American Lancet.
A. M. A. Bull. - Continued as Organization Section in Journal of the American Medical Association.
Am. M. Bi-Weekly - American medical bi-weekly.
Am. M. Compend - American medical compend.
Am. M. J. - American Medical Journal. (Cincinnati).
Am. M. Month. - American Medical Monthly.
Am. M. Recorder - American Medical Recorder.
Am. M. & S. J. - American Medical and Surgical Journal (Syracuse, N.Y.), Cincinnati v. 1-8 (1851-56), v.2 #1-10 as Am. J. Med., v.7 #1-2 as Syracuse M. & S. J. superseded by Am. M. J. (Cincinnati).
Am. M. Times - American Medical Times.
Am. M. Weekly - American Medical Weekly.
Am. Med. - American Medicine.
Am. Med.-Surg. Bull. - American Medico-Surgical Bulletin.
Am. Midland Naturalist. - American Midland Naturalist.
Am. Museum Novitates - American Museum Novitaves.
Am. Naturalist - American Naturalist.
Am. Phys. Educat. Rev. - American Physical Educattion Review.
Am. Pract. - American Practitioner.
Am. Pract. & News - American practitioner and news.
Am. Rev. Soviet Med. - American Review of Soviet Medicine.
Am. Rev. Tuberc. - American Review of Tuberculosis.
Am. Soc. Advance. Sc. - American Society for the Advancement of Science.
Am. Soc. Animal Production. - American Society of Animal Production.
Am. Therap. - American therapist.
Am. Vet. Rev. - American veterinary review-
Amatus - Amatus Lusitanus.
Amtl. Ber. ü. d. Versamml. deutsch. Naturf. u. Aerzte - Amtlicher bericht über die versammlung deutscher naturforscher und aerzte.
Amtl. med. Ber. d. Kantons (Zürich) -
An. r. Acad. de cien. méd...de la Habana -
An. Acad. y lab. de cien. méd. de Cataluna -
An. r. Acad. de méd. -
An. Acad. de méd. de Medellin -
An. de la Acad. de obst. -
An. argent de oftal. - Anales argentinos de oftalmologia.
An. d. Ateneo clin. quir. - Anales del Ateneo de clinica quirurgica.
An. de biol. - Anales de Biologia.
An. brasil. de dermat. e sif. - Anais brasileiros de dermatologia e sifilografia.
An. brasil. de ginec. - Annaes brasileiros de gynecologia.
An. Casa de Salud Valdecilla -
An. Cated. Clin. ginec. - Anales de la Cátedra de clínica ginecológica.
An. Cated. de pat. y clin. tuberc. - Anales de la Catedra de patologia y clinica de la tuberculosis.
An. d. centro de invest. tisiol. - Anales del centro de investigaciones tisiologicas.
An. de cir. - Anales de cirujia.
An. Clin. e Inst. enferm. infec. - Anales de la Clinica e Institute de enfermedades infecciasas.
An. Cong. brasil. ginec. e obst. -
An. Dispen. púb. nac. para enferm. d. ap. digest. - Anales del Dispensario publico nacional para enfermedades del aparto digestivo.
An. Fac. de cien. méd., (Asunción) - Anales de la Facultad de ciencias médicas, Universidad Nacional. (Asunción, Paraguay).
An. Fac. de med. de Montevideo - Anales de la Facultad de medicina de Montevideo.
An. Fac. de med. de Univ. de São Paulo - Annaes da Faculdade de medicina da Universidade de São Paulo.
An. Hosp. niños e inst. puericult. de Rosario. - Annales del Hospital de niños e Instituto de puericultura de Rosario.
An. Hosp. San Jose -
An. d. inst. matern. y asist. social. (Buenos Aires) - Anales del Instituto de maternidad y assistencia social (Buenos Aires).
An. Inst. med. trop. - Anais do Instituto de medicina tropical.
An. Inst. modelo de clin. med. - Anales del Instituto modelo de clinica médica.
An. méd. - Analecta médica.
An. med. gaditanos - Anales médicos gaditanos.
An. de obst. ginecopat. y pediat. (Madrid) - Anales de obstetricia, ginecopatia y pediatria (Madrid).
An. di ostet. Milano -
An. de oto-rino-laring. d. Uruguay - Anales de oto-rino-laringologia del Uruguay.
An. paulist. de med. e cir. - Anais paulistas de medicina e cirurgia.
An. Soc. biol. Bogotá - Anales de la Sociedad de biologia de Bogota.
An. Soc. ginec. españ., (Madrid) -
An. Soc. méd.-quir. d. Guayas - Anales de Sociedad médico-quirurgica del Guayas.
An. Soc. mex. de oftal. y oto-rino-laring. - Anales de la Sociedad mexicana de oftalmologia y oto-rino-laringologia.
An. Soc. puericult. Buenos Aires - Anales de la Sociedad de puericultura de Buenos Aires.
Anadolu klin. - Anadolu klinigi.
Analekt. f. Frauenkr. - Analekten für frauenkrankheiten.
Analyst - The Analyst.
Anat. Anz. - Anatomischer Anzeiger.
Anat. Hefte - Anatomische Hefte.
Anat. Rec. - Anatomical Record.
Andalucia méd. - Andalucia médica.
Anesthesiology - Anesthesiology.
Anesth. & Analg. - Current Researches in Anesthesia and Analgesia, 318 Hotel Westlake, Rocky River, Ohio.

Anesth. et analg. - Anesthésie et analgésie.
Anfiteatro anat. - Anfiteatro anatomico español.
Angew. Chemie - Angewandte Chemie. See: Ztschr. f. Angew. Chem.
Angle Orthodontist. - The Angle Orthodontist.
Anjou méd. - Anjou médical.
Ann. Acad. Sc. Tenn. - Annals of the Academy of Science of Tennessee.
Ann. Allergy - Annals of Allergy.
Ann. Am. Acad. Polit. & Social Sc. - Annals of the American Academy of Political and Social Science.
Ann. d'anat. path. - Annales d'anatomie pathologique et d'anatomie normale médico-chirurgicale.
Ann. Anat. & Surg. - Annals of anatomy and surgery.
Ann. Biochem. & Exper. Med. - Annals of Biochemistry and Experimental Medicine.
Ann. bot. Soc. zool., bot. fenn. Vanamo. -
Ann. brasil. de gynec. - Annaes brasileiros de gynecologia. (Continued as An. brasil. de ginec.).
Ann. et bull. Soc. roy. d. sc. méd. et nat. de Bruxelles - Annales et bulletin de la Société royale des sciences médicales et naturelles de Bruxelles.
Ann. der Chem. - Annalen der Chemie.
Ann. de la chir. franç. et étrang. - Annales de la chirurgie française et étrangère.
Ann. de chir. d'orthop. - Annales de chirurgie et d'orthopédie.
Ann. d. circ. méd. argent. -
Ann. clin. de Montpellier. - Annales cliniques de Montpellier.
Ann. dent. - Annals of Dentistry.
Ann. de dermat. et syph. - Annales de dermatologie et syphiligraphie.
Ann. de l'Ecole de méd. et pharm. de Marseille -
Ann. d'électrobiol. - Annales d'électrobiologie.
Ann. d'endocrinol. - Annales d'endocrinologie.
Ann. Eugenics - Annals of Eugenics.
Ann. Fac. franç. de méd. et de pharm. de Beyrouth. - Annales de la Faculté française de médecine et de pharmacie de Beyrouth.
Ann. d. Fac. di med. e mem. di Accad. med.-chir. di Perugia -
Ann. Gynaec. (Boston) - Annals of gynaecology (Boston).
Ann. Gynaec. & Pediat. - Annals of gynaecology and pediatry.
Ann. de gynéc. (Paris) - Annales de gynécologie (Paris).
Ann. de gynéc. et d'obst. - Annales de gynécologie et d'obstétrique.
Ann. de gynéc. et pediat. - Annales de gynécologie et de pédiatrique.
Ann. de Hosp. de Santa Creu i Sant Pau -
Ann. d'hyg. - Annales d'hygiène publique, industrielle et sociale.
Ann. d'hyg. et de med. colon. - Annales d'hygiène et de médecine coloniales.
Ann. d'ig. - Annali d'igiene.
Ann. Inst. d'actinol. - Annales de l'Institut d'actinologie.
Ann. de l'Inst. chir. de Bruxelles -
Ann. Inst. d'hydrol. - Annales de l'Institut d'hydrologie et de climatologie.
Ann. Inst. Pasteur - Annales de l'Institut Pasteur.
Ann. Int. Med. - Annales of Internal Medicine.
Ann. internat. de méd. phys. - Continued as Ann. de méd. phys.
Ann. di Ippocrate - Annali di Ippocrate.
Ann. Ist. Carlo Forlanini - Annali dell'Istituto Carlo Forlanini.
Ann. d. r. Ist. di clin. chir. di Roma - Annali del r. Istituto di clinica chirurgica di Roma.
Ann. ital. di chir. - Annali italiani di chirurgia.
Ann. d. klin. Anst. d. Univ. zu Bresl. f. Geburtsh. -
Ann. di laring., otol. - Annali di laringologia, otologia, rinologia e faringologia.
Ann. M. Hist. - Annals of Medical History.
Ann. d. mal. de l'oreille, du larynx - Annales des maladies de l'oreille, du larynx, du nez et du pharynx.
Ann. d. mal. d. org. génito-urin. - Annales des maladies des organes génito-urinaires.
Ann. d. mal. vén. - Annales des maladies vénériennes.
Ann. d. manic. prov. di Perugia -
Ann. d. manicom. prov. di Catanzaro -
Ann. de méd. - Annales de médecine.
Ann. de méd. belge - Annales de médecine belge et étrangère.
Ann. méd. de Caen - Année médical de Caen.
Ann. méd.-chir. - Annales médico-chirurgicales.
Ann. med.-chir. de l'Hôp. Sainte-Justine, (Montréal) - Les Annales médico-chirurgicales de l'Hôpital Sainte-Justine (Montréal).
Ann. de méd. et chir. inf. - Annales de médecine et chirurgie infantiles.
Ann. de méd. lég. - Annales de médecine légale, de criminologie, et de police scientifique, médecine sociale, et toxicologie.
Ann. di med. nav. e colon. - Annali di medicina navale e coloniale.
Ann. de méd. phys. - Annales de médecine physique, de physio-biologie et de rhumatisme.
Ann. méd.-psychol. - Annales médico-psychologiques.
Ann. de méd. scient. et prat. - Annales de médecine scientifique et pratique.
Ann. de méd. vét. - Annales de médecine vétérinaire.
Ann. de microg. - Annales de micrographie.
Ann. New York Acad. of Sciences - Annals of the New York Academy of Sciences.
Ann. Obst. & Gynaec. Brit. Emp. - Annals of obstetrics and gynaecology of the British Empire, (London).
Ann. d'ocul. - Annales d'oculistique.
Ann. d'ocul. et gynéc. (Charleroi) - Annales d'oculistique et de gynécologie (Charleroi).
Ann. d'orthop. et de chir. prat. - Annales d'orthopédie et de chirurgie pratique.
Ann. osp. psichiat. di Perugia - Annali dell'ospedale psichiatrico di Perugia.
Ann. di ostet. e ginec. - Annali di ostetricia e ginecologia e pediatrica.
Ann. d'oto-laryng. - Annales d'oto-laryngologie.
Ann. Otol., Rhin. & Laryng. - Annals of Otology, Rhinology and Laryngology.
Ann. di ottal. e clin. ocul. - Annali di ottalmologia e clinica oculistica.
Ann. paediat. - Annales paediatrici. (International Review of Pediatrics).
Ann. de parasitol. - Annales de parasitologie humaine et comparée.
Ann. paulist. de med. e cir. - Annaes paulistas de medicina e cirurgia. (Continued as An. paulistas de medecina, e cirurgia. (Sao Paulo).
Ann. de physiol. - Annales de physiologie et de physico-chimie biologique.
Ann. de la Policlin. de Bordeaux - Annales de la policlinique de Bordeaux.
Ann. de la Policlin. de Paris - Annales de la policlinique de Paris.
Ann. Pract & News -
Ann. di radiol. diag. - Annali di radiologia diagnostica. (Continuation of Ann. di radiol. e fis. med.).
Ann. di radiol. e fis. med. - Annali di radiologia e fisica medica. (Continuation of Riv. di radiol. e fis. med.).
Ann. Rep. Chem. Soc. - Annual Reports of the Chemical Society.
Ann. Rep. Mem. Ophthalmic Lab., (Giza) - Annual Report of the Memorial Ophthalmic Laboratory, (Giza), See: Mem. Ophthalmic Lab. Giza, Ann. Rep.).
Ann. Rep. trans. S. Durham & Cleveland M. Soc. -
Ann. Rev. Biochem. - Annual Review of Biochemistry.
Ann. Rev. Physiol. - Annual Review of Physiology.
Ann. Rheumat. Dis. - Annals of the Rheumatic Diseases.
Ann. Sc. nat. Zool. - Annales des sciences naturelles; zoologie.
Ann. Soc. d'anat. path. (Brussels) - Annales de la société d'anatomie pathologique, (Brussels).
Ann. Soc. belge de chir. - Annales de la société belge de chirurgie, (Brussels).

Ann. Soc. belge de méd. trop. - Annales de la Société belge de médecine tropicale.
Ann. Soc. Entomol. de France - Annales de la société entomologique de France (Paris).
Ann. Soc. de méd. d'Anvers - Annales de la société de médecine d'Anvers.
Ann. Soc. méd.-chir. du Brabant - Annales de la société médico-chirurgicale du Brabant.
Ann. Soc. méd.-chir. de Liége - Annales de la Société médico-chirurgicale de Liége.
Ann. Soc. de méd. de Gand. - Annales de la société de médecine de Gand.
Ann. Soc. de méd.-prat. de Montpellier - Annales de la société de médecine-pratique de Montpellier.
Ann. Soc. de méd. de St.Etienne et de la Loire - Annales de la société de médecine de Saint-Etienne et de la Loire.
Ann. d. städt. allg. Krankenh. z. München - Annalen der städtischen allgemeinen krankenhäuser zu München.
Ann. Surg. - Annals of Surgery (St. Louis; Philadelphia).
Ann. Surg. Path. -
Ann. & Tr. Brit. Homoeop. Soc. (London) - Annals and transactions of the British homoeopathic society. (London).
Ann. Trop. Med. - Annals of Tropical Medicine and Parasitology.
Ann. de l'Univ. de Bruxelles, Fac. de méd. - Annales de l'université de Bruxelles, Faculté de médecine.
Ann. univ. di med. e chir. - Annali universali di medicina e chirurgia (Milan).
Ann. Univers.(Algérie) - Annales Universitaires, (Algérie).
Ann. White Russ. agr. Inst. -
Annalist - Annalist; a record of practical medicine in the city of New York.
Anno. d. insegn. chir. di F. Durante n. Univ. di Roma -
Annot. zool. japon. - Annotationes zoologicae japonenses.
Anthrop. Anz. - Anthropologischer Anzeiger.
Anthropophyteia - Anthropophyteia (Leipzig).
Antiseptic - The Antiseptic.
Anz. d. k. k. Gesellsch. d. Aerzte in Wien.-
Ap. respir. y tuberc.(Santiago) - Aparato respiratorio y tuberculosis (Santiago).
Apollonian (Boston) - Apollonian (Boston).
Appendix VI. Rep. of U. S. Commissioner of Fisheries -
Arb. a. d. anat. Inst. d. kaiserlich-japan. Univ. zu Sendai - Arbeiten aus dem anatomischen Institut der kaiserlich-japanischen Universität zu Sendai.
Arb. a. d. dritten Abt. d. anat. Inst. d. kaiserlich. Univ. Kyoto - Arbeiten aus der dritten Abteilung des anatomischen Institutes der kaiserlichen Universität Kyoto.
Arb. a. d. Geb. d. Geburtsh. u. Gynäk. z. Feier... v. Carl Ruge -
Arb. u. Jahresb. d. k. k. erst. chir. Univ. Klin. zu Wien -
Arb. a. d. Path. Inst. in Göttingen - Arbeiten aus der Pathologisches institut in Göttingen.
Arb. a. d. path. Inst. d. Tübingen - Arbeiten auf dem pathologisch-anatomischen institut der Tübingen.
Arb. a. d. path. Inst. d. Univ. Helsingfors - Arbeiten aus dem pathologischen Institut der Universität Helsingfors.
Arb. a. d. staatl. Inst. f. exper. Therap. - Arbeiten aus dem staatlichen Institut für experimentelle Therapie und dem Forschungsinstitut für Chemotherapie zu Frankfurt a. M.
Arb. a. d. ungar. biol. Forschngsinst. - Arbeiten aus der ungarisches biologisches forschungsinstitut.
Arb. a. d. zool.-zoot. Institut Würzburg - Arbeiten aus, der zoologisch-zootomisches institut.
Arbeitsphysiol. - Arbeitsphysiologie. Zeitschrift für die Physiologie des Menschen bei Arbeit und Sport.
Arch. am. de med. - Archivos américanos de medicina: revista américana de ciencias médicas.
Arch. f. Anat. u. Embryol. - Archiv für anatomie und embryologie.
Arch. f. Anat. u. Entwcklngsgesch. - Archiv für Anatomie und Entwicklungsgeschichte.
Arch. d'anat., d'histol. et d'embryol. - Archives d'anatomie, d'histologie et d'embryologie.
Arch. anat. e istol. pat. -
Arch. d'anat. micr. - Archives d'anatomie microscopique.
Arch. f. Anat. u. Physiol. - Meckel's Archiv für Anatomie und Physiologie. (Continued as Arch. f. Anat. Physiol. u. Wissensch. Med.).
Arch. f. Anat. Physiol. u. Wissensch. Med. - Archiv für anatomie, physiologie und wissenschaftliche medicin.
Arch. di antropol. crim. - Archivio di antropologia criminale, psichiatria e medicina legale.
Arch. argent. de enferm. d. ap. digest. y de la nutricion - Archivos argentinos de enfermedades del aparato digestivo y de la nutricion.
Arch. argent. de enferm. d. ap. respir. y tuberc. - Archivos argentinos de enfermedades del aparato respiratorio y tuberculosis.
Arch. argent. de neurol. - Archivos argentinos de neurologia.
Arch. argent. de pediat. - Archovis argentinos de pediatria.
Arch. argent. de tisiol. - Archivos argentinos de tisiologia.
Arch. Asoc. para evit. ceguera México - Archives de la Asociacion para evitar la ceguera en México.
Arch. ed atti d. Soc. ital. di chir. - Archivio ed atti della societa italiana di chirurgia.
Arch. f. Augenh. - Incorporated in Archiv. für Ophthalmologie.
Arch. belges du serv. de san. de l'armée - Archives belges du service de santé de l'armée. (Continuation of Archives médicales belges).
Arch. f. Berdauungskr. -
Arch. Biochem. - Archives of Biochemistry.
Arch. de biol., (Paris) - Archives de biologie (Paris).
Arch. brasil. de med. - Archivos brasileiros de medicina. (Rio de Janeiro).
Arch. f. Chir. -
Arch. clin. de Bordeaux - Archives cliniques de Bordeaux.
Arch. Clin. Cancer Research - Archives of clinical cancer research.
Arch. Clin. e Inst. endocrinol. - Archivos de la Clinica e Instituto de Endocrinologia.
Arch. Clin. obst. y ginec. ''Eliseo Cantón''. -
Arch. Clin. Surg. - Archives of clinical surgery.
Arch. cubanos cancerol. - Archivos cubanos de cancerologia.
Arch. Dermat. & Syph. - Archives of Dermatology and Syphilology.
Arch. f. Dermat. u. syph. - Archiv für Dermatologie und Syphilis.
Arch. de dermat. e syph. de São Paulo - Archivos de dermatologia e syphiligraphia de São Paulo.
Arch. Diagn. - Archives of diagnosis.
Arch. Dis. Childhood - Archives of Disease in Childhood.
Arch. de Doyen (Paris) - Archives de Doyen (Paris).
Arch. droit climat. et hyg. - Les archives du droit climatique et de l'hygiene (Supplement de la Gaz. méd de France).
Arch. droit méd. et hyg. - Les archives du droit médical et de l'hygiène. (Supplément de la Gaz. méd. de France).
Arch. d'électric. méd. - Archives d'électricité médicale; électrologie, radiologie, curielogie et de physiothérapie du cancer.
Arch. f. Entwcklngsmechn. d. Organ. - Wilhelm Roux' Archiv für Entwicklungsmechanik der Organismen.
Arch. españ. de pediat. - Archivos españoles de pediatría.
Arch. f. exper. Path. u. Pharmakol. - Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie.

Arch. f. exper. Zellforsch. - Archiv für experimentelle Zellforschung besonders Gewebezüchtung (Explantation).
Arch. Fac. de méd. de Zaragoza . Archivos, Facultad de medicina de Zaragoza.
Arch. di farmacol. sper. - Archivio di farmacologia sperimentale e scienze affini.
Arch. di fisiol. - Archivio di fisiologia.
Arch. Fisiopatologia ecc. -
Arch. franco-belges de chir. - Archives franco-belges de chirurgie.
Arch. f. Frauenk. - Archiv für frauenkunde und konstitutionsforschung.
Arch. gén. de chir. - Archives générales de chirurgie.
Arch. gén. d'hydrol. - Archives générale d'hydrologie de climatologie et de balnéothérapie.
Arch. gén. de Med. - Archives générales de médecine.
Arch. gen. neur., Nocera -
Arch. gen. di neurol., psichiat. e psicoanal. - Archivio generale di neurologia, psichiatria e psicoanalisi.
Arch. f. d. ges. Med. - Archiv für die gesammte medicin (Jena).
Arch. f. d. ges. Naturl. (Nuremberg) - Archiv für die gesammte naturlehre (Nuremberg).
Arch. f. d. ges. Physiol. - Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere.
Arch. f. d. ges. Psychol. - Archiv für die gesamte Psychologie.
Arch. f. Gesch. d. Med. - Sudhoffs Archiv für Geschichte der Medizin und der Naturwissenschaften.
Arch. f. Gewerbepath. u. Gewerbehyg. - Archiv für Gewerbepathologie und Gewerbehygiene.
Arch. de ginec. obst. y ped. - Archivos de ginecopatía, obstetricía y pediatría (Barcelona).
Arch. de ginec. y pediat. - Archivos de ginecología y pediatría.
Arch. f. Gynäk. - Archiv für Gynäkologie. (Berlin).
Arch. f. Heilkunde - Archiv für Heilkunde.
Arch. f. d. Holländ. Beitr. z. Nat.-u. Heilk. - Archiv für die holländischen beiträge zur natur- und heilkunde.
Arch. d. hosp. municip. de la Habana -
Arch. d. Hosp. Niños Roberto del Rio - Archivos del Hospital de niños Roberto del Rio.
Arch. f. Hyg. - Archiv für Hygiene und Bakteriologie.
Arch. Inst. biol. - Continued as Arq. Inst. biol., (São Paulo).
Arch. Inst. Pasteur de l'Afrique du Nord - See: Arch. Inst. Pasteur d'Algérie and Arch. Inst. Pasteur de Tunis.
Arch. Inst. Pasteur d'Algérie - Archives de l'Institut Pasteur d'Algérie.
Arch. Inst. Pasteur d'Indochine - Archives des Instituts Pasteur d'Indochine.
Arch. Inst. Pasteur de Tunis - Archives de l'Institut Pasteur de Tunis.
Arch. Inst. prophylac. - Archives de l'Institut prophylactique. (Continued as Trav. et publ. Inst. prophylac.).
Arch. Int. Med. - Archives of Internal Medicine.
Arch. internae. de la hidatid. - Archivas internacionales de la hidatidosis, Ministeris de salud publica.
Arch. internat. de laryng. - Archives internationales de laryngologie.
Arch. internat. de méd. expér. - Archives internationales de médecine expérimentale.
Arch. internat. de neurol. - Archives internationales de neurologie.
Arch. internat. de pharmacodyn. et de thérap. - Archives internationales de pharmacodynamie et de thérapie.
Arch. internat. de physiol. - Archives internationales de physiologie.
Arch. Ist. biochim. ital. - Archivio dello Istituto biochimico italiano.
Arch. ital. di anat. e di embriol. - Archivio italiano di anatomia e di embriologia.
Arch. ital. di anat. e istol. pat. - Archivio italiano di anatomia e istologia patologica.
Arch. ital. de biol. - Archives italiennes de biologie. (Ceased publication).
Arch. ital. di chir. - Archivio italiano di chirurgia.
Arch. ital. di dermat.,sif. - Archivio italiano di dermatologia sifilografia e venereologia.
Arch. ital. di ginec. - Archivio italiano di ginecologia.
Arch. ital. di laring. - Archivii italiani di laringologia.
Arch. ital. d. mal. d. app. diger. - Archivio italiano delle malattie dell'apparato digerente.
Arch. ital. per le mal. nerv. e ment. - Archivio italiano per le malattie nervose e mentali. See: Riv. sper. di freniat.
Arch. ital. di med. sper. - Archivio italiano di medicina sperimentale. (Continued as Med. sper., Arch. ital.).
Arch. ital. di otol. - Archivio italiano di otologia, rinologia e laringologia.
Arch. ital. di pediat. - Archivio italiano di pediatria.
Arch. ital. di Sc. farmacol. - Archivio italiano di scienze farmacologiche.
Arch. ital. di urol. - Archivio italiano di urologia.
Arch. f. jap. Chir. - Archiv für japanische Chirurgie.
Arch. d. Julius Klaus-Stiftg. f. Vererbungsforschg. - Archiv der Julius Klaus-Stiftung für Vererbungsforschung, Sozialanthropologie und Rassenhygiene.
Arch. f. Kinderh. - Archiv für Kinderheilkunde.
Arch. f. klin. Chir. - Archiv für klinische Chirurgie.
Arch. f. Kreislaufforsch. - Archiv für Kreislaufforschung Beihefte zur Zeitschrift für Kreislaufforschung.
Arch. f. Kriminol. - Archiv für Kriminologie.
Arch. f. Laryngol. u. Rhinol. - Archiv für laryngologie und rhinologie.
Arch. latino am. de cardiol. y hemat. - Archivos latino americanos de cardiologia y hematologia.
Arch. latino-am. de pediat. - Archivos latino-americanos de pediatria.
Arch. M. Hydrol. - Archives of Medical Hydrology; being the Journal of the International Society of Medical Hydrology.(London).
Arch. d. mal. de l'app. digestif - Archives des maladies de l'appareil digestif et des maladies de la nutrition.
Arch. d. mal. du coeur - Archives des maladies du coeur et des vaisseaux.
Arch. d. mal. profess. - Archives des maladies professionelles, hygiène et toxicologie industrielles.
Arch. méd. d'Angers - Archives médicales d'Angers.
Arch. méd. belges - Archives médicales belges.
Arch. méd.-Chir. de l'app. respir. - Archives médico-chirurgicales de l'appareil respiratoire.
Arch. di med., chir. ed ig. - Archivio di medicina, chirurgia ed igiene.
Arch. méd.-chir. de Province - Archives médico-chirurgicales de province (Poitiers). (Ceased publication).
Arch. de méd. d. enf. - Archives de médecine des enfants. (Ceased publication).
Arch. f. med. Erfahr. - Archiv für medizinische erfahrung.
Arch. de med. expér. et d'anat. path. - Archives de médecine expérimentale et d'anatomie pathologique.
Arch. méd. ferroc. - Archivos médicos ferrocarrileros.
Arch. de méd. inf. - Archivos de medicina infantil.
Arch. de med. int. - Archivos de medicina interna.
Arch. de med. leg. - Archivo de medicina legal.
Arch. de méd. (Madrid) - Archives de médecine (Madrid).
Arch. méd. mex. - Archivos médicos mexicanos.
Arch. de méd. et pharm. nav. - Archives de médecine et pharmacie navales.
Arch. mens. d'obst. et de gynéc. - Archives mensuelles d'obstétrique et de gynécologie.
Arch. f. Menschenk. - Archiv für menschenkunde.
Arch. mex. ven.-sif. y dermat. - Archivos mexicanos de venereosifilis y dermatologia.
Arch. Middlesex Hosp. - Archives of the Middlesex hospital.

Arch. f. mikr. Anat. - Archiv für mikroskopische Anatomie.
Arch. f. Mikrobiol. - Archiv für Mikrobiologie, Zeitschrift für die Erforschung der pflanzlichen Mikroorganismen.
Arch. de Morph. gén. et expér. - Archives de morphologie générale et expérimentale.
Arch. f. Naturgesch. - Archiv für naturgeschichte.
Arch. néerl. de physiol. - Archives néerlandaises de physiologie de l'homme et des animaux.
Arch. de neurol. - Archives de neurologie.
Arch. Neurol. & Psychiat. - Archives of Neurology and Psychiatry.
Arch. de oftal. de Beunos Aires - Archivos de oftalmologia de Buenos Aires.
Arch. f. Ohren-, Nasen- u. Kehlkopfh. - Archiv für Ohren-, Nasen- und Kehlkopfheilkunde sowie die angrenzenden Gebiete.
Arch. d'opht. - Archives d'ophtalmologie. (Ceased publication).
Arch. Ophth. - Archives of Ophthalmology.
Arch. f. Ophth. - Albrecht von Graefes Archiv für Ophthalmologie vereinigt mit Archiv für Augenheilkunde.
Arch. f. orthop. u. Unfall-Chir. - Archiv für orthopädische und Unfall-Chirurgie mit besonderer Berücksichtigung der Frakturenlehre und der orthopädisch-chirurgischen Technik.
Arch. di ortop. - Archivio di ortopedia.
Arch. di ostet. e ginec. - Archivio di ostetricia e ginecologia.
Arch. Otolaryng. - Archives of Otolaryngology.
Arch. di ottal. - Archivio di ottalmologia.
Arch. di pat. e clin. med. - Archivio di patologia e clinica medica.
Arch. Path. - Archives of Pathology.
Arch. f. path. Anat. - Archiv für pathologische anatomie und physiologie und klinische medizin.
Arch. Path. & Lab. Med. - Archives of Pathology and Laboratory Medicine.
Arch. Pediat. - Archives of Pediatrics.
Arch. de pediat. d. Uruguay - Archivos de pediatria del Uruguay.
Arch. physiol. Heilk. - Archiv für Physiologische heilkunde.
Arch. de physiol., norm. et path. - Archives de physiologie normale et pathologique.
Arch. phys. Therapy - Archives of Physical Therapy (Incorporating Physical Therapeutics) with International Abstract.
Arch. de physique biol. - Archives de physique biologique.
Arch. de la Policlin. -
Arch. d. prakt. Heilk. - Archiv der praktischen heilkunde für Schlesien und Südpreussen.
Arch. f. Protistenk - Archiv für Protistenkunde.
Arch. prov. de Chir. - Archives provinciales de chirurgie.
Arch. prov. de méd. - Archives provinciales de médecine.
Arch. f. Psychiat. - Archiv für Psychiatrie und Nervenkrankheiten.
Arch. de psychol. - Archives de psychologie.
Arch. di radiol. - Archivio di radiologia.
Arch. Radiol. & Electrother. - Archives of radiology and electrotherapy.
Arch. f. Rassen-u. Gesellsch.-Biol. - Archiv für rassen-und gesellschafts-biologie, einschliesslich rassen-und gesellschafts.
Arch. roum. de méd. et chir. - Archives roumaines de médecine et de chirurgie.
Arch. roum. de path. expér. et de microbiol. - Archives roumaines de pathologie expérimentale et de microbiologie.
Arch. di sc. biol. - Archivio di scienze biologiche (fisiologia, farmacologia, patologia sperimentale).
Arch. per le sc. med. - Archivio per le scienze mediche.
Arch. f. Schiffs-u. Tropen-Hyg. - Archiv für Schiffs-und Tropen-Hygiene. (Continued as Deutsche tropenmed. Ztschr.)
Arch. Soc. argent. de anat. norm. y pat. - Archivos de la Sociedad argentina de anatomia normal y patologica.
Arch. Soc. de biol. de Montevideo - Archivos de la Sociedad de biologia de Montevideo.
Arch. Soc. cirujanos hosp. - Archivos de la Sociedad de cirujanos de hospital.
Arch. Soc. estud. clin. Habana - Archivos de la Sociedad de estudios clinicos de la Habana.
Arch. Soc. ital. chir. - Archivio, Societa italiana di chirurgia, (Rome).
Arch. Soc. d. sc. méd. et biol. de Montpellier - Archives de la Société des sciences médicales et biologiques de Montpellier et du Languedoc Méditerranéen.
Arch. f. soziale Hyg. u. Demog. - Archiv für soziale hygiene und demographie. (Ceased publication).
Arch. per lo stud. d. fisiopat. e clin. d. ricambio - Archivio per lo studio della fisiopatologia e clinica del ricambio.
Arch. Surg. - Archives of Surgery.
Arch. de terap. de l. enferm. nerv. y ment. - Archivos de terapeutica de las enfermedades nerviosas y mentales.
Arch. f. Tierernährg. u. Tierzucht - Archiv für Tierernährung und Tierzucht.
Arch. f. Tierheilk. - Archiv für thierheilkunde.
Arch. de tisiol. - Archivos de tisiologia de Argentina. (Continued as Arch. argent. de tisiol.).
Arch. de tocol. et de gynéc. - Archives de tocologie et de gynécologie.
Arch. urug. de Ginec. -
Arch. urug. de med., cir. y especialid. - Archivos uruguayos de medicina, cirgia y especialidades.
Arch. "de Vecchi" per anat. pat. e med. clin. - Archivio "de Vecchi" per l'anatomie patologica e la medicina clinica.
Arch. venezol. puericult. y pediat. - Archivos venezolanos de puericultura y pediatria.
Arch. venezol. - Soc. de oto-rino-laring., oftal., neurol. - Archivos venezolanos de la Sociedad de oto-rino-laringologia, oftalmologia, neurologia.
Arch. d. Ver. f. Wissensch. -
Arch. f. Verdauungskr. - Archiv für verdauungskrankheiten, stoffwechselpathologie und diätetik.
Arch. vét. - Archives vétérinaires.
Arch. f. wissensch. u. prakt. Tierh. - Archiv für wissenschaftliche und praktische tierheilkunde.
Arch. f. Zeilforsch. - Archiv für zeilforschung.
Arch. zool. ital. - Archivio zoologico italiano.
Arch. Hemiju Tehnol. - Archiv za hemiju i tehnologiju.
Arizona Med. - Arizona Medicine.
Ark. Kemi Min. Geol. - Arkiv för kemi, mineralogi och geologi.
Arkh. Biol. Nauk. - Arkhiv biologicheskikh nauk.
Army M. Bull. - Army medical bulletin. (Continued as Bull. U. S. Army M. Dept.).
Arq. assist. psicopat. estad. São Paulo. - Arquivos de assistência a psicopatas do estado de São Paulo.
Arq. de biol. - Arquívos de biología.
Arq. brasil. de cir. e ortop. - Arquivos brasileiros de cirurgia e ortopedia.
Arq. brasil. nutrição. - Arquivos brasileiros de nutrição.
Arq. brasil. de oftal. - Arquivos brasileiros de oftalmologia.
Arq. brasil. urol. - Arquivos brasileiros de urologia.
Arq. de cir. clin. e exper. - Arquivos de cirurgia clinica e experimental.
Arq. de dermat. e sif. de São Paulo - Arquivos de dermatologia e sifiligrafia de São Paulo.
Arq. Esc. méd.-cir. de Nova Goa - Arquivos da Escola médico-cirurgica de Nova Goa.
Arq. de hig. - Arquivos de higiene.
Arq. de hig. e saúde púb., São Paulo - Arquivos de higiene a saúde pública.
Arq. indo-portug. de méd. e hist. nat. - Arquivos indo-portuguêses de medicina e historia natural. See: Arq. Esc. méd.-cir. de Nova Goa.

Arq. inst. bact. Câmara Pestana - Arquivos de Instituto bacteriologico Câmara Pestana.
Arq. Inst. Benjamin Baptista - Arquivos do Instituto Benjamin Baptista.
Arq. Inst. biol.,(São Paulo) - Arquivos do instituto biologico (São Paulo).
Arq. mineir. leprol. - Archivos mineiros de liprologia.
Arg. neuro-psiquiat.,(São Paulo) - Arquivos de neuro-psiquiatria (São Paulo).
Arq. de obst. e ginec. - Arquivo de obstetricia e ginecologia.
Arq. de pat. - Arquivo de patologia orgao do Instituto Portugues para o estudo do cancro.
Arq. policia civil São Paulo - Arquivos da policia civil de São Paulo.
Arq. rio grand. med. - Arquivos rio grandenses de medicina.
Arq. Serv. assist a menor. - Arquivos do Servico de assistencia a menores.
Arq. Serv. assist. psicopat. estad. São Paulo - Arquivos do Servico de assistencia a psicopatas do estado de São Paulo.
Arq. Serv. de pronto socor. do Recife - Arquivos do Serviço do pronto socorro do Recife.
Arq. trab. fac. med. do Porto -
Ars méd. (Barcelona) - Ars medica; revista de medicina, cirugia y especialidades.
Arsberätt. f. Sabbatsbergs Sjukh. i Stockholm -
Art méd. - Art médical.
Art. Ovaire -
Arte ostet. - Arte ostetrica.
Askeri sihhiye mecmuasi - Askeri sihhiye mecmuasi.
Asoc. ayuda y orient. invalido prim. Conf. argent. - Asociacion de ayuda y orientacion al invalido, primera Conferincia argentina.
Asoc. méd. d. Hosp. Durand. prim. reuniones extraord. - Asociacion de médicos del Hospital Durand, primeras reuniones extraordinarias.
Assoc. franç. p. l'avanc. d. sc. C.-r. - Association française pour l'avancement des sciences Compte rendu.
Assoc. franç. de chir. Proc.-verb. - Association française de chirurgie. Procès verbaux. (Paris).
Ateneo parmense - L'ateneo parmense.
Athena - Athena. Rassegna mensile di biologia - clinica e terapia.
Atlanta M. & S. J. - Atlanta medical and surgical journal.
Atlantic M. J. - Atlantic medical journal.
Atlantic Monthly - The Atlantic Monthly.
Atti.Accad. Fisiocritici Siena. -
Atti Accad. Gioenia di sc. nat. in Catania - Atti, Accademia gioenio di scienze naturali, Catania.
Atti d. r. Accad. med.-chir. di Napoli - Atti Accademia medico-chirurgico (Naples).
Atti d. Accad. med.-fis. fiorent. - Atti Accademia medico-fisica fiorentina, (Florence).
Atti Accad. med. Lombarda - Atti, accademia medica lombarda (Milan).
Atti d. Accad. med. di Roma - Atti, accademia medica di Roma.
Atti Accad. naz. Lincei - Atti, accademia nazionale dei Lincei (Rome).
Atti Accad. d. sc. med. e nat. di Ferrara - Atti, accademia delle scienze mediche e naturali di Ferrara.
Atti d. r. Accad. d. sc. med. in Palermo - Atti, accademia delle scienze mediche in Palermo.
Atti Cong. gen. d. Ass. med. ital. - Atti del congresso assoriazione medica italiana.
Atti d. cong. internaz. dei patologi-
Atti r. ist. Veneto di sc., lett. ed. arti. - Atti, istituto veneto di scienze, lettere ed arti, (Venice).
Atti med. Accad. Storia arte sanit. -
Atti e rendic. d. Accad. med.-chir. di Perugia- Atti e rendiconti della Accademia medico-chirurgica di Perugia.
Atti Rep. Tosco-Umbro-Emiliana di ostet. e ginec. -
Atti Soc. ital. di ostet. e ginec. - Atti della Societa italiana di ostetricia e ginecologia.
Atti d. Soc. lomb. di sc., med. e biol. - Atti Societa lombarda di scienze mediche e biologiche.
Atti Soc. med.-chir. (Padova) - See: Boll. Fac. med. Chir. R. Univ. Padova.
Atti d. xi Cong. med. internaz -
Attualità - Attualità medica.
Auk - The Auk.
Australasian J. Pharm. - Australasian journal of pharmacy.
Australasian M. Gaz. - Australasian medical gazette.
Australian J. Exper. Biol. & M. Sc. - Australian Journal of Experimental Biology and Medical Science.
Australian M. J. - Australian medical journal.
Australian & New Zealand J. Surg. - Australian and New Zealand Journal of Surgery.
Australian Pract. - Australian practitioner.
Ausz. Inaug. Diss., Med. Fak. Univ. Bern. -
Ausz. a. d. Uebers. d. Arb. u. Veränd. d. schles. Gesellsch. f. vaterl. Kult. Jahresb. d. med. Sect. -
Avenir méd. - L'avenir médical.
Avh. Norske Vid. Akad. Oslo -
Bact. Rev. - Bacteriological Reviews.
Bahia med. - Bahia medica.
Balneologe - Der Balneologe. (Continuation of Ztschr. f. d. ges. phys. Therap.).
Baltimore M. J. & Bull. - Baltimore medical journal and bulletin.
Beil. z. Monatschr. f. Geburtsh. u. Gynäk. -
Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres - Beiträge zur anatomie, physiologie, pathologie und praktischen Therapie der ohren. (Continued as Pract. oto-rhino-laryng.).
Beitr. z. Chir. Festschr. -
Beitr. z. Geburtsk. - Beitraege zur geburtskunde.
Beitr. z. Geburtsk. u. Gynäk. - Beitraege zur geburtskunde und gynaekologie.
Beitr. z. gerichtl. Med. - Beiträge zur gerichtichen Medizin.
Beitr. z. klin. Chir. - Bruns' Beiträge zur klinischen Chirurgie.
Beitr. z. Klin. d. Tuberk. - Beiträge zur Klinik der Tuberkulose und spezifischen Tuberkulose-Forschung.
Beitr. z. Lehre v. Stoffwechsel - Beitraege zur Lehre vom stoffwechsel des gesunden und kranken menschen.
Beitr. z. path. Anat. u. z. allg. Path. - Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie.
Beitr. z. prakt. u. theoret. Hals-, Nasen- u. Ohrenh. - Continued as Pract. oto-rhino-laryng.
Beitr. z. Probl. d. Gynäk. u. d. Karzinoms. -
Belarus. med. dumka - Belaruskaia medychnaia dumka.
Belgique méd. - Belgique médical.
Belmont M. J. - Belmont medical journal.
Benivenius's de abditis nonnullis, causis Florentiae -
Ber. u. Arb. a. d. geburtsh-gynäk. Klin. zu (Marburg) - Berichte und arbeiten Geburtshülflich-gynaekologische klinik. (Marburg).
Ber. deutsch. chem. Gesellsch. - Berichte der deutschen chemischen Gesellschaft.
Ber. u. d. Ereign. in d. k. gynäk. Univ.-Klin. zu Königsberg - Bericht über die ereignisse in k. Gynäkologische universitätsklinik. (Königsberg).

Ber. ü. d. ges. Gynäk. u. Geburtsh. - Berichte über die gesamte Gynäkologie und Geburtshilfe.
Ber. d. Kinderheilanst. zu Leipzig -
Ber. d. k. k. Krankenanst. d. Rudolph-Stiftung in Wien -
Ber. d. k. k. Krankenh. Wieden - Bericht der K. K. Krankenhaus Wieden (Vienna).
Ber. d. naturw.-med. Ver. in Innsbruck. - Berichte der naturwissenschaftlichmedizinischer verein, Innsbruck.
Ber. d. Oberhess. Gesellsch. f. Nat. u. Heilk.- Bericht der oberhessische gesellschaft für natur- und heilkunde, (Giessen).
Ber. d. phys.-med. Gesellsch. zu Würzburg.- Berichte der physikalisch-medizinischen Gesellschaft zu Würzburg. (Continuation of Verhandl. d. phys.-med. Gesellsch.).
Ber. d. ungar. physiol. Gesellsch. - Issued with Magyar orvosi archivum.
Ber. u. d. Verh. d. Gesellsch. f. Geburtsh. u. Gynäk. z. Berlin - Berichte über die verhandlungen, Gesellschaft für geburtshülfe und gynäkologie, (Berlin).
Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. - Berichte über die Versammlungen der deutschen ophthalmologischen Gesellschaft.
Ber. ü. d. Vet. Sach. - Bericht ueber das Veterinärwesen im Sachsen.
Berliner Beitr. Geburtsh. -
Berliner klin. Wchnschr. - Berliner klinische Wochenschrift.
Berliner med. Central. Ztg. - Berliner medicinische central-zeitung.
Berliner münch. tierärztl. Wchnschr. - Berliner und münchener tierärztliche Wochenschrift.
Bibliog. anat. de Paris - Bibliographie anatomique de Paris.
Bibliog. Gen. sc. méd. - Bibliographie générale des sciences médicales.
Bibliog. Med., - Bibliographia medica (Paris).
Bibliot. f. laeger - Bibliotek for laeger. Udgivet med understøttelse af det classenske litteraturselskab.
Bijdr. t. theor. en pract. geneesk. -
Billroth Chir. Klin. Wien. -
Biochem. J. - Biochemical Journal.
Biochem. Ztschr. - Biochemische Zeitschrift.
Biochim. e terap. sper. - Biochimica e terapia sperimentale. Supplemento: Pat. compar. d. tuberc.
Biog. méd. - Biographies médicales.
Biokhimiya - Biokhimiya.
Biol. Bull. - The Biological Bulletin.
Biol. Bull. (Woods Hole, Mass. Mar. Biol. Lab.) - Biological bulletin, (Woods Hole, Mass. Marine biological laboratory).
Biol. generalis - Biologia generalis.
Biol. J. - Biologisch jaarboek.
Biol. listy - Biologické listy.
Biol. med., (Milano) - Biologia medica (Milano), (Ceased publication).
Biol. méd., (Paris) - Biologie médicale (Paris).
Biol. Rev. - Biological Review.
Biol. Symposia - Biological Symposia.
Biol. Unters. - Biologische untersuchungen.
Biol. Zentralbl. - Biologisches Zentralblatt.
Bio-Morphosis - Bio-Morphosis. Internationale Zeitschrift für Morphologie und Biologie des Menschen und der höheren Wirbeltiere.
Bird-Banding - Bird-Banding.
Birmingham M. Rev. - The Birmingham Medical Review. (Temporarily discontinued, 1940).
Biull. eksp. biol. med. - Biulleten eksperimental' moi biologii i meditsiny.
Bol. Acad. nac. de med. de Buenos Aires - Boletin de la Academia nacional de medicina de Buenos Aires.
Bol. Acad. nac. de med. do Rio de Janeiro - Boletin Academia nacional de medicina do Rio de Janeiro.
Bol. d. Asilo de alien. en Oliva - Boletin del Asilo de alienados en Oliva.
Bol. Asoc. méd. de Puerto Rico - Boletin de la Asociacion médica de Puerto Rico.
Bol. Asoc. méd. Santiago - Boletin de la Asociacion médica de Santiago.
Bol. d. Ateneo de alumnos intern. de la Fac. de med. de Barcelona - Boletin d' Ateneo de alumnos internos de la Facultad de medicina.
Bol. d. centro antirreumat. - Boletin del centro antirreumatico.
Bol. clin., Univ. de Antioquia - Boletin clinico, Universidad de Antioquia.
Bol. Col. brasil de cirurgiões - Boletim do Colegio brasileiro de cirurgiões. See: Rev. brasil de cir.
Bol. d. Dep. salub. púb., (México) - Boletin del Departamento de salubridad pública (México).
Bol. d. hosp. (Caracas) - Boletin de los hospitales civiles del Distrito Federal (Caracas).
Bol. d. Hosp. Melchor Romero - Boletin del Hospital Melchor Romero.
Bol. d. Hosp. policia nac. - Boletin del Hospital de la policía nacional.
Bol. d. Hosp.-San. "El Peral" - Boletin del Hospital-Sanatorio "El Peral".
Bol. d. Hosp. de San Juan de Dios - Boletin del Hospital de San-Juan de Dios.
Bol. indust. animal - Boletim de industria animal.
Bol. Inst. clín. quir. - Boletin del Instituto de clínica quirúrgica.
Bol. Inst. internac. am. de protec. a la infancia - Boletin del Instituto internacional americano de proteccion a la infancia.
Bol. inst. invest. vet. - Boletin del Instituto de investigaciones veterinarias.
Bol. Inst. de Matern. - Boletin del Instituto de Maternidad Sociedad de beneficencia de la Capital.
Bol. Inst. de med. exper. para el estud. y trat. d. cáncer - Boletin del Instituto de medicina experimental para el estudio y tratamiento del cancer.
Bol. Inst. de puericult - Boletin do Instituto de puericultura.
Bol. Inst. radiol. cáncer, (Montevideo). - Boletin del Instituto de radiologia y centro de estudio y lucha contrall cancer (Montevideo).
Bol. Liga argent. contra el reumat. - Boletin de la Liga argentina contra el reumatisms.
Bol. Liga contra el cáncer - Boletin de la Liga contra el cáncer.
Bol. de med., cirug. y farm. - Boletin de medicina, cirugia y farmasia.
Bol. méd. d. Hosp. inf. (Mexico) - Boletin médico dei Hospital infantil (Mexico).
Bol. Ofic. san. panam. - Boletin de la Oficina sanitaria panamericana.
Bol. san. Dep. nac. hig., (Buenos Aires) - Boletin sanitario del Departamento nacional de higiene. (Buenos Aires).
Bol. san. Guatemala - Boletin sanitario de Guatemala.
Bol. San. São Lucas - Boletin do Sanatorio São Lucas.
Bol. Soc. de Biol. de Santiago de Chile - Boletin de la Sociedad de Biologia de Santiago de Chile.
Bol. Soc. chilena de obst. y ginec. - Boletin de la Sociedad chilena de obstetricia y ginecologia.
Bol. Soc. de cir. de Chile - Boletines de la Sociedad de cirugia de Chile.
Bol. Soc. de cir. de Rosario - Boletines de la Sociedad de cirugia de Rosario.
Bol. Soc. de cir. d. Uruguay - Boletin de la Sociedad de cirugia del Uruguay.
Bol. Soc. cubana de pediat. - Boletin de la Sociedad cubana de pediatria.
Bol. Soc. de Med. e Cir. de Rio de Janeiro -
Bol. Soc. de med. e cir. de São Paulo - Boletim da Soc. de medicina e cirurgia de São Paulo.
Bol. Soc. de obst. y ginec. de Buenos Aires - Boletin, Sociedad de obstetricia y ginecologia de Buenos Aires.

Bol. y trab., Acad. argent. de cir. - Boletines y trabajos, Academia argentina de cirugia. (Continuation of Bol. y trab., Soc. de cir. de Buenos Aires).
Bol. y trab., Soc. argent. de cirujanos - Boletines y trabajos, Sociedad argentina de cirujanos.
Bol. y trab., Soc. de cir. de Buenos Aires - Boletines y trabajos, Sociedad de cirugia de Buenos Aires. (Continued as Bol. y trab., Acad. argent. de cir.).
Bol. y trab., Soc. de cir. de Córdoba - Boletines y trabajos Sociedad de cirugia de Córboda.
Boll. d. r. Accad. med. - Bollettino, accademia medica.
Boll. d. r. Accad. med. di Genova - Bollettino d. r. Accademia medica di Genova.
Boll. d. Assoc. med. Triestina - Bollettino della associazione medica triestina (Trieste).
Boll. d. clin. - Bollettino delle cliniche.
Boll. Fac. med. Chir. r. Univ. Padova - See; Atti Soc. med-chir. (Padova).
Boll. d. Ist. sieroterap. milanese - Bollettino dell'Istituto sieroterapico milanese.
Boll. d. levatr. - Bollettino delle levatrici.
Boll. d. mal. d. orecchio, d. gola, d. naso - Bollettino delle malattie dell'orecchio, della gola, del naso di tracheobronco-esofagoscopia e di fonetica.
Boll. med. d. Svizzera ital. - Bollettino medico della Svizzera Italiana.
Boll. med. trentino - Bollettino medico trentino .
Boll. e mem. Soc. piemontese di chir. - Bollettino e memorie della Societa piemontese di chirurgia.
Boll. d'ocul. - Bollettino d'oculistica.
Boll. d. Osp. di S. Casa di Loreto-
Boll. d. Poliambul. di Milano - Bollettino d. Poliambulanza di Milano.
Boll. Sc. Fac. Chim. ind. Bologna - Bollettino scientifico Facultà di chimica industriale (Bologna).
Boll. d. sc. med. di Bologna - Bollettino delle scienze mediche.
Boll. Scient. - Bollettino scientifico.
Boll. d. sez. d. cult. d. sc. med. n. r. Acad. d. fisiocrit. di Siena. -
Boll. d. sez. ital. d. Soc. internaz. di microbiol. Bollettino della sezione italiana della Societa internazionale di microbiologia.
Boll. Soc. eustachiana - Bollettino della Societa eustachiana.
Boll. Soc. ital. biol. sper. - Bollettino della Societa italiana di biologia sperimentale.
Boll. Soc. ital. di med. e ig. trop. - Bollettino della Societa italiana di medicina e igiene tropicale.
Boll. Soc. ital. di microbiol. - Bollettino della Societa italiana di microbiologia.
Boll. Soc. med.-chir. di Modena - Bollettino della Societa medico-chirurgica di Modena.
Boll. Soc. med.-chir. (Pavia) - Bollettino della Societa medico-chirurgica (Pavia).
Boll. Soc. med. di Parma - Bollettino d. Societa medica di Parma.
Boll. Soc. piemont. Ostetr. - Bollettino, Società piemontese di ostetricia e ginecologia (Turin).
Boll. Soc. tosc. di ostet. e ginec. - Bollettino, Societa toscana di ostetricia e ginecologia, (Florence).
Boll. Soc. tra i cult. d. sc. med. in Siena - Bollettino, Società tra i cultori delle scienze mediche in Siena.
Boll. di Zool. - Bollettino di zoologia.
Bollettino - Bollettino, Opera Pia Poliambulanza "Giuseppe Ronzoni".
Bolnitsch. gaz. Botkina -
Bononiensi sc. et art. Inst. comment. - Bononiensi scientiarum et artium instituto atque academia commentarii.
Bordeaux chir. - Bordeaux chirurgical.
Boston M. J. - Boston Medical Journal.
Boston M. & S. J. - Boston Medical and Surgical Journal.
Bot. Z. Akad. Nauk URSR - Botanichnii zhurnal: Akademiia nauk URSR;
Botanical Gaz. - Botanical Gazette.
Bourgogne méd. - Bourgogne médicale.
Bozhl. v. chir. a Gynaek. (cast gynék.).
Brain - Brain, a Journal of Neurology.
Brasil-med. - Brasil-medico.
Bratisl. lek. listy. - Bratislavské lekarske listy.
Breslauer arztl. Ztschr. - Breslauer ärztliche zeitschrift.
Bristol Med.-Chir. J. - Bristol Medico-Chirurgical Journal.
Brit. -Am. J. M. & Phys. Sc. - The British-American Journal of Medical and Physiological Science.
Brit. Dent. J. - British Dental Journal.
Brit. Goat Soc. Month. J. - British Goat Society's Monthly Journal.
Brit. Gynaec. J. - British Gynaecological Journal.
Brit. Heart J. - British Heart Journal.
Brit. J. Anaesth. - British Journal of Anaesthesia.
Brit. J. Child. Dis. - British Journal of Children's Diseases.
Brit. J. Dermat. - British Journal of Dermatology and Syphilis.
Brit. J. Exper. Biol. - British Journal of Experimental Biology. (Changed to J. Exper. Biol. after vol. 6).
Brit. J. Exper. Path. - The British Journal of Experimental Pathology.
Brit. J. Indust. Med. - British Journal of Industrial Medicine.
Brit. J. M. Psychol. - British Journal of Medical Psychology.
Brit. J. Ophth. - The British Journal of Opahthalmology
Brit. J. Phys. Med. - British Journal of Physical Medicine.
Brit. J. Radiol. - British Journal of Radiology.
Brit. J. Rheumat. - The British Journal of Rheumatism.
Brit. J. Surg. - British Journal of Surgery.
Brit. J. Tuberc. - British Journal of Tuberculosis.
Brit. J. Urol. - British Journal of Urology.
Brit. J. Ven. Dis. - British Journal of Venereal Diseases.
Brit. M. J. - British Medical Journal.
Bronchoscop., oesophagoscop. et gastroscop. - Bronchoscopie, oesophagoscopie et gastroscopie.
Brooklyn Hosp. J. - Brooklyn Hospital Journal.
Brooklyn M. J. - Brooklyn medical journal.
Bruns Beitr. z. klin. Chir. - Bruns beitraege zur klinischen chirurgie. -See: Beitr. z. klin. Chir.
Bruxelles-méd. - Bruxelles-médical.
Bucuresti med. - Bucuresti medical.
Budapesti közkorh. evk. - Budapesti közkorhazainak evkönyve.
Budapesti k. Orvoseylsület - Budapesti kiralyi orvosegylsület Ertesitoje.
Budapesti orvosi ujság. - Budapesti orvosi ujság.
Buffalo M. J. - Buffalo medical journal.
Buffalo M. & S. J. - Buffalo medical and surgical journal and reporter.
Bull. Acad. de méd., (Paris) - Bulletin de l'Académie de médecine (Paris).
Bull. Acad. de méd. de Roumanie - Bulletin de l'Académie de médecine de Roumanie.
Bull. Acad. Med., (Toronto) - Bulletin of the Academy of Medicine (Toronto).
Bull. d. r. Acad. di Roma -
Bull. Acad. roy. de méd. de Belgique - Bulletin de l'Académie royale de médecine de Belgique.
Bull. Acad. Sc. Cracow -
Bull. Acad. sc. de Montpellier -
Bull. Acad. vét. de France - Bulletin de l'académie vétérinaire de France.
Bull. Am. A. M. Rec. Lib. - Bulletin of the American Association of Medical Record Librarians.
Bull. Am. Acad. Med. - Bulletin of the American Academy of Medicine.
Bull. Am. Acad. Tuberc. Physicians - Bulletin of the american academy of tuberculosis physicians. (Continued as Tuberculology).

Bull. Am. Cancer Soc. - Bulletin of the American Cancer Society.
Bull. Am. Coll. Surgeons - Bulletin of the American College of Surgeons.
Bull. Am. Hosp. A. - Bulletin of the American hospital association. (Continued as Hospitals).
Bull. Am. Mus. Nat. Hist. - Bulletin of the American Museum of Natural History.
Bull. Am. Psychoanalyt. A. - Bulletin of the American Psychoanalytic Association.
Bull. Am. Soc. Control Cancer - Bulletin of the American Society for the Control of Cancer. (Continued as Nat. Bull. Am. Soc. Control Cancer).
Bull. Assoc. d. Anat. -
Bull. Assoc. franç. p. l'étude du cancer - Bulletin de l'Association française pour l'étude du cancer.
Bull. Assoc. d. méd. de lang- franç. de l'Amérique du Nord - Incorporated in Union méd. du Canada.
Bull. Ayer Clin. Lab., Pennsylvania Hosp. - Bulletin of the Ayer Clinical Laboratory of the Pennsylvania Hospital.
Bull. biol. France & Belg. - Bulletin biologique de la France et de la Belgique.
Bull. biol. méd. expér. URSS - Bulletin de biologie et de médecine expérimentale de l'URSS.
Bull. Buffalo Gen. Hosp. - Bulletin of the Buffalo general hospital.
Bull. Charlotte Mem. Hosp. - Bulletin of the Charlotte Memorial Hospital.
Bull. Chicago M. Soc. - Bulletin of the Chicago medical society.
Bull. clin. - Bulletin clinique, suivi d'une revue analytique des sciences médicales.
Bull. d. Comit. med. cremonese -
Bull. Comité Polonais, p. l. lutte contre le cancer - Bulletin du Comité polonais pour la lutte contre le cancer néoplasmes.
Bull. Czechoslovak M. A. in Great Britain - Bulletin of the Czechoslovak Medical Association in Great Britain.
Bull. Dept. Health Commonwealth Kentucky - Bulletin of the Department of Health, Commonwealth of Kentucky.
Bull. El Paso Co. M. Soc. - Bulletin of the El Paso country medical society, (El Paso, Texas).
Bull. Fac. de méd. de Paris - Bulletin de la Faculté de médecine de Paris.-
Bull. Free Hosp. women -
Bull. gén. de thérap. - Bulletin général de thérapeutique.
Bull. Health. Organ.,League of Nations - Bulletin of the Health Organisation of the League of Nations.
Bull. Hist. Med. - Bulletin of the History of Medicine. (Continuation of Bull. Inst. Hist. Med.).
Bull. d'histol. appliq. à la physiol. - Bulletin d'histologie appliquée à la physiologie et à la pathologie et de technique microscopique.
Bull. Hosp. Joint Dis. - Bulletin of the Hospital for Joint Diseases.
Bull. Hyg. - Bulletin of Hygiene.
Bull. Inst. Hist. Med. - Continued as Bull. Hist. Med.
Bull. de l'Inst. internat. de statist. - Bulletin de l'institut international de statistique (Rome).
Bull. Inst. M. Research, Federated Malay States - Bulletins from the Institute for Medical Research, Federated Malay States.
Bull. Inst. Pasteur - Bulletin de l'Institut Pasteur.
Bull. Inst. Phys. Chem. Res. -
Bull. internat. Acad. polon. d. sc. et d. lett., Cl. méd. - Bulletin international de l'Académie polonaise des sciences et des lettre, Classe de médecine.
Bull. internat. Acad. d. sc. de Cracovie - Bulletin international de l'académie de sciences de Cracovie.
Bull. Internat. M. News - Bulletin of the International Medical News.
Bull. internat. serv. santé - Bulletin international des services de santé des armées de terre, de mer et de l'air. (Liége).
Bull. Jackson Mem. Hosp. - Bulletin of the Jackson Memorial Hospital. (Miami,Florida).
Bull. John D. Archbold Hosp. - Bulletin; John D. Archbold Memorial Hospital. (Thomasville, Ga.).
Bull. Johns Hopkins Hosp. - Bulletin of the Johns Hopkins Hospital. (Baltimore).
Bull. Kansas Bd. Health - Bulletin of the Kansas State Board of Health. (Topeka, Kansas).
Bull. League Red Cross Soc. - Bulletin (Monthly) (at head of tp.) League of Red Cross Societies. (Paris).
Bull. Lederle Lab. - Bulletin of Lederle Laboratories. (New York).
Bull. Los Angeles Co. M. Ass. - Bulletin of the Los Angeles County Medical Association. (Los Angeles).
Bull. Los Angeles Neurol. Soc. - Bulletin of the Los Angeles Neurological Society. (Los Angeles).
Bull. Lying-in-Hosp. N. York - Bulletin of the Lying-in-Hospital of the City of New York. (New York). See: Bull. Soc. Lying-in-Hosp. New York.
Bull. M. & Chir. Fac. Maryland - Bulletin of the medical and chirurgical faculty of the state of Maryland. (Baltimore).
Bull. M. Coll. Virginia - Bulletin; Medical College of Virginia. (Richmond, Va.)-
Bull. M. Library A. - Bulletin of the Medical Library Association. (Cleveland).
Bull. M. Soc. Co. Kings - Bulletin of the Medical Society of the County of Kings and Academy of Medicine of Brooklyn. (Brooklyn,N.Y.).
Bull. M. Soc. District of Columbia - Bulletin; The Medical Society of the District of Columbia. (Washington,D.C.).
Bull. M. Women Nat. Ass. - Bulletin (Quarterly) of the Medical Women's National Association. (Oak Park, Ill.).
Bull. Maryland Dep. Health - Bulletin (Monthly) (at head of tp.) Maryland State Department of Health. (Baltimore).
Bull. Massachusetts Agr. Exp. Sta. - Bulletin (Technical) (at head of tp.) Massachusetts Agricultural Experiment Station. (Amherst, Mass.).
Bull. Math. Biophysics - Bulletin of Mathematical Biophysics (Chicago).
Bull. Méd. de l'Aisne - Bulletin médical de l'Aisne.
Bull. méd. de l'Algérie - Bulletin médical de l'Algérie.
Bull. méd. du Nord - Bulletin médical du Nord de la France.
Bull. méd., (Paris) - Le bulletin médical. (Paris).
Bull. méd. de Québec - Bulletin médical de Québec. (Québec).
Bull. Mem. Hosp. Cancer, N.Y. - Bulletin of the Memorial for the Treatment of Cancer and Allied Diseases. (New York).
Bull. et mém. de la Sect. d'endocrinol., Soc. Roumaine de Neurol. Psych; Psychol. et Endocrinologie - Bulletins et mémories; section d'endocrinologie de la société roumaine de Neurologie, Psychiatrie, Psychologie et Endocrinologie.
Bull. et mém. Soc. Anat. de Paris - Bulletins et mémoires de la société anatomique de Paris.
Bull. et mém. Soc. de chir. de Bucarest - Bulletins et mémoires de la société de chirurgie de Bucarest. See: Rev. de chir., Bucuresti.
Bull. et mém. Soc. des chir. de Paris - Bulletins et mémoires de la Société des chirurgiens de Paris.
Bull. et mém. Soc. d'électro-radiol. méd. de France - Bulletins et mémoires de la Societe de électro-radiologie médicale de France.

Bull. et mém. Soc. d'endocrinol. - Bulletin et mémoire de la société d'endocrinologie. (Paris).(Continued as Bull. et mém. Soc. roumaine d'endocrinol.)

Bull. et mém. Soc. franc. d'opht. - Bulletins et mémoires de la Societe française d'ophtalmologie.

Bull. et mém. Soc. méd. et chir. de Bordeaux - Bulletins et mémoires de la Société de médecine et de chirurgie de Bordeaux. (Bordeaux).

Bull. et mém. Soc. méd. d. hop. de Paris - Bulletins et mémoires de la Société médicale des hopitaux de Paris. (Paris).

Bull. et mém. Soc. de méd. de Paris - Bulletins et mémoires de la Société de médecine de Paris.

Bull. et mém. Soc. nat. de chir. - Bulletins et mémoires de la société nationale de chirurgie. (Paris). (Continued as Mem. Acad. de chir.)

Bull. et mém. Soc. d'obst. et de gynec. de Paris - Bulletin et mémoires de la société d'obstétrique et de gynécologie de Paris. (Paris).

Bull. et mém. Soc. de radiol. méd. de France - Bulletin et memoires de la société de radiologie medicale de France. (Paris). (Continued as Bull. et mem. Soc. d'électro-radiol. med. de France).

Bull. et mém. Soc. roumaine d'endocrinol. - Bulletins et mémoires de la Société roumaine d'endocrinologie. (Continuation of Bull. et mém. Soc. d'endocrinol.)

Bull. Menninger Clin. - Bulletin of the Menninger Clinic. (Topeka, Kans.)

Bull. Milwaukee Health Dep. - Bulletin of the Milwaukee Health Department. (Milwaukee, Wis.).

Bull. Min. san. pub., Beograd - Bulletin mensuel du Ministère de la santé publique. (Beograd).

Bull. Minnesota M. Found. - The Bulletin of the Minnesota Medical Foundation.

Bull. Moses Taylor Hosp. - Bulletin of the Moses Taylor Hospital. (Scranton, Pa.).

Bull. Museum Comp. Zool. - Bulletin of the Museum of Comparative Zoology at Harvard College. (Cambridge, Mass.).

Bull. N. Carolina Bd. Charities - Bulletin; North Carolina State Board of Charities and Public Welfare. (Raleigh, N.C.).

Bull. N. York Tuberc. Ass. - Bulletin (at head of tp.) New York Tuberculosis and Health Association. (New York).

Bull. Nat. Res. Counc. Philippine Islands - Bulletin; National Research Council of the Philippine Islands. (Manila, P.I.).

Bull. Nav. M. A., Japan - Bulletin of the Naval Medical Association. (Tokyo).

Bull. Neurol. Inst. New York - Bulletin of the Neurological Institute of New York. (New York).

Bull. Nevada Bd. Health - Bulletin of the Nevada State Board of Health. (Carson City, Nevada).

Bull. New England M. Center. - Bulletin of the New England Medical Center.

Bull. New York Acad. Med. - Bulletin of the New York Academy of Medicine. (New York).

Bull. New York M. Coll., Flower and Fifth Ave. Hosps. - Bulletin of the New York Medical College, Flower and Fifth Avenue Hospitals.

Bull. New York Path. Soc. - Bulletin of the New York pathological society.

Bull. Off. Pract. - Bulletin of office practice. (Youngstown, Ohio).

Bull. Office internat. d'hyg. pub. - Bulletin de l'Office international d'hygiène publique. (Paris).

Bull. office Soc. franç. d'électrother. - Bulletin officiel de la Société française d'électrotherapie et de radiologie médicale. (Paris).

Bull. Ohio Agr. Exp. Sta. - Bulletin; Ohio Agricultural Experiment Station. (Wooster, Ohio.).

Bull. Oklahoma Dent. Soc. - Bulletin of the Oklahoma State Dental Society. (Perry, Okla.).

Bull. Ophth. Soc. Egypt - Bulletin of the Ophthalmological Society of Egypt.

Bull. Otolar. Clin. Beth Israel Hosp. - Bulletin of the Oto-Laryngological Clinics of the Beth Israel Hospital. (New York).

Bull. otorhin., Par. - Bulletin d'oto-rhino-laryngologie et de broncho-oesophagoscopie. (Paris).

Bull. Panamer. Union - Bulletin of the Panamerican Union. (Washington).

Bull. Pennsylvania Dep. Agr. - Bulletin; Pennsylvania Department of Agriculture. (Harrisburg, Pa.).

Bull. Philadelphia Coll. Pharm. - Bulletin of the Philadelphia College of Pharmacy and Science. (Philadelphia).

Bull. Philippine Dep. Off. Surg. - Bulletin (at head of tp.) Headquarters Philippine Department; Office of the Surgeon. (Manila, P.I.).

Bull. Pract. Ophth. - Bulletin of Practical Ophthalmology.

Bull. Quezon Inst. - The Bulletin of the Quezon Institute.

Bull. Rhode Island Bd. Health. - Bulletin of Rhode Island State Board of Health. (Providence).

Bull. Russian M. Soc. New York - Bulletin of the Russian Medical Society of New York.

Bull. S. Anthony Hosp., Okla. - Bulletin of S. Anthony's Hospital. (Oklahoma City, Okla.)

Bull. S. Juan Hosp. Manila - Bulletin of the San Juan de Dios Hospital of Manila. (Manila).

Bull. san. Algérie - Bulletin sanitaire de l'Algérie. (Alger.)

Bull. san., Montréal - Bulletin sanitaire. (Montreal).

Bull. sc. de la France et de la Belg. - Bulletin scientifique de la France et de la Belgique.

Bull. sc. med., Bologna - Bullettino delle scienze mediche (Bologna).

Bull. d. sc. pharmacol. - Bulletin des sciences pharmacologiques. (Paris).

Bull. School Med. Univ. Maryland - Bulletin of the School of Medicine, University of Maryland.

Bull. Schweiz. Gesundhamt. - Bulletin des Schweizerischen Gesundheitsamtes. (Bern).

Bull. Schweiz. Verein. Krebsbekampf. - Bulletin der Schweizerischen Vereinigung für Krebsbekämpfung. (Bern).

Bull. Scient. dép. du nord. - Bulletin scientifique du département du Nord et des pays voisins.

Bull. Scripps Inst. Oceanogr. - Bulletin of the Scripps Institution of Oceanography, La Jolla, Calif. (Berkeley, Calif.).

Bull. Sect. Endocrin. Soc. roum. Neur. - Bulletin Section d'endocrinologie Société roumaine de neurologie psychiatrie, psychologie et endocrinologie.

Bull. sect. sc. acad. roumaine - Bulletin section des sciences académie roumaine.

Bull. Soc. anat. -clin. de Lille - Bulletin de la société anatomo-clinique de Lille.

Bull. Soc. anat. de Nantes - Bulletins de la société anatomique de Nantes.

Bull. Soc. d'anat. et physiol. de Bordeaux - Bulletin de la société d'anatomie et de physiologie normale et pathologique de Bordeaux.

Bull. Soc. anthrop. Paris - Bulletins et memoires de la Société d'anthropologie de Paris. (Paris).

Bull. Soc. belge de gynec. et d'obst. - Bulletin de la société belge de gynécologie et d'obstétrique.

Bull. Soc. belge d'opht. - Bulletin de la Société belge d'ophtalmologie. (Bruxelles).

Bull. Soc. belge d'orthop. et de chir. de l'app. mot. - Bulletin de la Société belge d'orthopédie et de chirurgie de l'appareil moteur.

Bull. Soc. belge d'otol., rhinol., laryng. - Bulletin de la Société belge d'otologie, de rhinologie et de laryngologie.

Bull. Soc. centr. méd. vét. - Bulletin de la société centrale de médecine vétérinaire. (Paris).
Bull. Soc. chim. biol. - Bulletin de la Société de chimie biologique. (Paris).
Bull. Soc. chim. France - Bulletin de la Société chimique de France. (Paris).
Bull. Soc. de chir. de Lyon - Bulletin de la société de chirurgie de Lyon.
Bull. Soc. chir. de Paris - See Bull. et mém. Soc. des chir. de Paris.
Bull. Soc. clin. méd. ment., Par. - Bulletin de la Société clinique de médecine mentale. (Paris).
Bull. Soc. clin. de Paris - Bulletin de la société clinique de Paris.
Bull. Soc. form. humain., Par. - Bulletin de la Société d'étude des formes humaines. (Paris).
Bull. Soc. franç. de dermat. et syph. - Bulletin de la Société française de dermatologie et de syphiligraphie. (Paris).
Bull. Soc. franç. d'hist. de la méd.- Bulletin de la Société française d'histoire de la médecine et de ses filiales. (Paris).
Bull. Soc. franç. d'urol. - Bulletin de la Société française d'urologie. (Paris).
Bull. Soc. gynéc. et d'obst. - Bulletin de la Société de gynécologie et d'obstétrique.
Bull. Soc. japon. de syph. - Bulletin de la société japonaise de syphiligraphie. See Lues; Bull. Soc. japon. de syph.
Bull. Soc. Lying-in-Hosp. New York - Bull. of the society of the Lying-in-hospital. (New York).
Bull. Soc. M. Hist. Chicago - Bulletin of the Society of Medical History of Chicago.
Bull. Soc. méd.-chir. de la Drôme. - Bulletin de la société médico-chirurgicale de la Drôme et de l'Ardèche.
Bull. Soc. méd.-chir. de l'Indochine - Bulletin de la société médico-chirurgical de l'Indochine.
Bull. Soc. méd. du départ. du Nord - Bulletins de la société de médicine du département du nord.
Bull. Soc. méd. d. hôp. univ. de Québec - Bulletin de la société médicale des hôpitaux universitaires de Québec. (Québec).
Bull. Soc. de méd. de Gand - Bulletin de la société de médecine de Gand.
Bull. Soc. méd. hôp. Bucarest - Bulletins et memoires de la Société médicale des hôpitaux de Bucarest. (Bucuresti).
Bull. Soc. méd. d. hôp. de Lyon. - Bulletin de la la société médicale des hôpitaux de Lyon.
Bull. Soc. méd. Paris - Bulletins et mémoires de la Société de médecine de Paris. (Paris).
Bull. Soc. méd. Poitiers - Bulletin de la société de médecine de Poitiers.
Bull. Soc. de méd. -prat. de Paris - Bulletin de la société de médecine pratique de Paris.
Bull. Soc. méd. de Reims - Bulletin de la société médicale de Reims.
Bull. Soc. de méd. de Rouen - Bulletin de la société de médecine de Rouen.
Bull. Soc. méd. de Saint Luc - Bulletin de la société médicale de Saint Luc, Saint Côme, Saint Damien. (Bourges).
Bull. Soc. méd. de la Suisse Rom. - Bulletin de la société médicale de la Suisse romande.
Bull. Soc. méd. Vienne - Bulletin de la Société de medecine de la Vienne. (Poitiers).
Bull. Soc. méd. de l'Yonne - Bulletin de la société médicale de l'Yonne. (Auxerre).
Bull. Soc. nat. chir., Paris - Bulletin de la société nationale de chirurgie de Paris.
Bull. Soc. d'obst. et de gynéc. de Paris - Bulletin de la Société d'obstétrique et de gynécologie de Paris. (Paris).
Bull. Soc. opht. Egypte - Bulletin de la Société d'ophtalmologie d'Egypte. (Cairo).
Bull. Soc. d'opht. de Paris - Bulletin de la Société d'ophtalmologie de Paris. (Paris).
Bull. Soc. path. exot. - Bulletins de la Société de pathologie exotique. (Paris).
Bull. Soc. pédiat. de Paris - Bulletins de la Société de pédiatrie de Paris. (Paris).
Bull. Soc. philomat. de Par. - Bulletin de la société philomatique de Paris. (Paris).
Bull. de la Soc. Portugaise des Sc. Nat. - Bulletin de la société Portugaise des sciences naturelles.
Bull. Soc. Psychiat. de Bucarest - Bulletin de la Société de psychiatrie de Bucarest.
Bull. Soc. roumaine de neurol., psychiat., psychol. et endocrinol. - Bulletin de la Société roumaine de neurologie, psychiatrie, psychologie et endocrinologie.
Bull. Soc. roy. d. sc. med. et nat. de Bruxelles - Bulletin de la société royale des sciences médicales et naturelles de Bruxelles.
Bull. Soc. d. sc. méd. et biol. de Montpellier - Bulletin de la société des sciences médicales et biologiques de Montpellier et du Languedoc mediterranéen. (Montpellier).
Bull. Soc. d. sc. méd. du gr.-duche - Bulletin de la société des sciences médicales du grand-duche de Luxemburg.
Bull. Soc. d. sc. méd. de Lille - Bulletins de la société des sciences médicales de Lille.
Bull. Soc. d. sc. méd. et nat. de Bruxelles - Bulletin de la société des sciences médicales et naturelles de Bruxelles.
Bull. Soc. sc. méd. ouest - Bulletin de la Société scientifique et médicale de l'Ouest. (Rennes).
Bull. Soc. de sc. vet. de Lyon - Bulletin de la société des sciences vétérinaires de Lyon.
Bull. Soc. scient. d'hyg. aliment. - Bulletin de la Société scientifique d'hygiène alimentaire et d'alimentation rationnelle de l'homme. (Paris).
Bull. Soc. de sexol. - Bulletin de la Société de sexologie.
Bull. Soc. Vaudoise des Sc. nat. - Bulletin de la société vaudoise des sciences naturelles. (Lausanne).
Bull. Soc. zool. de France - Bulletin de la société zoologique de France. (Paris).
Bull. South. Pacific Gen. Hosp. - Bulletin of the Southern Pacific General Hospital. (San Francisco).
Bull. statist., Brux. - Bulletin de statistique. (Bruxelles).
Bull. statist., Sofia - Bulletin mensuel de la Direction général de la statistique. (Sofia, Bulgaria).
Bull. statist. Strasbourg - Bulletin statistique mensuel de la Ville de Strasbourg. (Strasbourg).
Bull. Synd. gén. méd. stomat. fr. - Bulletin officiel du Syndicat général des médecins stomatologistes français. (Paris).
Bull. Texas Dep. Health - Bulletin of the Texas State Department of Health. (Austin, Texas).
Bull. Truesdale Hosp. - Bulletin of the Truesdale Hospital and Earle P. Charlton Surgery. (Fall River, Mass.).
Bull. Tulane M. Fac. - The Bulletin of the Tulane Medical Faculty.
Bull. Union internat. tuberc., Par. - Bulletin de l'Union internationale contre la tuberculose. (Paris).
Bull. Univ. Asie centr., Tashkent - Bulletin de l'Université de l'Asie centrale. (Tashkent).
Bull. Univ. Hosp. (Georgia) - Bulletin of the University Hospital (Georgia).
Bull. Univ. Maryland School Med. - Bulletin of the University of Maryland school of Medicine. (Baltimore). (Continued as Bull. School. Med. Univ. Maryland).
Bull. U. S. Army M. Dept. - The Bulletin of the U. S. Army Medical Department.
Bull. U. S. Bur. Cens. - Bulletin; U. S. Bureau of Census. (Washington).
Bull. U. S. Bur. Fish. - Bulletin of the United States Bureau of Fisheries. (Washington).

Bull. U. S. Bur. Labor Statist. - Bulletin; United States Department of Labor; Bureau of Labor Statistics. (Washington,D.C.).
Bull. U. S. Bur. Mines - Bulletin; Department of Commerce; Bureau of Mines. (Washington,D.C.)
Bull. U. S. Bur. Stand. - Bulletin of the Bureau of Standards (at head of tp.) Department of Commerce. (Washington,D.C.).
Bull. U. S. Fed. Bd. Vocat. Educ. - Bulletin; Federal Board for Vocational Education. (Washington,D.C.).
Bull. U. S. Geol. Surv. - Bulletin (Geological Survey) (at head of tp. United States Department of Interior). (Washington, D.C.).
Bull. U. S. Labor Stand. - Bulletin; United States; Department of Labor;Division of Labor Standards. (Washington).
Bull. U. S. Nat. Inst. Health - Bulletin (at head of tp.) National Institute of Health. (Washington, D.C.).
Bull. U. S. Nat. Mus. - Bulletin; United States National Museum. (Washington,D.C.).
Bull. U. S. Nat. Res. Counc. - Bulletin of the National Research Council. (Washington,D.C.).
Bull. U. S. Navy Dep. Div. Prev. M. - Bulletin of the Unites States Navy Department; Division of preventive medicine. (Washington, D.C.)
Bull. U. S. Off. Educ. - Bulletin; Office of Education. (Washington,D.C.)
Bull. Vancouver M. A. - The Bulletin of the Vancouver Medical Association.
Bull. Virginia Dent. Ass. - Bulletin (The) of the Virginia State Dental Association.
Bull. Virginia State Libr. - Bulletin of the Virginia State Library. (Richmond, Va.)
Bull. War Med. - Bulletin of War Medicine.
Bull. Washington Univ. - Bulletin of Washington University. (Saint Louis, Mo.).
Bull. West. Reserve Univ. - Bulletin (at head of tp.) Western Reserve University. (Cleveland, Ohio).
Bull. Wistar Inst. - Bulletin of the Wistar Institute of Anatomy and Biology. (Philadelphia, Pa.)
Bull. Woman's Hosp. - Bulletin of the Woman's Hospital.
Butler Univ. Indianapolis, Ind., Botan. Stud.- Butler University, Indianapolis, Indiana. Botanical Studies.
Byull. eksper. biol. i med. - Byulleten eksperimentalnoy biologii i meditsiny.
C. A. M. E. P. - See Prensa méd. mex.
C. Rend. Congr. internat., lith. biliaire - Comptes rendus (Rapports) Congrès international de la lithiase biliaire, Vichy. (Paris).
C. Rend. Congr. internat. med. trop. - Comptes rendus. Congrès international de médecine tropicale et d'hygiène.
C. rend. Congr. méd. lég. fr. - Compte rendu; Congrès de médecine légale de langue française. (Paris).
C. rend. Convent. serv. san. Quebec - Compte rendu (at head of tp.) Convention annuelle des services sanitaires de la province de Québec. (Québec).
C. rend. Fed. dent. internat., Brux. - Compte rendu de la Fédération dentaire internationale. (Bruxelles).
C. rend. Lab. Carlsberg - Comptes rendus des travaux du Laboratoire Carlsberg. (København.)
Caducée - Le Caducée (Paris).
Cah. climatol. - Les cahiers de climatologie. Supplément de la Gaz. méd. de France.
Cah. gastro-enterol. - Les cahiers de gastro-enterologie. Supplément de la Gaz. méd. de France. (Paris).
Cah. d'hydrol. - Les cahiers d'hydrologie. Supplément de la Gaz. méd. de France.
Cah. radiol. - Les cahiers de radiologie et d'électrologie. (Paris) Supplement de la Gaz. méd. de France.
Cairo Sc. J. - Cairo scientific journal. (Cairo).
Calcutta M. J. - Calcutta Medical Journal. (Calcutta).
Calcutta M. Rev. - Calcutta Medical Review.
Calcutta School of Trop. Med. & Carmichael Hosp. for Trop. Dis., Ann. Rep. - Calcutta School of Tropical Medicine and the Carmichael Hospital for Tropical Diseases. Annual Report.
Caldasia. Bol. d. Inst. de Ciencias Nat. (Bogota) - Caldasia. Boletin del Instituto de Ciencias Naturales. (Bogota).
Caledon M. J. - Caledonian Medical Journal. (Glasgow).
Calendar Pharm. Soc. Gr. Britain - Calendar of the Pharmaceutical Society of Great Britain. (London).
California Acad. sc. - California Academy of Sciences. Occasional Papers (San Francisco).
California Bd. Health Month. Bull. - See: Bull. California Bd. Health.
California Citrograph (Los Angeles). -
California Eclect. M. J. - California eclectic medical journal. (Los Angeles).
California Fish and Game (Sacramento) -
California J. M. - California State journal of medicine. (San Francisco).
California M. J. - California Medical Journal (San Francisco).
California M. & S. Reporter - California Medical and Surgical Reporter.
California Sewage Works Journal (Berkeley). -
California State J. Med. - California State Journal of Medicine.
California & West. Med. - California and Western Medicine. (San Francisco).
Cambridge Philosoph. Soc., Biol. Rev. - Cambridge Philosophical Society, Biological Reviews.
Cambridge Univ. M. Soc. Mag. - Cambridge University Medical Society Magazine.
Camp. Notes (Cancer) - Campaign notes; American Society for the Control of Cancer. (New York).
Canad. Dairy & Ice Cream J. - Canadian Dairy and Ice Cream Journal (Toronto).
Canad. Entomol. - Canadian Entomologist (Guelph).
Canad. Field-Nat. - Canadian Field-Naturalist (Ottawa).
Canad. Geogr. J. - Canadian Geographical Journal (Ottawa).
Canad. Insect Pest Rev. - Canadian Insect Pest Review (Ottawa).
Canad. J. Comp. Med. - Canadian Journal of Comparative Medicine. (Quebec).
Canad. J. M. & S. - Canadian journal of Medicine and Surgery. (Toronto).
Canad. J. M. Technol. - The Canadian Journal of Medical Technology. (Ontario).
Canad. J. Ment. Hyg. - Canadian journal of mental hygiene. (Montreal).
Canad. J. Pub. Health - Canadian Journal of Public Health. (Toronto).
Canad. J. Research - Canadian Journal of Research. (Ottawa).
Canad. J. Res., Sect. A. Phys. Sc. - Canadian Journal of Research. Section A. Physical Sciences.
Canad. J. Res., Sect. B. Chem. Sc. - Canadian Journal of Research. Section B. Chemical Sciences.
Canad. J. Res., Sect. C. Botan. Sc. - Canadian Journal of Research. Section C. Botanical Sciences.
Canad. J. Res.,Sect. D. Zool. Sc. - Canadian Journal of Research. Section D. Zoological Sciences.
Canad. J. Res., Sect. E. M. Sc. - Canadian Journal of Research. Section E. Medical Sciences.
Canad. J. Res., Sect. F. Technol. - Canadian Journal of Research. Section F. Technology.
Canad. M. A. J. - Canadian Medical Association Journal (Montreal).
Canad. M. Month. - Canadian Medical Monthly. (Toronto).
Canad. M. Rev. - Canadian Medical Review.
Canad. M. & S. J. - Canadian Medical and Surgical Journal.

Canad. Nurse - Canadian nurse. (Ottawa, Can.)
Canad. Pharm. J. - Canadian Pharmaceutical Journal (Whitby).
Canad. Pract. - Canadian Practitioner (and Review). (Toronto).
Canad. Pract. & Rev. - Canadian Practitioner and Review.
Canad. Silver Fox & Fur. - Canadian Silver Fox and Fur.
Canada Lancet - Canada Lancet (Toronto).
Canada Lancet Pract. - Canada Lancet and Practitioner. (Toronto).
Canada M. J. - Canada Medical Journal.
Canada M. Rec. - Canada Medical Record.
Cancer, Bruxelles - Ceased publication.
Cancer, N. Y. - Cancer. (New York).
Cancer Research - Cancer Research. (Baltimore).
Cancer Rev. - Cancer Review; a journal of abstracts. (Bristol, England).
Cancro- Il Cancro. (Torino).
Candollea (Genova). -
Canner (Chicago). -
Canning Age (New York) -
Canning Trade (Baltimore) -
Capita zool., Gravenh. - Capita zoologica. 's Gravenhage.
Cardinal (Sewickley, Pa.).
Cardiologia - Cardiologia. Internationales Archiv für Kreislaufforschung. (Basel).
Caribbean Forester (Rio Piedras). -
Caribbean M. J. - Caribbean Medical Journal.
Carnegie Inst. Washington Publ. - Carnegie institution of Washington Publications.
Case Rec. Massachusetts Gen. Hosp. - Case records of the Massachusetts General Hospital. (Boston).
Časop. lék. česk. - Časopis lékaru českych. (Praha).
Casuist. Gynäk. Mitth. -
Cath. M. Guard., Lond. - Catholic medical guardian. (London).
Catholic Univ. Amer. Biol. Studies - Catholic University of America Biological Studies. (Washington, D.C.).
Cattleman (Ft. Worth, Texas).-
Cellule - La cellule. (Louvain).-
Cenco News Chats (Chicago). -
Centaur, Menasha - The Centaur of Alpha Kappa Kappa. (Menasha, Wis.).
Centaure - Le centaure. Supplément de la Gaz. méd. de France. (Paris).
Central States M. Monit. - Central States Médical Monitor.
Centralblatt - See; Zentralblatt.
Centre méd. et pharm. - Centre médical et pharmaceutique.
Cereal Chemistry - Cereal chemistry. (Lancaster,Pa.)
Cervello - Il Cervello. (Napoli).
Cesalpino - Il Cesalpino . (Arezzo).
Česka dermat. - Česka dermatologie.
Českoslov. gynaek. - Československá gynaekologie.
Ceylon J. Sc., Sect. D., M.Sc. - Ceylon Journal of Science, Section D., Medical Science. (Colombo).
Ceylon M. J. - Ceylon Medical Journal.
Character & Personality - Character and personality. (Durham, N.C.).
Charité-Ann. - Charité-annalen (Berlin).
Charleston M. J. & Rev. - Charleston Medical Journal and Reviews.
Charlotte M. J. - Charlotte (The new) medical journal. (Charlotte, N.C.).
Chem. & Drugg. - Chemist and druggist.
Chem. & Engin. News. Am. Chem. Soc. - Chemical and Engineering News, American Chemical Society.
Chem. & Industry - Chemistry and Industry.
Chem. Metallurg. Engin. - Chemical and metallurgical engineering. (New York).
Chem. News, Lond. - Chemical news and journal of industrial science. (London).
Chem. Rev. - Chemical Reviews. (Baltimore).
Chem. Warf. - Chemical warfare. (Edgewood Arsenal, Md.).
Chem. Warf. Bull. - Chemical Warfare bulletin. (Washington, D.C.).
Chem. Zentralbl. - Chemisches zentralblatt.
Die Chemie -
Chemie der Zelle - Chemie der Zelle und Gewebe. (Leipzig).
Chiba Igakukwai Zasshi - Chiba Igakukwai Zasshi.
Chicago Clinic - Chicago Clinic.
Chicago Clin. Rev. - Chicago Clinical Reviews.
Chicago Health - Chicago's Health. (Chicago).
Chicago M. Exam. - Chicago Medical Examiner.
Chicago M. J. & Exam. - Chicago Medical Journal and Examiner.
Chicago M. Rec. - Chicago Medical Recorder (Chicago).
Chicago M. Rev. - Chicago Medical Review.
Chicago M. Times - Chicago Medical Times.
Child - The child. (Washington,D.C.).
Child Develop. - Child development. (Baltimore).
Child Health Bull. - Child health bulletin. (New York).
Child Health Mag. - Child health magazine. (Washington).
Child Labor Bull. - Child labor bulletin. (New York).
Child, Lond. - Child (London).
Child Res. Clin. Ser. - Child Research Clinic series. (Langhorne,Pa.).
Chimica, Milano - Chimica e la medicina moderna. (Milano).
China M. J. - China medical Journal (Shanghai).
China M. Miss. J. - China Medical Mission Journal.
Chinese J. Physiol. - Chinese Journal of Physiology. (Peiping).
Chinese M. J. - Chinese Medical Journal. (Peiping).
Chinsei Iho Kumamoto - Chinsei iho kumamoto. (Tokyo).
Chir. Beob. a. d. Thurgau. Kantonsspit. Münsterlingen -
Chir. ernia - La Chirurgia dell'ernia e dell'addome. (Napoli).
Chir. Laitop. -
Chir. narz. ruchu. - Chirurgia narzadów ruchu i ortopedja polska.
Chir. d. org. di movimento - La chirurgia degli organi di movimento. (Bologna).
Chir. plast. - La chirurgia plastica. (Roma).
Chir. Reminisc. -
Chirurg - Der Chirurg. Zeitschrift für alle Gebiete der operativen Medizen. (Berlin).
Chirurgie - Chirurgie (Genève).
Chirurgija -
Chiugai Iji Shinpo -
Chromosoma - Chromosoma. Zeitschrift für Zellkern- und Chromosomenforschung.
Chron. méd. - Chronique medicale. (Asnières).
Chron. med. (Paris) - Chronique médicale (Paris).
Ciba Ztschr. - Ciba Zeitschrift (Basel).
Ciclo conf. sobre ident. d recien nacido. - Ciclo de conferencias sobre identificacion del recién nacido.
Ciencia - Ciencia. Revista hispano-americana de ciencias puras y aplicadas.
Cincinnati J. Med. - Cincinnati Journal of Medicine. (Cincinnati, Ohio).
Cincinnati Lancet - Clinic - Cincinnati Lancet-Clinic.
Cincinnati Lancet & Obst. - Cincinnati Lancet and Obstetrics.
Cincinnati Med. & Dent. - Cincinnati Medicine and Dentistry.
Cincinnati M. J.- Cincinnati Medical Journal (Cincinnati).
Cincinnati M. News - Cincinnati Medical News.
Cincinnati M. Obs. - Cincinnati medical observer.
Cincinnati M. Rep. - Cincinnati Medical Report.
Cir. California Agr. Exper. Sta. - Circular of the California Agricultural Experiment Station.
Cir. y cirujanos - Cirugia y cirujanos. (Mexico, D.F.).
Cir. ortop. y traumatol., Habana - Cirugia ortopédica y traumatologia.
Cleanliness J. - Cleanliness journal. (New York).
Cleveland Clin. Quart. - Cleveland Clinic Quarterly. (Cleveland, Ohio).
Cleveland J. Med. - Cleveland Journal of Medicine.
Cleveland M. Gaz. - Cleveland Medical Gazette.

Cleveland M. J. - Cleveland Medical Journal.
Clifton M. Bull. - Clifton Medical Bulletin.(Clifton Springs, N.Y.).
Clin. chir. - Clinica chirurgica (Milano).
Clin. chir. de la Pitie -
Clin. Cincinnati - Clinical Cincinnati.
Clin. Hist. - Clinical History.
Clin. d. hop. (Paris) - Clinique des hopitaux et de la ville (Paris).
Clin. igiene inf. - Clinica e igiene infantilie.(Torino).
Clin. J. - Clinical Journal. (London).
Clin. J. Chiropody - Clinical journal of chiropody, pediatry and pedic surgery. (Chicago).
Clin. y lab., - Clinica y laboratorio,revista mensual española de ciencias medicas.(Zaragaza).
Clin. Lect. - Clinical Lectures.
Clin. Lect. Dis. Women - Clinical Lectures on Diseases of Women.
Clin. Med. - Clinical medicine.(Chicago).
Clin. med. ital. - La clinica medica italiana.(Milano).
Clin. Med. & Surg. - Clinical Medicine and Surgery (Waukegan, Ill.)
Clin. mod. Pisa - Clinica moderna (Pisa).
Clin. mod. Zaragoza - Clinica moderna (Zaragoza).
Clin. News Phila. - Clinical news (Philadelphia).
Clin. opht.,Par. - Clinique ophtalmologique.(Paris).
Clin. ostet. - La clinica ostetrica e ginecologica.(Rome).
Clin. pediat.,Mod.- Clinica pediatrica.(Modena).
Clin. per tutti - Clinica per tutti. (Roma).
Clin. Proc. - Clinical Proceedings.
Clin. psicoped.,B.Air.- Clinica psicopedagogica. (Buenos Aires).
Clin. Recorder - Clinical Recorder.
Clin. Rep. Surg., Pract. Glasgow Roy. Infirm.-
Clin. Rev. Pittsburgh - Clinical reviews of the Pittsburgh Diagnostic Clinic. (Pittsburgh,Pa.)
Clin. Sc. - Clinical Science Incorporating Heart.(London).
Clin. Sketches London - Clinical sketches illustrative of practical medicine and surgery (London).
Clin. vet. - La clinica veterinaria (Milano).
Clinica - Clinica
Clinics - Clinics (Philadelphia) (Successor to Internat. Clin.).
Clinique (Bruxelles) - Clinique (Bruxelles).
Clinique (Chicago) - Clinique (Chicago).
Clinique, Montreal - La clinique (Montreal).
Clinique, Paris - La clinique. (Paris).
Cluj. med. - Cluj medical.(cluj, Romania).
Codex med. (Philadelphia) - Codex medicus (Philadelphia).
Coimbra med. - Coimbra medica (Coimbra).
Cold Spring Harbor symp. on Quant. Biol. - Cold Spring Harbor symposia on quantitative biology.
Coll. &Clin. Rec. - College and clinical record.
Coll. J. M. Sc. - College journal of medical science. (Continued from Am. M. J. Cincinnati).
Collect. acad. d. mem. (Dijon) - Collection academique, composee de l'histoire & des memoires, actes Journaux de plus celebres academies et societes litteraires de l'Europe.(Dijon).
Collect. de diff. pieces - Collection de differentes pieces.
Collect. Papers Austral. Inst. Trop. M. - Collected papers (at head of tp.) The Australian Institute of Tropical Medicine. (Townsville, Australia).
Collect. Papers Hall Inst. Res. Path. Melb. - Collected papers (at head of tp.) The Walter & Eliza Hall Institute of Research in Pathology and Medicine.(Melbourne).
Collect. Papers Henry Ford Hosp. - Collected papers by the Staff of the Henry Ford Hospital. (N. York).
Collect. Papers Inst. Biol. Johns Hopkins - Collect d Papers from the Institute for Biological Research of the Johns Hopkins University. (Baltimore).
Collect. Papers Marquette Univ. - Collected papers of the Marquette University School of Medicine. (Milwaukee, Wis.).
Collect. Papers, Mayo Clin. - Collected papers of the Mayo clinic. (Rochester).
Collect. Repr. Montefiore Hosp. N. York. - Collected reprints; Montefiore Hospital for Chronic Diseases, New York. (New York).
Collect. Repr. Williams Hooper Found. - Collected reprints from the George Williams Hooper Foundation; University of California. (San Francisco).
Collect. Stud. Chicago Mun. Tuberc. Sanit. - Collected Studies from the Chicago Municipal Tuberculosis Sanitarium. (Chicago, Ill.).
Colombia med. - Colombia médica. (Bogotá).
Colonial J., London - Colonial Jorunal. (London).
Colorado Med. - Colorado medicine (Denver). (Cont'd as Rocky Mountain Medical Journal).
Columbia Alumni News - Columbia alumni news. (New York).
Columbia Univ. Bull. Inform. - Columbia University bulletin of information.(New York).
Columbus M. J. - Columbus Medical Journal.
Comitato Talassografico Ital. Mem. - Comitato Talassografico italiano memoria.
Comment. Clin. di Pisa - Commentario clinico di Pisa.
Comment. Owensby Clin. - Commentator of the Owensby Clinic, Atlanta,Ga.
Comment. soc. regiae scient. Gottingensis. Commentationes societatis regiae scientiarum Gottingensis.
Commonhealth, Bost. - Commonhealth Boston.
Commun. Inst. sérothér. Danois. - Communications de l'Institut sérothérapique de l'Etat Danois. (København).
Communicat. M. Soc. Connecticut - Communications of the medical Society of Connecticut.
Comp. Psychol. Monogr. - Comparative psychology monographs. (Baltimore).
Compend Med. & Surg. - Compend of medicine and surgery. (San Francisco).
Compilador med. - Compilador medico.
Compt. rend. Acad. med. de belge -
Compt. rend. Acad. d. sc. - Comptes rendus hebdomadaires des séances de l'Académie des sciences. (Paris).
Compt. rend. Acad. sc. U.R.S.S. - Comptes rendus Académie des sciences de U. R. S. S.
Compt. rend. de l'Assoc. d. anat. - Comptes rendus de l'association des anatomistes.
Compt. rend. Soc. des Anat. (Marseilles). -
Compt. rend. Soc. de biol. - Comptes rendus des séances de la Société de biologie. (Paris).
Compt. rend. Soc. franç. de gynéc. - Comptes rendus de la Société française de gynécologie.
Compt. rend. Soc. de méd. de Nancy - Compte rendu de la société de medecine de Nancy
Compt. rend. Soc. méd. du prem. arrond. de Paris - Compte-rendu de la société médicale du premier arrondissementd de Paris.
Compt. rend. Soc. obst. et gynéc. Moscou - Compte rendu de la société d'obstetrique et de gynécologie Moscou.
Compt. rend. Soc. d'obst. de gynéc. et de pédiat. de Paris - Comptes rendus de la société d'obstetrique et de gynécologie et de pédiatrique de Paris.
Compt. rend. Soc. Phys. Hist. Nat. -(Genève Compte rendu de la société de physique et d'histoire naturelle de Genève.
Compt. rend. Soc. d. sc. de Varsovie - Compte rendu de la société des sciences de Varsovie.
Compt. rend. d. trav. du lab. Carlsberg. serie physiol. - Comptes rendus des travaux du laboratoire Carlsberg, serie physiologique.
Concilium ophthalmologicum 1937 Egypte - See Internat. Ophth. Cong.
Concours Méd. - Concours médical.
Conf. Bull., Cincin. - Conference bulletin. (Cincinnati, Ohio).

Conf. M. Res. Workers Calcutta - Conference of medical research workers held at the School of Tropical Medicine, Calcutta. (Simla, Calcutta).
Conf. prat. urol., Milano - Conferenze pratiche d'urologie. (Milano).
Confer. clin. chir. Paris -
Confinia neurol. - Confinia neurologica.
Cong. franç. de chir.,Proc.-verb. etc. - Congrès français de chirurgie procès-verbaux, mémoires et discussions.
Cong. gynéc. d'obst. et pédiat. Bordeaux. -
Cong. internat. de bains de mer -
Cong. internat. de méd. C.r., sect. de méd. de l'enf. - Congrès international de médecine compe-rendu section de médecine des enfants (Paris).
Cong. internat. de méd. trop. et d'hyg.,Compt. rend. -
Cong. méd. région, ligure -
Cong. nat. périod. de gynéc. d'obst. et de pédiat. Mém. et disc. -
Cong. nat. périod. de gynéc. Rouen -
Cong. paulist. de psiol.,neurol.,psiquiat. endocrinol.,ident.,med. leg e criminol.,atos.-
Cong. périod. de gynéc. et d'obst.-
Cong. périod. internat. gynéc. et d'obst. Bruxelles -
Cong. périod. internat. d. sc. méd. -
Congr. argent. cir. - Congreso argentino de cirugia.
Congr. brazil. hyg. - Congresso brasileiro de hygiene, (Rio de Janeiro) See; Ann. Congr. brasil. hgy.).
Congr. med. cir. nav. mil. Chile - Congreso de medicina y cirugia naval y militar de Chile.
Congr. nac. cir.,Valparaiso - Congreso nacional de cirugía. (Valparaiso, Chile).
Connecticut Health Bull. - Connecticut health bulletin. (Hartford,Conn.)
Connecticut M. J. - Connecticut Medical Journal.
Conrad Printing Co., Tacoma, Washington -
Consulti med. -
Contact point - Contact point. (San Francisco).
Contr. Bermuda Biol. Sta. - Contributions from the Bermuda biological Station for Research. (Cambridge,Mass.).
Contr. Dep. Pub. Health Yale - Contributions from the Anna M. R. Lauder Department of Public Health;Yale University; School of Medecine. (New Haven, Conn.).
Contr. Inst. Physiol. Nat. Acad. Peiping - Contributions from the Institute of Physiology; National Academy of Peiping. (Peiping).
Contr. Lab. Vertebr. Genet. Univ. Michigan - Contributions from the Laboratory of Vertebrate Genetics; University of Michigan. (Ann Arbor).
Contr. Peking Union M. Coll. - Contributions from the Peiping Union Medical College (Peiping).
Contr. Penrose Res. Lab. - Contributions from the Penrose Research Laboratory. (Philadelphia).
Contr. Tuberc. Nat. Jew Hosp., Denver - Contributions to the study of tuberculosis by the Research Department; National Jewish Hospital for Consumptives. (Denver,Colo.).
Contrib. to Embryol.,Carnegie Inst. Washington. Contributions to Embryology, Carnegie Institute of Washington. (Washington).
Contrib. M. Res. -
Copeia - Copeia-
Cor.-Bl. d. allg. ärztl. Ver. v. Thüringen Weimar -
Cor. - Bl. d. allg. mecklenb. Aerztever -
Cor.-Bl. f. d. Ärzte u. Apoth. d. Grossenherz. Oldenburg.- Korrespondenzblatt für die äerzte und apotheker des grossherzogthums Oldenburg.
Cor.-Bl. d. ärztl. Ver. d. Rhein-Prov.-
Cor.-Bl. f. schweiz. Äerzte - Korrespondenzblatt für schweizer äerzte.
Cor.-Bl. f. Zahnärzte . Korrespondenzblatt für zahnäerzte.
Cornell Univ. M. Bull. - Cornell University medical bulletin. (New York).
Cornell Univ. Stud. Anat. - Cornell university studies from the department of Anatomy.
Cornell Vet. - Cornell (The) veterinarian. (Ithaca).
Correio med. de Lisboa - Correio medico de Lisboa.
Correo med. castellano - Correo medico castellano.
Corresp. méd. - Correspondencia médica. (Madrid).
Correspondenzblatt - See: Korrespondenzblatt.
Corriere san.,(Milano) - Corriere sanitario (Milano).
Corriere san. Settim. -
Courrier méd. - Courrier médical.
Crippled Child - Crippled Child. (Lorain, Ohio).
Cron. Clin. med. Genova - Cronaca della Clinica medica di Genova. (Genova).
Crón. méd. Lima - La crónica médica. (Lima).
Crón. méd. mexicana - Cronica medica mexicana. (Mexico).
Crón. méd.-quir. de la Habana - Crónica médico-quirúrgica de la Habana. (La Habana).
Crón. méd. (Valencia) - Crónica médica. (Valencia).
Crouse Irving Bull. - Crouse-Irving bulletin. (Syracuse, N.Y.).
Crusader - Crusader of the Wisconsin Anti-tuberculosis Association. (Milwaukee, Wis.).
Cruz roja - Cruz roja. (Madrid).
Cult. med. mod. Pal. - Cultura (La) medica moderna (Palermo).
Cultura - Cultura.
Cultura méd. - Cultura médica.
Cuore e circolaz. - Cuore e circolazione. (Roma).
Current Leg. Thought - Current legal thought. (New York).
Current Researches in Anesth. & Analg.- Current researches in anesthesia and analgesia. (Elmira, New York). (See Anesth. & Analg.)
Cycl. Anat. & Physiol. -
Cytologia - Cytologia.
Czasopismo lék. (Lodz) - Czasopismo lékarskie.(Lodz).
Dairen Hosp. - Dairen hospital. (Dairen).
Dallas M. J. - The Dallas Medical Journal (Dallas,Texas).
Daniel's Texas M. J. - Daniel's Texas Medical Journal.
Dansk. dermat. selsk. forh. - Dansk dermatologisk selskabs forhandlinger. (København). (Supplement of Hospitalstidende).
Dauphin M. Acad. - Dauphin medical academician. (Harrisburg, Pa.).
Dauphine méd.(Grenoble) - Dauphine médical. (Grenoble).
Debrec. Tisza István Tud. Társ. II. Oszt. Munkai - Debreceni Tisza István tudományos tarsaság, Debrecen. II. Orvos-természettudomanyi osztályának Munkái.
Delaware State M. J. - Delaware State Medical Journal. (Wilmington,Del).
Dem. Sitzg. med. Ges. Magdeburg -
Dementia Praecox Stud. - Dementia praecox studies. (Chicago).
Denkschr. Akad. Wiss. Wien - Denkschriften (at head of tp.) Akademie der Wissenschaften in Wien; mathematisch-naturwissenschaftliche Klasse. (Wien).
Dental Bull., Carlisle - Dental bulletin. (Carlisle Barracks,Pa.).
Dental Cosmos - Dental (The) Cosmos (Philadelphia). (Ceased publication).
Dental Craftsman - Dental craftsman. (Chicago).
Dental Digest. - Dental digest. (Pittsburgh,Pa.).
Dental Facts - Dental facts.(Chicago).
Dental Forum - Dental forum. (Pittsburgh,Pa.).
Dental Gaz. - The Dental Gazette.
Dental Items - Dental items of interest. (Brooklyn,N.Y.).
Dental J. Australia - Dental journal of Australia. (Sydney).
Dental News - Dental news. (Minneapolis, Minn.).
Dental Rec.,Lond. - Dental (The) Record (London).
Dental Reg. - Dental register. (Cincinnati).
Dental Rev. - Dental review. (Chicago).
Dental Summary - Dental summary. (Toledo,Ohio).
Dental Surv. - Dental survey. (Minneapolis).
Dentoscope Bull.,Wash. - Dentoscope (at head of tp.) (Howard University Bulletin) Washington,D.C.

Denver M. Times - Denver Medical Times.
Dermat. Wchnschr. - Dermatologische Wochenschrift. (Leipzig).
Dermat. Zb. - Dermatologisches Centralblatt.(Berlin).
Dermat. Ztschr. - Dermatologische Zeitschrift.(Berlin).
Dermatologica - Dermatologica.
Dermosifilografo - Dermosifilografo (Il). (Torino).
Desgranges Leçons de clin. chir. Paris -
Detroit Clinic - Detroit clinic.
Detroit Lancet - Detroit lancet.
Detroit M. J. - Detroit (The) Medical Journal. (Detroit, Mich.).
Detroit Rev. Med. & Pharm. - Detroit review of medicine and pharmacy.
Detsk. bolez. - Detskikh boleznei. (Leningrad).
Deutsche Äerzte Ztg. - Deutsche Äerzte-Zeitung. (Berlin).
Deutsche Dent. - Der Deutsche Dentist. (Berlin).
Deutsche Heilpflanze - Die Deutsche Heilpflanze. (Munchen).
Deutsche Klin. - Deutsche Klinik.
Deutsche Krüppelhilfe - Deutsche Krüppelhilfe; Ergängungshelfte der Zeitschrift für Kruppelfürsorge. (Leipzig).
Deutsche med. Wchnschr. - Deutsche medizinische Wochenschrift. (Leipzig).
Deutsche Med.-Ztg. - Deutsche medizinal-zeitung.
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Deutsche Militar- Der Deutsche Militararzt. (Berlin).
Deutsche Monatschr. f. Zahnheilk. - Deutsche Monatsschrift für Zahnheilkande. (Berlin).
Deutsche Prax. - Deutsche praxis.
Deutsche Rev. - Deutsche Revue. (Stuttgart).
Deutsche tierärztl. Wchnschr. - Deutsche tierärztliche Wochenschrift. (Hannover).
Deutsche tropenmed. Ztschr. - Deutsche tropenmedizinische Zeitschrift.
Deutsche Tuberk. Bl. - Deutsches Tuberkulose-Blatt. (Leipzig).
Deutsche Vjschr. f. Zahnchir. - Deutsche Vierteljahrsschrift für Zahnchirurgie.(München).
Deutsche Zahn-Mund-Kiefer-heilk.- Deutsche Zahn-Mund-und Kieferheilkunde.(Leipzig).
Deutsche zahnärztl.Wchnschr. - Deutsche zahnärztliche wochenschrift.
Deutsche Zahnh. - Deutsche Zahnheilkunde.(Leipzig).
Deutsche Ztschr. f. Chir. - Deutsche Zeitschrift für Chirurgie. (Berlin).
Deutsche Ztschr. f. d. ges. gerichtl. Med. - Deutsche Zeitschrift für die gesamte gerichtliche Medizin.(Berlin).
Deutsche Ztschr. f. Nervenh. - Deutsche Zeitschrift für Nervenheilkunde.(Berlin).
Deutsche Ztschr. öff. Gesundhpfl. - Deutsche Zeitschrift für öffentliche Gesundheitspflege. (Berlin).
Deutsche Ztschr. f. prakt. Med. - Deutsche zeitschrift für praktische Medizin.
Deutsche Ztschr. f. Thiermed. - Deutsche zeitschrift fur thiermedizin und vergleichende pathologie.
Deutsche Ztschr. f.Verdauungs-und Stoffwechselkrankh. - Deutsche zeitschrift für verdauungs-und stoffwechselkrankheiten.
Deutsches Arch. f. klin. Med. - Deutsches Archiv für klinische Medizin. (Berlin).
Deutsches Arch. f. Physiol. - Deutsches archiv für die physiologie.
Deutsches Tuberk. -Bl. Deutsches Tuberkulose-Blatt. (Leipzig).
Día méd. - El día médico (Buenos Aires).
Día méd. urug. - Día médico uruguayo. (Montevideo).
Diabetes,N.Y. - Diabetes.(New York).
Diag. Anat. Clin. (Lecéne,P.) -
Diag. e tec. di lab. - Diagnostica e tecnica di laboratorio. (Napoli). (Continuation of Folia clin. chim. et micr.).
Diag. ther. Irrtüm. - Diagnostische und therapeutische Irrtümer und deren Verhütung.(Leipzig).
Diag. et Trait. - Diagnostics et Traitements.
Diagnosi - Diagnosi (Bologna).
Dict. d. Sc. méd. - Dictionnaire encyclepédique des sciences médicales.
Diet. Admin. Ther. - Dietary administration and therapy. (Cleveland, Ohio).
Diet. encycl. d. sc. méd. -
Difesa med. leg. lavoro - Difesa medico-legale del lavoro. (Torino).
Difesa sociale - Difesa sociale. (Roma).
Digest Phys. Ther. - Digest of physical Therapy. (Battle Creek, Mich.).
Diplomate. - The Diplomate. (Philadelphia).
Diritto vet. - Diritto veterinario.(Torino).
Dis. of Chest. - Diseases of the Chest. (El Paso,Tex.)
Dis. Eye Ear, Nose & Throat - Incorporated in Eye Ear, Nose & Throat Monthly.
Dis. Nerv. System - Diseases of the Nervous System.
Discovery, Lond. - Discovery.(London).
Dixie Doct. Atlanta - Dixie doctor Atlanta.
Dnevnik syezda Obsh. russk. vrach. v. pamyat Pirogova -
Dnipropetr. med. J. - Dnipropetrovsky medichiny jurnal. (Dnipropetrovsk).
Dodici mesi di chir. n. osp. Costanze Mazzoni -
Dodonaeus, R.,Med. obs. exampla rara, Lugd. Bat. -
Dominion Dent. J. - Dominion Dental Journal (Toronto).
Dominion M. J. - Dominion Medical Journal.
Dominion M. Month. - Dominion Medical Monthly.(Toronto).
Dresd. Statist. - Dresdner Statistik. (Dresdan).
Drug. Trade Week. - Drug Trade weekly. (New York).
Dublin Hosp. Gaz. - Dublin Hospital Gazette.
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Dublin J. Med. - Dublin Journal of Medicine.
Dublin M. Press - Dublin Medical Press.
Dublin Quart J. M. Sc. - Dublin Quarterly Journal of Medical Science.
Duncan Clin. Lect. Dis. Women. -
Duodecim. - Duodecim, lääketieteellinen aikakauskirja.
Durham Mus. Catal. -
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Eating Your Way to Health - Eating your way to health. (Oakland, Calif.).
Ebd. clin. di Bologna - Ebdomadario clinico di Bologna.
Echo Méd. - Echo médical.
Echo méd. d. Cevennes - Echo médical des Cevennes.
Echo méd. du Nord - L'echo médical du Nord (Lille).
Echo méd. Toulouse - Echo médical de Toulouse.
Eclect. M. J. - The Eclectic medical journal. (Cincinnati, Ohio).
Eclect. M. & S. J. - Eclectic medical and surgical journal. (Des Moines).
Eclect. Repert. - Eclectic repertory and analytical review.
Ecole prat. d. hautes études - Ecole pratique des hautes études Paris.
Econom. Proc. R.Dublin Soc. - The economic proceedings of the Royal Dublin Society.(Dublin).
Edinburgh Hosp. Rep. - Edinburgh Hospital Reports.
Edinburgh J. M. Sc. - Edinburgh Journal of Medical Science.
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Edinburgh M. & S. J. - Edinburgh Medical and Surgical Journal).
Eira - Eira
Wjened. jour. "Prakt. Med."-
Ejened. klin. gaz.-
Ejenedelnik -
Eksper. med. - Eksperimentalna meditsina.
Elme-és idegkórt.- Elme-és idegkórtan
Emory Med. Rev. - Emory medical review.(Atlanta,Ga.).
Encéphale - L'encéphale, journal de neurologie et de psychiat chiatrie. Supplément; l'hygiene mentale. (Paris).

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Endocrin. Gynec. si Obst. - Endocrinologie, gynecologie, si, Obstetrica.
Endocrine Round Table -
Endocrine Survey - (Continuing the International Digest of Organotherapy) Publ. in Glendale, Calif.
Endocrinol. e pat. costit. - Endocrinologia e pathologia costituzionale, (Bologna).
Endocrinologia - Endocrinologia
Endocrinology - Endocrinology (Los Angeles).
Endokrinologie - Endokrinologie (Leipzig).
Engin. & Contracting - Engineering and contracting. (Chicago).
Ensayo med.- Ensayo medico.
Entwickl. Med. -
Enzymologia - Enzymologia
Eos, Wien - Eos Zwitschrift für die Erkenntnis und Behandlung jugendlicher Abnormer. (Wien).
Epidemiol. Rep., League of Nations - (Ceased publication).
Erbbl. f. d. Hals-, Nasen-u. Ohrenarzt: See Hals. Nasen-u. Ohrenarzt.
Erdball - Die Erdball Berlin-Lichterfelde.
Ergebn. d. allg. Path. u. path. Anat. - Ergebnisse der allgemeinen Pathologie und pathologischen Anatomie des Menschen und der Tiere. (München).
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Ergebn. d. ges. Med. - Ergebnisser der gesamten Medizin (Berlin).
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Ergebn. d. inn. Med. u. Kinderh. - Ergebnisse der inneren Medizin und Kinderheilkunde. (Berlin).
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Ergebn. d. Path. -
Ergebn. d. phys. - diät. Therap. - Ergebnisse der physikalisch-diätetischen Therapie.
Ergebn. d. Physiol. - Ergebnisser der Physiologie biologischen Chemie und experimentellen Pharmakologie. (München).
Ergebn. sozial. Hyg. - Ergebnisse der sozialen Hygiene und Gesundbeitsfürsorge. (Leipzig).
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Erkrank. Beweg. App., Wien. - Die Erkrankungen des Bewegungsapparates. (Wien).
Eschenbach's Obst. anat. chir.-med. rariora Rostoch -
Escuela de med. - Escuela de medinina.
España méd. - España médica.
Essais et obs. de méd. de la Soc. d'Edinb. - Essais et observations de médecine de la société d'Edinbourg.
Essays in Biology -
Ethnographie, Par. - Ethnographie. (Paris).
Ethnol. Anz. - Ethnologischer Anzeiger. (Stuttgart).
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Eugen. News - Eugenical news. (Cold Spring Harbor, N.Y.)
Eugen. Rev., Lond. - Eugenics review. (London).
Eugenik, Berl. - Eugenik. (Berlin).
Everybody's Health - Everybody's health. (Chicago).
Evolution méd.-chir. - Evolution médico-chirurgicale. (Paris).
Evolution thér. - Evolution thérapeutique. (Paris).
Exc. méd. S.C.O.P. - Excerta médica de la S.C.O.P.
Exper. Med. & Surg. - Experimental Medicine and Surgery.
Exper. Station Rec., Wash. - Experiment station record (at head of tp.: U. S. Department of Agriculture). (Washington, D.C.)
Expérience - Expérience
Exposé d. trav. de la Soc. d. Sc. méd. de la Moselle Metz - Exposé des travaux de la société des sciences médicales de la Moselle, Metz.
Extension Serv. News, Ithaca - Extension service news. (Ithaca, N.Y.)
Extension Universitaria -
Extr. Rec. Boston Soc. M. Improve.- Extracts from records of the Boston society for medical improvement.
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Eye Sight Conserv. Bull. - Eye sight conservation bulletin. (New York).
Fabriksfeuerwehr, Wien - Fabriksfeuerwehr. (Wien).
Far East Sc. Bull. - Far Eastern Science Bulletin.
Farmakol. i Toksikol. - Farmakologiia i toksikologiia.
Farmers Bull. - Farmers'bulletin (at head of tp.: U.S. Department of Agriculture) (Washington, D.C.)
Fasc. Cestriensis -
Federation Bull. - Federation Bulletin (Chicago)-
Federation Proc. - Federation Proceedings
Feestb. opgedr. aan. H. Treub -
Feldscher - Feldscher.
Fermentforsch. - Fermentforschung. (Berlin).
Festschr. v. Carl. v. Kupffer -
Feuerwehr, Wien - Die Feuerwehr Wien. (See Fabriksfeuerwehr).
Field Mus. Natur. Hist. - Field Museum of Natural History, (Chicago) (See also Publ. Field Mus. Natur. Hist.)
Filip. Nurse - Filipino nurse. (Manila, P.I.)
Financ. Statist. Cities - Financial statistics of the cities. (Washington, D.C.)

Financ. Statist. States - Financial statistics of the states. (Washington, D.C.).
Finska läk. - sallsk. handl. - Finska läkaresällskapet Handlingar (Helsingfors).
Firenze (Rass.) - Firenze; rassegna mensile del comune (Firenze).
Fisiol. e med. - Fisiologia e medicina (Roma).
Fiziol. zhur. - Fiziologicheskii zhurnal, U.S.S.R. (Moscow).
Fol. med. (B. Air.) - Folha medica. (Buenos Aires).
Fol. med. (Rio)- Folha medica. (Rio de Janeiro).
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Folia anat. Univ. conimb. - Folia anatomica universitatis conimbrigensis (Coimbra).
Folia biol., (B. Air.) - Folia biologica. (Buenos Aires).
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Folia clin. chim. et micros. - Folia clinica, chimica, et microscopica. (Bologna).
Folia clin. orient. - Folia clinica orientalia.
Folia demogr. gynec. (Genova)- Folia demografica-gynaecologica. (Genova).
Folia Endocrinol. Japon.- Folia endocrinologica japonica.
Folia gynaec. - Folia gynaecological (Genova).
Folia gynaec. demogr., (Genova) - Folia gynaecologica demographica. (Genova)
Folia gynec., (Pavia)- Folia gynaecologica (Pavia).
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Food Research - Food Research (Champaign, Ill.).
Forening f. Gynec. og. Obst. -
Forh. kir. foren. Kristiania - Forhandlinger kirurgiske foreningi Kristiania. See: (Forh. kir. foren. i Oslo).
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Forh. Nord. derm. foren. - Forhandlinger ved Nordisk dermatologisk forenings. (Oslo).
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Frankfurt. Ztschr. f. Path.- Frankfurter Zeitschrift für Pathologie. (München).
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Frauenarzt- Frauenarzt (Berlin).
Freedmen Hosp. Bull.- Freedmen's Hospital Bulletin. (Washington, D. C.)
French M. Rev., (Par.)- French medical review. (Paris).
Fukuoka acta med.- Fukuoka acta medica. (Fukuoka-Ikwadiagaku-Zasshi) (Fukuoka).
Fukuoka-ikwadaigaku-Zasshi- See Fukuoka acta medica.
G. Univ. Sofia, Med. Fak.- Godishnik universitet Sofia, Meditsinski fakultet.
Gac. de l. hosp. Valencia- Gaceta de los hospitales Valencia.
Gac. méd. de Caracas.- Gaceta médica de Caracas. (Caracas, Venezuela).
Gac. méd. catal.- Gaceta médica catalana.
Gac. méd. centroam.- Gaceta médica centroamericana.
Gac. méd. de Granada- Gaceta médica de Granada.
Gac. méd. de Lima- Gaceta médica de Lima.
Gac. méd. de México- Gaceta médica de México (México).
Gac. méd. mil., Méx.- Gaceta médico militar. (México, D. F.)
Gac. med. d. Norte Bilbao-
Gac. med. d. Sur. de españa- Gaceta medica del sur de España.
Gaceta-
Gaifami's Convers. & lez. ostet. ginec. Roma-
Gaillard's M. J.- Gaillard's Medical Journal.
Galen (C.) Liber de plenitudine, Parisiis-
Galvani- Galvani (Bologna).
Gann- Gann. The Japanese Journal of Cancer Research. (Tokyo).
Gastroenterologia- Gastroenterologia.
Gastroenterology- Gastroenterology.
Gaz. clin.- Gazeta clinica (São Paulo).
Gaz. eaux- Gazette des eaux. (Paris).
Gaz. de gynéc.- Gazette de gynécologie.
Gaz. hebd. de méd.- Gazette hebdomadaire de médecine. et de chirurgie.
Gaz. hebd. d. sc. méd. de Bordeaux- Gazette hebdomadaire des sciences médicales de Bordeaux (Bordeaux).
Gaz. hebd. d. sc. méd. de Montpellier- Gazette hebdomadaire des sciences médicales de Montpellier.
Gaz. d. hôp.- Gazette des hôpitaux (civils et militaires) (Paris).
Gaz. d. hôp. de Toulouse- Gazette des hôpitaux de Toulouse.
Gaz. lék.- Gazeta Lékarska.
Gaz. méd.- Gazette médical.
Gaz. med. da Bahia- Gazeta medica da Bahia.
Gaz. méd. belge- Gazette médicale Belge.
Gaz. méd. de Bordeaux- Gazette médicale de Bordeaux.
Gaz. méd. du centre, (Tours)- Gazette médicale du Centre (Tours).
Gaz. méd. et chir. (Paris)-
Gaz. méd.-chir. de Toulouse- Gazette médico-chirurgicale de Toulouse.
Gaz. méd. de France- Gazette médicale de France et des pays de langue française (Paris).
Gaz. méd. de Lyon- Gazette médicale de Lyon.
Gaz. méd. de Nantes- Gazette médicale de Nantes.
Gaz. méd. d'Orient.- Gazette médicale d'Orient (Pera).
Gaz. méd. de Paris- Gazette médicale de Paris.

Gaz. méd. de Picardie - Gazette médicale de Picardie
Gaz. méd. de Strasbourg. - Gazette médicale de Strasbourg (Strasbourg).
Gaz. obst. de Paris - Gazette obstétricale de Paris.
Gazz. d. clin. Torino - Gazzetta delle cliniche di Torino
Gazz. internaz. di med. - Gazzetta internazionale di medicina.
Gazz. internaz. med. - chir. - Gazzetta internazionale di medicina e chirurgia. (Napoli).
Gazz. méd. ital. - Gazzetta médica italiana (Torino).
Gazz. med. ital. lomb. - Gazetta medica italiana lombarda. (Milano).
Gazz. med. ital. prov. venete - Gazzetta medica italiana provincie venete.
Gazz. med. Napolet. - Gazzetta medica napoletana (Napoli).
Gazz. med. Roma - Gazzetta medica di Roma (at head of tp.: Malpighi) (Roma).
Gazz. med. sicil. - Gazzetta medica siciliana.(Catania).
Gazz. d. osp. - Gazzetta degli ospedali e delle cliniche. (Milano).
Gazzetta - Gazzetta
Geburtsh. u. Frauenh. - Geburtshilfe und Frauenheilkunde.
Gegenbaurs morphol. Jahrb. - Gegenbaurs morphologisches jahrbuch (Leipzig).
Gem. deutsche Ztschr. f. Geburtsk. - Gemeinsame deutsche zeitschrift für geburtskunde.
Gen.-Ber. d. k. rhein. Med.-Coll. Koblenz -
Gen. Practitioner - The General Practitioner of Australia and New Zealand.
Genees-i hell-, ... Kundige Verhandel. v. h. k. -nederl. Inst. v. wetensch. - Genees-, hell-,vroed-,schei-ennaturer-kundige verhandelingen v. h. K. Nederlandsch instituut van wetenschappen, letterkunde en schoone kunsten, Amsterdam.
Geneesk. bl. u. klin. en lab. v. d. prakt. - Geneeskundige bladen uit kliniek en laboratorium voor de praktijk (Haarlem).
Geneesk. gids. - Geneeskundige gids. (Den Haag).
Geneesk. Mag. - Geneeskundig magazijn.
Geneesk. tijdschr. v. België - Geneeskundig tijdschrift voor België.
Geneesk. tijdschr. v. Nederl. -Indië - Geneeskundig tijdschrift voor Nederlandsch-Indië (Batavia).
Geneesk. Verhandel. a. d. K. Sweed. Acad. (Sandifort) -
Genesis,(Roma)- Genesis; rassegna di studi sessuali, demografia ed eugenica.(Roma).
Genet. Psychol. Monogr. - Genetic Psychology Monographs. (Worcester, Mass.)
Genetica - Genetica; Nederlandsch tijdschrift voor erfelijk heids- en afstammingsleer 's Gravenhage.
Genetics - Genetics (Menasha, Wisc.)
Génio méd. -quir. - Génio médico-quirurgico.
George Washington Univ. Bull. - George Washington University Bulletin.
Georgia Health - Georgia's health. (Atlanta, Ga.).
Georgia M. Companion - Georgia medical companion.
Georgia N. M. & Surg. - Georgia North Medical and Surgery.
Ges. Arb. -
Ges. Geburtsh. u. Gynäk.(St. Petersburg)- Gesellschaft für geburtshülfe und gynäkologie.
Ges. Würzburg -
Gesellsch. f. Nat.-u. Heilk. - Gesellschaft für natur- und heilkunde,(Dresden.)
Gesundh. u. Erziehg. - Gesundheit und erziehung (Leipzig) (Ceased publication).
Gesundheitsführung. - Die Gesundheitsführung.
Gesundheitslehrer - Gesundheitslehrer; Zeitschrift gegen Misstände im Heilwesen für Aerzte und Behörden. (Ausgabe A-B.) (Berlin).
Gesundhfürs. Kindesalt. - Gesundheitsfürsorge für das Kindesalter.(Berlin).
Gesundh.-Ingenieur - Gesundheits-Ingenieur. (München).
Gig. bezopas. pat. truda - Gigiena bezopasnost i patologia truda. (Moskva).
Gig. epidem. - Gigiena i epidemiologia.(Moskva).
Gig. sotsial. zdrav. - Gigiena i sotsialisticheskoe zdravookhranenie.
Ginecol. mod. - Ginecologia moderna
Ginecologia - La ginecologia
Ginek. polska - Ginekologja polska
Ginek. (russ.) - Ginekologia
Gior. d. r. Accad. di med. di Torino - Giornale della reale Accademia di medicina di Torino. (Cirie).
Gior. d. Ass. napole. di med. e nat. - Giornale d. associazione napoletana di medici e naturalisti,(Naples).
Gior. di batteriol. e immunol. - Giornale di batteriologia e immunologia. (Torino).
Gior. biol. appl. - Giornale di biologia applicata alla industria chimica ed alimentare. (Bologna).
Gior. biol. indust. - Giornale di biologia industriale, agraria ed alimentare. (Bologna).
Gior. di biol. e med. sper. - Giornale di biologia e medicina sperimentale (Torino).
Gior. di clin. med. - Giornale di clinica medica (Parma).
Gior. di clin. e terap. - Giornale di clinica e terapia.
Gior. crit. di med. anal. - Giornale critico di medicina analatica.
Gior. di elett. med. - Giornale di elettricità medica.
Gior. di ginec. e di pediat. - Giornale di ginecologia e di pediatria.
Gior. internaz. d. sc. med. - Giornale internazionale delle scienze mediche.
Gior. ital. Anest. - Giornale italiano di anestesia e di analgesia.
Gior. ital. clin. trop. - Giornale italiano di clinica tropicale. (Napoli).
Gior. ital. di dermat. e sif. - Giornale italiano di dermatologia e sifilologia. (Milan).
Gior. ital. mal. esot. - Giornale italiano di malattie esotiche e tropicali ed igiene coloniale. (Torino).
Gior. ital. mal. vener. - Giornale italiano delle malattie veneree e della pelle. (Milano).
Gior. med. d. Alto Adige - Giornale medico dell'Alto Adige. (Bolzano).
Gior. med. Alto Adige - Giornale medico dell'Alto Adige. (Torino).
Gior. med. ferrov. - Giornale di medicina ferroviaria. (Prato & Firenze).
Gior. med. d. Marca trevig. - Giornale medico della Marca trevigiana. (Treviso).
Gior. di med. mil. - Giornale di medicina militare. (Roma).
Gior. d. med. prat. - Giornale del medico pratico (Napoli).
Gior. med. di Roma - Giornale medico di Roma (Rome).
Gior. med. vet. - Giornale di medicina veterinaria. (Torino).
Gior. morf. - Giornale per la morfologia dell'uomo e dei primati. (Pavia).
Gior. ocul. - Giornale di oculistica.(Napoli).
Gior. di psichiat. clin. e tecn. manic.- Giornale di psichiatria clinica e tecnica manicomiale.
Gior. di psichiat. e di neuropat. - Giornale di psichiatria e di neuropatologia.(Terrara).
Gior. per serv. a storia rag. d. med. - Giornale per servire alla storia ragionata della medicina di questo secolo.
Gior. Soc. ital. igiene - Giornale della R. Societa italiana d'igiene (etc.) (Milano).
Gior. d. terap. oftal. - Giornale di terapia oftalmologica (Napoli).
Gior. tisiol. - Il Giornale di tisiologia. (Napoli).
Gior. veneto di sc. med. - Giornale veneto di scienze mediche.
Giza Mem. Ophthalmic Lab. Ann. Rep. - See Mem. Ophthalmic Lab.,Giza, Ann. Rep.
Glasgow M. J. - Glasgow Medical Journal (Glasgow).
Good Health - Good health. (Battle Creek, Mich.)
Good Health Clin. - Good-health clinic. (Syracuse,N.Y.)
Göteborgs Läk. sällsk. Förh. - Göteborgs läkaresällskap Förhandlingar.
Grace Hosp. Bull.,(Detr.)- Grace Hospital bulletin. (Detroit,Mich.)
Graefe's Arch. f. Ophthal. - Graefe's archiv für ophthalmologie.
Grèce méd.(Syra)- Grèce médicale
Grenzfr. Nervenleb.- Grenzfragen des Nerven- und Seelenlebens. (München).

Groene & witte kruis - Het Groene en het witte kruis (Utrecht).
Growth - Growth. A Journal of Studies of Development and Increase.
Guarigione Clin. chir. -
Guerra,(Madr.) - Guerra y su preparacion. (Madrid).
Guglielmo da Saliceto - Guglielmo da Saliceto.
Gulf States J. Med. & Surg. - Gulf states journal of medicine and surgery.
Gun idan zasshi - Gun' idan-zasshi. (Tokyo).
Guthrie Clin. Bull. - Guthrie Clinic Bulletin. (Sayre, Pa.)
Guy's Hosp. Gaz. - Guy's Hospital Gazette (London).
Guy's Hosp. Rep. - Guy's Hospital Reports (London).
Gyermekgyógyászat - Gyermekgyógyászat (Budapest).
Gynaec. Helvet. - Gynaecologia helvetica.
Gynaek. og obst. Med. - Gynaekologiske og obstetriciske meddelelser.
Gynaekologia - Gynaekologia.
Gynäk. Rundschau - Gynaekologische rundschau.
Gynäk. Tagesfr. -
Gynec. i Accoucheurstovo Moscou-
Gynec. catal.(Barcel.) - Gynecologia catalana(Barcelona).
Gynéc. et Obst. - Gynécologie et obstétrique (Paris).
Gynec. a Obst. Monographies London -
Gynéc. et Sem. gynéc. - Gynécologie et Semaine gynécologique des Practiciens. (Now called gynécologie).
Gynec. Tr. -
Gynecol. (rum.) -
Gynecologia - Gynecologia (Barcelona).
Gynecologie - La gynécologie (Paris).
Gyógyászat - Gyógyászat (Budapest).
Gyógysz. hetil - Gyógyszerészi hetilap. (Budapest).
Haematologica - Haematologica Archivio (Pavia).
Hahneman. Monthly - The Hahnemannian Monthly. (Philadelphia).
Halbmonatschr. f. Frauen. u. Kinderkr. - Halbmonatsschrift für frauen- und kinderkrankheiten.
Haller. Disp. ad. morb. Lausannae -
Hals-, Nasen- u. Ohrenarzt - Der Hals-, Nasen- und Ohrenarzt. (Leipzig).
Hamburg. Wschr. Aerzte - Hamburger Wochenschrift für Aerzte und Zahnärzte. (Hamburg).
Hamburgs Verwalt. - Aus Hamburgs Verwaltung und Wirtschaft. (Hamburg).
Handel. v. h. Nederl. Nat.-en Geneesk. Cong. - Handelingen Haarlem. Nederlandsch natureren geneeskundig congres.
Handel. vlaamsch nat.-en geneesk. Cong.,(Ghent) Handelingen, Vlaamsch natuur- en geneeskundig congres (Ghent).
Hannover Ann. f. d. ges. Heilk. - Hannoversche annalen für die gesammte heilkunde.
Harefuah - Harefuah: The medical journal of the Palestine Jewish Medical Association.(Tel-Aviv).
Harofé Haivri - See Hebrew M. J.
Harper Hosp. Bull. - Harper Hospital Bulletin (Detroit)
Harper's - Harper's Magazine.
Harvard M. Alumni Bull. - Harvard medical alumni bulletin. (Boston, Mass.)
Harvey Lect. - Harvey Lectures.
Hawaii M. J. - Hawaii Medical Journal.
Hawkins Path. & Surg. -
Hbd. d. Anatomie -
Health Bull.,(Brookline)- Health bulletin. (Brookline, Mass.).
Health Bull.,(Melb.)- Health Bulletin. (Melbourne).
Health Bull.,(Newark)- Health bulletin. (Newark, N.J.).
Health Bull.,(Raleigh) - Health bulletin. (Raleigh,N.C.).
Health Bur.,(Rochester) - Health bureau. (Rochester, N.Y.).
Health,(Canberra)- Health. (Canberra, Australia).
Health,(Chic.)- Health; a national magazine for home, school and industry. (Chicago).
Health,(Concord)- Health. (Concord,N.H.).
Health Cult.,(N.Y.)- Health culture.(New York).
Health Educ.,(Wash.) - Health education (U.S.) Bureau of Education. (Washington).
Health Exam.(N.Y.)- Health examiner.(New York)
Health & Happiness - Health and happiness.(San Antonio,
Health,(N. Haven)- Health. (New Haven, Conn.).
Health News,(Albany)- Health news, (Albany,N.Y.)
Health Notes,(Jacksonville)- Health notes. (Jacksonville, Fla.)
Health Officer - The Health Officer. (Washington). (Ceased publication).
Health Officer Bull.,(Alb.)- Health officers' bulletin. (Albany, N.Y.)
Health Shoe Digest - Health shoe digest. (Boston,Mass.)
Health,(Toronto)- Health (Toronto, Can.).
Healthy Home Q.,(Athol.)- Healthy home quarterly. (Athol, Mass.).
Heart - Heart (London) (Continued as Clinical Science).
Heating Piping - Heating, piping and air conditioning. (Chicago).
Hebrew M. J. - The Hebrew Medical Journal
Hebrew Physician - Hebrew physician (New York) (Continued as Hebrew Medical Journal).
Hefte Unfallh. - Hefte zur Unfallheilkunde. (Berlin).
Heidelberg.klin. Ann. - Heidelberger klinische annalen.
Heigakkwai Syashi -
Heilkunde - Heilkunde.
Helvet. chim. acta - Helvetica Chimica Acta.
Helvet. med. acta - Helvetica medica acta. (Basel).
Helvet physiol. et pharmacol. acta - Helvetica physiologica et pharmacologica acta.
Herald of Health,(N.Y.)- Herald of health and naturopath. (New York).
Heraldo med.,(Bogotá)- Heraldo médico.
Hereditas,(Lund.)- Hereditas; genetiskt arkiv. (Lund).
Hihu-to-Hitunyo - Hihu-to-Hitunyo.
Hippokrates,(Stuttg.)- Hippokrates; Zeitschrift für Einheitsbestrebungen in der Medicin. (Stuttgart).
Hist. Acad. roy. d. sc. - Histoire de l'académie royale des sciences
Hist. Soc. roy. de méd. - Histoire de la société de médecine de Paris.
Hoja tisiol. - Hoja tisiologica.
Holsts Beitr. Gynäk. u. Geburtsh. -
Homoeop. J. Obst. - Homoeopathic journal of obstetrics.
Homoeop. News. - Homoeopathic news.
Homoeop. Recorder - Homoeopathic Recorder (Glendale, Calif.).
Honved Allategészseguggi Evkönyv -
Hôp. d'enf. Ste. Olga à Mosc. -
Hôpital. - L'hôpital. (Paris).
Hoppe Seyler's Ztschr. f. physiol. Chem. - See Ztschr. f. physiol. Chem.
Hora med.(Rio de Janeiro.)- Hora medica do Brasil.
Hormones,(Lond.)- Hormones. (London)
Hornsby Hosp. Mag. - Hornsby's hospital magazine. (Chicago)
Hosp. argent. -
Hosp. Bull. Univ. Maryland- Hospital Bulletin of the University of Maryland
Hosp. Corps Quart. - The Hospital Corps Quarterly. (Washington)
Hosp. Counc. Bull. - Hospital Council Bulletin.
Hosp. General - Hospital General; revista mexicana de sciencias medicas (Mexico).
Hosp. & Health Rev.,(Lond.) - Hospital and health review (London).
Hosp. Management - Hospital Management. (Chicago).
Hosp. News,(Wash.) - Hospital news. (Washington,D.C.)
Hosp. Progr. - Hospital Progress (Milwaukee)
Hosp. Social Serv. - Hospital social service. (New York).
Hosp. -Tid. Kjøbenh. -
Hosp. World,(Toronto)- Hospital world. (Toronto,Can.).
Hospital,(London)- The Hospital. (London).
Hospital,(Rio de Janeiro)- O Hospital.
Hospitals. - Hospitals. (Chicago).
Hospitalstid. - Hospitalstidende (København.).(Published in Nord. med.).
Howard M. News - Howard medical news,(Washington).
Hudson Co. Health Rec. - Hudson County health record. (Jersey City, N.J.)
Hufeland's J. - Hufelands journal der praktischen heilkunde.
Human Biol. - Human biology. (Baltimore).
Human Fertility- Human Fertility
Hyg. ment. - L'hygiène mentale, (Paris)
Hyg. Rdsch. - Hygienische Rundschau. (Berlin).

Hyg. scol., (Par.) - Hygiène scolaire. (Paris.)
Hygeia - Hygeia (Chicago).
Hygiea - Hygiea (Stockholm) (Published in Nord.med.).
I. C. N., (Genève) - I. C. N. (International Council of Nurses) (Genève)
Idr. clim. - Idrologia la climatologia e la terapia fisica. (Pisa)
Igaku Chuwo Zasshi - Igaku chuwo zasshi
Igiene della scuola - Igiene della scuola. (Genova).
Igiene mod. - Igiene moderna. (Genova).
Igiene e vita - Igiene e la vita (Torino).
Iji Shinbun Tokio - Iji shinbun Tokyo.
Iji Shinshi -
Illinois Arrow - Illinois arrow. (Springfield, Ill.).
Illinois Biol. Monogr. - Illinois biological monographs (at head of tp; University of Illinois bulletin) (Urbana, Ill.)
Illinois Dent. J. - Illinois dental journal. (Chicago).
Illinois Health Mess. - Illinois health messenger. (Springfield, Ill.)
Illinois Health News - Illinois health news. (Springfield, Ill.)
Illinois Health Q. - Illinois health quarterly. (Springfield, Ill.)
Illinois M. J. - Illinois Medical Journal (Oak Park, Ill.)
Illinois Psychiat. J. - Illinois Psychiatric Journal Department of Public Welfare.
Illust. med. ital. - Illustrazione medica italiana (Genova).
Illust. Quart. M. a. S. - Illustrated quarterly of medecine and surgery
Ilust. méd. - Ilustração médica.
Imago - Continued as Internat. Ztschr. f. Psychoanal. u. Imago.
Imparziale - Imparziale
Inat. M. S. Anat. -
Incurabili - Incurabili (Gli') (Napoli).
Indépend. méd. - Indépendence médicale.
Indépend. méd. et méd. orient. - Indépendance médicale et la Médecine orientale.
Independent Pract. - Independent practitioner.
Independente, (Torino) -
Index analyt. cancer., (Par.) - Index analyticus cancerologiae (Paris).
Index neurol. y psiquist. - Index de neurologia y psiquiatria.
Indian Ann. M. Sc. - Indian annals of medical science.
Indian Homeop. Rev. - Indian homeopathic review. (Calcutta).
Indian J. M. Research - Indian Journal of Medical Research. (Calcutta)
Indian J. Med. - Indian journal of medicine. (Calcutta).
Indian J. Ophth. - Indian Journal of Ophthalmology.
Indian J. Pediat. - Indian Journal of Pediatrics.
Indian J. Surg. - Indian Journal of Surgery.
Indian J. Ven. Dis. - Indian Journal of Venereal Diseases.
Indian J. Vet. Sc. & Animal Husband. - The Indian Journal of Veterinary Science and Animal Husbandry.
Indian Lancet - Indian lancet
Indian M. Chir. Rev. - Indian medico-chirurgical review.
Indian M. Gaz. - Indian Medical Gazette. (Calcutta).
Indian M. J. - The Indian Medical Journal.
Indian M. Rec. - The Indian Medical Record. (Calcutta).
Indian M. Research Mem. - Indian Medical Research Memoires. Supplementary Series to Indian Journal of Medical Research. (Calcutta)
Indian Physician. - The Indian Physician
Indiana M. J. - Indiana Medical Journal
Indianapolis M. J. - Indianapolis Medical Journal (Indianapolis)
Indipendente - Indipendente.
Individ. Psychol. M. Pamphl., (Lond.) - Individual psychology medical pamphlets. (London).
Indust. Doctor - The Industrial Doctor.
Indust. & Engin. Chem. (Indust. Ed.) - Industrial and Engineering Chemistry. (Industrial Edition) (Easton, Pa.)
Indust. Hyg. Bull. - Industrial Hygiene Bulletin. (Albany, N.Y.).
Indust. Med. - Industrial Medicine. (Beloit, Wisc.).
Inf. anorm., Milano - Infanzia anormale, (Milano).
Infirm. fr. - Infirmière française. (Paris).
Inform. aliénist. - Informateur des aliénistes et des neurologistes. (Paris)
Inform. bull., (Par.) - Information bulletin (at head of tp.: League of Red Cross Societies) (Paris).
Inform. enferm. ven. - Información sobre enfermedades venéreas.
Inform. méd. - Informaciones médicas. (Valladolid).
Insecutor, (Wash.) - Insecutor inscitiae menstruus. (Washington, D.C.).
Inst. M. Research. Federated Malay States, Bull. - See Bull. Inst. M. Research, Federated Malay States.
Inst. M. Research, Federated Malay States, Studies - See Studies Inst. M. Research, Federated Malay States.
Institution Q., (Springf.) - Institution quarterly, (Springfield, Ill.).
Intercolon. M. Cong. Australasian Tr. - Intercolonial medical congress of Australasia.
Intercolon. M. J. Australasia - Intercolonial medical journal of Australasia.
Intercolon. Quart. J. Med. a. S. - Intercolonial Quarterly Journal of Medicine and Surgery.
Interméd. d. biol. - Intermédiaire des biologistes et de médecins.
Internat. A. M. Museums Bull. - See J. Tech. Methods.
Internat. Abstr. Surg. - See Surg., Gynec. & Obst.
Internat. Beitr. z. Wiss. Med. (Virchow Festschr.).
Internat. Bull. M. Research. & Pub. Hyg. - The International Bulletin for Medical Research and Public Hygiene. (Continuation of Internat. Bull. Econ. M. Research & Publ. Hyg.).
Internat. Clin. - International Clinics. (Philadelphia) (Continued as Clinics).
Internat. Cong. Med. London -
Internat. Cong. Verlosk. en Gynaec. Amsterdam 4-8 Mei. -
Internat. Cong. of Zool., (Moscow) -
Internat. Digest Organ - International Digest of Organotherapy Publ. in Glendale, Calif.
Internat. Encycl. Surg. (Ashhurst) -
Internat. J. Gastro-enter. - International journal of gastro-enterology. (New York).
Internat. J. Individ. Psychol. - International journal of individual psychology. (Ceased publication).
Internat. J. Leprosy - International Journal of Leprosy (Manila, P.I.).
Internat. J. Med. & Surg. - International journal of medicine and surgery. (New York).
Internat. J. Orthodontia - International journal of orthodontia and oral surgery. (St. Louis, Mo) (Continued as Am. J. orthodontics.).
Internat. J. Psycho-Analysis - International Journal of of Psycho-Analysis. (London).
Internat. J. Pub. Health. (Genève) - International journal of public health (Genève).
Internat. J. Surg. - International journal of Surgery. (New York), (See: Internat. J. M. & S.).
Internat. klin. Rundschau - Internationale klinische rundschau.
Internat. M. Digest - International Medical Digest.
Internat. M. Mag. - International medical magazine.
Internat. Monatschr. f. Anat. u. Physiol. - Internationale monatsschrift für Anatomie und Physiologie.
Internat. Nurs. Rev., (Genève) - International nursing revue. (Genève)
Internat. Ophth. Cong. - International Ophthalmological Congress.
Internat. Rev. Agr. Econom., (Roma) - International review of Agricultural economics. (Roma).
Internat. Rev. Educ. Cinemat. (Roma) - International review of educational cinematography. (Roma).
Internat. Rev. Hydrobiol. - Internationale Revue der gesamten Hydrobiologie und Hydrographie. (Leipzig).
Internat. Rev. Sc. Agr., (Roma.) - International review of the science and practice of agriculture. (Roma).

Internat. S. Digest. - International Surgical Digest.
Internat. Zentralbl. exper. Phonet. - Internationales Zentralblatt für experimentelle Phonetik. (Berlin).
Internat. Zentralbl. Laryng. - Internationales Centralblatt für Laryngologie,Rhinologie, und verwandte Wissenschaft. (Berlin).
Internat. Zentralbl. f. Ohrenh. - Internationales zentralblatt für ohrenheilkunde und rhinolaryngologie. (Leipzig). (Continued as Hals-, Nasen- u. Ohrenarzt.)
Internat. Zentralbl. Tuberkforsch. - Internationales Centralblatt für die gesamte Tuberkuloseforschung (See: Zbl. ges. Tuberkforsch.)
Internat. Ztschr. f. Individualpsychol. - Internationale zeitschrift für individual-psychologie. (Ceased publication).
Internat. Ztschr. f. Psychoanal. u. Imago - Internationale Zeitschrift für Psychoanalyse und Imago. (London).
Internat. Ztschr. Psychoanal. (Wien) - Internationale Zeitschrift für Psychoanalyse. (Wien)
Interstate M. J. - Interstate Medical Journal (St. Louis).
Iowa Dent. Bull. - Iowa dental bulletin. (Cedar Rapids, Iowa).
Iowa M. J. - Iowa Medical Medical Journal.
Iowa Pub. Health Bull. - Iowa public health bulletin. (Des Moines, Iowa).
Iowa State M. Reporter - Iowa State Medical Reporter.
Ipek, (Par.) - Ipek; annuaire d'art préhistorique et ethnographique. (Paris).
Ippocratico - See Raccoglitore medico.
Irish Hosp. Gaz. - Irish Hospital Gazette.
Irish J. M. Sc. - Irish Journal of Medical Science. (Dublin).
Irrenfreund - Irrenfreund.
Irrt. allg. Diagn. - Irrtümer der allgemeinen Diagnostik und Therapie sowie deren Verhütung. (Leipzig).
Isis - Isis. (Bruges).
Ist. di san. pub. - Instituto di sanita pubblica. (See: Rend. Ist. di san. pub., Roma.).
Italia med. - Italia medica (Pisa).
Italia san. - Italia sanitaria . (Roma).
Izv. Imp. Voyenno-Med. Akad. (St. Petersberg)-
Izv. naucn. Lesgafta -
Izv. Petr. N. Inst. -
Izv. Tomsk. univ. - Izvestia (Imperatorskovo) Tomskovo Universiteta. (Tomsk.).
J. A. Am. M. Coll. - Journal of the Association of the American Medical Colleges. (Chicago,Ill.).
J. A. M. A. - Journal of the American Medical Association (Chicago).
J. A. Off. Agric. Chem. - Journal of the Association of Official Agricultural Chemists.
J. Abnorm. & Social Psychol. - Journal of Abnormal and Social Psychology. (Albany, N.Y.).
J. d'accouch. - Journal d'accouchements; (et revue de medécine et de chirurgie pratiques).
J. Advanc. Ther. - Journal of advanced therapeutics.
J. Agric.Chem. Soc. Japan -
J. Agric. Res. - Journal of agricultural research. (Washington, D.C.).
J. akush. - Jurnal akusherstva i zhenskikh boleznei. (Leningrad).
J. Alabama Acad. - Journal of the Alabama Academy.
J. Allergy - The Journal of Allergy. (S. Louis).
J. Alumni Assoc. Coll. Phys. -
J. Am. A. Chicago -
J. Am. A. Med.-Phys. Research - Journal of the American Association for Medico physical Research. (Lewistown, Pa.).
J. Am. A. Promot. Hyg. - Journal of the American Association for Promoting Hygiene and Public Baths.
J. Am. Chem. Soc. - Journal of the American Chemical Society. (Easton, Pa).
J. Am. Coll. Dentists- Journal of the American College of Dentists. (Baltimore, Md.).
J. Am. Coll. Proct. - Journal of the American College of Proctology. (Los Angeles).
J. Am. Dent. A. - Journal of the American Dental Association and the dental cosmos.(Chicago,Ill.),
J. Am. Dietet. A. - Journal of the American Dietetic Association. (Baltimore).
J. Am. Electron. Research A. - Journal of the American Electronic Research Association. (Indianapolis, Ind.).
J. Am. Folklore - Journal of American Folk-lore. (New York).
J. Am. Inst. Crim. - Journal of the American Institute of Criminal Law and Criminology.(Chicago, Ill.).
J. Am. Inst. Homeop. - Journal of the American Institute of Homeopathy. (New York).
J. Am. M. Ed. A. - Journal of the American Medical Editors Association. (New York)
J. Am. M. Hydr. - Journal of American medical hydrology. (Chicago).
J. Am. Optometr. A.-Journal of the American Optometric Association. (Faribault, Minn.).
J. Am. Osteop. A. - Journal of the American osteopathic Association. (Chicago, Ill.).
J. Am. Pharm. A. - Journal of the American Pharmaceutical Association. (Easton, Pa.).
J. Am. Soc. Heat. Ventil. Engin. - Journal of the American Society of Heating and Ventilating Engineers. (Easton, Pa.).
J. Am. Statist. A. - Journal of the American Statistical Association.(Menasha, Wis.).
J. Am. Vet. M. A. - Journal of the American Veterinary Medical Association. (Chicago).
J. Anat. - Journal of Anatomy. (London).
J. Anat. & Physiol. - Journal of anatomy and physiology.
J. de l'Anat. et de la Physiol. - Journal de l'anatomie et de la physiologie.
J. Animal Science - Journal of Animal Science
J. Anthrop. Soc. Bombay - Journal of the Anthropological Society of Bombay. (Bombay).
J. Appl. Psychol. - Journal of applied psychology. (Athens, Ohio).
J. Arkansas M. Soc. - Journal of the Arkansas Medical Society. (Little Rock, Ark.).
J. k. arztl. Fortbld. - Jurnal der königlichen ärztlichen Fortbildung.
J. Aviation Med. - The Journal of Aviation Medicine. (S. Paul, Minn.).
J. Ayurveda - Journal of Ayurveda or the Hindu system of medicine. (Calcutta).
J. Bact. - Journal of Bacteriology. (Baltimore).
J. belge de neurol. et de psychiat. - Journal belge de neurologie et de psychiatrie. (Bruxelles).
J. belge d'urol. - Journal belge d'urologie.
J. Bengal Cancer Inst. - Journal of the Bengal Cancer Institute.
J. Biochem. - Journal of Biochemistry. (Tokyo).
J. Biol. Chem. - Journal of Biological Chemistry. (Baltimore).
J. Biol. Photographic A. - The journal of the Biological Photographic Association. (Baltimore).
J. Biophysics, (Tokyo) - Journal of biophysics. (Tokyo).
J. Bone & Joint Surg. - Journal of Bone and Joint Surgery. (Boston).
J. Botany - Journal of Botany.
J. Bowman Gray School Med. - The Journal of the Bowman Gray School of Medicine of Wake Forest College.
J. California Dent. Ass. - Journal of the California State Dental Association. (San Francisco).
J. Canad. Dent. Ass. - Journal of the Canadian Dental Association. (Toronto).
J. Canad. M. Serv. - The Journal of the Canadian Medical Services.
J. Cancer, (Dubl.) - Journal of cancer. (Dublin).
J. Cancer Res. - Journal of Cancer Research (Lancaster, Pa.).
J. Cancer Res. Com. Univ. Sydney - Journal of the Cancer Research Committee of the University of Sydney. (Sydney).
J. Cell. & Comp. Physiol. - Journal of Cellular and Comparative Physiology. (Philadelphia).
J. Ceylon Br., Brit. M. A. - The Journal of the Ceylon Branch of the British Medical Association. (Colombo).
J. Chem. Educ. - Journal of chemical education. (Easton, Pa.).

J. Chem. Ind. - Journal of chemical industry.
J. Chem. Soc. - Journal of the chemical society.
J. Chemother. - Journal of chemotherapy and advanced therapeutics. (North Chicago, Ill.).
J. Chemotherapy - Journal of chemotherapy. (Ceased publication).
J. Chim. phys., (Par.) - Journal de chimie physique et revue générale des colloïdes. (Paris).
J. de chir. - Journal de chirurgie. (Paris).
J. de chir. et ann. Soc. belge de chir. - Journal de chirurgie et annales de la Société belge de chirurgie.
J. d. Chir. u. Augenh. -
J. d. chir., (Brux.) - Journal de chirurgie. (Bruxelles).
J. Chosen M. A. - The Journal of the Chosen Medical Association. (Keijo, Chosen).
J. Christian M. A. - Journal of the Christian Medical Association of India, Burma and Ceylon.
J. d. Clin. - Jornal dos clinicos. (Rio de Janeiro).
J. Clin. Endocrinol. - Journal of Clinical Endocrinology.
J. Clin. Investigation - Journal of clinical investigation. (Lancaster, Pa.).
J. Clin. Investigation - Journal of Clinical Investigation. (New York).
J. Clin. Psychopath. - Journal of Clinical Psychopathology and Psychotherapy.
J. Coll. Surg. Australasia - Journal of the College of Surgeons of Australasia. (Sydney).
J. Colorado Dent. A. - Journal of the Colorado Dental Association. (Denver).
J. Comp. Neurol. - Journal of Comparative Neurology. (Philadelphia).
J. Comp. Path. & Therap. - The Journal of Comparative Pathology and Therapeutics. (London)
J. Comp. Psychol. - Journal of Comparative Psychology. (Baltimore).
J. Compl. du dict. d. sc. méd. - Journal complimentaire du dictionnaire des sciences médicales.
J. d. conn. méd. - chir. - Journal des connaissances médico-chirurgicales.
J. d. conn. méd. prat. - Journal des connaissances médicales pratiques.
J. Connecticut M. Soc. - Journal of the Connecticut State Medical Society. (New Haven, Conn.).
J. Contraception. - The Journal of Contraception. (New York).
J. Council Scient. & Indust. Research - Journal of the Council for Scientific and Industrial Research. (Melbourne).
J. Crim. Law & Criminol. - Journal of Criminal Law and Criminology. (Chicago).
J. Crim. Psychopath. - Journal of Criminal Psychopathology.
J. Dairy Sc. - Journal of dairy science. (Baltimore).
J. Delinq. - Journal of delinquency. (Whittier, Calif.)
J. Dent. belge - Journal dentaire belge. (Bruxelles).
J. Dent. Hyg. Ass. N. York. - Journal of the Dental Hygienists Association of the City of New York. (New York).
J. Dent. Research - Journal of Dental Research. (New York).
J. Dept. Agr., (Pretoria) - Journal of the Department of Agriculture. (Pretoria, S. Afr.).
J. dlya normal i patal. gistologii. -
J. dlya usov. vrach. - Jurnal dlya usovershenstvovania vrachei. (Leningrad).
J. Egyptian M. A. - Journal of the Egyptian Medical Association. (Cairo).
J. Egyptian Publ. Health A. - The Journal of the Egyptian Public Association.
J. eksper. biol. - Jurnal eksperimentalnoi biology i meditsiny. (Moskva).
J. Electrotherap. Journal of Electro-therapeutics.
J. Elisha Mitchell Science Soc. - Journal of the Elisha Mitchell Scientific Society. (Chapel Hill, N.C.).
J. Endocrinol. - The Journal of Endocrinology.
J. epidem. i mikrob., (Moskva) - Jurnal epidemiology i mikrobiology. (Moskva).
J. Exper. Biol. - The Journal of Experimental Biology. (London), (Before vol. 6 called Brit. J. exper. Biol.).
J. Exper. Med. - Journal of Experimental Medicine. (Baltimore).
J. Exper. Psychol. - Journal of experimental Psychology. (Lancaster, Pa.).
J. Exper. Ther., Tokyo - Journal of experimental therapeutics. (Tokyo).
J. Exper. Zool. - Journal of Experimental Zoology. (Philadelphia).
J. Fac. Sc., Hokkaido Imp. Univ. - Journal of the faculty of science, Hokkaido imperial university (Sapporo, Japan).
J. Fac. of Sc., Univ. Tokyo - Journal of the Faculty of Science; Imperial University of Tokyo (several sections) (Tokyo).
J. Florida M. A. - Journal of the Florida Medical Association. (Jacksonville, Fla.).
J. Franklin Inst. - Journal of the Franklin Institute. (Philadelphia, Lancaster, Pa.).
J. f. Geburtsh. (Frankfurt) - Journal für geburtshelfer. (Frankfurt).
J. f. Geburtsh., (Frankf. a. M.) - Journal für geburtshülfe frauenzimmer- und kinderkrankheiten (Frankfurt a. M.).
J. Gen. Chem. - Journal of General Chemistry USSR.
J. gén. de méd., Chir. et pharm. - Journal général de médecine, de chirurgie et de pharmacie.
J. Gen. Physiol. - Journal of General Physiology. (Worcester, Mass.).
J. Gen. Psychol. - The Journal of General Psychology. (Worcester, Mass.).
J. Genet. Psychol. - The Pedagogical Seminary and Journal of Genetic Psychology.
J. Genetics. - Journal of Genetics. (Cambridge, Engl.).
J. Gynaec. Soc. Boston - Journal of gynaecology of the Society of Boston.
J. Gynec. (Toledo) - Journal of gynaecology (Toledo). (See: Am. Gynec. J.).
J. H. Pratt. Anniv. Vol. -
J. Health & Phys. Educ. - Journal of Health and Physical Education. (Ann Arbor, Mich.).
J. hebd. d. progr. d. sc. méd. - Journal hebdomadaire des progrès des sciences et institutions médicales.
J. Helminthol. - Journal of Helminthology. (S. Albans, Engl.).
J. Hered. - Journal of Heredity. (Baltimore, Md.).
J. Home Econ. - Journal of Home Economics. (American Home Economics Association). (Baltimore).
J. de l'Hôtel-Dieu de Montréal - Le Journal de l'Hôtel-Dieu de Montréal. (Montréal)
J. Hyg. - Journal of Hygiene. (London).
J. Illinois Hist. Soc. - Journal of the Illinois Historical Society. (Springfield, Ill.).
J. Immunol. - Journal of Immunology. (Baltimore).
J. Indian M. A. - Journal of the Indian Medical Association. (Calcutta).
J. Indiana M. A. - Journal of the Indiana State Medical Association. (Indianapolis, Ind.).
J. Indust. Chem. - Journal of industrial and engineering chemistry. (Easton, Pa.).
J. Indust. Hyg. & Toxicol. - Journal of Industrial Hygiene and Toxicology. (Baltimore, Md.)
J. Infect. Dis. - Journal of Infectious Diseases. (Chicago).
J. Inst. Actuaries, (Lond.) - Journal of the Institute of Actuaries. (London).
J. Internat. de Chir. - Journal international de chirurgie.
J. Internat. Coll. Surgeons - The Journal of the International College of Surgeons.
J. Intraven. Ther. - Journal of intravenous therapy. (New York).
J. Invest. Dermat. - The Journal of Investigative Dermatology.
J. Iowa M. Soc. - Journal of Iowa State Medical Society. (Des Moines, Iowa).
J. izuch. rann. detsk. vozr. - Jurnal izuchenia rannevo detskovo vozrasta. (Moskova).
J. Jap. Soc. Vet. Sc. - Journal of the Japanese society of veterinary science. (Tokyo).
J. Juvenile Research. - Journal of juvenile research. (Claremont, Calif.) (Ceased publication).
J. Kansas M. Soc. - Journal of the Kansas Medical Society. (Topeka, Kan.).
J. Kumamoto M. Soc. - The Journal of the Kumamoto Medical Society.
J. Lab. & Clin. Med. - Journal of Laboratory and Clinical Medicine. (S. Louis).

J. Lancet - Journal lancet. (Minneapolis).
J. Laryng. & Otol. - Journal of Laryngology and Otology. (London).
J. Linn. Soc. - Journal of Linnean society of London.
J. Louisiana State Univ. School Med. - Journal of the Louisiana State University School of Medicine.
J. M. A. Alabama - Journal of the Medical Association of the State of Alabama. (Montgomery).
J. M. A. Georgia - Journal of the Medical Association of Georgia. (Atlanta).
J. M. A. South Africa - Journal of the Medical association of South Africa. (Cape Town).
J. M. Coll. Keijo - Journal of the Medical College of Keijo.
J. M. Coll. Ohio - Journal of the Medical college of Ohio.
J. M. Pract. - Journal of medical practice. (Philadelphia).
J. M. Res. - Journal of medical research.(Boston).
J. M. Soc. - Journal of medical society of Arkansas. (Little Rock, Ark.).
J. M. Soc. New Jersey - Journal of the Medical Society of New Jersey. (Orange, N.Y.).
J. Maine M. A. - Journal of the Maine Medical Association.
J. Malaya Br., Brit. M. A. - Journal of the Malaya Branch of the British Medical Association.
J. Mammal. - Journal of mammalogy.
J. Marine Biol. A., U. K. - Journal of the marine biological association of the United Kingdom.
J. Med. - Journal of Medicine. (Cincinnati). (v. 1-7 #10 as Cincinnati J. Med.)
J. Med. A. Formosa - Journal of the medical association of Formosa. (See Taiwan Igakkai Zasshi.).
J. méd. - biol.,(Moskva) - Journal médico-biologique. (Moskva).
J. de méd. de Bordeaux - Journal de médecine de Bordeaux et du Sud-Ouest. (Bordeaux).
J. de méd. de Bruxelles - Journal de médecine de Bruxelles.
J. de méd., chir. et pharm. - Journal de médecine, chirurgie et pharmacie.
J. de méd. et chir. prat. - Journal de médecine et de chirurgie pratiques. (Paris).
J. méd. franç. - Le journal médical français. (Paris).
J. Med. Kiev. - Journal medical (Russian) Kiev.
J. de méd. de Lyon - Le journal de médecine de Lyon. (Lyon).
J. de méd. de l'ouest. - Journal de médecine de l'ouest.
J. de méd. de Paris - Journal de médecine de Paris. (Paris).
J. de méd. vét. de Paris - Journal de médecine vétérinaire de Paris.
J. de méd. vét. et zootech. - Journal de médecine vétérinaire et de zootechnie.
J. Ment. Sc. - Journal of Mental Science. (London).
J. Michigan M. Soc. - Journal of Michigan State Medical Society. (S.Paul).
J. mikrob. i. immunobiol. (Moskva) - Jurnal mikrobiology i immunobiology. (Moskva).
J. mikrob., (Moskva) - Jurnal mikrobiology, pathology i infektsionnykh boleznei. (Moskva).
J. Minist. Agric. -
J. Missouri M. A. - Journal of Missouri State Medical Association. (Fulton, Mo.).
J. Morphol. - Journal of Morphology. (Philadelphai).
J. Morphol. Physiol. - Journal of morphology and physiology. (Philadelphia).
J. Mt. Sinai Hosp. - Journal of the Mount Sinai Hospital. (New York).
J. Nat. A.Chiropod. - Journal of the National Association of Chiropodists.(New York, N.Y.).
J. Nat. A. Railway Surg. - Journal of national association of railway surgeons.
J. Nat. Cancer Inst. - Journal of the National Cancer Institute.
J. Nat. M. A. - Journal of the National Medical Association. (New York).
J. Nat. Malaria Soc. - The Journal of the National Malaria Society.
J. Nerv. & Ment. Dis.- Journal of Nervous and Mental Disease. (New York).
J. Nerv. & Ment. Dis. - Journal of nervous and mental diseases. (Richmond, Va.).
J. Neurol., Neurosurg. & Psychiat. - Journal of Neurology, Neurosurgery and Psychiatry. (London). (Continuation of J. Neurol. & Psychiat.).
J. Neurol. & Psychiat. - Journal of Neurology and Psychiatry. (Bruxelles). (Continued as J. Neurol. Neurosurg., & Psychiat.).
J. Neurol. Psychopath.,(Lond.) - Journal of neurology and psychopathology. (London).
J. Neuropath. & Exper. Neurol. - Journal of Neuropathology and Experimental Neurology.
J. Neurophysiol. - Journal of Neurophysiology.
J. Neurosurg. - Journal of Neurosurgery.
J. vevropat. psikhiat.(Moskva) - Jurnal nevropatology i psikhiatry. (Moskva).
J. New England Water Works A. - Journal of the New England Water Works Association. (Boston, Mass.).
J. New York Acad. Dent. - Journal of New York academy of dentistry. (Albany). (Continued as Ann. Dent.).
J. Nutrition - The journal of Nutrition.
J. Obst. & Gynaec. Brit. Emp. - Journal of Obstetrics and Gynaecology of the British Empire. (Manchester).
J. Obst. & Gynac. Soc. North India - Journal of the Obstetric & Gynaecological Society of Northern India.
J. d'obst. et de gynéc. prat. - Journal d'obstétrique et de gynécologie pratiques. (Lille).
J. Ohio Dent. Soc. - Journal of the Ohio Dental Society.
J. Oklahoma M. A. - Journal of Oklahoma State Medical Association.(McAlester, Okla.).
J. Omaha Mid-West. Clin. Soc. - The Journal of the Omaha Mid-West Clinical Society.
J. d'opht. sociale - Journal d'ophtalmologie sociale.
J. Ophth. Otol. & Laryng.- Journal of ophthalmology, otology and laryngology. (New York).
J. Optic. Soc. America - Journal of the Optical Society of America. (Lancaster, Pa.).
J. Oral Surg. - Journal of Oral Surgery.
J. Org.Chem. - Journal of Organic Chemistry.
J. Organother. - Journal of organotherapy. (New York).
J. Orient. Med. - The Journal of Oriental Medicine. (Dairen).
J. Orific. Surg. - Journal of Orificial Surgery.
J. für Ornithologie- Journal für ornithologie.
J. Orthop. Surg. - Journal of orthopaedic surgery. (Lincoln Neb.).
J. Outdoor Life-Journal of the outdoor life.(Camden, N.J.).
J. Parasitol. - Journal of Parasitology. (Lancaster,Pa.).
J. Path. - Journal of pathology.
J. Path. & Bact. - Journal of Pathology and Bacteriology. (London).
J. Pediat. - The Journal of Pediatrics.(S.Louis).
J. Periodont. - Journal of periodontology. (Birmingham, Mich).
J. Personnel Res. - Journal of personnel research. (Baltimore).
J. Pharm. Belg. - Journal de pharmacie de Belgique.
J. de Pharm. et chim. - Journal de pharmacie et de chimie. (Paris).
J. Pharm. Soc. Japan - Journal of the pharmaceutical society of Japan.
J. Pharm. Toz. USSR. -
J. Pharmacie - Journal de pharmacie.
J. Pharmacol. & Exper. Therap. - Journal of pharmacology and Experimental Therapeutics. (Baltimore).
J. Philippine Islands M. A. - Journal of the Philippine Islands Medical Association. (Manila).
J. Philos - Journal of philosophy. (Lancaster, Pa.).
J. Phys. Chem. - Journal of physical chemistry. (Baltimore).
J. Phys. Educ. - Journal of physical education. (New York).
J. Phys. radium,(Par.) - Journal of physique et le radium. (Paris).
J. Physiol.- Journal of Physiology. (London).
J. de physiol. et de path. gén. - Journal de physiologie et de pathologie générale. (Paris).

J. Physiol. USSR. - See: Fiziol. zhur.
J. d. pract. Arzneyk. u. Wundarznk. - Journal der practischen arzneykunde und wundarzneykunst.
J. d. pract. Heilk. - Journal der practischen Heilkunde.
J. d. praticiens - See: Rev. gén. de clin. et de thérap. (Paris).
J. Prev. Med. - Journal of preventive medicine. (Baltimore).
J. Proc. Roy. Soc. New South Wales - Journal and proceedings of the Royal Society of New South Wales. (Sydney).
J. de psychiat. inf. - Journal de psychiatrie infantile. (See: Ztschr. f. Kinderpsychiat.).
J. Psycho-Asthenics - Journal of psycho-asthenics. (See: Proc. Am. A. Ment. Deficiency).
J. Psychol. - The Journal of Psychology. (Provincetown, Mass.)
J. f. Psychol. u. Neurol. - Journal für Psychologie und Neurologie. (Leipzig).
J. psychol. neurol. (Moskva) - Journal de psychologie, de neurologie et de médecine mentale, (Moskva) (Russian).
J. de psychol. norm. et path. - Journal de psychologie normale et pathologique. (Paris).
J. Quekett Micr. Club. - Journal of the Quekett Microscopical Club. (London).
J. Radiol. - Journal of radiology. (Omaha, Neb.).
J. de radiol. et d'électrol. - Journal de radiologie et d'électrologie. (Paris).
J. rann. detsk. vozr. - Journal po rannemu detskomu vozrastu. (Moskva).
J. Röntg. Soc., Lond. - Journal of the Röntgen Society (London).
J. Roy. Agric. Soc. (Cairo) - Journal of the Royal Agricultural Society (Cairo).
J. Roy. Agric. Soc. of England (London) - Journal of the Royal Agricultural Society of England (London).
J. Roy. Agric. Soc. of New South Wales (Sydney). - Journal of the Royal Agricultural Society of New South Wales (Sydney).
J. Roy. Anthrop. Inst. Great Britain & Ireland - Journal of the Royal Anthropological Institute of Great Britain and Ireland (London).
J. Roy. Army M. Corps - Journal of the Royal Army Medical Corps. (London).
J. Roy. Army Vet. Corps - Journal of the Royal Army Veterinary Corps. (London).
J. Roy. Asiat. Soc. Gr. Britain - Journal of the Royal Asiatic Society of Great Britain and Ireland. (London).
J. Roy. Inst. Publ. Health & Hyg. - Journal of the Royal Institute of Public health and Hygiene Incorporating Journal of State Medicine.
J. Roy. Microscop. Soc. London - Journal of the royale microscopical society. (London).
J. Roy. Nav. M. Serv. - Journal of the Royal Naval Medical Service. (London).
J. Roy. San. Inst. - Journal of the Royal Sanitary Institute. (London).
J. Roy. Soc. Arts - Journal of the Royal Society of Arts.
J. Roy. Statist. Soc. - Journal of the royal statistical society. (London).
J. Roy. Unit. Serv. Inst. - Journal of the Royal United Service Institution. (London).
J. Sc. Hiroshima Univ. - Journal of science of the Hiroshima University. (Hiroshima, Japan).
J. de sc. méd. - Journal des sciences médicales.
J. d. sc. méd. de Lille - Journal des sciences médicales de Lille.
J. d. sc. méd. de Louvain - Journal des sciences médicales de Louvain.
J. d. scavans. - Journal des scavans.
J. Severance Union M. Coll. - Journal of Severance Union Medical College. (Seoul).
J. Sex. Psychanal. - Journal of sexology and psychanalysis. (New York).
J. Shanghai Sc. Inst. - The Journal of the Shanghai Science Institute.
J. de sif. e urol. - Journal de sifilis e urologia.
J. Soc. Chem. Industry - Journal of the society of chemical industry. (London).
J. Soc. de méd. et pharm. de la Haute Vienne - Journal de la société de médecine et de pharmacie de la Haute-Vienne.
J. Soc. de méd. et pharm. de l'Isère - Journal de la société de médecine et de pharmacie de l'Isère.
J. Soc. nat. horticult. France - Journal de la Société nationale d'horticulture de France. (Paris).
J. Soc. de sc. méd. de Lisbon - Journal de la Société des sciences médicales de Lisbon.
J. Social Hyg. - Journal of Social Hygiene. (Albany, N.Y.).
J. Social Psychol. - The Journal of Social Psychology.
J. South Afr. Vet. M. A. - Journal of the South African Veterinary Medical Association. (Pretoria).
J. South Carolina M. A. - Journal of South Carolina Medical Association. (Greenville, S.C.).
J. State Med. - Journal of State medicine. (London) (Continued as J. Roy. Inst. Pub. Health & Hyg.).
J. Surg. Gynec. & Obst. - Journal of surgery, gynecology and obstetrics.
J. Tech. Methods - Journal of Technical Methods and Bulletin of the International Association of Medical Museums. (Toronto, Ont.).
J. Tennessee M. A. - Journal of Tennessee State Medical Association. (Nashville, Tenn.).
J. Teor. prakt. med. - Jurnal teoreticheskoi i prakticheskoi meditsiny. (Baku).
J. Thoracio Surg. - The Journal of Thoracic Surgery. (S. Louis, Mo.).
J. Trop. Med. - Journal of Tropical Medicine and Hygiene. (London).
J. Univ. et hebd. de méd. et de chir. prat. et inst. méd. de Paris - Journal universel et hebdomadaire de médecine et de chirurgie pratiques et des institutions médicales de Paris.
J. Urol. - The Journal of Urology. (Baltimore).
J. d'urol. - Journal d'urologie médicale et chirurgicale. (Paris).
J. vét. de Lyon -
J. Washington Acad. Sc. - Journal of the Washington Academy of Science. (Washington, D. C., Menasha, Wis.).
Jackson Co. M. J. - Jackson County medical journal. (Kansas City, Mo.).
Jackson Mem. Hosp. - See: Bull. Jackson Mem. Hosp.
Jahrb. d. Charakt. - Jahrbuch der Charakterologie. (Berlin).
Jahrb. Diss. Med. Fak. Tübingen - Jahrbuch der Auszüge aus den Dissertationen der Medizinischen Fakultät zu Tübingen. (Tübingen).
Jahrb. f. ges. Krankenhauswes. - Jahrbuch für das gesamte Krankenhauswesen. (Berlin).
Jahrb. f. Kinderh. - Jahrbuch für kinderheilkunde. (Berlin), (Continued as Ann. paediat.).
Jahrb. f. Morphol. u. mikr. Anat. Abt. I - Jahrbuch für morphologie und mikroskopische anatomie. Abt. I. See: Morphol. Jahrb. Abt. II: See; Ztschr. f. mikr.-anat. Forsch.
Jahrb. f. Psychiat. u. Neurol. - Jahrbücher für Psychiatrie und Neurologie. (Wien).
Jahrb. f. sex. Zwischenst. - Jahrbuch für sexuelle Zwischenstufen. (Leipzig).
Jahrb. d. Wien. k. k. Kranken-anst. -
Jahrb. f. wiss. prakt. Tierzucht - Jahrbuch für wissenschaftliche und praktische Tierzucht. (Hannover).
Jahresb. ü. d. chir. Abth. d. Spit. zu Basel -
Jahresb. d. chir. Klin. -
Jahresb. ü. d. chir. Thätigk. im Cölner Städt. Bürger Hosp. -
Jahresb. f. Gesellsch. Natur. Heilk. Dresden - Jahresbericht der Gesellschaft für Natur- und Heilkunde in Dresden. (Dresden).
Jahresb. d. Kurashiki-Zentralhosp. - Jahresbericht des Kurashiki-Zentralhospitals.
Jahresb. Schles. Gesellsch. vaterl. Cult. - Jahresbericht der Schlesischen Gesellschaft für vaterländische Cultur. (Breslau).
Jahresb. u. d. Verwalt. d. Med. -Wes. -d. Krankenanst d. Stadt Frankfurt. - Jahresbericht über die verwaltung des medizinalwesens die krankenanstalten und die öffentlichen gesundheitsverhältnisse des stadt Frankfurt.

Jahresb. Vet-Med. - Jahresbericht Veterinär-Medizin. (Berlin).
Jahresk. f. ärztl. Fortbild. - Jahreskurse für ärztliche Fortbildung. (München).
Jamaica Pub. Health - Jamaica public health. (Kingston).
Janus - Janus. (Leiden).
Jap. centrarev. med. - Japana centrarevuo medicina. (Tokio).
Jap. J. Dermat. & Urol. - Japanese journal of Dermatology and Urology. (Tokyo).
Jap. J. Exper. Med. - Japanese Journal of Experimental Medicine. (Tokyo).
Jap. J. Gastroenterol. - Japanese Journal of Gastroenterology. (Kyoto).
Jap. J. M. Sc. - Japanese Journal of Medical Sciences. (Tokyo).
Jap. J. Math. - Japanese journal of mathematics (at head of tp.: National Research Council of Japan). (Tokyo).
Jap. J. Obst. & Gynec. - Japanese Journal of Obstetrics and Gynecology. (Kyoto).
Jap. J. Zool. - Japanese journal of zoology. (Tokyo).
Jap. M. Literat. (Shanghai) - Japanese medical literature. (Shanghai).
Jap. Ztschr. Dermat. Urol. - Japanische Zeitschrift für Dermatologie und Urologie. (Tokio).
Jap. Ztschr. Krebsforsch. - Japanische Zeitschrift für Krebsforschung. (Tokio).
Jap. Ztschr. Naturwiss., (Jena) - Japanische Zeitschrift für Naturwissenschaft. (Jena).
Jap. Ztschr. Verdauungskr. - Japanische Zeitschrift für Verdauungs-Krankheiten. (Tokio).
Japan M. World - Japan medical world. (Tokyo).
Japan Mag. - Japan magazine. (Tokyo).
Japan Times - Japan times. (Tokyo).
Jenaer med. hist. Beitr. - Jenaer medizin-historische Beiträge. (Jena).
Jenaische Ann. f. Physiol. u. med. - Jenaische annalen für physiologie und medicin.
Jenaische Ztschr. f. Naturwiss. - Jenaische Zeitschrift für Naturwissenschaft. (Jena).
Jo-san-no Shiori - Jo-san-no shiori. (Osaka).
Johns Hopkins Alumni Mag. - Johns Hopkins alumni magazine. (Baltimore).
Johns Hopkins Hosp. Rep. - Johns Hopkins hospital. Reports.
Johns Hopkins Nurs. Alumnae Mag. - Johns Hopkins nurses alumnae magazine. (Baltimore.).
Johns Hopkins Univ. Circ. - Johns Hopkins university circular. (Baltimore).
Journal-Lancet - Journal-Lancet.
Jundendo Ijikuken Kwai hoko -
Juntendo Iji Kenkiu Kwai Zasshi - Juntendo iji kenkiu kwai, Tokyo Zasshi.
Juventud méd. - Juventud médica. (Guatemala, C.A.).
K. Akad. v. Wetensch. te Amst. Proc. - K. Akademie van wetenschappen, Amsterdam. Proceedings.
K. Akad. d. Wissensch. - K. Akademie der wissenschaften.
K. Vetensk.-Akad. n. Handl. - K. vetenskopsakademien, Handlingar. (Stockholm).
Kaibogaku Zassi -
Kampf gegen Geschlkr. - Kampf gegen die Geschlechtskrankheiten. (Berlin).
Kansas City M. Index-Lancet - Kansas City medical index. (Fort Scott).
Kansas City M. Rec. - Kansas City medical record.
Kansas M. J. - Kansas Medical Journal.
Kazan. med. J. - Kazansky meditsinsky jurnal. (Kazan).
Keio-Röntgenarch. - Keio-Röntgenarchiv. (Tokyo).
Keizyo J. Med. - The Keizyo Journal of Medicine.
Kekkaku - Kekkaku (Tuberculosis)(Tokyo).
Kentucky M. J. - Kentucky Medical Journal. (Kentucky).
Kenya East Afr. M. J. - Kenya and East African medical journal. (Nairobi).
Key Reporter - Key reporter; the Phi Beta Kappa news magazine. (Concord, N.H.).
Kgl. danske Vidensk. Selsk. biol. Med. -
Kgl. Fysiograf. Sallskap. Lund. -
Kharkov M. J. - Kharkov Medical Journal.
Khirurgiya - Khirurgiya. (Moskva).
Kinderärztl. Praxis - Kinderärztliche Praxis. (Leipzig).
Kindertuberkulose - Kindertuberkulose. (München).
King's Coll. Hosp. Rep. - King's College Hospital Report.
Kinki Fujink. Gakk. Zassi - Kinki fujinka gakkai zassi. (Kyoto).
Kitasato Arch. Exper. Med. - Kitasato Archives of Experimental Medicine. (Tokyo).
Klin. Fortbild. - Klinische fortbildung. (Berlin).
Klin. J. Saratov - Klinichesky jurnal Saratovskovo Universiteta. (Saratov).
Klin. med. - Klinicheskaya meditsina. (Moskva).
Klin. Monatsbl. f. Augenh. - Klinische Monatsblätter für Augenheilkunde und für augenärztliche Fortbildung. (Stuttgart).
Klin.-therap. Wchnschr. - Klinisch-therapeutische wochenschrift in Wien.
Klin. Wchnschr. - Klinische Wochenschrift. (Berlin).
Klin. Ztschr. f. Chir. u. Augenh. - Klinische zeitschrift für chirurgie und augenheilkunde.
Kolloid-Beihefte - Kolloid-Beihefte. (Dresden).
Kolloid-Ztschr. - Kolloid-Zeitschrift. (Dresden).
Komplex Biochemie - Die Komplex-Biochemie. (Berlin).
Kongrzbl. inn. Med. - Kongresszentralblatt für die gesamte innere Medizin und ihre Grenzgebiete. (Berlin).
Korbl. Allg. ärztl. Verein. Thüringen - Korrespondenz-Blätter des Allgemeinen ärztlichen Vereins von Thüringen. (Berlin).
Korbl. Verein. Aerzte Reichenberg - Correspondenzblatt des Vereins deutscher Aerzte in Reichenberg und Umgebung (Reichenberg).
Korbl. f. Zahnärzte - Korrespondenzblatt für Zahnärzte. (Berlin).
Korin no Siwori -
Korresp.-bl. Schweiz. Arzte - Korrespondenzblatt für Schweizer aerzte.
Koseikwan Iji Kenyu Kwai Zasshi - Koseikwan iji kenkyu kwai zasshi.
Kosmos - Kosmos.
Közl. összehas. élet, & kórt. - Közlemények az összehasonlító élet- es kórtan köréböl (Publications of comparative biology and pathology). (Budapest).
Krankenfreund - Kranken-Freund. (Karlsruhe).
Krankheitsforschung - Krankheitsforschung. (Leipzig).
Krebsbekämpfung - Krebsbekämpfung. (Leipzig).
Kron. lek. (Warsaw) - Kronika lekarska. (Warsaw).
Ksiega pamiatkowa wyd. w 25. roczn. Wydz. Lek. Lwow -
Kuban. nauch.-med. J. - Kubansky nauchno-meditsinsky jurnal. (Krasnodar).
Kuban. nauch.-med. vest. - Kubansky nauchno-meditsinsky vestnik. (Krasnodar).
Kyklos, (Lpz.) - Kyklos; Jahrbuch des Instituts für Geschichte der Medizin an der Universität Leipzig. (Leipzig).
Kyoto Igakkwai Zasshi - Kyoto-igakkwai zasshi.
Kyoto-Ikadaigaku-Zasshi - See: Mitt.a. d. med. Akad. zu Kioto.
Lab. d'histol. du Coll. de France. Trav. - Laboratoire d'histologie du collège de France. Travaux.
Lab. Stud. Mem. Hosp., (N.Y.) - Laboratory studies of the Memorial Hospital. (New York).
Labor méd., (Méx.) - Labor médica. (México).
Lahey Clin. Bull. - The Lahey Clinic Bulletin.
Laitop. khirurg. Obsh. v. Mosk. -
Laitop. russk. chir. -
Lancet - Lancet (London).
Lancet-Clinic - Lancet clinic. See: Cincinnati Lancet Clinic.
Languedoc méd.-chir. - Languedoc médico-chirurgicale.
Lantbruks-Högskolans Ann. -
Laryngoscope - Laryngoscope. (S. Louis).
Lattante - Il lattante. (Parma).
Latv. arstu Z. - Latvijas arstu zurnals. (Riga).
Latv. Univ. rak. - Latvijas universitates raksti. See: Acta Univ. Latv.
Lav. Ist. anat. pat. Univ. Catania - Lavori degli istituti di anatomia patologica delle Regi Università di Catania e di Palermo. (Palermo).

Lav. d. Ist. di clin. med. di Padova -
Lav. Lab. fisiol. Univ. Padova - Lavori del Laboratorio di fisiologia; R. Università di Padova. (Padova).
Laval méd. - Laval médical. (Québec).
Lavori d. cong. di med. int. -
Lavoro - Lavoro (Milano).
Lavoro Umano - Lavoro umano.
Leavenworth M. Herald - Leavenworth Medical Herald.
Leçons de clin. chir. -
Leech - The Leech. (Cardiff, Wales).
Legge dei simili - Legge dei simili. (Arezzo).
Lék. wojsk. - Lékarz wojskowij. (Warszawa).
Lenin-Akad. Landw. Wiss., Inst. Tierz. -
Leprosy Rev. - Leprosy Review.(British Empire Leprosy Relief Association) (London).
Lett. oftalm. - Lettura oftalmologica (Verona).
Leudet's Etudes de path. et de clin. méd. (Paris) -
Library A. Rec. - Library Association Record.
Lichtheilgrüsse - Lichtheilgrüsse. (Hamburg).
Liec. viestnik. - Liecnicki viestnik. See: Lijecn. viestnik u Zagrebu.
Liége méd. - Liége médical. (Liége).
Life & Health, (Wash.) - Life and health. (Washington).
Ligaria med. -
Lijecn. viestnik u Zagrebu - Lijecnicki viestnik u Zagrebu. See: Lijecn. vjes.
Lijecn. vjes. - Lijecnicki vjesnik.
Lilly Scient. Bull. - Lilly scientific bulletin. (Indianapolis).
Limousin méd. - Limousin médical.
Linacre Quart. - Linacre quarterly. (New York).
Lisboa méd. - Lisboa médica. (Lisbon).
Liverpool & Manchester M. & S. Rep. - Liverpool and Manchester Medical and Surgical Reports.
Liverpool Med.-Chir. J. - Liverpool Medico-Chirurgical Journal. (Liverpool).
Living Tissue - Living Tissue. (Boston).
Ljetopgiss russk. Chir. -
Loire méd. - Loire médicale (Lyon).
London & Edinburgh Month. J. M. Sc. - London and Edinburgh Monthly Journal of Medical Science.
London J. Med. - London Journal of Medicine.
London M. Gaz. - London Medical Gazette.
London M. & Phys. J.- London Medical and Physiological Journal.
London M. Rec. - London Medical Record.
London M. Reposit.- London medical repository and review.
Long Island M. J. - Long Island Medical Journal. (Brooklyn).
Lotta tuberc. - Lotta contro la tubercolosi. (Roma).
Louisville M. Monthly - Louisville medical monthly.
Louisville M. News - Louisville medical news.
Louisville Month. J. Med. & Surg. - Louisville monthly journal of Medicine and Surgery.
Louvain Diss.,(Louvanii)
Lucina - Lucina (Bologna).
Lues: Bull. Soc. japon. de syph. - Lues: Bulletin de la Société japonaise de syphiligraphie. (Kyoto).
Luftfahrtmedizin - Luftfahrtmedizin. (Berlin).
Lunds läk. säll. förh. - Lunds läkaresällskap förhandlingar. (Göttenborg).
Lyon chir. - Lyon chirurgical. (Paris).
Lyon méd. - Lyon Médical. (Lyon).
M. Age - Medical age.
M. Ann. District of Columbia - Medical annals of the District of Columbia. (Baltimore, Md.).
M. Ann. District of Columbia - Medical annals of the District of Columbia. (Washington, D.C.).
M. Arts - Medical arts; Indianapolis medical journal. (Indianapolis).
M. besieda -
M. Brief - Medical brief. (S. Louis).
M. Bull.(Bombay) -The Medical Bulletin. (Bombay).
M. Bull.(N.Y.) - Medical bulletin. (New York).
M. Bull. North African Theat.Op. - Medical Bulletin of the North African Theater of Operations.
M. Bull. (Philadelphia) - Medical bulletin (Philadelphia).
M. Bull. Univ. Cincinnati - Medical bulletin; University of Cincinnati. (Cincinnati).
M. Bull. Vet. Admin. - The Medical Bulletin of the Veterans' Administration. (Washington, D. C.).
M. Care - Medical care.
M. Century - Medical century.
M. Chron. (Manchester) - Medical chronicle (Manchester).
M. Circ. - Medical circular.
M. Classics - Medical Classics.
M. Clin. Chicago - Medical clinics of Chicago.
M. Clin. North America - The Medical Clinics of North America. (Philadelphia).
M. Comment. - Medical comment. (Johnstown).
M. Comment. Edinburgh & London - Medical commentaries (Edinburgh; London).
M. Communicat.(London) - Medical communications. (London).
M. Communicat. Mass. M. Soc. - Medical communications. Boston Massachusetts medical society.
M. Council (Phila.) - Medical council. (Philadelphia).
M. Counselor - Medical counselor.
M. Critic - Medical critic (New York).
M. Critic & Guide- Medical critic and guide. (New York).
M. Econom. - Medical economics. (Rutherford, N.J.).
M. Exam. - Medical examiner.
M. Fortnightly - Medical fortnightly.
M. Free Press. - Medical free press.
M. Gaz. - Medical gazette.
M. Herald - Medical herald. (Portland, Oreg.).
M. Insur. - Medical insurance. (Austin, Tex.).
M. J. Australia - Medical Journal of Australia. (Sydney).
M. J. & Rec. - Medical journal and record. (New York).
M. J. Siam. Red Cross - Medical journal of Siamese Red Cross; Chulalonkorn Memorial Hospital. (Bangkok).
M. J. South Africa - Medical journal of South Africa. (Johannesburg).
M. J. Surg. - Medical Journal of Surgery.
M. Life - Medical life. (New York).
M. Mag. - Medical magazine (Boston).
M. Mentor - Medical mentor. (Baltimore).
M. Mirror - Medical mirror.
M. News - Medical news. (Philadelphia). -
M. News & Libra. - Medical news and library.
M. observ. Soc. Phys. London - Medical observations and inquiries; Society of Physicians in London.
M. Officer - The Medical Officer. (London).
M. Pickwick - Medical pickwick. (S. Louis).
M. Press - Medical Press and Circular. (London).
M. Progress - Medical progress. (Louisville, Ky.).
M. Rec., Houston - Medical record and annals. (Houston, Tex.).
M. Rec. - Medical Record. (New York).
M. Rec. & Ann. - Medical record and annals.
M. Reg. - Medical register.
M. Reporter - Medical reporter.
M. Reposit. - Medical repository.
M. Rev. - Medical review (London).
M. Rev. of Rev. - Medical review of reviews. (New York).
M. & S. Monitor - Medical and surgical monitor.
M. & S. Rep. Episc. Hosp., (Phila.) - Medical and surgical reports of the Episcopal Hospital. (Philadelphia).
M. & S. Reporter - Medical and surgical reporter.
M. & S. Yearb. Physicians Hosp. Plattsburgh - Medical and surgical year-book of the Physicians Hospital, Plattsburgh. (Plattsburgh, N.Y.).
M. San. Rep., (Hong Kong) - Medical and sanitary report Medical Department. (Hong Kong).
M. Sc. Abstr.(Lond.) - Medical science, abstracts and reviews (Medical research council) (London).
M. Scient. Arch. Adelaide Hosp. - Medical and scientific archives of the Adelaide Hospital. (Adelaide).
M. Sentinel - Medical sentinel. (Portland, Oreg.).
M. Soc. New Jersey - Medical Society of New Jersey.
M. Soc. Rep., (Scranton) - Medical society reporter. (Scranton, Pa.).

M. Standard - Medical standard. (Chicago).
M. Statist. Bull. Sel. Serv. Syst. - Medical Statistics Bulletin. Selective Service System.
M. Summary - Medical Summary (Philadelphia).
M. Times & Gaz. - Medical times and gazette (London).
M. Times & Hosp. Gaz. - Medical times and hospital, gazette.
M. Times, (London) - Medical Times, (London) See: M. Times & Gaz. (London.).
M. Times. (New York) - Medical Times. The Journal of the American Medical Profession, including Long Island Medical Journal and Western Medical Times.
M. Times Philadelphia - Medical times philadelphia.
M. Tr. Roy. Coll. Phys. - Medical transactions of the Royal college of physicians. (London).
M. Visitor - Medical visitor.
M. Woman's J. - Medical Woman's Journal. (Cincinnati).
M. World - Medical world. (Philadelphia).
Maandber. Bur. statist. Amsterdam - Maandbericht van het Bureau van statistick der gemeente Amsterdam (Amsterdam).
Maandschr. v. Kindergeneesk. - Maandschrift voor kindergeneeskunde (Leiden).
Madras M. J. - Madras medical journal. (Madras).
Madras Month. J. M. Sc. - Madras monthly journal of medical science.
Madras Quart. J. M. Sc. - Madras quaterly journal of medical science.
Mag. f. d. ges. Heilk. - Magazin für die gesammte heilkunde.
Mag. London School M. Women - Magazine of the London Royal Free Hospital School of Medicine for Women. (London).
Magyar Nögyogy. -
Magyar orvosi arch. - Magyar orvosi archivum. (Budapest).
Magyar orv. nagyhét jegyzökve - Magyar orvosi nagyhét ...jegyzökönyve (Budapest).
Magyar Orvosok Term.-viszgalok - Magyar orvosok és természetvizsgalok.
Magyar röntgen köz. - Magyar röntgen közlöny. (Budapest).
Magyar statiszt. szemle - Magyar statisztikai szemle. (Budapest).
Maimonides Bull. - Maimonides bulletin. (Detroit).
Maimonides Month. - Maimonides monthly. (Detroit).
Maine M. J. - Maine Medical Journal. (Portland).
Maine M. & S. Reporter - Maine medical and surgical reporter.
Mal. cuore - Malattie del cuore. (Roma).
Malariologia, (Nap.) - Malariologia. (Napoli).
Malayan M. J. - Malayan Medical Journal. (Singapore).
Malthusian, (Lond.) - Malthusian. (London).
Man, (Lond.) - Man. (London).
Manchester M. & S. Rep. - Manchester medical and surgical reports.
Manhattan Eye a. Ear. Hosp. Rep. - Manhattan Eye and Ear Hospital Report.
Manicomio - Il Manicomio (Nocera Inferiore).
Manitoba M. A. Rev. - Manitoba Medical Association review. (Winnipeg, Can.).
Manitoba M. Bull. - Manitoba medical bulletin. (Winnipeg, Can.).
Manitoba M. Rev. - The Manitoba Medical review.
Manpower - Manpower (Volkskragte).
Marcuse's Handwörterb. Sexualwiss. -
Marineärztl. Kriegserfahr. - Marineärztliche Kriegserfahrungen. (Jena).
Maritime M. News - Maritime medical news.
Marquette M. Rev. - The Marquette Medical Review.
Marriage Hyg. - Marriage Hygiene. (Bombay).
Marseille-méd. - Marseille-médical. (Marseille).
Mary Fletcher Hosp. Bull. - Mary Fletcher Hospital Bulletin (Burlington, Vt.).
Maryland M. J. - Maryland medical journal.
Maryland Psychiat. Quart. - Maryland psychiatric quarterly. (Baltimore).
Mask, (Menasha) - Mask Kappa Psi Pharmaceutical Fraternity. (Menasha, Wisc.).
Massachusetts Gen. Hosp. News. - Massachusetts General Hospital News. (Boston).
Massachusetts Health J. - Massachusetts health journal. (Boston).
Massachusetts M. J. - Massachusetts medical journal.
Mat. & Child Welf., (Lond.) - Maternity and child welfare. (London).
Matér. ét. calam., (Genève) - Matériaux pour l'étude des calamités. (Genève).
Matlakowski (w) Ksiega panisetkowa .....Hayerowi Worsgawa. -
Mbl. vervalsch. - Maanblad tegen de vervalschingen. (Amsterdam).
McGill M. J. - McGill Medical Journal.
McGregor Clin. Bull. - McGregor Clinic Bulletin.
Meckel's Arch. f. Anat. u. Physiol. - Meckel's Archiv für anatomie und physiologie. (Leipzig). See: Arch. f. Anat. u. Physiol.
Méd. anecdot. - Médecine anecdotique, historique littéraire.
Med. Ann. - Medicinische annalen. (Heidelberg).
Med. Arch. - Medical archives.
Med. argent. - La medicina argentina.
Med. Besieda, Voronezh. -
Med. biol. J., - Mediko-biologichesky jurnal. (Leningrad).
Med. chir. Centralbl. - Medicinisch-chirurgisches centralblatt.
Med. Chir. Cor.-Bl. f. Deutsch.-Am. Aerzte - Medicinisch-chirurgisches correspondenzblatt für deutsch-amerikanische aerzte.
Med. chir., (Nap.) - Medicina e chirurgia del medico pratico. (Napoli).
Med. Chir. Quart. - Medico-chirurgical quarterly.
Med.-chir. Tr. - Medico-chirurgicale transactions.
Med. u. chir. Wehrnehm. -
Med. cir. pharm. - Medicina-cirugia-pharmacia.
Med. clin. - Medicina clinica.
Med. colon. (Madrid.) - La medicina colonial. (Madrid).
Med. contemp., (Lisb.) - Medicina contemporanea. (Lisboa).
Med. Cor.-Bl. bayer. Aerzte - Medicinisches correspondenz-blatt bayerischer aerzte.
Med. dóswiadcz. i spot. - Medycyna dóswiadczalna i spoteczna. (Warszawa).
Med. español. - Medicina española.
Méd. exp. (russ.) - Médecine expérimentale.
Med. fenn. - Medicina fennica. (Helsinki).
Med. heldigt Udfald. -
Med. d. Lavoro - La medicina del lavoro.
Med. ibera - La medicina ibera; revista semanal de medicina y cirugia. (Madrid).
Méd. inf. - La médecine infantile. (Paris).
Med. inf., (Roma) - Medicina infantile. (Roma).
Méd. internat. - La médecine internationale. (Paris).
Med. ital. - Medico italiano (Milano).
Med. J., (Moskva) - Meditsinsky jurnal. (Moskva).
Med. Jahrb. f. d. Herzogth. Nassau, (Wiesb.) - Medicinische jahrbücher für das herzogthum Nassau (Wiesbaden).
Med. Jahrb. d. k. k. österr. Staates - Medicinische jahrbücher des K. K. österreichischen staates.
Med. Klin. - Medizinische Klinik. (Berlin).
Med. Klin. Beihefte - Beihefte zur Medizinischen Klinik.
Med. Korresp.-bl. württemb. - Medizinisches korrespondenzblatt für württemberg. (Stuttgart).
Med. Korresp.-Bl. württemb. Ärztl. Ver. (Stuttgart) - Medizinischers korrespondenzblatt für Württembergischer ärztlicher verein (Stuttgart).
Med. kron. lek., (Warsz.) - Medycyna i kronika lekarska. (Warszawa).
Med. d. lavoro - La medicina del lavoro. (Milano).
Med.-Leg. & Criminol. Rev. - The Medico-Legal and Criminological Review.
Med.-Leg. J., (N.Y.) - Medico-legal journal. (New York).
Med. Liter., (Lpz.) - Medizinische Literatur. (Leipzig).
Med. mil. español. - Medicina militar española.
Med. Mil. Rev., (Wash.) - Medico-military review. (Washington, D. C.).
Med. misl. (Rostov) - Meditzinskaia misl. (Rostov na Donu).
Med. misl, (Tashkent) - Meditzinskaia misl uzbekistana i turkmenistana. (Tashkent).

Med. Mitt. (russ.) -
Méd. mod. - Médecine moderne (Paris).
Med. Monatschr. - Medicinische monatsschrift.
Med. napried.,Sofiya -
Med. ninos - Medicina de los ninos. (Barcelona).
Med. nuova - Medicina nuova. (Roma).
Med. Obozr. - Medicinskoje Obozrenije (Moskow).
Méd. orient.(Paris) - Médecine orientale. (Paris).
Med. otchet. rodovsp. zaved. Imp. Moskov. Vosp. Doma -
Med. parazitol. i parazit. bolez. - Meditsinskaya parazitologiya i parazitarniya bolezni. (Moskva).
Med. & Phys. J. - Medical and physical journal.
Med. prat., (Nap.) - Medicina pratica. (Napoli).
Med. prat. (Paris) - Médecine pratique (Paris).
Med. prev.,(Tor.) - Medicina preventiva. (Torino).
Med. pribav. k marsk. sbarniku -
Med. Rev. f. Belneol. - Medicinische revue für balneologie hydro-und mechano-therapie, diätetik und hygiene.
Med. rev.,(Bergen) - Medicinsk revue. (Bergen).
Med. Rev. of Rev. (N.Y.) - - Medical review of reviews (New York).
Med. Sbornik,(Tiflis). - Meditsinskii sbornik (Tiflis).
Méd. scolaire (Par.) - Médecine scolaire. (Paris).
Med. sociale,(Nap.) - Medicina sociale (Napoli).
Med. sper., Arch. ital. - Medicina sperimentale; archivio italiano. (Turin).
Med. statist. Mitt. Reichsgesundhamt. - Medizinal-statistische Mitteilungen aus dem Reichsgesundheitsamte. (Berlin).
Med. statist. Nachr.,(Berl.) - Medizinalstatistische Nachrichten. (Berlin).
Méd. stomat. (Par.) - Médecin stomatologiste. (Paris).
Med. Students Mag. - Medical students magazine. (Kansas City).
Med. Suggestions - Medical suggestions. (St. Louis).
Med. & Surg. - Medicine and Surgery.
Med.-Surg. Suggestions,(Madras) - Medico-surgical suggestions. (Madras).
Med. Today & Tomorrow - Medicine today and Tomorrow.
Med. trabajo - Medicina del trabajo e higiene industrial. (Madrid).
Med. Viestnik - Meditsinskii viestnik.
Med. Weekbl. Noord-en Zuid-Nederl. - Medish weekblad voor Noord en Zuid-Nederland. (Amsterdam).
Med. Welt - Die medizinische Welt. (Berlin).
Med. Woche - Medicinische woche.
Med. zhur. - Medichniy zhurnal.
Med. Zhur. Akad. Nauk U.R.S.R. - Medichnii zhurnal Akademia nauk URSR.
Med. Ztg. Russlands - Medizinische zeitung Russlands.
Médecin.prat. - Médecine pratique.
Mededeel. v. dienst. d. volksgezondh. in Nederl.-Indië - Mededeelingen van den dienst der volksgezondheit in Nederlandsch-Indië. (Batavia).
Médecine - La médecine. (Paris).
Medd. Grønland - Meddelelser om Grønland. (København).
Mededeel. Geneesk. lab. Weltevreden - Mededeelingen uit het Geneeskundig laboratorium te Weltevreden. (Batavia).
Mededeel. Inst. v. trop. geneesk. - Mededeelingen Institutt voor tropische geneeskunde (Leyden). See; Acta leidensia scholae med. trop.
Mededeel. Rijks Inst. pharm. ther. onderzoek. - Mededeelingen van het Rijks-Instituut voor pharmaco-therapeutisch onderzoek. (Leiden).
Medica, Matanzas- Medica. Organo official de la Sociedad de medicina y cirugia de Matanzas.
Medicina, (Buenos Aires) - Medicina (Buenos Aires).
Medicina, (Kaunas) - Medicina. (Kaunas).
Medicina, (Madrid) - Medicina. (Madrid).
Medicina, (México) - Medicina (México).
Medicine - Medicine, Analytical Reviews of General Medicine, Neurology and Pediatrics. (Baltimore).
Medicine (Detroit) - Medicine (Detroit).
Medicinskoje Obozrenije -
Medico-Surgical Tributes to Harold Brunn -
Meditsina (St. Petersburg) - Meditsina (St.Petersburg).
Medycyna - Medycyna See: Medycyna i kron. lek.
Medycyna i Kron. Lek. - Medycyna i kronika lekarska.
Mélanges biol. Acad. imp. d. sc. (St.Petersburg) - Mélanges biologiques académie impériale des sciences. (St. Petersburg).
Mélanges de chir. - Mélanges de chirurgie étrangere. (Geneva).
Mém. Acad. de chir. - Mémoires; Académie de chirurgie (Paris).
Mém. Acad. cienc. Barcelona - Memorias de la Academia de ciencias y artes de Barcelona. (Barcelona).
Mém. Acad. de méd. - Mémoires; académie de médecine. (Paris).
Mém. Acad. nac. cienc. Antonio Alzate - Memorias y revista de la Academia nacional de ciencias Antonio Alzate. (México).
Mém. Acad. polon. sc. - Mémoires de l'Académie polonaise des sciences et des lettres. (Krakow).
Mém. Acad. roy. de chir. - Mémoires de l'académie royale de chirurgie. (Paris).
Mém. Acad. roy. de méd. de Belgique - Mémoires; Académie royale de médecine de Belgique. (Bruxelles).
Mém. Acad. sc. Montpellier - Mémoires; Académie des sciences et lettres de Montpellier. (Montpellier, France).
Mem. Accad. Italia - Memorie della R. Accademia d'Italia- (Classe di scienze fisiche, matematiche e naturali. (Roma).
Mem. Accad. sc. Ist. Bologna - Memorie della R. Accademia delle scienze dell'Istituto di Bologna. (Bologna).
Mem. Am. Acad. Arts & Sc. - Memoirs; American academy of arts and sciences. (Boston).
Mem. Am. Anthrop. Ass. - Memoirs of the American Anthropological Association. (Menasha, Wis.).
Mém. et bull. Soc. de méd. et chir. de Bordeaux - Mémoires et bulletins de la société de médecine et de chirurgie de Bordeaux.
Mem. Carnegie Museum - Memoirs of Carnegie museum.
Mém. et compt.-rend. Soc. d. sc. méd. de Lyon - Mémoires et comptes-rendus de la société des sciences médicales de Lyon.
Mém. d. concours...Acad. Roy. de méd. de Belg. - Mémoires des concours et des savants étrangers de l'académie royale de médecine de Belgique.
Mem. Congr. venezol. med. - Memoria; Congreso venezolano de medicina.
Mém. couron. Acad. méd. Belgique - Mémoires couronnés et autres mémoires; Académie royale de médecine de Belgique. (Bruxelles).
Mem. Hosp. de Juquery - Memorias do Hospital de Juquery.
Mem. do Instituto Biol. Ezequiel Dias - Memorias do Instituto biologico Ezequiel dias (Belo Horizonte).
Mem. Inst. Butantan - Memorias do Instituto de Butantan. (São Paulo).
Mém. Inst. Égypte - Mémoires présentés à l'Institut d'Égypte. (Le Caire).
Mem. Inst. Oswaldo Cruz. - Memorias do Instituto Oswaldo Cruz. (Rio de Janeiro).
Mem. Ist. venet. sc. - Memorie del R. Istituto veneto di scienze, lettere ed arti. (Venezia).
Mem. Liverpool School Trop. M. - Memoir; Liverpool School of Tropical Medicine. (Liverpool).
Mem. London School Hyg. - Memoir; London School of Hygiene and Tropical Medicine. (London).
Mem. M. Soc. London - Memoires of the medical society of London.
Mem. Nat. Acad. sc. U. S. - Memoirs of the National Academy of Sciences of the United States. (Washington).
Mem. Ophthalmic Lab. Giza, Ann. Rep. - Ceased publication.
Mem. Soc. Antonio Alzate - Memorias y revista de la Sociedad cientifica "Antonio Alzate" (Mexico).
Mém. Soc. de biol. (Paris) - Mémoires de la société de biologie. (Paris).

Mém. Soc. de chir. de Paris - Mémoires de la société de chirurgie de Paris.
Mém. Soc. méd. d'émulat. de Paris - Mémoires de la société médicale d'émulation de Paris.
Mém. Soc. de méd. de Nancy - Mémoires de la société de médecine de Nancy.
Mém. Soc. de méd. de Strasbourg - Mémoires de la société de médecine de Strasbourg.
Mém. Soc. sc. Bordeaux - Mémoires de la Société des sciences physiques et naturelles de Bordeaux. (Bordeaux).
Mém. Soc. d. sc. méd. de Lille - Mémoires de la société des sciences médicales de Lille.
Mém. Soc. sc. natur. méd. Seine-et-Oise - Mémoires de la Société des sciences naturelles et médicales de Seine-et-Oise. (Versailles).
Mém. Univ. of California - Memoires of the University of California.
Mem. Univ. Michigan Mus. Paleont. - Memoirs of the University of Michigan Museums; Museum of Paleontology. (Ann Arbor).
Memorabilien - Memorabilien.
Memphis M. J. - Memphis Medical Journal. (Memphis, Tenn.).
Memphis M. Month. - Memphis medical monthly. (Memphis, Tenn.).
Ment. Health - Mental health. (Toronto).
Ment. Hyg. - Mental Hygiene. (Albany, N.Y.).
Ment. Health Bull., (Danville) - Mental health bulletin. (Danville, Pa.).
Ment. Hyg., (Concord) - Mental hygiene. (Concord, N.H.).
Ment. Welfare - Mental Welfare (London).
Merck Rep. - Merck report. (Rahway, N.J.).
Mercredi méd. - Mercredi médicale.
Messenger - Messenger (New York).
Metabolist - Metabolist. (New York).
Meth. M. Educ. - Methods and problems of medical education. (New York).
Metron, (Rovigo) - Metron. (Rovigo).
Michigan M. News - Michigan medical news.
Michigan Out of Doors - Michigan out-of-doors. (Ann Arbor).
Michigan Pub. Health - Michigan public health. (Lansing).
Michigan State M. Soc. J. - Michigan State Medical Society Journal.
Michigan Univ. M. J. - Michigan University Medical Journal.
Middlesex Hosp. J. - The Middlesex Hospital Journal. (London).
Middlesex Hosp. Rep. - Middlesex hospital reports. (London).
Midi méd. (Toulouse) - Midi médical. (Toulouse).
Midland Druggist - Midland druggist and pharmaceutical review. (Columbus, Ohio).
Midland M. J. - Midland Medical Journal. (Bermingham).
Midland M. & S. Reporter - Midland medical and surgical reporter.
Mikrobiologia, (Moskva) - Mikrobiologia. (Moskva).
Mikrob. J., (Leningr.) - Mikrobiologichesky jurnal. (Leningrad).
Mikrochim. Acta - Mikrochimica acta.
Mikrokosmos - Mikrokosmos. (Stuttgart).
Mil. Dent. J. - Military dental journal. (Washington, D.C.).
Mil. Engin. - Military engineer. (Washington, D.C.).
Mil. geneesk. tschr. - Militair-geneeskundig tijdschrift. (Haarlem).
Mil. spectator (Haag) - Militaire spectator. (Den Haag).
Mil. Surgeon - Military Surgeon (Washington, D.C.).
Mil. Wbl., (Berl.) - Militär-Wochenblatt. (Berlin).
Mil. wiss. Mitt., (Wien) - Militärwissenschaftliche Mitteilungen. (Wien).
Milbank Mem. Fund Quart. - Milbank Memorial Fund Quarterly
Militaerlaegen - Militaerlaegen. (København).
Milwaukee M. J. - Milwaukee medical journal.
Mind, (Lond.) - Mind. (London).
Minerva med. - Minerva medica (Torino).
Minnesota M. Mirror - Minnesota medical mirror.
Minnesota Med. - Minnesota medicine. (Minneapolis).
Minnesota Med. - Minnesota Medicine. (St. Paul).
Minutes Am. Roentg. Soc. - Minutes of the American Roentgen Ray Society. (Chicago, Ill.).
Misc. Acad. nat. curios - Miscellanea curiosa medico-physica Academiae naturae curiosorum.
Misc. Contr. Com. Costs M. Care - Miscellaneous contributions of the Committee on the Costs of Medical care. (New York).
Misc. Pub. Univ. Michigan Mus. Zool. - Miscellaneous publications; University of Michigan, Museum of zoology. (Ann Arbor).
Mision estud. pat. reg. argent. - See: Univ. Buenos Aires mision estud. pat. reg. argent.
Mississippi Doctor - The Mississippi Doctor.
Mississippi Valley M. J. - Mississippi Valley Medical Journal. (Louisville, Ky.).
Mississippi Valley M. Month. - Mississippi Valley medical Monthly.
Missouri Agr. Exper. Station, Res. Bull. -
Missouri State M. A. - Missouri State Medical Association.
Mitt. ü. allg. Path. u. path. Anat. - Mitteilungen über allgemeine Pathologie und pathologische Anatomie. (Sendai, Japan).
Mitt. Anthrop. Ges. Wien. - Mitteilungen der Anthropologischen Gesellschaft in Wien. (Wien.).
Mitt. Biochem. - Mitteilungen über Biochemie. (Lage).
Mitt. Deut. Ges. Naturk. Ostasiens (Tokyo) - Mitteilungen der Deutschen Gesellschaft für Natur-und Völkerkunde Ostasiens. (Tokyo).
Mitt. a. d. Geb. d. Lebensmittelunt. u. Hyg. - Mitteilungen aus dem Gebiete der Lebensmitteluntersuchung und Hygiene.
Mitt. Gesch. Med. Naturwiss. - Mitteilungen zur Geschichte der Medizin und der Naturwissenschaften. (Leipzig).
Mitt. Gesellsch. f. Geburtsh. u. gyn. zu (Leipz.) - Mittheilungen; Gesellschaft für geburtshülfe und gynäkologie. (Leipzig).
Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien - Mitteilungen; Gesellschaft für innere medizin und kinderheilkunde in Wien.
Mitt. a. d. Grenzgeb. d. Med. u. Chir. - Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie. (Jena).
Mitt. gynäk. Klin. Engström - Mitteilungen; Gynaekologische klinik des Prof. Dr. Otto Engström (Helsingfors, Finland).
Mitt. Inst. Radiumforsch., (Wien) - Mitteilungen des Institutes für Radiumforschung. (Wien).
Mitt. Jap. Gesellsch. f. Gynäk. -
Mitt. Justus Perthes Anst. - Mitteilungen aus Justus Perthes' geographischer Anstalt. (Gotha).
Mitt. Klin. u. med. Inst. Schweiz. -
Mitt. Lebensmitteluntersuch., (Bern) - Mitteilungen aus dem Gebiete der Lebensmitteluntersuchung und Hygiene. (Bern).
Mitt. a. d. med. Akad. zu Kioto - Mitteilungen aus der medizinischen Akademie zu Kioto. (Kioto).
Mitt. med. Fac. Kyushu - Mitteilungen faculty of medicine; Kyushu imperial university. (Fukuoka, Japan).
Mitt. med. Fak. Tokyo - Mitteilungen aus der medizinischen fakultät der kaiserlichen universität zu Tokyo.
Mitt. med. Gesellsch. Chiba - Mitteilungen der medizinische gesellschaft zu Chiba.
Mitt. d. med. Gesellsch. zu Tokio - Mitteilungen der medicinische Gesellschaft zu Tokio.
Mitt. Oesterr. Ges. Bevölkpolit. - Mitteilungen der Oesterreichischen Gesellschaft für Bevölkerungspolitik und fürsorgewesen. (Wien.)
Mitt. Path. (Sendai) - Mitteilungen pathologisches institut (Sendai, Japan).
Mitt. a. d. Sitz. Protok. d. Gesellsch. f. Geburtsh. - Mitteilungen aus den sitzungsprotokollen. Gesellschaft für geburtshülfe und gynäkologie. (Berlin).
Mitt. Statist. Staatsamt. Cech. - Mitteilungen des Statistischen Staatsamtes der Cechoslovakischen Republik. (Praha).
Mitt. Stazione Zool. Naples - Mitteilungen stazione Zoologica Naples.

Mitt. d. Ver. d. Aerzte in Steiermark - Mitteilung des Vereins der Aerzte in Steiermark. (Graz).
Mitt. Ver. badisch. Tierärzte - Mitteilungen des Vereins badischer Tierarzte. (Karsruhe).
Mitt. Ver. Erdk. Dresden - Mitteilungen des Vereins für Erdkunde zu Dresden. (Dresden).
Mitt. d. Verhandl. d. Aerzte in Nied.-Oest. Wien -
Mitt. f. d. Verhandl. Schesw.-Holst. Aerzte. Kiel -
Mitt. Volksgesundhamt.,(Wien)- Mitteilungen des Volksgesundheitsamtes im Bundesministerium für soziale Verwaltung. (Wien).
Mitt. d. Wien. med. Doct.-Coll. -
Mitt. d. wissensch. Kom. z. Erforsch.'u. Bekämpf. d. Kreislaufstör. - Mitteilungen des wissenschaftlichen Komitees zur Erforschung und Bekämpfung der Kreislaufstörungen.
Mitt. Zool. Station zu Neaple - Mitteilungen zoologische station zu Neaple. See: Mitt. Stasione zool. Naples.
Mod. Concepts Card. Dis. - Modern concepts of cardiovascular disease. (New York, N.Y.).
Mod. Hosp. - Modern Hospital. (Chicago).
Mod. Med. & Bacteriol. Rev. - Modern medicine and bacteriological review.
Mod. Med. (Chic.) - Modern medicine. (Chicago).
Mod. Pharm. - Modern pharmacy.
Monatsber. Statist.Amt.Breslau - Monatsberichte des Statistischen Amts der Stadt Breslau. (Breslau).
Monatsber. Statist. Amt. Dresden - Monatsberichte des Statistischen Amts der Stadt Dresden. (Dresden).
Monatsbl. Gesundhpfl. - Monatsblatt für Gesundheitspflege. (Braunschweig).
Monatschr. Elektr. Compl. Homöop. - Monatsschrift für Elektro-Komplex-Homöopathie. (Regensburg).
Monatschr. f. Geburtsh. u. Gynäk. - Monatsschrift für Geburtshülfe und Gynäkologie. (Berlin).
Monatschr. f. Geburtsk. u. Frauenk. - Monatsschrift für geburtskunde und frauenkrankheiten.
Monatschr. Harnkr. sex. Hyg. - Monatsschrift für Harnkrankheiten und sexuelle Hygiene. (Stuttgart).
Monatschr. f. Kinderh. - Monatsschrift für Kinderheilkunde (Berlin).
Monatschr. f. Krebsbekämpf. - Monatsschrift für Krebsbekämpfung. (München)
Monatschr. f. Krim.-biol. - Monatsschrift für Kriminalbiologie und Strafrechtsreform. (München).
Monatschr. f. Krim.-Psychol. - Monatsschrift fur Kriminalpsychologie und Strafrechtsreform.
Monatschr. f. Ohrenh. - Monatsschrift für Ohrenheilkunde und Laryngo-Rhinologie. (Wien).
Monatschr. f. Psychiat. u. Neurol. - Monatsschrift für Psychiatrie und Neurologie. (Berlin).
Monatschr. f. Unfallh. - Monatsschrift für Unfallheilkunde und Versicherungsmedizin. (Berlin).
Monatschr. ungar. Med. - Monatsschrift ungarischer Mediziner. (Budapest)
Monatsh. prakt. tierh. - Monatshefte der praktischen Tierheilkunde. (Stuttgart).
Monde méd., (Paris) - Monde médical. (Paris).
Mondo med. - Mondo medico. (Roma).
Monist,(Chic.) - Monist. (Chicago).
Monit. Endocrinologia - Monitore di endocrinologia per il medico pratico (Roma).
Monit. d. hôp. (Paris) - Moniteur des hôpitaux. (Paris).
Monit. ostet. ginec. - Monitore ostetrico-ginecologico. (Bologna).
Monit. zool. ital. - Monitore zoologico italiano. (Firenze).
Monogr. act. derm., (Kyoto) - Monographiae actorum dermatologicorum. (Kyoto).
Monogr. Frauenk. - Monographien zur Frauenkunde und Eugenetik, Sexualbiologie und Vererbungslehre. (Leipzig).
Monogr. Inst. Hig. (Popotla) - Monografias del Instituto de higiene. (Popotla).
Monogr. Neur. Psychiat., (Berl.) - Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie. (Berlin).
Monogr. Rockefeller Inst. f. M. Res. - Monographs of the Rockefeller institute for medical research. (New York).
Monog. Soc. Res. Child Develop. - Monographs of the Society for Research in Child Development.
Month. Bull. Alberta Dep. Health - Monthly bulletin; Alberta Department of Health. (Alberta).
Month. Bull. Bd.Health California - Monthly bulletin of the State Board of Health of California. (Sacramento, Calif.).
Month. Bull. Bd.Health Indiana - Monthly bulletin of the State Board of Health of Indiana. (Indianapolis).
Month. Bull. Dep. Health City N. York - Monthly bulletin of the Department of Health for the City of New York. (New York).
Month. Bull. Dep. Health New Haven - Monthly bulletin of the Department of Health of New Haven. (New Haven, Conn.).
Month. Bull. Indiana Div. Pub. Health - Monthly bulletin; Indiana Division of Public Health. (Indianapolis, Ind.).
Month. Bull. Min. Health & Emerg. Pub. Health Lab. Serv. - Monthly Bulletin of the Ministry of Health and the Emergency Public Health Laboratory Service.
Month. Bull. (New York)State Dep. Health - Monthly bulletin (New York) State Department of Health. (Albany, N.Y.).
Month. Bull. Ohio Agr. Exp. Sta. - Monthly bulletin of the Ohio Agricultural Experiment Station. (Wooster, Ohio).
Month. Bull. Philadelphia Dep. Pub. Health. - Monthly bulletin: Philadelphia Department of Public Health. (Philadelphia, Pa.).
Month. Bull. Philippine Health Serv. - Monthly bulletin of the Philippine Health Service. (Manila, P. I.).
Month. Bull. Truesdale Hosp. - Monthly bulletin of the Truesdale Hospital and Earle P. Charlton Surgery. (Fall River, Mass.).
Month. Cycl. & M. Bull. - Monthly Cycle and Medical Bulletin.
Month. Digest Nat. Health Counc. - Monthly digest of the National Health Council. (New York).
Month. Epidem. Rep. League of Nat. - Monthly epidemiological report of the Health section of the Secretariat. League of Nations. (Genève).
Month. Homoeop. Rev. - Monthly homoeopathic review.
Month. J. M. Sc. (London & Edinburgh) - Monthly journal of medical science. (London and Edinburgh).
Month. Labor Rev. - Monthly labor review. (Washington D.C.).
Month. News Lett. Suffolk Co. M. Soc. - Monthly news letter of the Suffolk County Medical Society. (Riverhead).
Month. Rel. Com. Nurs. Schools - Monthly releases of the Committee on Grading of Nursing Schools. (New York).
Month. Summary Internat. Labor Org. - Monthly Summary of the International Labour Organization. (Genève).
Month. Summary League of Nat. - Monthly summary of the League of Nations. (Genève).
Month. Vit. Statist. Rev.(Alb.) - Monthly vital statistics review. (Albany).
Month. Weather Rev., (Wash.). - Monthly weather review; U. S. Weather Bureau. (Washington, D. C.).
Montpellier méd. - Montpellier médical. (Montpellier). France).
Montreal Gen. Hosp. Rep. - Montreal general hospital pathological reports.
Montreal M. J. - Montreal medical journal.
Morgagni - Morgagni. (Ceased publication).
Morphol. Jahrb. - Morphologisches Jahrbuch. (Leipzig).

Mort. Statist. U. S. Bur. Cens. - Mortality statistics of the U. S. Bureau of Census. (Washington).
Moscow M. J. - Moscow Medical Journal.
Mosk. med. J. - Moskovsky meditsinsky jurnal. (Moskva).
Mother & Child - Mother and child. (Baltimore).
Mouth Health Quart. - The Mouth Health Quarterly.
Mouvement hyg. - Mouvement hygiénique.
Movimento - Movimento.
Mun. Engin.,(Lond.) - Municipal engineering and sanitary record. (London).
Mun. Facts, (Denver) - Municipal facts. (Denver, Colo.).
München. Gynäk. Gesellsch. -
München. med. Wchnschr. - Münchener medizinische Wochenschrift. (München).
München. tierärztl. Wchnschr. - Münchener tierärztliche wochenschrift (München).
Mus. Work, (Provid.) - Museum work. (Providence, R.I.).
Museu. - Museu.
Mycologia, (Lancaster) - Mycologia. (Lancaster, Pa.).
Naar het volle leven - Naar het volle leven. (Amsterdam.).
Nachr. Gesellsch. Wiss. Gött. - Nachrichten; Gesellschaft der wissenschaften zu Göttingen. (Berlin).
Nachr. Gesellsch. d. Wissensch. Math.-phys. Kl. - Nachrichten. Gesellschaft der wissenschaften. Mathematisch-physikalische klasse.
Nachr. Mil. med. Akad. -
Nachrbl. Reichsaussch. hyg. Volksbelehr. - Nachrichtenblatt des Reichsausschusses für hygienische Volksbelehrung (etc.).(Dresden).
Nagasaki Igakkwai Zassi - Nagasaki Igakkwai Zassi.
Nagoya J. M. Sc. - Nagoya Journal of Medical Science. (Nagoya).
Narkose u. Anaesth. - Narkose und anaesthesie. (Berlin). (Continued as Schmerz Narkose-Anaesth.
Nashville J. M. & S. - Nashville journal of medicine and surgery.
Nat. Assoc. Study & Prev. Tuberc. Tr. - National association for the study and prevention of tuberculosis. (See: National tuberculosis association transactions, N.Y.).
Nat. Bd. Bull., (Phila.) - National Board bulletin. (Philadelphia).
Nat. Bull. Am. Soc. Control Cancer - National bulletin of American society for the control of cancer. (Continuation of Bull. Am. Soc. Control Cancer).
Nat. Eclect. M.A. Quart. - National eclectic medical association quarterly (Cincinnati).
Nat. Health Counc. - National Health Council. (New York).
Nat. Health Rev. (Ottawa) - National Health review. (Ottawa, Can.).
Nat. Humane Rev. - National humane review. (Albany, N.Y.).
Nat. Inst. Health Bull. - National Institute of Health Bulletin. (Continuation of Hygiene Laboratory Bulletin Series).
Nat. Inst. Soc. Sc. - National institute of social sciences.
Nat. M. J. China - National medical journal of China (Peiping). (Continued as Chinese M. J.).
Nat. M. Rev. Washington - National medical review Washington.
Nat. Negro Health News - National negro health news. (Washington, D.C.).
Nat. Provisioner - National provisioner. (Chicago, Ill.).
Nat. Red. Cross. (Bangkok). - National Red Cross. (Bangkok).
Nat. Safety News - National safety news. (Chicago, Ill.)
Nat. Tijdschr. -
Nat. Tuberc. A. Tr. - National Tuberculosis Association Transactions.
Nat. Vet. M. Ass. Gr. Britain - National Veterinary Medical Association of Great Britain and Ireland.
Nation's Health, (Chic.) - Nation's health. (Chicago).
Native M. Pract., (Suva) - Native medical practitioner. (Suva).
Natur. (Lpz.) - Natur. (Leipzig).
Natura dux. Gravenh. - Natura dux. 's Gravenhage.
Naturärztl. Rdsch. - Naturärztliche Rundschau. (Stuttgart).
Nature, (London) - Nature. (London).
Nature, (Par.) - Nature. (Paris).
Nature's Path. - Nature's path. (New York).
Naturopath. (N.Y.) - Naturopath. (New York).
Naturwissenschaften - Naturwissenschaften (Die). (Berlin).
Nauch. Besedy Tiflis Zakavkazsk. Povival. Inst. - Nauchnyia besiedy, tiflis Zakavkazskii povival'nyi institut.
Naunyn-Schmiedeberg's Archiv - Naunyn-Schmiedeberg's Archiv für experimentelle pathologie und pharmakologie (Leipzig). (Continued as Archiv für experimentelle Pathologie und Pharmakologie).
Nebraska M. J. - Nebraska State Medical Journal. (Lincoln).
Nebraska M. J. - Nebraska State Medical Journal (Norfolk, Nebr.).
Nederl. maandschr. v. Geesk. - Nederlandsch maandschrift voor geneeskunde. (Leiden).
Nederl. maandschr. v. verlosk. en vrouwenz., en v. Kindergeneesk. - Nederlandsch maandschrift voor verloskunde en vrouwenziekten en voor kindergeneeskunde. (Leiden).
Nederl. Monatschr. v. geneesk. -
Nederl. tijdschr. v. dierk. - Nederlandsch tijdschrift voor de dierkunde.
Nederl. tijdschr. v. geneesk. - Nederlandsch tijdschrift voor geneeskunde. (Amsterdam).
Nederl. tijdschr. v. Heel-en Verlosk. - Nederlandsch tijdschrift voor heel- en verloskunde
Nederl. tijdschr. v. hyg. microb. - Nederlandsch tijdschrift voor hygiene, microbiologie en serologie. (Leiden).
Nederl. tijdschr. v. natuurk. - Nederlandsch tijdschrift voor natuurkunde. 's Gravenhage.
Nederl. tijdschr. v. verlosk. en gynaec. - Nederlandsch tijdschrift voor verloskunde en gynaecologie. (Haarlem).
Nederl. Weekbl. v. Geneesk. - Nederlandsch weekblad voor geneeskundigen.
Néoplasmes - Néoplasmes (Paris).
Neopsichiatria - Neopsichiatria.
Nerv. Child. - The Nervous Child.
Nerv. Ment. Dis. Monogr. - Nervous and mental disease monograph series. (New York).
Nervenarzt - Der Nervenarzt. (Berlin).
Neue Generation - Die Neue Generation. (Berlin).
Neue Jahrb. d. deutsch. Med. u. Chir. - Neue jahrbücher der deutschen medicin und chirurgie.
Neue Ztschr. f. Geburtsk. - Neue zeitschrift für geburtskunde.
Neues Arch. f. med. Erfahr. - Neues archiv für medizinische erfahrung.
Neues Mag. f. Aerzte - Neues magazin vor aerzte.
Neurobiologia - Neurobiologia.
Neurol. Bull., (N.Y.). - Neurological bulletin. (New York).
Neurol. polska - Neurologia polska.
Neurol. Zentralbl. - Neurologisches Zentralblatt. (Leipzig).
Neurologica, (Nap.) - Neurologica. (Napoli).
Neurotherapie, (Amst.) - Neurotherapie. (Amsterdam).
Nevrol. Viestnik. (Kazan) - Nevrologicheskii viestnik. (Kazan.).
Nevropat. i psikhiat. - Nevropatologiya i psikhiatriya.
New Albany M. Herald - New Albany medical herald. (New Albany, Ind.).
Newcastle & Gateshead Path. Soc. Communicat. - Newcastle and Gateshead pathological society Communications).
Newcastle M. J. - The Newcastle Medical Journal. (Newcastle-upon-Tyne).
New Charlotte M. J. - New Charlotte medical journal. (Charlotte, N.C.).
New England J. Med. - New England Journal of Medicine. (Boston).
New England J. Med. & Surg. - New England journal of medicine and surgery.
New England M. Center - New England medical Center.

New England M. Gaz. - New England medical gazette.
New England M. Month. - New England medical monthly and the prescription.
New Generation, (Lond.) - New Generation.(London).
New Hampshire J. M. - New Hampshire journal of medicine.
New Internat. Clin. - New International clinics. (See: Internat. Clin.).
New Jersey J. Pharm. - New Jersey journal of pharmacy. (Sommerville, N.J.).
New Jersey M. Reporter - New Jersey medical reporter.
New Orleans M. News & Hosp. Gaz. - New Orleans Medical News and Hospital Gazette.
New Orleans M. & S. J. - New Orleans Medical and Surgical Journal. (New Orleans, La.).
New Philos.,(Lancaster) - New Philosophy. (Lancaster, Pa.).
New Republic -
New South Wales M. Gaz. - New South Wales medical gazette.
New York & Chicago M. & S. J. - New York and Chicago medical and surgical journal.
New York J. Dent. - New York journal of dentistry. (Brooklyn, N.Y.).
New York J. Gynec. & Obst. - New York journal of gynaecology and obstetrics.
New York J. Med. - New York journal of medicine.
New York J. Pharm. - New York journal of pharmacy. (New York).
New York M. Coll. & Flower Hosp. Bull.- New York medical college and Flower and Fifth Avenue hospitals Bulletin (New York). (Continued as Bull. New York M. Coll.Flower & Fifth Ave. Hosps.).
New York M. Gaz. - New York medical gazette.
New York M. Gaz. & J. Health - New York medical gazette and journal of health.
New York M. J. - New York Medical Journal (New York).
New York M. J. & Obst.Rev. - N. Y. Medical Journal and Obstetric Review.
New York M. M. - New York medical monthly.
New York Med. & Phys. J. - New York medical and physical journal.
New York M. Press. - New York medical press.
New York Polyclin. J. - New York polyclinic journal.
New York State J. Med. - New York State Journal of Medicine. (Albany, N.Y.).
New York Zool. Soc. - New York Zoological Society.
New Yorker med. Monatschr. - New Yorker medicinische monatsschrift.
New Zealand M. J. - The New Zealand Medical Journal. (Wellington).
News Lett. (Blindness)(N.Y.)- News letter (Committee for the Prevention of Blindness) (New York).
News Lett. (Ment. Hyg.) (N. Y.) - News letter (National Committee for Mental Hygiene) New York.
News Lett. Suffolk Co. M. Soc. - News letter of the Suffolk County Medical Society. (Port Jefferson).
News Rel. Indiana M. A. - News release; Indiana Medical Association.(Indianapolis).
Nice-med. - Nice-medical.
Nicolett Clin. Bull. - Nicolett Clinic Bulletin.
Nihon Byori Gakkwai Kwaishi -
Nipiologia, (Nap.) - Nipiologia. (Napoli).
Nippon fujinkagakkai zassi - Nippon fujinkagakkai zassi. (Tokyo).
Nippon no ikai sha - Nippon no ikai sha (See:Japan M. World).
Nord. Arch. f. Nat. u. Arzneywiss.,(Copenhagen)- Nordisches archiv für natur und arzneywissenschaft und chirurgie (Copenhagen).
Nord. hyg. tidskr. - Nordisk hygienisk tidskrift. (Lund).
Nord. med. - Nordisk medicin.
Nord. med. (Lille) - Nord medical. (Lille).
Nord. med. tidskr. - Nordisk medicinsk tidskrift. (Published in Nord. med).
Nordmandie méd. (Rouen)- Normandie médicale (Rouen).
Norsk mag. f. laegevidensk. - Norsk magasin for laegevidenskaben. (Oslo).
Norsk tskr. mil. med. - Norsk tidsskrift for militaermedicin. (Oslo).
North America Arch. M. & S. Sc. - North American archives of medical and surgical science.
North America J. Homoeop. - North American journal of homoeopathy. (New York).
North American M.-Chir. Rev. - North American Medical-Chirurgical Review.
North America Pract. - North American practitioner.
North. American Vet. - North American veterinarian. (Chicago,Ill.).
North Carolina M. J. - North Carolina Medical Journal.
North England Obst. & Gynaec. Soc. (Manchester) - North of England Obstetrical & Gynecological Society (Manchester).
North. J. M. - Northern journal of medicine.
Northumberland & Durham M. J. - Northumberland and Durham medical journal.
Northwest. Lancet - Northwestern lancet.
Northwest. M. J. - Northwestern medical journal.
Northwest. M. & S. J. - Northwestern medical and surgical journal.
Northwest Medicine, (Seattle) - Northwest Medicine. (Seattle,Wash.).
Northwestern. Univ. Bull.,Med. School. - Northwestern University Bulletin of the medical school.
Nosokomeion - Nosokomeion (Quarterly Hospital Review). (Stuttgart).
Nosokomos, (Amst.) - Nosokomos. (Amsterdam).
Note psichiat.,(Pesaro) - Note e riviste di psichiatria. (Pesaro).
Note riv. clin. -terap. -
Note e riv. di psichiat. - Note e riviste di psichiatria.
Notes in Med. & Surg. -
Nourrisson - Le nourrisson. (Paris)
Nouv. arch. ital. de biol. - Nouvelles archives italiennes de biologie.(Continued as Rev. arch. ital. de biol.).
Nouv. Arch. d'obst. et de gynéc. - Nouvelles archives d'obstétrique et de gynécologie.
Nouv. dict. de méd. et chir. prat. - Nouveau dictionnaire de médecine et de chirurgie pratiques.
Nouv. J. de méd. chir., pharm.- Nouveau journal de médecine, chirurgie,pharmacie, etc.(Paris).
Nouv. Montpellier méd. - Nouveau Montpellier médical.
Nov. khir.,(Moskva)- Novaia khirurgia. (Moskva).
Nova Scotia M. Bull. - The Nova Scotia Medical Bulletin.
Novy khir. arkhiv. - Novy khirurgicheskiy arkhiv. (Dnepropetrovsk).
Nowiny lek. - Nowiny lekarskie.
Nuntius radiol.,(Siena) - Nuntius radiologicus.(Siena).
Nuova riv. clin. psichiat. - Nuova rivista di clinica ed assistenza psichiatrica e di terapia applicata (at head of tp.: Villa Russo (Etc.) (Milano), (Napoli).
Nuova vet. - Nuova veterinaria.
Nuovo Ercolani - Nuovo Ercolani (Torino).
Nuovo Progr. internaz. med.-chir. - Nuovo progresso internazionale medico-chirurgico.
Nursing J. China - Nursing journal of China. (Nanking).
Nursing J. India - Nursing journal of India. (Kilpauk, (Madras).
Nursing Mirror, (Lond.) - Nursing mirror and midwives journal.(London).
Nursing Rec. - Nursing record.
Nutrition - Nutrition, annales cliniques, biologiques, thérapeutiques. (Paris).
Nutrition Abstr. & Rev. - Nutrition Abstracts and reviews.
Nutrition Rev. - Nutrition Reviews.
Objazat. pat. anat. izslied. stud. med. imp. Charkov Univ. -
Observ. med.,(Mex.)- Observador medico. (Mexico).
Obst. Gaz. (Cincinnati)- Obstetric gazette (Cincinnati).
Obst. y Ginec. latino-americanas - Obstetricia y Ginecologia latino-Americanas.
Obst. J. Great Britain & Ireland - Obstetrical journal of Great Britain and Ireland.
Obstétrique - Obstétrique.
Occas. Papers Univ. Michigan Mus. Zool. - Occasional papers of the Museum of Zoology, University of Michigan. (Ann Arbor).

Occidental M. Times - Occidental medical times.
Occup. Therapy - Occupational Therapy and Rehabilitation. (Baltimore).
Odes. Med. Zhur. - Odesskii meditsinski zhurnal (Odessa).
Odess. med. J. - See: Odes. Med. Zhur:
Odont. Bl. - Odontologische blätter.
Odont. Stomat.,(Moskva) - Odontologia i stomatologia (Moskva).
Odontologie - Odontologie (Paris).
Oeff. Gesundhdienst - Oeffentliche gesundheitsdienst. (Leipzig).
Oeff.Gesundhpfl. - Oeffentliche Gesundheitspflege. (Braunschweig).
Oesterr. ärztl. Vereinsztg. - Oesterreichische aerztliche vereinszeitung.
Oesterr. med. Wchnschr. - Oesterreichische medicinische wochenschrift.
Off. Army Reg. - Official army register. (Washington).
Off. Bull. Chicago M. Soc. - Offical bulletin of the Chicago Medical Society. (Chicago).
Off. Yearb. Union S. Africa - Official year book of the Union of South Africa. (Pretoria).
Öffentl. Gesundhdienst. - Der öffentliche Gesundheitsdienst.
Ogata Byo-in Iji kwai Ho - Ogata byo-in, Iji kwai ho.
Oglethorpe M. & S. J. - Oglethorpe Medical and Surgical Journal.
Ohio Health News - Ohio health news. (Columbus).
Ohio M. J. - Ohio Medical Journal (Columbus).
Ohio M. Recorder - Ohio Medical Recorder.
Ohio M. & S. J. - Ohio Medical and Surgical Journal.
Ohio Pub. Health J. - Ohio public health journal. (Columbus).
Ohio State M. J. - Ohio State Medical Journal. (Columbus).
Ohrenh. Gegenwart - Ohrenheilkunde der Gegenwart und ihre Grenzgebiete. (München).
Okajimas Folia anat. japon. - Okajimas Folia anatomica japonica. (Tokyo).
Okayama-Igakkai-Zasshi - Okayama-Igakkai-Zasshi. (Okayama).
Okhr. zdorov. diet. - Okhrana zdorovia dietei i podrostkov. (Moskva).
Oklahoma M. J. - Oklahoma Medical Journal.
Oklahoma M. News-J. - Oklahoma Medical News-Journal.
Old Dominion J. Med. & Surg. - Old Dominion journal of medicine and surgery.
Omaha Clin. - Omaha clinic.
Omnia med. - Omnia medica.
Omsky med. J. - Omsky meditsinsky jurnal.(Omsk).
Onderstepoort J. Vet. Sc. - Onderstepoort journal of veterinary sciences and animal industry. (Pretoria).
Ons. mbl. - Ons maanblad. (Amsterdam).
Ontario J. Neuropsychiat. - Ontario journal of neuropsychiatry. (Toronto,Can.).
Ophtalmos.- Ophtalmos.
Ophth. ibero am. - Ophthalmologia ibero americana.
Ophth. Liter.,(Denver)- Ophthalmic literature.(Denver).
Ophth. Rec. - Ophthalmic Record. (Chicago).
Ophth. Yearb. - Ophthalmic yearbook. (Denver).
Ophthalmologica - Ophthalmologica.
Opinion med.,(Zaragoza)- Opinion medica. (Zaragoza).
Optic. J.(N.Y.) - Optical journal and review of optometry. (New York).
Optometr. Week. - Optometric weekly (Chicago).
Oral Health, (Toronto) - Oral health. (Toronto,Can.).
Oral Hyg.,(Pittsb.) - Oral hygiene. (Pittsburgh).
Orient. J. Dis. Infants - Oriental Journal of Diseases of Infants. (Kyoto).
Ormoni - Ormoni
Ornithol. Monatsber. - Ornithologische Monatsberichte.
Orsz. Közegészs. Int. közl. - M. Kir. Országos Közegészségügyi Intezet összegyüjtött közleményei. (Budapest).
Ortop. i travmatol. - Ortopediya i travmatologiya. (Kharkoo).
Orvos. koz. (Budapest) - Orvostudomanyi kozlemenyek. (Budapest).
Orvosi hetil. - Orvosi hetilap. (Budapest).
Orvosi heti szemle - Orvosi heti szemle.
Orvosképzès - Orvosképzès (Budapest).
Osaka Igaku Kenk. Zasshi - Osaka igaku kenkyukwai zasshi. (Osaka).
Osaka Koigakusha Geppo - Osaka koigakusha geppo.
Osp. Mag. - Ospedale Maggiore (Milano).
Osp. maggiore Novara - Ospedale maggiore di Novara. (Novara).
Osp. psichiat. - Ospedale psichiatrico.
Oss. di patol. e clin. chir. -
Osservatore - Osservatore.
Osservatore Med. - Osservatore medico.
Osteopath. J. - Osteopathic journal of laboratory diagnosis. (Los Angeles, Calif.).
Osteopath. Mag. - Osteopathic magazine. (Chicago).
Osteopath. Phys. Ther. - Osteopathic physical therapeutist. (Upper Darby, Pa.).
Österr. med. Wchnschr. - Oesterreichische medicinische wochenschrift.
Österr.-ung. Vjschr. Zahnheilk. - Oesterreichisch-ungarische vierteljahrsschrift für zahnheilkunde.
Österr. Ztschr. f. prakt. Heilk. - Oesterreichische zeitschrift für praktische heilkunde.
Otchot o dieyateln. khirurg. klin.-
Otolar. slav.,(Praha) - Otolaryngologia slavica.(Praha).
Oto-rhino-laryng. - Oto-rhino-laryngologia.
Oto-rhino-laryng. internat. - Oto-rhino-larynologie internationale. (Lyons; Paris).
Oto-rino-laring. ital. - Oto-rino-laringologia italiana. (Bologna).
Outlook for Blind - Outlook for the blind(Camden, N.J.)
P.-verb. Congr. fr. chir. - Procès-verbaux, Congrès français de chirurgie.
P.-verb. Congr. internat. gastroentér. - Procès-verbaux. Congrès international de gastro-entérologie.
P.-verb. Soc. sc. phys. natur. Bordeaux - Procès-verbaux des séances de la Société des science physiques et naturelles de Bordeaux. (Bordeaux).
Pacific Coast J. Homeop. - Pacific coast journal of homeopathy. (Berkeley).
Pacific Coast. J. Nurs. - Pacific Coast journal of nursing. (San Francisco, Calif.).
Pacific Coast Med. - Pacific Coast medicine. (San Francisco).
Pacific Dent. Gaz. - Pacific dental gazette. (San Francisco).
Pacific M. J. - Pacific Medical Journal.
Pacific M. & S. J. - Pacific Medical and Surgical Journal. (San Francisco).
Pam. N. I. Studenskago Sborn. statei...Kazan-
Pam. Towarz. Lek. Warszaw. - Pamietnik: Towarzystwo lekarskie warszawskie (Warsaw).
Pamphl. M. Field Serv. School - Pamphlets of the medical Field Service School. (Carlisle Barracks, Pa.).
Panama Canal Rec. - Panama Canal record. (Balboa Heights, C.Z.).
Pantherapist,(Chic.) - Pantherapist. (Chicago).
Papers Dep. Marine Biol. Carnegie Inst. - Papers from the Department of Marine Biology of the Carnegie Institution of Washington, (Washington,D.C.).
Papers & Disc. Ann. Cong. M. Educ. - Papers and Discussions presented at the Annual Congress on Medical Education and Licensure.
Papers Internat. Vet. Congr. - Papers of the International Veterinary Congress (v.p.).
Papers James MacKenzie Inst., (S. Andrews) - Papers from the Weekly Staff Meetings (at head of tp.: The James MacKenzie Institute for Clinical Research) (S. Andrews).
Papers Mayo Found. - Papers of the Mayo Foundation. (Philadelphia).
Papers Michigan Acad. Sc. - Papers of the Michigan Academy of Science, Arts and Letters. (Ann Arbor).
Papers Tortugas Lab.,(Wash.)- Papers: Tortugas Laboratory. (Washington,D.C.).
Paradentium - Paradentium;Zeitschrift für die Grenzfragen der Medizin und Odontologie.(Berlin.)

Parasitology - Parasitology. (London).
Paris chir. - Paris chirurgical. (Paris).
Paris méd. - Paris médical. (Paris).
Passow-Schaefer Beitr. - Passow-Schaefer Beiträge zur Anatomie, Physiologie & c. (See: Beitr. Anat. Ohr.).
Passow-Schaefer Beitr. z. prakt. u. theoret. Hals-.Nasen- u. Ohrenh. - See; Pract. oto-rhino-laryng.
Pasteur - Pasteur. (Mexico).
Pat.-anat. kasuist.....Kharkov. Univ. - Patologo-anatomicheskaia kazuistika iz nauchnykh sovieshchanii vrachéi. Kharkov Universitet. (Moscow).
Pat. compar. d. tuberc. - Patologia comparata della tubercolosi.
Pathologica - Pathologica; rivista mensile. (Genova).
Pathologist- Pathologist.
Pau méd. - Pau médical.
Pedagog. Semin. & J. Genet. Psychol. - See: J. Genet. Psychol.
Pediat. Bull. - Pediatric bulletin. (Baltimore).
Pediatria - Pediatria. Archivio di pathologia e clinica pediatria. (Napoli).
Pediatria - La pediatria. Rivista mensile di medicina e di chirurgia dell'infanzia. (Napoli).
Pediatria - Pediatria. Rivista quindicinale d'igiene, medicina e chirurgia dell'infanzia. (Napoli).
Pediatria Américas - Pediatria de las Américas.
Pediatria españ. - Pediatria española. (Madrid).
Pediatria med. prat.,(Tor.) - Pediatria del medico pratico. (Torino).
Pediatria, (Moskva) - Pediatria. (Moskva).
Pediatria polska - Pediatria polska.
Pediatria prat.,(Modena)- Pediatria pratica. (Modena).
Pediatria prat., (São Paulo) - Pediatria pratica. (São Paulo).
Pediatrics - Pediatrics.
Peninsular. J. Med. (Ann Arbor) - Peninsular journal of medicine. (Ann Arbor).
Pennsylvania Health - Pennsylvania's health. (Harrisburg).
Pennsylvania Hosp. Rep. - Pennsylvania Hospital reports.
Pennsylvania M. J. - Pennsylvania Medical Journal. (Harrisburg).
Pensamiento peruano - Pensamiento peruano.
Pensiero med. - Pensiero medico. (Milano).
Peoria M. Month. - Peoria Medical Monthly.
Period. Acad. de med. de Mexico- Periodico; Academia de medicina de Mexico.
Periodical, (Oxf.) - Periodical. (Oxford).
Perm. med. J. - Permsky meditsinsky jurnal. (Perm).
Permanente Found. M. Bull. - Permanente Foundation Medical Bulletin.
Personnel J. - Personnel journal. (Baltimore).
Pest. med.-chir. Presse - Pester medicinisch-chirurgische presse. (Budapest).
Petermanns Mitt. - Petermanns Mitteilungen. (Gotha).
Petersburg. med. Wchnschr. - St. Petersburger medicinische Wochenschrift.
Petersburg. med. z. - Petersburger medicinische zeitschrift.
Pflüger's Arch. f. d. ges. Physiol. - See: Arch. f. d. ges. Physiol.
Pharm. Acta Helv. - Pharmaceutica Acta Helvetiae.
Pharm. Adv. - Pharmacal advance. (New York).
Pharm. Era - Pharmaceutical era. (New York).
Pharm. J., (Lond.) - Pharmaceutical journal. (London).
Pharm. i Pharmacol. - Pharmacija i Pharmacologija. (USSR).
Pharmazeutisch Weekblad. v. Nederl.- Pharmazeutisch weekblad voor Nederland. (Amsterdam).
Phi Chi Quart. (Menasha) - Phi Chi Quarterly. (Menasha).
Phi Lambda Kappa Quart. - Phi Lambda Kappa quarterly. (Philadelphia).
Phil. Tr. Roy. Soc. London - Philosophical Transactions of the Royal Society of London. (London).
Philadelphia M. J. - Philadelphia Medical Journal.
Philadelphia M. Museum - Philadelphia Medical Museum.
Philadelphia M. Times - Philadelphia Medical Times.
Philippine J. Sc. - Philippine Journal of Science. (Manila).
Philippine Statist. Rev. - Philippine statistical review. (Manila).
Phys. Clin. Med. (San Franc.) - Physico-clinical medicine and clinics of Dr. Albert Abrams. (San Francisco)
Phys. u. med. Abhandl. Akad. d. Wissensch. (Berlin) - Physikalische und medicinische abhandlungen; Akademie der Wissenschaften. (Berlin).
Phys. Ther. - Physical therapeutics. (Elmira, N.Y.).
Phys. Ther. Electrosurg. Digest. - Physical therapy and electrosurgery digest. (Milton, Wis,)
Phys. Training - Physical training. (New York).
Physiatrie (Berl.) - Physiatrie. Naturärztliche Rundschau. (Berlin).
Physician & Surg. - Physician and surgeon. (Detroit; Ann Arbor).
Physicians Times Mag. - Physicians times magazine. (Bridgeport, Conn.).
Physiol. Abstr.,(Lond.) - Physiological abstracts. (London).
Physiol. Rev. - Physiological Reviews. (Baltimore).
Physiol. Zoöl. - Physiological Zoölogy. (Chicago).
Physiotherapy Rev. - Physiotherapy Review. (Chicago).
Phytopathology - Phytopathology. (Lancaster, Pa.).
Piedmont Hosp. Bull. - Piedmont Hospital bulletin. (Baltimore).
Pittsburgh M. Bull. - Pittsburgh Medical Bulletin. (Pittsburgh).
Pittsburgh M. J. - Pittsburg medical journal.
Pittsburgh M. Rev. - Pittsburg medical review.
Plantation Health - Plantation Health.
Plastica Chirurgica - Plastica chirurgica.
Plexus, (Chicago) - Plexus. (Chicago).
Plumber & Steam Fitter - Plumber and steam fitter. (New York).
Poitou méd. - Poitou médical.
Policlin. Bruxelles - Policlinique. (Bruxelles).
Policlinico - Il Policlinico. (Rome).
Polish Sc. & Learn. - Polish Science and Learning Bureau of Animal Population.
Polit. anthrop. Monatschr. - Politisch-anthropologische Monatsschrift. (Leipzig).
Polska gaz. lek. - Polska gazeta lekarska. (Lwow).
Polski przegl. rajol. - Polski przeglad rajologiczny. (Warszawa).
Polskie arch. med. wewnetr. - Polskie archiwum medycyny wewnetrznej. (Warszawa).
Polyclin. Dairen - Polyclinica Dairen. (Dairen).
Polyclinic - Polyclinic (Philadelphia).

Polyclinique - Polyclinique
Pop. Health Dent. Suppl. - Popular health dental supplement. (Minneapolis).
Pop. Health Dent. Surv. - Popular health dental survey. (Minneapolis).
Pop. Health mag. - Popular health magazine and child welfare. (Minneapolis).
Porto Rico Health Rev. - Porto Rico health review. (San Juan).
Porto Rico J. Pub. Health - Porto Rico journal of public health and tropical medicine. (San Juan).
Porto Rico Rev. Pub. Health - Porto Rico review of public health and tropical Medicine. (San Juan).
Portsmouth Health Rep.- Portsmouth health report. (Portsmouth).
Porvenir (Mexico) - Porvenir, (Mexico).
Post- Grad. Bull. - The Post-Graduate Bulletin.
Post-Grad M. J. - The Post-Graduate Medical Journal. (London).
Post-Graduate, New York - Post-graduate New York.
Poultry Sc. - Poultry Science.
Pract. Gynec.-
Pract. Med. (Delhi) - Practical medicine. (Delhi, India).
Pract. Med. & Surg. - Practical medicine and surgery. (Austin).

Pract. oto-rhino-laryng. - Practica oto-rhino-laryngologica.
Practica d. med. -
Practice - Practice. (Richmond).
Practitioner - Practitioner. (London).
Prag. Arch. Tiermed. - Prager archiv für tiermedizin und vergleichende pathologie. (Praha).
Prag. med. Wchnschr. - Prager medizinische wochenschrift.
Prag. tierarztl. Arch. - Prager tierärztliches Archiv. (Prag).
Prag. Vjschr. prakt. Heilk. -
Prag. Ztschr. f. Heilk. - Prager Zeitschrift für heilkunde. (Prague).
Prakt. Arztfrau - Praktische Arztfrau. (Berlin).
Prakt. Desinfekt. - Der Praktische Desinfektor. (Dresden).
Prakt. Erg. Geburtsh. - Praktische Ergebnisse der Geburtshilfe und Gynäkologie. (München).
Prakt. lek. - Praktyka lekarska. (Supplement to Polska gaz. lek.).
Prakt. med. (Leningr.) - Prakticheskaia meditsina. (Leningrad).
Prakt. Vrach. - Prakticheskii vrach.
Prat. chir. - La pratica chirurgica e delle discipline affini. (Arezzo).
Prat. méd. franç. - La pratique médicale française. (Paris).
Prat. pediat. - La pratica pediatrica. (Milano).
Praticien - Praticien.
Praticien du Nord de l'Afrique - Le praticien du Nord de l'Afrique.
Pratique jour.- Pratique journalière. (Lille).
Praxis - Praxis (Schweizer Rundschau für Medizin) (Bern).
Prensa méd. argent. - La prensa médica argentina. (Buenos Aires).
Prensa méd.,(Habana) - Prensa médica. (La Habana).
Prensa méd. (La Paz) - Prensa médica. (La Paz).
Prensa méd. mex. - La prensa médica mexicana.
Prescriber - Prescriber. (Edinburgh).
Prescription (Danbury) - Prescription. (Danbury, Conn.).
Presse méd. - La presse médicale. (Paris).
Presse méd. belge - Presse médicale belge.
Presse therm. clim. - Presse thermale et climatique. (Paris).
Prev. Med. - Prevention Medicine.
Prim. Conf. argent. Asoc. ayuda y orient. invalido - See; Asoc. ayuda y orient. invalido. prim. Conf. argent.
Prim. reuniones extraord.,Asoc. méd. d. Hosp. Durand - See; Asoc. méd. d. Hosp. Durand, prim. reuniones extraord.
Priroda, (Leningr.) - Priroda. (Leningrad).
Prob. Nutr. - Problemi della nutrizione. (Roma).
Probl. aliment. - Il problema alimentare. (Roma).
Probl. Endocrin. -
Probl. tuberk. - Problemy tuberkuleza. (Moskva).
Proc. A. Am. M. Coll. - Proceedings of the Association of American Medical Colleges.
Proc. A. Life Insur. M. Dir. America - Abstract of the Proceedings of the Association of Life Insurance Medical Directors of America.
Proc. A. Life Insur. Pres. - Proceedings of the Association of Life Insurance Presidents. (New York).
Proc. A. Research Nerv. & Ment. Dis. - See: A. Research Nerv. & Ment. Dis., Proc.
Proc. Acad. Natur. Sc. Philadelphia - Proceedings of the Academy of Natural Sciences of Philadelphia.
Proc. Akad. wet. Amsterdam - Proceedings of the section of sciences. Koninklijke Akademie van wetenschappen te Amsterdam. (Amsterdam).
Proc. All-India Ophth. Soc. - Proceedings of the All-India Ophthalmological Society. (Madras).
Proc. Alumni A. M. School Univ. Oregon - Proceedings of the ... annual meeting of the Alumni Association; Medical School; University of Oregon. (Portland, Ore.).
Proc. Am. A. Coll. Pharm. - Proceedings of the American Association of Colleges of Pharmacy.
Proc. Am. A. Dent. Schools - Proceedings of the ....annual meeting of the American Association of Dental Schools.
Proc. Am. A. Instruc. Blind - (Proceedings) ..... Biennial convention (at head of tp.: American Association of Instructors of the Blind).
Proc. Am. A. Med.-Phys. Res. - Proceedings of the American Association for Medico-Physical Research.
Proc. Am. A. Ment. Deficiency - Proceedings and Addresses of the American Association on Mental Deficiency. (Formerly American Association for the Study of the Feebleminded) Comprising the Journal of Psycho-Asthenics.
Proc. Am. A. Study of Feebleminded - See: Proc. Am. A. Ment. Deficiency.
Proc. Am. Acad. Art. Sc. - Proceedings of the American Academy of Arts and Sciences. (Boston).
Proc. Am. Conf. Pharm. - Proceedings of the American Conference of Pharmaceutical Faculties.
Proc. Am. Diabetes A. - Proceedings of the American Diabetes Association.
Proc. Am. Drug. Manuf. A. - Proceedings of the annual meeting of the American Drug. Manufacturers Association.
Proc. Am. Fed. Hard of Hearing - Proceedings of the .....annual meeting of the American Federation of Organizations for the Hard of Hearing. (Washington).
Proc. Am. Pharm. Manuf. A. - Proceedings of the American Pharmaceutical Manufacturers' Association.
Proc. Am. Philos. Soc. - Proceedings of the American Philosophical Society (etc.) (Philadelphia).
Proc. Am. Soc. Animal Product - Proceedings of the American Society of Annual Production.
Proc. Am. Soc. Biol. Chem. - Proceedings of the American Society of Biological Chemistry.
Proc. Am. Student Health A. - Proceedings of the American Student Health Association.
Proc. Ann. Cong. M. Educ. - Proceedings of the Annual Congress on Medical Education, Medical Licensure and Hospitals.
Proc. Antimalar. Advis. Com. - Proceeding of the Antimalarial Advisory Commission.
Proc. Arkansas M. Soc. - Proceedings of the Arkansas Medical Society.
Proc. Boston Soc. Nat. Hist. - Proceedings of the Boston Society of Natural History.
Proc. California Acad. Med. - Proceedings of the California Academy of Medicine. (San Francisco).
Proc. Central Soc. Clin. Res. - Proceedings of the Central Society for Clinical Research.
Proc. Charaka Club. - The Proceedings of the Charaka Club.
Proc. Conf. Health Author . North America - Proceedings of the ... annual meeting of the Conference of State and Provincial Health Authorities of North America.
Proc. Congr. M. Educ. - Proceedings of the Congress on Medical Education.
Proc. Connecticut M. Soc. - Proceedings of the Connecticut State medical society.
Proc. Dublin Obst. Soc. - Proceedings of the Dublin obstetrical society.
Proc. Helminth. Soc. Washington - Proceedings of the Helminthological Society of Washington (Washington).
Proc. Homeop. M. Soc., Ohio - Proceedings of the Homeopathic medical society of the state of Ohio.
Proc. Imp. Acad. (Tokyo) - Proceedings of the imperial academy. (Tokyo).
Proc. Indiana M. Soc. -
Proc. Inst. Med. Chicago - Proceedings of the Institute of Medicine of Chicago. (Chicago).
Proc. internat. Assemb. inter-State Post Grad M. A. North America - See: Proc. interst. Postgrad M.A. North America.
Proc. Internat. Conf. Health Trop. America - Proceedings of the International Conference on Health Problems in Tropical America.

Proc. Internat. Conf. Women Physicians - Proceedings of the International Conference of Women Physicians.
Proc. Internat. Congr. Alcohol - Proceedings of the International Congress on Alcoholism.
Proc. Internat. Congr. Genet. - Proceedings of the ....International Congress of Genetics.
Proc. Internat. Congr. Ment. Hyg. - Proceedings of the International Congress of Mental Hygiene.
Proc. Internat. Congr. Plant. Sc. - Proceedings of the International Congress of Plant Sciences.
Proc. Internat. Congr. Sex. Res. - Proceedings of the International congress on Sex Research.
Proc. Interst. Postgrad. M. A. North America - Proceedings of the International Assembly of the Inter-State Post-Graduate Medical Association of North America. (Freeport, Ill.).
Proc. Iowa Conf. Child Health - Proceedings of the Iowa White House Conference of Child Health. (Des Moines).
Proc. Leeds Phil. Lit. Soc. - Proceedings of the Leeds philosophical and literary society.
Proc. Life Ext. Exam. - Proceedings of the Life Extension Examiners.
Proc. Liverpool Biol. Soc. - Proceedings and transactions of the Liverpool Biological Society. (Liverpool).
Proc. M. A. Canal Zone - Proceedings of the Medical Association of the Isthmian Canal Zone. (Mount Hope, C. Z.).
Proc. M. Soc. - Proceedings of the Medical Society.
Proc. M. Soc. County Kings - Proceedings of the society of the county of Kings.
Proc. Maryland-Delaware Water Sewer A. - Proceedings of the Maryland-Delaware Water and Sewer Association
Proc. Med.-Chir. Soc. Montreal - Proceedings of the medico-chirurgical society of Montreal.
Proc. Missouri Pharm. A. - Proceedings. Missouri Pharmaceutical Association.
Proc. Nat. Acad. Sc. - Proceedings of the National Academy of Sciences. (Washington, D.C.).
Proc. Nat. Acad. Sc. U. S. - Proceedings of the National Academy of Sciences of the United States of America. (Easton, Pa.).
Proc. Nat. Conf. Social Work - Proceedings of the National Conference of Social Workers.
Proc. Nat. Congr. Tuberc.,(Manila) - Proceedings of the....National Congress on Tuberculosis (at head of tp.: Philippine Islands Antituberculosis Society) (Manila).
Proc. Nat. Safety Counc. - Proceedings of the National Safety Council. (Chicago).
Proc. Nebraska M. Soc. - Proceedings of the Nebraska Medical Society.
Proc. New Jersey Mosquito Exterm. A. - Proceedings New Jersey Mosquito Extermination Association.
Proc. New York Indust. Safety Congr. - Proceedings of the New York State Industrial Safety Congress.
Proc. New York Path. Soc. - Proceedings of the New York Pathological Society.
Proc. Nova Scot. Inst. Sc. - Proceedings of the Nova Scotian Institute of Science. (Halifax, N.S.).
Proc. Oklahoma Acad. Sc. - Proceedings of the Oklahoma Academy of Science.
Proc. Oregon M. Soc. - Proceedings of the Oregon Medical Society.
Proc. Panpacific Sc. Congr. - Proceedings of the Pan-Pacific Science Congress.
Proc. Path. Soc. - Proceedings of the Pathological Society.
Proc. Path. Soc. Dublin - Proceedings of the Pathological Society of Dublin.
Proc. Path. Soc. Philadelphia - Proceedings of the Pathological Society of Philadelphia. (Philadelphia).
Proc. Philadelphia Co. M. Soc. - Proceedings of the Philadelphia County Medical Society.
Proc. Physiol. Soc. - Proceedings of the Physiological Society of Philadelphia.
Proc. Round Table, Nutrition & Pub. Health - Proceedings of the Round Table on Nutrition and Public Health.
Proc. Roy. Acad. Amsterdam - Proceedings of the Royal Academy of Amsterdam.
Proc. Roy. Canad. Inst. - Proceedings of the Royal Canadian Institute.
Proc. Roy. Inst. Great Britain - Proceedings of the Royal Institution of Great Britain. (London).
Proc. Roy. Irish Acad. - Proceedings of the Royal Irish Academy. (Dublin).
Proc. Roy. M. & Chir. Soc. - Proceedings of the Royal Medical and Chirurgical Society.
Proc. Roy. Philos. Soc. Glasgow - Proceedings of the Royal Philosophical Society of Glasgow. (Glasgow).
Proc. Roy. Soc. Canada - Proceedings and transactions of the Royal Society of Canada.
Proc. Roy. Soc. Edinburgh - Proceedings of the Royal Society of Edinburgh. (Edinburgh).
Proc. Roy. Soc. Lond. - Proceedings of the Royal Society of London.
Proc. Roy. Soc., London, s. B. - Proceedings of the Royal Society, series B. (Biological Sciences).
Proc. Roy. Soc. Med. - Proceedings of the Royal Society of Medicine. (London).
Proc. Roy. Soc. South Africa - Proceedings of the Royal Society of South Africa.
Proc. Seventh World's Poultry Congr. & Exposition - Proceedings of the Seventh World's Poultry Congress and Exposition.
Proc. Soc. Exper. Biol. & Med. - Proceedings of the Society for Experimental Biology and Medicine. (Ultica, N.Y.).
Proc. Soc. Med.-Sect. Obstetr. a. Gynaec, - Proceedings of the Royal Society of Medicine-Section obstetric and gynecology.
Proc. Soc. Psychic. Res.,(Lond.) - Proceedings of the Society for Psychical Research. (London).
Proc. South. Sociol. Congr. -(Proceedings)Southern Sociological Congress (U.S.).
Proc. Staff Meet. Clin. (Honolulu) - Proceedings of the Staff Meeting of the Clinic. (Honolulu).
Proc. Staff Meet., Mayo Clin. - Proceedings of the Staff Meetings of the Mayo Clinic. (Rochester, Minnesota).
Proc. U. S. Nat. Immigr. Conf. - Proceedings of the (U. S.) National Immigration Conference.
Proc. U. S. Nat. League Nurs. Educ. - Proceedings of the ... Annual convention of the (U. S.) National League of Nursing Education.
Proc. U. S. Nat. Mus. - Proceedings of the United States National Museum. (Washington).
Proc. U. S. Nav. Inst. - Proceedings; United States Naval Institute. (Annapolis, Md.).
Proc. Zool. Soc. London - Proceedings of the general meetings for scientific business of the zoological Society of London. (London).
Profess. Papers U. S. Geol. Surv. - Professional papers of the (U.S.) Geological Survey. (Washingtin).
Profess. pat. gig. - Professionalnaia patologia i gigiena. (Moskva).
Profil. med.,(Kharkov) - Profilakticneskaia meditsina. (Kharkov).
Profilassi - Profelassi. (Milano).
Progr. med. Philadelphia - Progressive medicine. (Philadelphia).
Progrès méd. belge - Progrès médical belge.
Progrès méd. - Le progrès médical. (Paris).
Progreso ginec. - Progreso ginecológico y pediatria. (Valencia).
Progreso méd. - Progreso médico. (Habana).
Progresos clin. (Madr.) - Progresos de la clinica. (Madrid).
Progresso med. - Progresso medico. (Napoli).
Prophyl. antivénér. - La prophylaxie antivénérienne. (Paris).

Protok. Obsh. russk. vrach. v. St. Petersberg - Protokoly; Obshchestvo russkikh vrachei v S. - Petersburgfe.
Protok. Soobsh. i S. - Peterb. med. Obsh. - Protokolyi soobshcheniia; Sankt-Peterburgskoe meditsinskoe obshchestvo.
Protok. i trudy Obsh. Arkhangel. vrach - Protokoly i trudy; Obshchestvo Arkhangel skikh vrachei (Archangel).
Protok. i trudy russk. chir. Obsh. Pirogova St. Petersb. - Protokoly zasiedanii i trudy; Russkoe khirurgicheskoe obshchestvo imeni N. I. Pirogova.
Protok. zassie d. akush. - ginek. Obsh. v. Kiev - Protokoly zasiedanii; Akushersko-ginekologicheskoe obshchestvo, universitet Kiev.
Protok. zasie d. Kavkazs. med. Obsh. - Protokoly zasiedanii; Kavkazskoe medecinskoe obshchestvo.
Protok. Zasied., Kievsk. Sifilidol. i Dermat. Obsh., Univ. Izv. (Kieve) - Protokoly zasiedanii; Kievskoe sifilidologicheskoe i dermatologicheskoe obshchestvo; Universitetskiia izviestiia (Kieve).
Protoplasma Lpz. - Protoplasma. Internationale Zeitschrift für physikalische Chemie des Protoplasten. (Leipzig).
Prov. M. J. (Halifax) - Provincial medical journal. (Halifax).
Prov. M. J. (Leicester) - Provincial medical journal (Leicester).
Prov. M. & S. J. - Provincial medical and surgical journal.
Prov. San. - Ber. k. Med. -Coll. zu Königsb. - Provinzial-sanitäts-berichte; K. Medicinalcollegium zu Koenigsberg.
Province méd. (Lyon) - Province médicale. Lyon.
Province méd. (Paris) - Province médicale (Paris).
Przegl. chir. i ginek. - Przeglad chirurgiczyn i ginekologiczny.
Przegl. dermat. Warsz. - Przeglad dermatologi (Warszawa).
Przegl. lek. (Cracow) - Przeglad lekarski (Cracow).
Psiquiat. y criminol. - Psiquiatria y criminologia. (continued as Rev. de psiquiat. y criminol.)
Psyche & Eros. (N.Y.) - Psyche and eros. (New York)
Psyche J. Entom. - Psyche; a journal of entomology. (Boston).
Psyche, (Lond.) - Psyche. (London).
Psychiat. en neurol. bl. - Psychiatrische en neurologische bladen uitgegeven door de nederlandsche vereeniging voor psychiatrie en neurologie.
Psychiat. et Neurol. jap. - Psychiatria et neurologia japonica. (Tokio).
Psychiat.-neurol. Wchnschr. - Psychiatrisch-neurologische Wochenschrift. (Halle a. S.).
Psychiat. Quart. - Psychiatric (The) Quarterly. (Utica, N.Y.).
Psychiatry - Psychiatry.
Psychic Res. Quart. (Lond.) - Psychic research quarterly. (London).
Psychoanalyt. Quart. - Psychoanalytic Quarterly.
Psychoanal. Rev. - Psychoanalytic Review. (Albany).
Psychobiology - Psychobiology. (Baltimore).
Psychol. Abstr. - Psychological abstracts. (Princeton, N.J.).
Psychol. Arb. - Psychologische Arbeiten. (Berlin).
Psychol. Bull. - Psychological bulletin. (Princeton,N.J.).
Psychol. Clin. - Psychological clinic. (Lancaster,Pa.).
Psychol. Forsch. - Psychologische Forschung. Zeitschrift für Psychologie und ihre Grenzwissenschaften. (Berlin).
Psychol. Index - Psychological index. (Princeton,N.J.).
Psychol. & Med. - Psychology and Medicine.
Psychol. & Med. (Stuttg.) - Psychologie und Medizin. (Stuttgart).
Psychol. Monogr.(Princeton) - Psychological Monographs. (Princeton, N.J.).
Psychol. Rev. - Psychological Review. (Lancaster,Pa).
Psychosom. Med. Monographic Series - Psychosomatic medicine. Monographic Series.
Psychossomatic Med. - Psychossomatic Medicine.
Psychother. Prax., Wien - Psychotherapeutische Praxis. Vierteljahresschrift für praktische ärztliche Psychotherapie. (Wien).
Pub. Am. Statist. A. - Publication of the American Statistical Association
Pub. Health, (Lond.) - Public Health (London).
Pub. Health Bull. Bost. - Public Health Bulletin. (Boston).
Pub. Health. Bull., (Wash.) - Public health bulletin (Washington).
Pub. Health J., Toronto - Public health journal. (Toronto, Can.).
Pub. Health Michigan - Public health, Michigan. (Lansing, Mich.).
Pub. Health News, (Trenton) - Public health news. (Trenton, N.J.).
Pub. Health Nurs. - Public health Nursing. (Utica,N.Y.).
Pub. Health Rep. Wash- - Public Health Reports. (Washington).
Pub. Health. Rep. Supp. - Public health Reports, Supplements.
Pub. Health Rev. (Ann Arb.) - Public Health reviews (Ann Arbor).
Pubb. Lab. chim. biol. Univ. Padova - Pubblicazioni del Laboratorio di chimica bioligica della R. Universita di Padova. (Padova).
Pubb. Staz. zool. Napoli - Pubblicazioni della Stazione zoologica di Napoli. (Roma).
Publ. biol. Ec. vét., Brno - Publications biologiques de l'Ecole des hautes études vétérinaries (Brno).
Publ. centro de Invest. tisiol. - Publicaciones del centro de investigaciones tisiológicas.
Publ. Clark Univ. Libr. - Publications of the Clark University Library. (Worchester, Mass.).
Publ. Colorado Coll. - Publications of the Colorado College. (Colorado Springs).
Publ. Com. Costs M. Care. - Publications of the Committee on the Costs of Medical Care. (New York).
Publ. Cornell Univ. Anat. - Publications of Cornell University Medical College: Studies from the Department of Anatomy. (New York).
Publ. Dep. Pediat. Univ. Toronto - Publications. Department of Pediatrics. University of Toronto (Toronto, Can.).
Publ. Dep. Surg. Univ. Pennsylvania - Publications of the Department of Surgery: University of Pennsylvania. (Philadelphia).
Publ. Egypt. Univ. Fac. Med. - Publications of the Egyptian University, Faculty of Medicine, (Cairo).
Publ. Field Mus. Natur. Hist. - Publications (At head of tp.: Field Museum of Natural History (Anthropoligical) series: Botanical series Report series: Anthropology, Memoires) (Chicago).
Publ. Inst. Neurol. Northwestern Univ. - Publications: Institute of Neurology: Northwestern University. (Chicago).
Publ. Macausland Orthop. Clin. - Publications of the Macausland Orthopedic Clinic. (New York).
Publ. Massachusetts Gen. Hosp. - Publications of the Massachusetts general hospital.
Publ. McGill Univ. - Publications of the McGill University. (Montreal,Can.).
Publ. med. São Paulo - Publicações medicas. (São Paulo).
Publ. Nat. Quarant. Serv. (Shanghai) - Publications of the National Quarantine Service. (Shanghai).
Publ. Smithson. Inst. - Publication: Smithsonian Institution, (Washington).
Publ. South Afr. Inst. M. Res. - Publications of The South African Institute for Medical Research (Johannesburg).
Publ. Univ. Pittsburgh School Med. - Publications from the University of Pittsburgh: School of Medicine.
Publ. Wellcome Chem. Res. Lab. - Publications. Wellcome Chemical Research Laboratories (London).

Puerto Rico J. Pub. Health & Trop. Med. - Puerto Rico Journal of Public Health and Tropical Medicine.
Quaderni di psichiat. - Quaderni di psichiatria. (Genova).
Quaderni radiol. - Quaderni di radiologia.
Quart. Bull. Bd. Health New Hampshire - Quarterly bulletin of the State Board of Health of New Hampshire. (Concord).
Quart. Bull. California Bd. Health - Quarterly bulletin California State Board of Health. (Sacramento).
Quart. Bull. Health Organ., League of Nations - Quarterly bulletin of the Health organization, League of Nations. (Genève) (Continued as Bull. Health Organ.)
Quart. Bull. Indiana Univ. M. Center. - Quarterly Bulletin Indiana University Medical Center.
Quart. Bull. Kansas City Clin. Soc. - Quarterly bulletin of the Kansas City Clinical Society. (Kansas, City).
Quart. Bull. Louisiana Bd. Health. - Quarterly bulletin, Louisiana State Board of Health (New Orleans, La.).
Quart. Bull. M. Women Nat. A. - Quarterly bulletin of the Medical Women's National Association. (Oak Park. Ill.).
Quart. Bull. Michigan Agr. Coll. - Quarterly bulletin. Michigan Agricultural College. (East Lansing).
Quart. Bull. Milbank Mem. Fund. - Quarterly bulletin. Milbank Memoiral Fund (New York).
Quart. Bull. New York Dep. Health - Quarterly bulletin: New York Department of Health (New York).
Quart. Bull. New York Hist. Soc. - Quarterly bulletin of the New York Histological Society.
Quart. Bull. North Western Univ. M. School. - Quarterly Bulletin, North Western University Medical School.
Quart. Bull. Rockefeller Found. - Quarterly bulletin (at head of tp.) The Rockefeller Foundation. (New York).
Quart. Bull. Sea View Hosp. - The Quarterly Bulletin of Sea View Hospital. (N.Y.).
Quart. Bull. St. Louis Coll. Pharm. - Quarterly bulletin of The St. Louis College of Pharmacy. (S. Louis).
Quart. Bull. Univ. Hawaii - Quarterly bulletin. University of Hawaii. (Honolulu).
Quart. J. Exper. Physiol. - Quarterly Journal of Experimental Physiology and Cognate Medical Sciences.
Quart. J. M. Sc. - Quarterly Journal of Medical Science.
Quart. J. Med. (Oxf.) - Quarterly Journal of Medicine. (Oxford).
Quart. J. Micr. Sc. - Quarterly Journal of Microscopical Science (London).
Quart. J. Pharm. & Pharmaecol. - Quarterly Journal of Pharmacy and Pharmacology. (London).
Quart. J. Speech - The Quarterly Journal of Speech.
Quart. J. Stud. Alchol . - Quarterly Journal of Studies on Alcohol.
Quart. Phi Beta Pi M. Fratern. - Quarterly of the Phi Beta Pi Medical Fraternity.
Quart. Pub. Am. Statist. A. - Quarterly publications of the American Statistical Association.
Quart. Rev. Biol. - Quarterly Review of Biology. (Baltimore).
Queen Nurs. Mag. (Lond.) - Queen's nurses' magazine. (London).
Quelle - Quelle. Monatschrift für Körper und Geistespflege. (Hamburg).
Quellen Gesch. Naturwiss. Med. - Quellen und Studien zur Geschichte der Naturwissenschaften und der Medizin. (Berlin).
Quest. méd. d'actual. (Par.) - Questions médicales d'actualité. (Paris).

Raboti hosp. khirurg. klin. Dyakonova-
Raboty fiziol. lab. Med. Fak. Univ. Warsaw- Raboty, fiziologicheskaia laboratoria, meditsinski fakultet, universitet Warsaw.
Rac. di scritti ostet.-ginec.-
Raccoglitore med.- Raccoglitore medico (Forli, Fano).
Raccoglitore med. di Fano- Raccoglitore medico di Fano.
Rad. Med.- Radyanska meditsina.
Radiobiologia (Venez.)- Radiobiologia (Venezia).
Radiochirurg. (Nap.) - Radiochirurgia (Napoli).
Radiog. & Clin. Photog.- Radiography and Clinical Photography (Rochester, N.Y.).
Radiography (Lond.)- Radiography (London).
Radiol. med.- La radiologia medica (Milano).
Radiography- Radiography.
Radiol. Rdsch.- Radiologische Rundschau; Röntgen, Radium, Licht (Berlin).
Radiol. Rev. & Mississippi Valley M. J.- Radiological review and Mississippi Valley medical journal (Quincy, Ill.) (Continued as Mississippi Valley M. J.)
Radiología- Radiología.
Radiology- Radiology.
Radiophys. et radiothérapie- Radiophysiologie et radiothérapie.
Radium (Pittsburgh)- Radium (Pittsburgh).
Radium Rep. Mem. Hosp. (N.Y.)- Radium Report of the Memorial Hospital (New York).
Radium Ther. (Denver)- Radium therapist (Denver).
Raggi ultraviol.- Raggi ultravioletti (Milano).
Railw. Surg. J.- Railway surgical journal (Chicago).
Rapp. Conf. internat. rhumat. chron.- Rapports. Conférence scientifique internationale du rhumatisme chronique, progressif, généralisé.
Rapp. Congr. fr. méd.- Rapports du congrès français de médecine.
Rapp. Congr. internat. asthme- Rapport du Congrès international de l'asthme.
Rapp. Congr. Soc. internat. chir.- Rapports du Congrès de la Société internationale de chirurgie.
Rassegna clin.-sc.- Rassegna clinico-scientifica (Milano).
Rassegna clin. terap.- Rassegna di clinica terapia.
Rassegna Clin., Therap. Sc. affini- Rassegna di clinica, terapia e scienze affini (Roma).
Rassegna di fisiopat. clin. e terap.- Rassegna di fisiopatologia clinica e terapeutica.
Rassegna internaz. di clin. e terap.- Rassegna internazionale di clinica e terapia.(Napoli).
Rassegna internaz. oto-rino-lar.- Rassegna internazionale di oto-rino-laringologia (Roma).
Rassegna Ist. med. prev. (Tor.)- Rassegna dell'Istituto di medicina prevnetiva (Torino).
Rassegna ital. oto-rino-lar.- Rassegna italiana di oto-rino-laringologia (Napoli).
Rassegna ital. d'ottal.- Rassegna italiana d'ottalmologia (Torino).
Rassegna med.- Rassegna medica.
Rassegna di med. indust.- Rassegna di medicina industriale.
Rassegna med. lavoro indust.- Rassegna di medicina applicata al lavoro industriale (Torino).
Rassegna med. sarda.- Rassegna medica sarda (Cagliari).
Rassegna mens. (Tor.)- Rassegna mensile (Torino).
Rassegna di neurol. veget.- Rassegna di neurologia vegetativa.
Rassegna d'ostet. e ginec.- La rassegna d'ostetricia e ginecologia (Napoli).
Rassegna d. previd. sociale.- Rassegna della previdenza sociale (Roma).
Rassegna sc. biol.- Rassegna delle scienze biologiche (Firenze).
Rassegna di sc. med.- Rassegna di scienze mediche.
Rassegna Soc. ital. igiene- Rassegna della Reale Societa italiana d'igiene (Milano).
Rassegna di studi psichiat.- Rassegna di studi psichiatrici (Siena).
Rassegna di studi sess.- Rassegna di studi sessuali demografia ed wugenica. (Roma).
Rassegna di terap. e pat. clin.- Rassegna di terapia e patologia clinica (Napoli). (Continued as Rassegna di fisiopat. clin. e terap.).

Rec. Bost. Soc. M. Improve- Records of Boston society for medical improvement.
Rec. Canterbury Mus.- Records of the Canterbury Museum (Christ Church, N.Z.).
Rec. Malaria Surv. India- Records of the Malaria Survey of India (Calcutta).
Rec. de méd. vét.- Recueil de médecine vétérinaire (Paris).
Rec. de méd. école vét. d'Alfort- Recueil de médecine de l'école vétérinaire d'Alfort.
Rec. méd. vét. exot.- Recueil de médecine vétérinaire exotique (Paris).
Rec. de mem. de méd...mil.- Recueil de memoires de médecine, de chirurgie et de pharmacie militaires.
Rec. Oceanogr. Works japan- Records of Oceanographic Works in Japan (Tokyo).
Rec. spec. accid. trav.- Recueil spécial des accidents du travail (Paris).
Rec. Trav. chim. Pays-Bas- Recueil des travaux chimiques des Pays-Bas et de la Belgique.
Rec. trav. sc. méd. Congo belge- Recueil de travaux de sciences médicales au Congo belge.
Rec. d. trav. Soc. méd. dept. d'Indre-et-Loire- Recueil des travaux de la société médicale du département d'Indre-et-Loire.
Rec. d. trav. Soc. méd. d'obst. de Paris- Recueil des travaux de la société médicale d'observation de Paris.
Recherches clin. et thérap. sur l'épileps.- Recherches cliniques et thérapeutiques sur l'épilepsie, l'hystérie et l'idiotie.
Rechiedei, Mailand-
Red Cross Bull.- Red Cross bulletin (Washington).
Red Cross Courier- Red Cross courier (Washington).
Red.Cross Mag.- Red Cross magazine (Washington).
Reddingwezen- Reddingwezen (Amsterdam).
Ref. J. klin. med. (Moskva)- Referati jurnala klinicheskaia meditsina (Moskva).
Reforma med. (Lima)- Reforma medica (Lima).
Reg. Kentucky Hist. Soc.- Register of the Kentucky Historical Society (Frankfort, Ky.).
Regeneración méd.- Regeneración médica.
Reichsgesundhbl.- Reichs-Gesundheitsblatt (Berlin).
Reichs-Med.-Anz.- Reichs-medicinal-anzeiger.
Rel. Com. Nurs. Schools- Releases of Committee on the Grading of Nursing Schools (New York).
Rend. Accad. sc. Ist. Bologna - Rendiconto delle sessioni della R. Accademia delle scienze dell' Istituto di Bologna (Bologna).
Rend. d. Ass. med.-chir. di Parma- Rendiconti, Associazione medico-chirurgica di Parma.
Rend. Ist. di san. pub. Roma- Istituto di sanita pubblica rendiconti. (Roma).
Rep. Austral. Cancer Conf.- Report of Australian Cancer Conference.
Rep. Bd.Health (Cambr.)- Report of the Board of Health (Cambridge).
Rep. Bd.Health Kentucky- Reports of the State Board of Health of Kentucky (Bowling Green).
Rep. Bd. Health Michigan- Reports of the State Board of Health of Michigan (Lansing).
Rep. Bd.Health New Jersey- Reports of the Board of Health of the State of New Jersey (Trenton).
Rep. Bd.Health Ohio- Reports of the State Board of Health of Ohio (Columbus).
Rep. Bd.Health Rhode Island- Reports of the State Board of Health of Rhode Island (Providence).
Rep. Brit. A. Advance. Sc.- Report of the meetings of the British Association for the Advancement of Science (London).
Rep. Chief U. S. Weather Bur.- Report of the Chief of the Weather Bureau. U.S. Department of Agriculture (Washington).
Rep. Columbia Inst. Deaf (Washington)- Report of the Columbia Institute for the Deaf (Washington, D.C.).
Rep. Connecticut Bd.Health- Report of the Connecticut State Board of Health (New Haven).
Rep. Dep. Health Iowa- Reports of the State Department of Health of Iowa (Des Moines).
Rep. Dep. Health Maine- Reports of the State Department of Health of Maine. (Augusta, Me.).
Rep. Dep. Health Maryland- Reports of the State Department of Health of Maryland (Annapolis, Md.).
Rep. Dep. Health Montreal- Report of the Department of Health of Montreal (Montreal).
Rep. Dep. Pub. Health Illinois- Reports of the Department of Public Health of Illinois (Springfield).
Rep. Dir. Pub. Health (N.S. Wales)- Report of the Director-General of Public Health (N. S. Wales).
Rep. Dir. Vet. Educ. (Pretoria)- Reports of the Director of Veterinary Education and Research (Pretoria).
Rep. Gav. Bur. Microbiol.-
Rep. Hackney M. Off. Health- Report of the Hackney Medical Officer of Health (Hackney, Engl.).
Rep. Health of Army (Lond.)- Report on the health of the Army (London).
Rep. Health Manchester- Report on the health of the City of Manchester (Manchester, Engl.).
Rep. Helmuth House New York-
Rep. Henry Phipps Inst. Tuberc.- Report of the Henry Phipps Institute for the Study of Tuberculosis (Philadelphia).
Rep. Inst. Sc. Labour (Kurasiki)- Report of the Institute of Science and Labour (Kurasiki, Japan).
Rep. Internat. Conf. Goiter- Report of the International Conference on Goiter in Berne.
Rep. Internat. Congr. Mil. Med. Pharm.- Report on International Congress of Military Medicine and Pharmacy.
Rep. Internat. Neo-malthus. Conf.- Report of the International Neo-Malthusian and Birth Control Conference.
Rep. Johns Hopkins Hosp.- Report of the Johns Hopkins Hospital (Baltimore).
Rep. Kansas Bd.Health -Reports of Kansas State Board of Health (Topeka).
Rep. Lahey Clin.- Report of the Lahey Clinic (Boston).
Rep. Lancashire Tuberc. Off.- Report of the Lancashire Central. Tuberculosis Officer of the Lancashire County Council (Liverpool).
Rep. M. Miss. Soc. in China, Hongkong-
Rep. M. Off. Health Glasgow- Report of the Medical Officer of Health, City of Glasgow (Glasgow).
Rep. M. Res. Counc. (Lond.)- Report of the Medical Research Council (London).
Rep. Massachusetts Gen. Hosp.- Reports (Annual) of the Massachusetts General Hospital (Boston).
Rep. Matern. Hosp. Manchester- Report of the Maternity Hospital, Manchester (Manchester, Engl.).
Rep. Michigan Acad. Sc.- Report of the Michigan Academy of Science (Lansing).
Rep. Murdock Free Surg. Hosp. f. Women(Boston)-
Rep. Nat. Acad. Sc. U.S.- Reports of the National Academy of Sciences of the United States of America (Washington).
Rep. Nat. Quarant. Serv.- Reports of the National Quarantine Service Republic of China. (Ceased publication).
Rep. Nat. Res. Counc. Japan- Report; National Research Council of Japan (Tokyo).
Rep. New York State Dep. Health- Report of the State Department of Health of New York. (Albany).
Rep. New York StateWoman's Hosp.-Reports of the New York State Woman's Hospital (New York).
Rep. North Carolina Bd.Health- Reports of the North Carolina Board of Health (Raleigh).
Rep. North Manchur. Plague Prev. Serv.- Report of the North Manchurian Plague Prevention Service (Tientsin).
Rep. Peter Bent Brigham Hosp.- Reports of the Peter Bent Brigham Hospital (Cambridge, Mass).
Rep. Philadelphia Gen. Hosp.- Reports of the Philadelphia General Hospital (Philadelphia).
Rep. Proc. Aluminae A. Woman's M. Coll. Penn.-
Rep. Proc. Am. Soc. San. Engin.- Report of proceedings of American Society of Sanitary Engineering.
Rep. proc. M. Soc. New castle upon Tyne- Report of the Proceedings of the Medical Society of New Castle on Tyne.

Rep. Proc. Northumb. & Durham M. Soc.- Report of the Proceedings of the Northumberland and Durham Medical Society.
Rep. Pub. Health (Lond.)- Reports on public health and medical subjects (London).
Rep. Rhode Island Health Com.- Reports (Biennial) of the Rhode Island Health Commission (Providence).
Rep. S. Andrews Inst. Clin. Res. (Lond.)- Report of the S. Andrews Institute for clinical research. (London).
Rep. S. Barth. Hosp. (Lond.)- Reports of S. Bartholomew's Hospital (London).
Rep. S. Thomas Hosp. (Lond.)- Reports of the S. Thomas Hospital (London).
Rep. Secr. U. S. Dep. Agr.- Report of the Secretary of the (U.S.) Department of Agriculture. (Washington).
Rep. Secr. U. S. Navy- Reports of the Secretary of (U.S.). Navy (Washington).
Rep. Superint. Johns Hopkins Hosp.- Report of the Superintendent of Johns Hopkins Hospital (Baltimore).
Rep. Surg.-Gen. Army-
Rep. Surg. Staff Woman Hosp. (S. Louis)- Report of the surgical staff of the Woman's Hospital (S. Louis).
Rep. Surg. Staff Woman Hosp. State N. York.- Report on the Scientific Work of the Surgical Staff of the Woman's Hospital in the State of New York (New York).
Rep. Ther. Res. Com. Am. M. A.- Report of the investigation of the therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association (Chicago).
Rep. U.S. Fed. Bd. Vocat. Educ.- Reports of the (U.S.) Federal Board for Vocational Education (Washington).
Rep. Wayne Co. M. Soc.- Report of the Wayne County (Mich.) Medical Society (Ann Arbor).
Repert. de med. y cir.- Repertorio de medicina y cirugia (Bogota).
Répert. pharm.- Répertoire de pharmacie (Paris).
Repert. de thérap.- Répertoire de thérapeutique (Paris).
Report méd.-
Repr. Michigan Dep. Health - Reprints series. Michigan Department of Health (Lansing).
Repr. Nat. Res. Counc. (Wash.)- Reprint and circular series of the National Research Council (Washington).
Repr. Presbyter. Hosp. New York.- Reprints from medical and surgical report of the Presbyterian Hospital in the City of New York (New York).
Research Bull. Univ. Missouri Agr. Exper. Station- Research bulletin. University of Missouri. College of agriculture. Agricultural Experiment Station (Columbus, Mo.).
Research Publ., A. Nerv. & Ment. Dis.- See: A. Research Nerv. & Ment. Dis. Proc.
Research Quart.- The Research Quarterly.
Researches London Hops.- Researches of the London Hospital (London).
Resenha clin-cient.- Resenha clinico-cientifica (São Paulo).
Resoc. R. Accad. med. chir. di Napoli- Resoconto delle adunanze; R. Accademia medico-chirurgica di Napoli.
Resoc. d. op. eseg. Clin. chir.-
Resoc. san sped. civ. di Trieste- Resoconto sanitario; Spedale civici di Trieste.
Resumpt. genet. Gravenh.- Resumptio genetica's Gravenhage.
Rev. d'actino. (Par.)- Revue d'actinologie et de physiothérapie (Paris) (Continued as Rev. de physiothérap.)
Rev. anthrop. (Par.)- Revue anthropologique (Paris).
Rev. Appl. Entom (Lond.)- Review of applied entomology (London).
Rev. arch. ital. de biol.- Revue des archives italiennes de biologie (Pisa, Italia).
Rev. argent. de cardiol.- Revista argentina de cardiologia.
Rev. argent. dermatosif.- Revista argentina de dermatosifilologia (Buenos Aires).
Rev. argent. hig. social y med. prev.- Revista argentina de higiene social y medicina preventiva.
Rev. argent. hist. med.- Revista argentina de historia de la medicina.
Rev. argent. de neurol. y psiquiat.- Revista argentina de neurologia psiquiatria y medicina legal (Buenos Aires).
Rev. argent. norteam. clen. méd.- Revista argentino-norteamericana de ciencias médicas.
Rev. argent. Obst.- Rivista argentina de obstetrica y ginecologia (Buenos Aires).
Rev. argent. de oto-rino-laring.- Revista argentina de oto-rino-laringologia.
Rev. argent. de reumatol.- Revista argentina de reumatologia.
Rev. argent. de tuberc- Revista argentina de tuberculosis.
Rev. argent. de urol.- Revista argentina de urologia.
Rev. Asoc. argent. dietol.- Revista de la Asociacion argentina de dietologia.
Rev. Asoc. med. argent.- Revista de la Asociación medica argentina (Buenos Aires).
Rev. Assoc. paulista de med.- Revista da Associação paulista de medicina. (Continued as Rev. paulista de Med.). (São Paulo).
Rev. belge sc. méd.- Revue belge des sciences médicales (Louvain).
Rev. belge tuberc.- Revue belge de la tuberculose.
Rev. biol. e hyg.- Revista de biologia e hygiene (São Paulo).
Rev. brasil. de biol.- Revista brasileira de biologia.
Rev. brasil de cir.-Revista brasileira de cirurgia.
Rev. brasil. de leprol.- Revista brasileira de leprologia de São Paulo.
Rev. brasil. med.- Revista brasileira de medicina.
Rev. brasil. med. farm.- Revista brasileira de medicina e farmacia (Rio de Janeiro).
Rev. brasil. del ortop. e traumatol.- Revista brasileira de ortopedia e traumatologia.
Rev. brasil. de oto-ring-laring.- Revista brasileira de oto-rino-laringologia.
Rev. brasil. de tuberc.- Revista brasileira de tuberculose.
Rev. canad. de Biol.- Revue canadienne de Biologie.
Rev. chilena de hig. y med. prev.- Revista chilena de hygiene y medicina prevnetiva.
Rev. chilena de pediat.- Revista chilena de pediatria.
Rev. de chir. (Bucuresti)- Revista de chirurgie si Bulletins et mémoires de la Société de chirurgie de Bucarest. (Bucuresti).
Rev. de chir. (Paris)- Revue de chirurgie (Paris).
Rev. de chir. plast. (Brux.)- Revue de chirurgie plastique (Bruxelles).
Rev. de chir. structive- Revue de chirurgie structive (Bruxelles).
Rev. de cien. méd.- Revista de ciencias médicas (Buenos Aires).
Rev. de cien. méd. (Mex.)- Revista de ciencias médicas (Mexico).
Rev. de cir. de Buenos Aires- Revista de cirugia de Buenos Aires.
Rev. de cir. de Barcelona- Revista de cirurgia de Barcelona (Barcelona).
Rev. de cir. Hosp. Juarez (Méx.)- Revista de cirugía; Hospital Juarez (México).
Rev. de cir. de São Paulo- Revista de cirurgia de São Paulo.
Rev. d. Circ. méd. argent. y Centro estud méd.- Revista del Circulo médico argentino y Centro estudiantes de medicina (Buenos Aires).
Rev. d. Circ. méd. Córdoba- Revista del Círculo médico de Córdoba (Córdoba).
Rev. d. Circ. mil (S. Salvador)- Revista del Círculo militar (S. Salvador).
Rev. clin. d'androl. et de gynéc.- Revue clinique d'andrologie et de gynécologie (Paris).
Rev. clin. espaf.- Revista clinica española.

Rev. de la clin. d. mal. d. femmes de la Fac. de méd. de Lyon-
Rev. clin. de São Paulo.- Revista clínica de São Paulo.
Rev. Clin. Stomat.- Review of clinical stomatology (New York).
Rev. d. Col. farm. Habana- Revista del Colegio farmaceutico de la Habana (La Habana).
Rev. de criminol. psiquiat.- Revista de criminologia, psiquiatria y medicina legal (Buenos Aires)
Rev. crit. path (Par.)- Revue critique de pathologie et de thérapeutique (Paris).
Rev. Cruz Roja colomb.- Revista de la Cruz. Roja colombiana.
Rev. cubana de cardiol.- Revista cubana de cardiologia.
Rev. cubana de obst. y ginec.- Revista cubana de obstetricia y ginecologia (Havana).
Rev. cubana de oftal.- Revista cubana de oftalmologia (La Habana).
Rev. cubana de oftal. oto-rin-lar.- Revista cubana de oftalmologia y oto-rino-laringologia (La Habana).
Rev. cubana de oto-neuro-oftal.- Revista cubana de oto-neuro-oftalmiatria (Habana).
Rev. dermat. argent.- Revista dermatológica argentina (Buenos Aires).
Rev. dermat. (B. Air.)- Revista dermatólogica. (Buenos Aires).
Rev. españ. de dermat. y sif.- Revista española de dermatologia y sifiligrafia.
Rev. españ. Farmacol. y Terapeut.-
Rev. españ. med. cir.- Revista española de medicina y cirugia (Barcelona).
Rev. españ. Obst.- Revista española de obstetricia y ginecologia (Valladolid).
Rev. españ. Obst.- Revista española de obstetricia y ginecologia (Madrid).
Rev. españ. de tuberc.- Revista española de tuberculosis.
Rev. espec. (B. Air.)- Revista de especialidades (Buenos Aires).
Rev. estud. mil. (Madr.)- Revista de estudios militares (Madrid).
Rev. Fac. de med. (Bogotá)- Revista de la Facultad de medicina (Bogotá).
Rev. farm. Buenos Aires.- Revista farmacéutica.
Rev. filipina de med. y farm.- Revista filipina de medicina y farmacia (Manila).
Rev. flum. de med.- Revista fluminense de medicina.
Rev. franç. de dermat. et de vénéréol.- Revue française de dermatologie et de vénéréologie (Paris).
Rev. franç. d'endocrinol.- Revue française d'endocrinologie (Paris).
Rev. franç. de gynéc. et d'obst.- Revue française de gynécologie et d'obstetrique (Paris).
Rev. franç. de pediat.- Revue française de pediatrie (Paris).
Rev. franç. de phoniatrie- Revue française de phoniatrie.
Rev. franç. de Psychanal.- Revue française de psychanalyse (Paris).
Rev. franç. de puericult.- Revue française de puericulture.
Rev. frenopat. españ.- Revista frenopatica española (Barcelona).
Rev. Gastroenterol.- The Review of Gastroenterology (New York).
Rev. de gastro-enterol. de México- Revista de gastro-enterologia de México.
Rev. de gastro-enterologia São Paulo- Revista de gastro-enterologia de São Paulo.
Rev. gén. de clin. et de thérap.- Revue générale de clinique et de thérapeutique (Paris) (See: J. prat. Paris).
Rev. gén. méd. vét.- Revue générale de médecine vétérinaire (Toulouse).
Rev. gén. opth. (Genève)- Revue générale d'ophtalmologie (Genève).
Rev. gén. sc. pur.- Revue générale des sciences pures et appliquées (Paris).
Rev. de gynéc. et d'obst.- Revista de gynecologia e d'obstetricia (Rio de Janeiro).
Rev. de gynéc.- Revue de gynécologie et de chirurgie abdominale (Paris).
Rev. de gynéc. et de chir. abdom.- See: Rev. de Gynéc.
Rev. de gynéc. e d'obst. (Rio de Janeiro)- Revista de gynecologia e d'obstetricia (Rio de Janeiro).
Rev. hebd. de laryngol.- Revue hebdomadaire de laryngologie, d'otologie et de rhinologie.
Rev. de hig (Bogotà)- Revista de higiene (Bogotà).
Rev. hig. y med. esc.- Revista de Higiene y medicina escolares.
Rev. hig. tuberc. (Valencia)- Revista de higiene y de tuberculosis (Valencia).
Rev. d'hyg.- Revue d'hygiène et de médecine préventive (Paris).
Rev. d'hyg. et de méd. sociales- Revue d'hygiène et de médecine sociales.
Rev. hyg. prophyl. social.- Revue d'hygiène et de prophylaxie sociales (Paris).
Rev. hyg. social. Strasbourg- Revue d'hygiène sociale de Strasbourg (Strasbourg).
Rev. de l'hypnot. et psychol. physiol.- Revue de l'hypnotisme, de psychothérapie et de psychologie.
Rev. Ibero-Am. de cien. méd.- Revista ibero-americana de ciencas médicas (Madrid).
Rev. d'immunol.- Revue d'immunologie (Paris).
Rev. Inst. Adolfo Lutz.- Revista do Instituto Adolfo Lutz.
Rev. d. Inst. bact. Buenos Aires- Revista del Instituto bacteriologico del Departamento nacional de higiene.
Rev. d. Inst. bact. de Chile- Revista del Instituto bacteriologico de Chile.
Rev. d. Inst. salub. y enferm. trop.- Revista del Instituto de salubridad y enfermedades tropicales.
Rev. interall. mutil. guerre- Revue interalliée pour l'étude des questions intéressant les mutilés de la guerre (Paris).
Rev. internat. de la Croix-Rouge- Revue internationale de la Croix-Rouge (Genève).
Rev. internat. hyg. pub. (Genève)- Revue internationale d'hygiène publique (Genève).
Rev. internat. de méd. et de chir.- Revue internationale de médecine et de chirurgie.(Paris) (Ceased publication).
Rev. internat. de méd. profess. et sociale - Revue internationale de médecine professionnelle et sociale.
Rev. internat. du trachome- Revue internationale du trachome (Paris).
Rev. de laryng.- Revue de laryngologie, otologie, rhinologie (Bordeaux).
Rev. leprol. dermat. y sif.- Revista de leprologia, dermatologia y sifilografia.
Rev. Liga puertorriq. contra el cáncer.- Revista de la Liga puertorriquena contra el cáncer.
Rev. d. mal de la nutrition- Revue des maladies de la nutrition (Paris).
Rev. de med. y alimentacion- Revista de medicina y alimentacion.
Rev. med. Angola- Revista medica de Angola (Loanda).
Rev. med. Bahia- Revista medica da Bahia (Bahia).
Rev. méd. de Barcelona- Revista médica de Barcelona (Barcelona).
Rev. Méd. de Bogotá- Revista medica de Bogota (Bogotá).
Rev. méd. brasil.- Revista médica brasileira.
Rev. méd. du centre-ouest- Revue médicale du centre-ouest (Poitiers).
Rev. méd. de Chile- Revista médica de Chile (Santiago).
Rev. méd.-chir. d. mal. d. femmes- Revue médico-chirurgicale des maladies des femmes (Paris).
Rev. méd.-chir. d. mal. du foie- Revue médico-chirurgicale des maladies du foie, du pancréas et de la rate (Paris).
Rev. méd.-chir. de Paris.- Revue médico-chirurgicale de Paris (Paris).
Rev. med. cienc. afines (Buenos Aires)- La revista de medicina y ciencias afines (Buenos Aires).
Rev. de med. y cir. (Barranquilla)- Revista de medicina y cirugia. (Barranquilla).

Rev. med.-cir. do Brasil- Revista medico-cirurgica do Brasil (Rio de Janeiro).
Rev. de med. y cir. Habana- Revista de medicina y cirugia de la Habana (La Habana).
Rev. med.-cir. mil. (Rio de Jan.)- Revista medico-cirurgica militar (Rio de Janeiro).
Rev. de méd. y cir. pract.- Revista de medicina y cirugía practicas.(Madrid).
Rev. med. e cir. de São Paulo- Revista de medicina e cirurgia de São Paulo.
Rev. med. y clen. afines (México)- Revista de medicina y ciencias afines. (México).
Rev. med. Colombia- Revista medica de Colombia (Bogotá).
Rev. méd. de Córdoba- Revista médica de Córdoba.
Rev. méd. Corrientes.- Revista médica de Corrientes.
Rev. méd. Costa Rica.- Revista médica de Costa Rica.
Rev. méd. cubana- Revista médica cubana (La Habana).
Rev. méd. de l'est.- Revue médicale de l'est (Nancy) (Continued as Rev. méd. de Nancy).
Rev. méd. exper. (Lima)- Revista de médicina experimental.(Lima)
Rev. méd.-farm. de Aragon (Zaragoza)- Revista médico-farmaceutica de Aragón. (Zaragoza).
Rev. méd. franç.- Revue médicale française. (Paris).
Rev. méd. franç. et étrang.- Revue médicale française et étrangère (Paris).
Rev. méd. franç. d'Extrême-Orient.- Revue médicale française d'Extrême-Orient.
Rev. méd. franç. Moyen-Orient - Revue médicale française du Moyen-Orient.
Rev. med. german-ibero-am.- Revista medica germano-ibero-americana (Leipzig).
Rev. méd. Hamburgo- Rev. médica de Hamburgo (Hamburg).
Rev. méd. hondur.- Revista médica hondureña (Tegucigalpa).
Rev. méd. d. Hosp. gen.- Revista médica del Hospital general.
Rev. med. hyg. mil. Rio.- Revista de medicina e hygiene militar (Rio de Janeiro).
Rev. de med. et d'hyg. trop.- Revue de médecine et d'hygiène tropicales (Paris).
Rev. méd. latino-am.- Revista médica latino-americana. (Buenos Aires).
Rev. med. leg. Cuba- Revista de medicina legal de Cuba (La Habana).
Rev. med. leg. y jurisp. méd.- Revista de medicina legal y jurisprudencia médica.
Rev. méd. de Limoges.-Revue médicale de Limoges (Limoges).
Rev. méd. Louvain- Revue médicale de Louvain (Louvain).
Rev. méd. (Managua)- Revista médica (Managua).
Rev. méd. munic. (Rio de Janeiro)- Revista Médica Municipal (Rio de Janeiro, Brazil).
Rev. méd. de Nancy- Revue médicale de Nancy (Nancy).
Rev. méd. de Normandie- Revue médicale de Normandie (Rouen).
Rev. méd. d. Paraguay- Revista médica del Paraguay.
Rev. de méd. (Paris)- Revue de médecine (Paris).
Rev. med. de Pernambuco- Revista medica de Pernambuco.
Rev. med. peruana- Revista medica peruana.
Rev. méd.-profes (Barcel.)- Revista médico-profesional (Barcelona).
Rev. méd. (Puebla)- Revista médica (Puebla).
Rev. méd.-pharm. (Constantinople)- Revue médico-pharmaceutique (Constantinople).
Rev. méd.-quir.- Revista médico-quirúrgica (Buenos-Aires).
Rev. méd. quir. hosp. Bogotá- Revista médico-quirurgica de los hospitales (Bogotá).
Rev. med. quir. de Oriente.- Revista medico-quirugica de Orient .
Rev. méd.-quir. de Pat. fem.- Revista medico-quirurgica de patologia femenian.
Rev. méd.-quir. (Tegucigalpa)- Revista médico-quirúrgica (Tegucigalpa).
Rev. méd. de Rosario- Revista médica de Rosario. (Rosario de Santa Fé).
Rev. med. Rosario- Revista de médicina (Rosario de Santa Fé).
Rev. méd. roumaine- Revue médicale roumaine (Bucuresti).
Rev. méd. San José.- Revista médica San José (Costa Rica) (See: Rev. méd. Costa Rica).
Rev. méd. (S. Paulo)- Revista de médicina (São Paulo).
Rev. méd. social san y benef. munic.- Revista médico-social de la sanidad y beneficencia municipal.
Rev. méd.-sociale de l'enf.- Revue médico-sociale de l'enfance.
Rev. méd. de la Suisse Rom.- Revue médicale de la Suisse Romande (Lausanne).
Rev. de méd. tchèque- Revue de médecine tchèque (Prague).
Rev. méd. de Toulouse- Revue médicale de Toulouse (Toulouse).
Rev. méd. trop (Bogotá)- Revista de medicina tropical. (Bogotá).
Rev. de med. trop. y parasitol., bacteriol., clin. y lab.- Revista de medicina tropical y parasitologia, bacteriologia clinica y laboratorio.
Rev. Méd. Uruguay - Revista médica del Uruguay (Montivideo).
Rev. méd. veracruz.- Revista médica veracruzana (Veracruz).
Rev. med. vet. (B. Air.)- Revista de medicina veterinaria. (Buenos Aires).
Rev. méd. de Yucatán- Revista médica de Yucátan (Merida).
Rev. mens. de gynéc. d'obst. et de pédiat.- Revue mensuelle de gynécologie, d'obstétrique et de pédiatrie (Paris; Bordeaux).
Rev. mens. de gynéc. d'obst. et pédiat. de Bordeaux- Revue mensuelle de gynécologie obstétrique et paediatrie de Bordeaux (Bordeaux, Paris).
Rev. mens. de méd. et chir.- Revue mensuelle de médecine et de chirurgie (Paris).
Rev. mex. de biol.- Revista mexicana de biología (México).
Rev. mex. de cir., ginec. y cáncer- Revista mexicana de cirugía, ginecologia y cáncer (Mexico).
Rev. mex. de pediat.- Revista mexicana de pediatria.
Rev. Mex. Psiquiat, neurol. y med. leg.- Revista mexicana de psiquiatria, neurologia y medicina legal.
Rev. mex. puericult.- Revista mexicana de puericultura (México).
Rev. mex. de tuberc.- Revista mexicana de tuberculosis y enfermedades del'aparato respiratorio (México).
Rev. mil. (B. Air.)- Revista mexicana de puericultura (México).
Rev. mil. (La Paz)- Revista militar (La Paz, Bolivia).
Rev. Neoplasms- Published in the Southern Surgeon.
Rev. neurol.- Revue neurologique (Paris).
Rev. neurol. de Buenos Aires- Revista neurologica de Buenos Aires.
Rev. neurol. Psychiat. (Praha)- Revue v neurologii a psychiatrii (Praha).
Rev. neurol. e psychiat. de São Paulo- Revista de neurologia e psychiatria de São Paulo.
Rev. neuro-psiquiat.-Revista de neuro-psiquiatria.
Rev. neuropsychopath. (Praha)- Revue neuropsychopathologie (etc.) (Praha).
Rev. obst. y ginec. (Caracas)- Revista de obstetricia y ginecologia.
Rev. de obst. et ginec. de São Paulo- Revista de obstetricia e ginecologia de São Paulo.
Rev. d'obst. et de gynéc.- Revue d'obstétrique et de gynécologie.
Rev. odont. (Par.)- Revue odontologique (Paris).
Rev. de ophtal. de São Paulo- Revista de ophtalmologia de São Paulo
Rev. d'orthop.- Revue d'orthopédie et de chirurgie de l'appareil moteur (Paris).
Rev. ortop. y traumatol.- Revista de ortopedia y traumatologia.
Rev. oto-laring. de São Paulo- Revista oto-laringologica de São Paulo.
Rev. oto-neuro-oftal.- Revista oto-neuro-oftalmologica y de cirugia neurologica sud-americana (Buenos Aires).

Rev. d'oto-neuro-opht. - Revue d'oto-neuro-ophtalmologie. (Paris).
Rev. otorrinolaring. - Revista de otorrinolaringologia.
Rev. otorrinolaring. d. litoral. - Revista de otorrinolaringologia del litoral.
Rev. de parasitol., clín. y lab. - Revista de parasitologia, clínica y laboratorio. (Continued as Rev. de med. trop. y parasitol., bacteriol, clin. y lab.).
Rev. de path. comparée - Revue de pathologie comparée et d'hygiène générale.
Rev. paulista de med. - Revista paulista de medicina.
Rev. paulista de tisiol. - Revista paulista de tisiologia.
Rev. pediat. si puericult. - Revista de pediatrie si puericultura.
Rev. philanthrop.,(Par.) - Revue philanthropique. (Paris).
Rev. philos. France - Revue philosophique (de la France et de l'étranger). (Paris).
Rev. phot. d. hôp. de Paris - Revue photographique des hôpitaux de Paris.
Rev. de phtisiol. - Revue de phtisiologie thérapeutique et sociale. (Paris).
Rev. de physiothérap. - Revue de physiothérapie.
Rev. Policlín.(Caracas.) - Revista de la Poliklinica (Caracas).
Rev. port. de estomatol. - Revista portuguesa de estomatologia.
Rev. prat. de biol. appliq. - Revue pratique de biologie appliquée à la clinique et à la thérapeutique. (Paris).
Rev. prat. hyg., mun.,(Nancy) - Revue pratique d'hygiène municipale urbaine et rurale. (Nancy).
Rev. prat. d. mal. d. pays chauds - Revue pratique des maladies des pays chauds. (Paris).
Rev. prat. d'obst. et de gynéc. - Revue pratique d'obstétrique et de gynécologie. (Paris).
Rev. prat. d'obst. et de pédiat. - Revue pratique d'obstétrique et de paediatrie. (Paris).
Rev. Presse méd. belge - Revue de la presse médicale belge.
Rev. psicoanál. - Revista de psicoanálisis.
Rev. de psiquiat. y criminol. - Revista de psiquiatria y criminologia.
Rev. psiquiat. Neurol. (Habana) - Revista de psiquiatria y neurologia. (La Habana).
Rev. psychol. appl., (Par.) - Revue de psychologie appliquée. (Paris).
Rev. radiol.,(Berl.) - Revista de radiologia. (Berlin).
Rev. radiol. y fisioterap. - Revista de radiologia y fisioterapia. (Chicago).
Rev. san. y asist. social. - Revista de sanidad y asistencia social.
Rev. san. benef. munic. - See: Rev. méd.-social san y benef. munic.
Rev. san. mil.,(Asunción) - Revista de sanidad militar. (Asunción, Paraguay).
Rev. san. mil.,(Bucuresti) - Revista sanitara militara. (Bucuresti).
Rev. san. mil.(Buenos Aires) - Revista de la sanidad militar (Buenos Aires).
Rev. san. mil.,(Caracas) - Revista de sanidad militar.
Rev. san. mil. (Chile) - Revista de la sanidad militar. (Santiago de Chile).
Rev. san. mil. (Habana) - Rebista de la sanidad militar.
Rev. san. mil.,(Lima) - Revista de sanidad militar: (organo del Servicio de Sanidad militar del Peru.). (Lima).
Rev. san. mil. (Madr.) - Revista de sanidad militar. (Madrid).
Rev. san. de policía. - Revista de la sanidad de policía.
Rev. sc. méd. Franc. du Moyen-Orient. - Revue de la science médicale française du Moyen-Orient .
Rev. d. sc. méd. pharm. et vét. l'Afrique franç. libre. - Revue des sciences médicales p pharmaceutiques et vétérinaires de l'Afrique française libre.
Rev. scient. - Revue scientifique. (Paris).
Rev. scient. Instruments - Review of Scientific Instruments. (Lancaster,Pa.).
Rev. serv. de san. mil. - Revue du service de santé militaire. (Paris).
Rev. Soc. argent. de biol. - Revista de la Sociedad argentina de biologia y sus filiales la Sociedad de biologia de Rosario y la Sociedad de biologia de Cordoba. (Buenos Aires).
Rev. Soc. argent. neurol. - Revista de la Sociedad argentina de neurologia y psichiatria. (Buenos Aires).
Rev. Soc. argent. nipiol. - Revista de la Sociedad argentina de nipiologia. (Buenos Aires).
Rev. Soc. argent. Oftal. - Revista de la Sociedad argentina de oftalmologia. (Buenos Aires).
Rev. Soc. argent. otorrinolar. - Revista de la Sociedad argentina de otorrinolaringologia. (Buenos Aires).
Rev. Soc. argent. radio electr. - Revista de la Sociedad argentina de radio- y electrologia. (Buenos Aires).
Rev. Soc. argent. tisiol.- Revista de la Sociedad argentina de tisiologia. (Buenos Aires).
Rev. Soc. argent. urol. - Revista de la Sociedad argentina de urologia. (Buenos Aires).
Rev. Soc. hig. microbiol. (B. Air.) - Revista de la Sociedad de higiene y microbiologia. (Buenos Aires).
Rev. Soc. med. argent. - Revista de la Sociedad medica argentina.
Rev. Soc. med. int.,(B. Air.) - Revista de la Sociedad de medicina interna y de Sociedad de tisiologia. (Buenos Aires).
Rev. Soc. méd. - quir. Zulia - Revista de la Sociedad médico-quirúrgica del Zulia. (Maracaibo).
Rev. Soc. pediat. de Rosario - Revista de la Sociedad de pediatria de Rosario.
Rev. Soc. Puericult.Buenos Aires - Revista de la Sociedad de puericultura de Buenos Aires.
Rev. stiint. med. - Revista stiintelor medicale. (Bucuresti).
Rev. de stomatol. - La revue de stomatologie. (Paris).
Rev. sud. -am. de endocrinol. - Revista sud-americana de endocrinologia, immunologia y quimioterapia. (Buenos Aires).
Rev. sud-am. de méd. et de chir. - Revue sud-americaine de médecine et de chirurgie. (Paris).
Rev. suisse Zool. - Revue suisse de zoologie. (Geneva).
Rev. techn. chir.,(Par.) - Revue de la technique chirurgicale. (Paris).
Rev. de thérap. méd.- chir. - Revue thérapuetique médico-chirurgicale. (Paris).
Rev. thérap. du Medi- (Montpel.) - Revue thérapeutique du Midi (Marseilles).
Rev. de tisiol. pract. - Revista de tisiologia practica.
Rev. d. trab. - Revista del trabajo.
Rev. trachome, (Par.) - Revue de trachome.(Paris).
Rev. de la tuberc. - Revue de la tuberculose. (Paris).
Rev. tuberc. (Habana) - Revista de tuberculosis.
Rev. de tuberc. d. Uruguay - Revista de tuberculosis del Uruguay. (Montevideo).
Rev. tumor Therapy. - Combined with The Southern Surgeon.
Rev. tunis. sc. méd. - Revue tunisienne des sciences médicales. (Tunis).
Rev. Univ. B. Aires - Revista de la Universidad de Buenos Aires. (Buenos Aires).
Rev. de la Univ. Nac. de Cordoba - Revista de la Universidad nacionale de Cordoba.
Rev. Univ. rio. - Ribista do Universidade do Rio de Janeiro. (Rio de Janeiro).
Rev. urol. - Revista de urologia.
Rev. valenc. cienc. med. - Revista valenciana de ciencias medicas. (Valencia).
Rev. vet. mil. (Bucur.) - Revista veterinara militara. (Bucuresti).
Rev. vét. mil.,(Par.) - Revue vétérinaire militaire. (Paris).
Rev. vět. slave, (Brno) - Revue vétérinaire slave. (Brno).
Rev. zootecn. (B. Air.) - Revista zootecnica. (Buenos Aires).

Rhein. Monatschr. prakt. Ärzte - Rheinische Monatsschrift für praktische Aerzte. (Cologne).
Rheumat. Dis. - Rheumatic diseases. (Continued as Ann. Rheumat. Dis.).
Rhode Island M. J. - Rhode Island Medical Journal. (Providence, R.I.).
Ric. Sci. Progr. tecn. Econ. naz. - Ricerca scientifica ed il progresso tecnico nell' economia nazionale. (Rome).
Ricerche di fisiol. e. sc. affini ded. al Prof. L. Luciani -
Ricerche lab. di anat. norm. Univ. di Roma - Ricerche; laboratorio di anatomia normale, Università di Roma.
Ricerche di Morfol. - Ricerche di morfologia. (Rome).
Ricerche morf. biol. anim. - Ricerche di morfologgia e biologia animale. (Napoli).
Richmond Hosp. Rec. - Richmond Hospital Record.
Richmond & Louisville M. J. - Richmond and Louisville medical journal.
Riforma med. - La riforma medica. (Napoli).
Rinasc. med. - Rinascenza medica. (Napoli).
Rinnovamento med. Sez. 3: - Rinnovamento medico. (Naples). (See: Gior. ital. di clin. trop.).
Rinsho shika - Rinsho shika. (Osaka, Japan).
Risveglio, (Reggio-Calabria) - Risveglio (Reggio-Calabria).
Riv. antrop. - Rivista di antropologia. (Roma).
Riv. Biol. - Rivista di biologia. (Perugià).
Riv. di chir. Como - Rivista di chirurgia. (Como).
Riv. chir., (S. Onofrio) - Rivista di chirurgia. (Saint Onofrio).
Riv. di clin. di Bologna -
Riv. di clin. med. - Rivista di clinica medica. (Firenze)
Riv. di clin. pediat. - Rivista di clinica pediatrica. (Firenze).
Riv. clin. Univ. di Napoli - Rivista clinica: Universita di Napoli.
Riv. crit. clin. med. - Rivista critica di clinica medica (Firenze).
Riv. crit. lavoro - Rivista critica (del diritto del lavoro e della responsabilita civile). (Milano).
Riv. espedal. -
Riv. di idroclimat., talassol. e terap. fis. - Rivista di idroclimatologia, talassologia e terapia fisica. (Milano).
Riv. idrol. clim. - Rivista di idrologia, climatologia e terapia fisica. (Turin).
Riv. immun. - Rivista di immunologia e scienze affini. (Milano).
Riv. ingegn. san. - Rivista di ingegneria sanitaria. (Torino).
Riv. internaz. ingegn. san. - Rivista internazionale di ingegneria sanitaria ed urbanistica.(Milano).
Riv. internaz. di med. e chir. - Rivista internazionale di medicina e chirurgia. (Naples).
Riv. ital. actin. - Rivista italiana di actinologia. (Milano).
Riv. ital. di ginec. - Rivista italiana di ginecologia. (Bologna).
Riv. ital. neuropat. - Rivista italiana di neuropatologia, psichiatria ed elettroterapia. (Catania).
Riv. ital. stomat. - Rivista italiana di stomatologia. (Parma).
Riv. ital. di Terap. - Rivista italiana di terapia ed igiene. (Piacenza).
Riv. di malariol. - Rivista di malariologia. (Roma).
Riv. med. - Rivista medica. (Milano).
Riv. di med. aeron. - Rivista di medicina aeronautica. (Rome).
Riv. di med. di chirurg. - Rivista di medicina di chirurgia e di terapeutica (Milan).
Riv. di med. dosim. - Rivista di medicina dosimetrica (Turin).
Riv. di med. leg. - Rivista di medicina legale e di giurisprudenza medica (Milan).
Riv. med. leg. - Rivista di medicina legale e di giurisprudenza medica. (Siena).
Riv. med.-social. tuberc. - Rivista medico-sociale della tuberclulosi. (Palermo).
Riv. mens. mun.,(Tor.) - Rivista mensile municipale. (Torino).
Riv. di neurol. - Rivista di neurologia. (Napoli).
Riv. nipiol. - Rivista di nipiologia. (Napoli).
Riv. osp. - Rivista ospedaliera; giornale di medicina e chirurgia.
Riv. d'ostet. e ginec. prat. - Rivista d'ostetricia e ginecologia pratica. (Milano).
Riv. oto-neuro-oftal. - Rivista oto-neuro-oftalmologica. (Bologna).
Riv. di parassitol. - Rivista di parassitologia. (Rome).
Riv. pat. app. resp. - Rivista di patologia dell' apparato respiratorio. (Archo).
Riv. di pat. e clin. d. tuberc. - Rivista di patologia e clinica della tubercolosi. (Bologna).
Riv. di pat. nerv. - Rivista di patologia nervosa e mentale. (Florence).
Riv. pat. nerv. - Rivista di patologia nervosa e mentale. (Siena).
Riv. di pat. sper. - Rivista di patologia sperimentale. (Naples).
Riv. pat. sper. - Rivista di patologia sperimentale. (Torino).
Riv. pellagr. ital. - Rivista pellagrologica italiana (etc.) (Udine).
Riv. psicol. - Rivista di psicologia. (Bologna).
Riv. Radiol. - Rivista di radiologia e fisica medica. (Bologna).
Riv. san. siciliana - Rivista sanitaria siciliana. (Palermo). (Continued as Sett. med.).
Riv. sicil. ostet. - Rivista siciliana d'ostetricia e ginecologia pratica. (Palermo).
Riv. sper. di franiat. - Rivista sperimentale di freniatria e medicina legale delle alienazioni mentali (Archivio italiano per le malattie nervose e mentali). (Reggio-Emilia).
Riv. di storia d. sc. med. e nat. - Rivista di storia delle delle scienze mediche e naturali. (Siena).
Riv. veneta di sc. med. - Rivista veneta di scienze mediche. (Venice).
Roc. ceskoslov. kardiol. spol. - Rocenka ceskoslovenske kardiologiche spolecnosti za rok 1933.
Rocky Mountain M. J. - Rocky Mountain Medical Journal. (Denver).
Rocky Mountain M. Rev. - Rocky Mountain Medical Review. (Denver).
Rocznik lek. - Rocznik lekarski. (Krakow).
Rocznik psychjat. - Rocznik psychjatryczny. (Warsaw).
Romania med. - Romania medicala. (Bucharest).
Röntgenpraxis - Röntgenpraxis. Beihefte zu Fortschritte auf dem Gebiete der Röntgenstrahlen. (Leipzig).
Roosevelt Wild Life Ann. - Roosevelt wild life annals. (Syracuse).
Roosevelt Wild Life Bull. - Roosevelt wild life bulletin. (Syracuse).
Rotes Kreuz - Das Rote Kreuz. (Berlin).
Roux' Arch. - Wilhelm Roux' Archiv für Entwicklungsmechanik der Organismen. (Berlin).(See: Archiv für Entwicklungsmechanik der Organismen).
Roy. Berkshire Hosp. Rep. - Royal Berkshire Hosp. ital. Reports.
Roy. Infirmary, Edinburgh M. Times & Gaz. -
Roy. Melbourne Hosp. Clin. Rep. - Royal Melbourne Hospital Clinical Reports.
Rozhl. v. chir. - Rozhledy v chirurgii (Prague).
Rozpr. ceské Akad. cís. Františka Josefa -
Rozpr. wydz. mat. przyrod. Polska Akad. - Rozprawy wydzialu matematyczno-przyrodniezego (at head of tp.) Polska Akademja umiejet nosci. (Krakow).
Rural Med.,Proc. - Rural Medicine. Proceedings of the Conference Held at Cooperstown, New York, October 7 and 8, 1938.
Russ. Ärzteztg. -
Russ. J. Koshn. vener. bolezn. -
Russ. Med. - Russian Medicine.
Russk. arkh. anat. - Russky arkhiv anatomy gistology i embriology. (Leningrad).
Russk. chir. Arch. -
Russk. J. trop. med. - Russky jurnal tropichesskoy meditsiny. (Moskva).
Russk. Klin. - Russkaia klinika (Moskva). See: Sovetskaia klinika.

Russk. Med. (St. Petersburg) - Russkaia meditsina (St. Petersburg).
Russk. oftalm. Z. - Russkii oftalmologicheskii zhurnal. (Moscow).
Russk. vrach. - Russkii vrach. (Petrograd).
Rusts Magazin -
S. Clin. North America - Surgical Clinics of North America.
S. M. S., (Par.) - A. M. A. (Syndicat des médecins de la Seine. (Paris).
Sächs. Hebam.-Ztg. - Sächsische Hebammen-Zeitung. (Dresden).
Safety Engin. - Safety engineering. (New York).
Saisei Gakusha Iji Shimpo - See: Iji shimpo (Tokyo).
Saito Ho-on Kai Monogr. Ser. - Saito ho-on Kai monograph series. (Sendai).
Sällskapet för Veterinarmedicinsk Forskning -
Salubridad, (Méx.) - Salubridad. (México).
Salud, (Santa Crux de Tenerife) -
Samml. klin. Vortr. - Sammlung klinischer Vorträge (Leipzig).
Samml. wissensch. Arb. a. d. Grenzgeb. d. Gynäk. u. Geburtsh. Prof. W. Orlow Gew. -
Samml. zwangl. Abhandl. a. d. geb. d. Derm. - Sammlung zwangloser Abhandlungen aus dem Gebiete der Dermatologie und Syphilidologie (Halle).
Samml. zwangl. Abhandl. a. d. Geb. d. Nerven- u. Geisteskr. - Sammlung zwangloser Abhandlungen aus dem Gebiete der Nerven- und Geisteskrankheiten. (Halle).
Samml. zwangl. Abhandl. a. d. Geb. d. Verdauungs.-u. Stoffwechs.-Krankh. - Sammlung zwangloser Abhandlungen aus dem Gebiete der Verdauungs- und Stoffwechselkrankheiten (Halle).
San. & benef. (Habana) - Sanidad y beneficencia. (La Habana).
San.-Ber. d. k. Med.-Coll. zu Posen -
San Francisco M. Press. - San Francisco Medical Press.
San Francisco West. Lan. - San Francisco western lancet. (San Francisco).
San. mil., (Habana) - Sanidad militar. (Habana).
San. Rec. (Lond.) - Sanitary record. (London).
Sanatorium, (Denver) - Sanatorium. (Denver).
Sang - Le sang. (Paris).
Sankwa Fujinkwa Gaku Zasshi - Sankwa fujinkwa gaku zasshi (Tokyo).
Sankwa Fujinkwa Kenkiu Kwai Kwai ho - Sankwa fujinkwa kenkiu kwai kwai ho. (Tokyo).
São Paulo méd. - São Paulo médico.
Saviard Obs. in Surg. London -
Savoir, (Par.) - Savoir. (Paris).
Sborn. lék. - Sborník lékařsky. (Praha).
Sc. Rep. Tôhoku Univ. - Science reports of the Tôhoku Imperial University. (Sendai, Japan).
Scalpel, (Brux.) - Scalpel. (Bruxelles).
Scalpel, (N. Orl.) - Sclapel. (New Orleans, La.).
Schizofrenie - Schizofrenie. (Racconige, Italia).
Schizofrenie - Schizofrenie. (Torino).
Schmerz Narkose-Anaesth. - Schmerz Narkose-Anaesthesie. (Leipzig).
Schmidts Jahrb. - Schmidt's Jahrbücher der in- und ausländischen gesamten Medizin. (Leipzig).
School Health News - School health news. (New York).
School Health Stud. - School health studies. (Washington).
School Hyg., (Lond.) - School hygiene. (London).
School Hyg. Rev. - School hygiene review. (Worcester, Mass.)
School Life - School life. (Washington).
School Physicians Bull. - School physician's bulletin. (Albany, N.Y.).
School & Soc. - School and society. (New York).
Schriften Naturwiss. Verein. Schl.-Holstein - Schriften des Naturwissenschaftlichen Vereins für Schleswig-Holstein. (Kiel).
Schriften d. physik.-ökon. Gesellsch. Königsberg - Schriften der physikalisch-oekonomische gesellschaft, Königsberg.
Schulzahnpflege - Schulzahnpflege. (Berlin).
Schweiz. Arch. f. Neurol. u. Psychiat. - Schweizer Archiv für Neurologie und Psychiatrie. (Zürich).
Schweiz. Arch. f. Tierh. - Schweizer archiv für tierheilkunde (Zürich).
Schweiz. med. Wchnschr. - Schweizerische medizinische Wochenschrift. (Basel).
Schweiz. Monatschr. Zahnheilk. - Schweizerische monatsschrift für zahnheilkunde. (Zürich).
Schweiz. Rdsch. Med. - Schweizerische rundschau für medizin. (Bern).
Schweiz. Vjschr. f. Zahnheilk. - Schweizerische vierteljahrsschrift für zahnheilkunde. (Genève).
Schweiz. Ztschr. f. allg. Path. u. Bakt. - Schweizerische Zeitschrift für allgemeine Pathologie und Bakteriologie. (Basel; Leipzig).
Schweiz. Ztschr. f. Med. Chir. u. Geburtsh. - Schweizerische zeitschrift für medicin, chirurgie und geburtshülfe. (Bern, Zürich).
Schweiz. Ztschr. f. Natur.-u. Heilk. - Schweizerische zeitschrift für natur- und heilkunde (Zürich, Heilbronn).
Schweiz. Ztschr. f. Path. u. Bakt. - Schweizerische Zeitschrift für Pathologie und Bakteriologie.
Schwester - Schwester. (Berlin).
Science - Science. (Lancaster, Pa.).
Science - Science. (New York).
Science Leaflet - Science leaflet. (Lancaster, Pa.).
Science News Lett. - Science news letter. (Washington).
Science Progr., (London) - Science progress. (London).
Science Stud. - Science studies.
The Science Teacher -
Sciences, (Par.) - Sciences; revue de l'Association française pour l'avancement des sciences. (Paris).
Sciencia med., (Rio) - Sciencia medica. (Rio de Janeiro).
Scient. Agric. - Scientific Agriculture.
Scient. Am. - Scientific American. (New York).
Scient. Month. - Scientific monthly. (Lancaster, Pa.).
Scient. Monthly - Scientific Monthly. (New York).
Scient. Pap. Inst. Phys. Chem. Res. - Scientific papers of the Institute of physical and chemical research. (Tokyo).
Scient. Proc. Roy. Dublin Soc. - Scientific proceedings of the Royal Dublin Society. (Dublin).
Scient. Rep. Cancer Res. Fund. (Lond.) - Scientific report on the investigations of the Imperial Cancer Research Fund. (London).
Scient. Rep. Inst. Infect. Dis. (Tokyo) - Scientific reports from the Government Institute for Infectious Diseases. Tokyo Imperial University. (Tokyo).
Scient. Ther., (Lewist.) - Scientific therapy and practical research. (Lewistown, Pa.).
Scientia (Bologna) - Scientia. (Bologna).
Scientia - Scientia (Milano).
Scott. M. J. - Scottish medical journal. (Edinburgh).
Scott. M. & S. J. - Scottish medical and surgical journal. (Edinburgh).
Scripta. Soc. radiol. jap. -
Scritti biol. - Scritti biologici raccolti da Luigi Castaldi.
Scritti med. in omaggio a A. Murri -
Scuola positi. - Scuola positiva. (Milano).
Seara méd. - Seara médica. Revista de ciencias medicas e human is mo. (Sao Paulo).
Seattle Health - Seattle health and sanitation. (Seattle).
Sebeszet. (Budapest) -
Sei i kwai - Sei i kwai medical journal. (Tokyo).
Selecta med. Francof. - Selecta medica francofurtensia. (Frankfurt).
Semaine dent. - Semaine dentaire.
Semaine gynéc. - Semaine gynécologique. (Paris).
Semaine d. hôp. de Paris - Semaine des hôpitaux de Paris. (Paris).
Semaine méd. - Semaine médicale. (Paris).
Semana méd. - La semana médica. (Buenos Aires).
Semana méd. españ. - Semana medica española. (Madrid).
Semi-Month. J. Proc. Path. Soc. - Semi-Monthly Journal of the Proceedings of the Pathological Society.
Serv. Bull. U. S. Bur. Fish. - Service bulletins of the (U.S.) Bureau of Fisheries. (Washington).

Serv. Pub. Dept. Health Melbourne - Service publications of the Department of Health of Melbourne. (Melbourne).
Serv. Pub. indust. Hyg., (Melb.) - Service publications (Division of industrial hygiene) (Melbourne).
Serv. Pub. Trop. Div. (Melb.) - Service publication. (Tropical division) (Melbourne).
Sett. med. - La settimana medica. (Palermo, Milan).
Seuchenbekämpfung, (Wien) - Seuchenbekämpfung. (Wien).
Sex.-Probleme - Sexual-probleme; Zeitschrift für sexualwissenschaft und sexualpolitik. (Frankfurt a. M.).
Sexology - Sexology. (New York).
Sheffield M. J. - Sheffield Medical Journal.
Shield (Lond.) - Shield. (London).
Shikwa gakuho - Shikwa gakuho. (Tokyo).
Sibirsk. Vrach (Tomsk) - Sibirskii vrach (Tomsk).
Sibirsk. Vrach. Viedom. - Sibirskia vrachebnyia viedomosti. (Krasnoyarsk).
Sicilia med. - Sicilia medica. (Palermo; Turin).
Sierra Leone Roy. Gaz. - Sierra Leone royal gazette. (Freetown).
Sight-Saving Rev. - Sight-Saving Review. (New York).
Sight-Saving Rev. - Sight-saving review. (Philadelphia).
Siglo méd. - Siglo médico. (Madrid).
Sigma Xi Quart - Sigma Xi Quarterly. (Burlington, Vt.).
Signal Corps Bull. - Signal corps bulletins. (War Department) (Washington).
Simpson Contrib. Obstet. Pat. (etc.) Edinburgh. -
Simpson Works (Dis. of Women) Edinburgh - Simpson works (Diseases of women)(Edinburgh).
Sind. M. J. - The Sind Medical Journal. (Karachi).
Sitzungsb. d. Akad. Wissensch. Wien - Sitzungsberichte der Akademie der Wissenschaften in Wien. (Wien).
Sitzungsb. d. ärztl. Ver. - Sitzungsberichte der aerztlicher verein. (Munich).
Sitzungsb. d. ärztl. Ver. Nürnberg - Sitzungsberichte der aerztlicher verein Nürnberg. (München).
Sitzungsb. d. geburtsh. gynäk. Gesellsch. in Wien - Sitzungsberichte der Geburtshilflich-gynäkologische gesellschaft in Wien.
Sitzungsb. d. Gesellsch. f. Gynäk. in München - Sitzungsberichte der gesellschaft für gynäkologie in München.
Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. Sitzungsberichte der gesellschaft für morphologie und physiologie. (Munich).
Sitzungsb. d. Gesellsch. Naturwiss. Marburg. - Sitzungsberichte der Gesellschaft zur Beförderung der gesamte Naturwissenschaften zu Marburg. (Berlin).
Sitzungsb. d. Kaiserl. Akad. d. Wissensch. in Wien, Mathem.-Naturw. Classe - Sitzungsberichte der kaiserlichen Akademie der Wissenschaften in Wien, Mathem.-naturw. Classe. (Wien).
Sitzungsb. d. math.-naturwiss. Abt. Bayer. Akad. Wissensch. - Sitzungsberichte der mathematisch-naturwissenschaftlichen Abteilung der Bayerischen Akademie der Wissenschaften zu München. (München).
Sitzungsb. d. med. Gesellsch. Magdeburg. -
Sitzungsb. d. med.-naturw. Ver. (Tübingen) -
Sitzungsb. d. naturforsch. Gesellsch. Leipzig - Sitzungsberichte der naturforschende gesellschaft. (Leipzig).
Sitzungsb. d. Otolar. Gesellsch. Berlin - Sitzungsberichte der Oto-laryngologischen Gesellschaft zu Berlin. (Leipzig).
Sitzungsb. d. phys. med. Gesellsch. (Würzburg) - Sitzungsberichte der physikalisch-medicinische gesellschaft. (Würzburg).
Sitzungsb. d. phys.-med. Soz. zu Erlangen - Sitzungsberichte der physikalisch-medizinischen Sozietät zu Erlangen. (Erlangen).
Sitzungsb. d. Preuss. Akad. Wissensch. - Sitzungsberichte der Preussischen Akademie der Wissenschaften. (Berlin).
Sitzungsb. d. Preuss. Akad. Wissensch. - Sitzungsberichte der Preussischen Akademie der Wissenschaften. (Berlin).
Sitzungsb. d. Ver. d. Aerzte in Steiermark - Sitzungsberichte der verein der aerzte in Steiermark(Gratz)-
Skandinav. Arch. f. Physiol. - Skandinavisches Archiv für Physiologie. (Berlin).
Smithsonian Inst.,-Annual Rep. - Annual report of the Board of Regents of the Smithsonian Institution. (Washington, D. C.).
Smithsonian Miscell. Collections - Smithsonian Miscellaneous Collections.
Soc. Alumni City Hosp. Tr. (New York) -
Soc. bavaroice de gynéc. -
Soc. belge de chir. - Société belge de chirurgie. (Brussels).
Soc. benef. Cap. Bol. Inst. de matern. - See: Bol. Inst de matern.
Soc. de cir. de Cordoba, Bol. y trab. - See Bol. y trab. -
Soc. de dermatol. et syphiligraphie -
Soc. fr. prophyl. san. - Société française de prophylaxie sanitaire et morale. (Paris).
Soc. internaz. di microbiol.,Boll. d. sez. ital. - Societa internazionale di microbiologia. See: Boll. d. sez. ital. d. Soc. internaz di microbiol.
Soc. méd. d'Amiens. (Bull) - Bulletin des travaux de la société médicale d'Amiens.
Soc. med. Havn. collect. -
Soc. de méd. mil. franç., Bull. mens. - Société de médecine militaire française.
Soc. de méd. de Nancy, C.-rendu Mém. - Société de médecine de Nancy, Compte rendu et mémoires. See: Compt.-rend. & mém. Soc. méd. de Nancy.
Soc. méd. de Strasbourg - Société de médecine de Strasbourg.
Soc. d'obst. et de gynéc. - Société d'obstétrique et de gynécologie de Paris.
Soc. philomat. de Paris C.-r. - Société philomatique de Paris (compte-rendu).
Soc. Roumaine de Neurol. Psych. et Endocrinol. Société Roumaine de Neurologie, Psychiatrie, psychologie et Endocrinologie.
Soc. d. sc. méd. de Gannat. Compt. rend. - Société des sciences médicales de Sannat. (Compte-rendu).
Social Hyg. Bull. - Social hygiene bulletin. (New York).
Sociologus, (Stuttg.) - Sociologus. (Stuttgart).
South. African J. M. Sc. - The South African Journal of Medical Sciences. (Johannesburg).
South African M. J. - South African Medical Journal. (Cape Town).
South African M. Rec. - South African Medical Record. (Cape Town).
South African Nurs. Rec. - South African nursing record. (E. London, S. Africa).
South. Calif. Pract. - Southern California practitioner. (Los Angeles).
South. Clinic. - Southern clinic. (Richmond).
South. Hosp. Rec., (Atlanta) - Southern Hospital Record. (Atlanta, Ga.).
South. J. Med. & Pharm. - Southern journal of Medicine and Pharmacy.
South. M. J. - Southern Medical Journal. (Birmingham, Ala.).
South. M. Rec. - Southern Medical Record. (Atlanta, Ga.).
South. M. Rev. - Southern medical review. (Houston).
South. M. & S. J. - Southern Medical and Surgical Journal (Augusta, Ga.).
South. Med. & Surg. - Southern Medicine and Surgery. (Charlotte, N.C.).
South. Pract. (Nashville) - Southern practitioner. (Nashville).
South. Surgeon - The Southern Surgeon. (Atlanta, Ga.).
South Texas M. Rec. - South Texas medical record. (Houston, Tex.).
Southwest J. Med. & Surg. - Southwest journal of medicine and surgery. (El Reno, Okla.).
Southwest. M. & S. Rep. - Southwestern Medical and Surgical Reporter. (Fort Worth).
Southwestern Med. - Southwestern Medicine. (Phoenix, Ariz).
Sovet. khir. - Continued as Khirurgiya.

Sovet. klin. - Sovetskaia klinika. (Moscow).
Sovet. med. - Sovetskaya meditsina. (Moskva).
Sovet. nevropat. - Sovetskaia nevropatologia, psikhiatria psikhogigiena. (Moskva).
Sovet. pediat. - Sovetskaia pediatria.
Sovet. psikhonevrol. - Sovetskaya psikhonevrologiya. (Kharkov).
Sovet. stomat. - Sovetskaia stomatologia. (Moskva).
Sovet. vestnik oftal. - Sovetskii vestnik oftalmologii. (Moskva). (Continued as Vestnik oftal.).
Sovet. vestnik vener. - Sovetsky vestnik venerology i dermatology. (Moskva).
Sovet. Vet. - Sovetskaia veterinaria (Moscow).
Sovet. vrach. gaz. - Sovetsky vrachebny gazeta. (Leningrad).
Sovet. vrach. gaz. - Sovetskaia vrachebnaia gazeta. (Moscow).
Sovet. vrach. zhur. - Sovetskiy vrachebniy zhurnal. (Leningrad).
Sovet. zdravookh. Turkmenii. - Sovetskoe zdravookhranenie Turkmenii.
Sovrem. med. - Sovremennaia meditsina (Warsaw).
Sovrem. psikhonevr. - Sovremennaia psikhonevrologia. (Moskva).
Sowjetruss. ärztl. Z. - Sowjetrussische ärztliche Zeitschrift.
Soziale Prax. - Soziale Praxis. (Jena).
Spallanzani - Spallanzani. (Rome).
Spec. Bull. Dep. Health Montana - Special bulletin Department of Health of Montana. (Helena, Mont.).
Spec. Rep. M. Res. Counc.,(Lond.) - Special report series; Medical Research Council. (London).
Speech Monogr.- Speech Monographs.
Sperimentale, Arch. di biol. - Lo sperimentale. Archivio di biologia normale e patologica. (Organo dell'Accademia medico-fisico fiorentina).(Firenze).
Spizy lek. fak. Masaryk. Univ. - Spisy lekarske fakulty Massarykovy University. (Brno).
Spitals-Ztg. - Spitals-zeitung. (Vienna).
Spitalul - Spitalul (Bucharesti).
Sportmedizin - Sportmedizin. (Halle).
Squibb Mem. - Squibb memoranda. (New York).
St. Barth. Hosp. J. - St. Bartholomew's Hospital Journal. (London).
St. Barth. Hosp. J.,War. Ed. - St. Bartholomew's hospital journal. War edition. (Ceased publication).
St. Barth. Hosp. Rep. - St. Bartholomew's Hospital Reports.
St. George's Hosp. Rep. - St. George's Hospital Report.
St. Louis Cour. Med. - St. Louis courier of medicine (St. Louis).
St. Louis M. Reporter - St. Louis Medical Reporter (St. Louis).
St. Louis M. Rev. - St. Louis Medical Review. (St. Louis).
St. Louis M. & S. J. - St. Louis Medical and Surgical Journal.
St. Luke Hosp. Staff Clin. Bull. - St. Luke Hospital Staff Clinical Bulletin.
St. Mary Hosp. Gaz. (London) - St. Mary's Hospital gazette. (London).
St. Michael's Hosp. M. Bull. - St. Michael's Hospital Medical Bulletin (Toronto).
St. Paul M. J. - St. Paul Medical Journal.
St. Petersburg. med. Wchnschr. - St. Petersburger medicinische wochenschrift.
St. Petersburg med. Ztschr. - St. Petersburger medicinische zeitschrift. (St. Petersburg).
St. Thomas's Hosp. Gaz. - St. Thomas's Hospital Gazette.(London).
St. Thomas's Hosp. Rep. - St. Thomas's Hospital Reports. (London).
Stain Technol. - Stain Technology. (Geneva).
Stalpartius van der Wiel's Obst. rar. med. anat. chir., Lugd. Bat. -
Stanford M. Bull. - Stanford Medical Bulletin.
Stanford Univ. Publ. Univ. Series M. Sc. - Stanford University Publications, University Series, Medical Sciences. (California).
Starry Cross - Starry cross. (Philadelphia).
Stat. therm. franç. - Les stations thermales françaises. Supplément de la Gaz. méd. de France.
State Bd. Health Bull. Wisconsin - See: Bull. Bd. Health Wisconsin.
State Hosp. Q. (Utica) - State Hospital quarterly. (Utica, N.Y.).
Statist. Bull. Metrop. Life Insur. Co. - Statistical Bulletin Metropolitan Life Insurance Company. (New York).
Statist. obzor - Statisticky obzor. (Praha).
Staub. - Staub.
Stethoscope, (Bristol) - Stethoscope. (Bristol).
Stethoscope & Virginia M. Gaz. - Stethoscope and Virginia Medical Gazette.
Stomaco - Stomaco. (Napoli).
Stomatol. (Athénes) - Stomatologie.
Stomatol. ital. - La stomatologia italiana. (Rome).
Stomatologia, (Mod.) - Stomatologia. (Modena).
Strahlentherapie - Strahlentherapie. (Berlin).
Strahlentherapie, Sonderband (Berlin) -
Strasbourg méd. - Strasbourg médical, Gazette médicale de Strasbourg. (Strasbourg).
Strasbourg. med. Ztg. - Strassburger medizinische Zeitung. (Strasbourg).
Stud. Connaught Lab. - Studies from the research division of the Connaught Antitoxin Laboratories University of Toronto. (Toronto).
Stud. Dep. Anat. Cornell Univ. - Studies from the department of anatomy (at head of tp.) Publication of Cornell University Medical College (New York).
Stud. Dep. Path. Columbia Univ. - Studies from the department of Pathology of the College of Physicians and Surgeons. Columbia University. (New York).
Stud. Dep. Path. Cornell Univ. - Studies from the departments of pathology, bacteriology, hygiene (at head of tp.) Publications of Cornell University Medical College. (New York).
Stud. Dep. Path. Univ. Pennsylvania - Studies from the Department of Pathology; University of Pennsylvania. (Philadelphia).
Stud. Dep. Pediat. Washington Univ. School. Med. - Studies from the Department of Pediatrics of the Washington University School of Medicine and S. Louis Children's Hospital (S. Louis).
Stud. Div. Lab. N. York State Dep. Health - Studies from the Division of Laboratories and Research of the New York State Department of Health. (Albany,N.Y.).
Stud. Inst. Divi Thomae -
Stud. Lab. Philadelphia Gen. Hosp. - Studies from the laboratories of the Philadelphia General Hospital. (Philadelphia).
Stud. Ment. Ineffic.,(Lond.) - Studies in mental inefficiency (London).
Stud. Morphol. Lab. Univ. Cambridge - Studies; morphological laboratory university of Cambridge (England).
Stud. path. Entwcklng - Studien zur pathologie der entwicklung (Jena).
Stud. Psychol. Cath. Univ. America - Studies in psychology and psychiatry from the Catholic university of America,(Washington,Baltimore).
Stud. Rockefeller Inst. M. Res. - Studies from the Rockefeller Institute for Medical Research. (New York).
Stud. St. Louis Child. Hosp. - Studies from the St. Louis Children's Hospital. (St. Louis).
Studi Sassaressi - Studi sassaressi (Sassari).
Studies Inst. M. Research, Federated Malay States - Studies from the Institute for Medical Research Federated Malay States.
Studium - Studium. Rivesta di scienza medica (Napoli).
Sudeb. med. ekspertiza - Studebno-meditsinskaia ekspertiza. (Moskva).
Sudhoffs Arch. f. Gesch. d. Med. - Sudhoffs archiv für geschichte der medizin. (Leipzig). (See Arch. f. Gesch. d. Med.).
Summ. d. neuest. a d. ges. Med. - Summarium des neuesten aus der gesammten medicin (Leipzig).

Sunti Congr. internaz. fisiol. - Sunti; Congresso internazionale di fisiologia. (Roma).
Suppl. al Policlin. -
Surg. Clin. - Surgical clinic (Chicago).
Surg. Clin. Chicago - Surgical clinics of Chicago (Philadelphia; London).
Surg. Clin. North America - Surgical Clinics of North America. (Philadelphia).
Surg.,Gynec. & Obst. - Surgery, Gynecology and Obstetrics with International Abstract of Surgery. (Chicago).
Surg. J. - Surgical Journal. (Chicago).
Surgery - Surgery (S. Louis).
Survey - The Survey. (New York).
Survey Graphic - Survey graphic. (Concord, N.H.).
Survey Graphic - Survey graphic. (New York).
Sven. farm. tskr. - Svensk farmaceutisk tidskrift. (Stockholm).
Svenska läk.-sällsk. förh. - Svenska läkaresällsak apet; Förhandlingar (Stockholm).
Svenska läk. -Sällsk. handl. - Svenska läkaresällskapet handlingar. (Stockholm).
Svenska läk.-tidning - Svenska läkartidningen. (Stockholm).
Sydney Univ. Repr. - Sydney University reprints. (Sydney).
Syezd. rossiysk. khirurg. -
Symposium on Blood, Univ. Wisconsin - See:Univ. Wisconsin, Symposium on Blood.
Synops. clin. surg., Salt Lake City -
Syphilis, Paris - Syphilis. (Paris).
Syracuse, M. & S. J. - Syracuse Medical and Surgical Journal.
Syst. Gynec. (Mann) -
Syst. Med. (Reynolds) Lond -
Syst. Pract. M. (Tweedie) -
Tabulae biol. - Tabulae biologicae. (Berlin).
Tabulae biol., (Haag) - Tubulae biologicae periodicae. (Den Haag).
Tagebl. d. 52. Versamml. deutsch. Naturf. u. Ärzte, Baden-Baden - Tageblatt der 52. Versammlung deutscher Naturforscher u. Ärzte. Baden-Baden.
Tagebl. d. Versamml. deutsch. Naturf. u. Ärzte zu Cassel - Tageblatt der Versammlung deutscher Naturforscher u. Aerzte zu Cassel.
Tägl. Prax.,(Wien)- Die Tägliche Praxis. (Wien).
Taiwan Igakkai Zasshi - The Taiwan Igakkai Zasshi. (Formosa).
Tech. Bull. U. S. Dep. Agr. - Technical bulletins of the (U.S.) Department of Agriculture. (Washington).
Tech. chir. - Technique chirurgicale, (Paris).
Tech. Gemeindebl. - Technisches Gemeindeblatt. (Berlin).
Tech. Papers U. S. Dep. Commerce - Technical papers of the (U.S.) Department of Commerce (Bureau of Mines). (Washington).
Tech. san. mun.,(Par.) - Technique sanitaire et municipale, (Paris).
Tech. Supp. Am. J. Clin. Path. - Technical supplement of the american journal of clinical pathology (Baltimore).
Ted. klin. ve lab. derg. -
Tegen de tuberculose - Tegen de tuberculose. (Den Haag).
Temperance Cause - Temperance cause. (Boston).
Terap. arkh. - Terapevtichesky arkhiv. (Moskva).
Terap. Obozr. (Odessa) - Terapevticheskoe obozrienie. (Odessa).
Terapia - Terapia. (Milan).
Texas Cour. Rec. Med.- Texas courier-record of medicine (Fort Worth).
Texas Rep. Biol. & Med. - Texas Reports on Biology and Medicine.
Texas Sanitarian - Texas sanitarian.
Texas State J. Med. - Texas State Journal of Medicine. (Fort Worth, Tex.).
Thai Sc. Bull. - Thai science bulletin (Bangkok).
Therap. Diet. Age. - Therapeutic and dietetic age. (Elmira, N.Y.).
Therap. Gaz. - Therapeutic gazette (Detroit).
Therap. d. Gegw.- Therapie der Gegenwart (Berlin, Vienna).
Therap. Halbmhefte - Therapeutische Halbmonatshefte. (Leipzig).
Therap. Monatsh. - Therapeutische monatshefte.
Therap. Notes, (Detr.) - Therapeutic notes. (Detroit).
Therapia - Therapia. (Budapest).
Tidskr. mil. hälsov. - Tidskrift i militar hälsovard (Lund).
Tidskr. Norsk. laegeforen. - Tidsskrift for den Norske laegeforening. (Kristiania).
Tierärztl. Rdsch. - Tierärztliche Rundschau (Berlin).
Tijdschr. v. Diergeneesk. - Tijdschrift voor diergeneeskunde. (Utrecht,Amsterdam). (See: Nederl. tijdschr. v. dierk.).
Tijdschr. v. prakt. verlosk. - Tijdschrift voor praktische verloskunde, hoofdzaheligk ten dienste van vroedvrouwen (Haarlem, Amsterdam).
Tijdschr. v. sociale hyg. - Tijdschrfit voor sociale hygiene. (Zwolle).
Tijdschr. v. tandheelk. - Tijdschrift voor tandheelkunde. (Utrecht).
Tijdschr. Vereen. homeop. geneesh. - Tijdschrift van de Vereeniging van homeopathische geneesheeren in Nederland.
Times & Reg. - Times and register (Philadelphia).
Times & Surg. - Times and Surgery.
Tisiol.,Univ. nac. de Cordoba - Tisiologia, Universidad nacional de Cordoba.
Tohoku J. Exper. Med. - The Tohoku Journal of experimental Medicine. (Sendai, Japan).
Tohoku Univ. Sc. Rep. - Tohoku Imperial University science reports (See Sc. Rep. Tohoku Univ.).
Tokei Zasshi - Tokei Zasshi (Osaka).
Toko-ginec. Pract. - Toko-ginecologia practica.(Madrid).
Tokyo Igakkwai Zasshi - Tokyo Igakkwai Zasshi.
Tokyo-Iji-Shinski - Tokyo-iji-shinshi kyoku. (See Tokyser medizinische ..... Wochenschrift).
Tokyoer med. Wchnschr. - Tokyoer medizinische Wochenschrift (Tokaki).
Toledo City J. - Toledo City Journal. (Toledo City, Ohio).
Toledo M. Compend. - Toledo Medical Compend.(Toledo).
Toledo M. & S. J. - Toledo Medical and Surgical Journal (Toledo, Ohio).
Tommasi - Tommasi (Naples)
Torin no Siwori, (Fukuoka,Japan) -
Torino (Riv.) - Torino; Rivista mensile municipale. (Torino).
Toulouse-méd. - Toulouse-médicale. (Toulouse.)
Tr. A. Am. Physicians - Transactions of the Association of American Physicians,(Philadelphia).
Tr. A. Am. Teach. Dis. Child- Transactions of the Association of American Teachers of the Diseases of Children.
Tr.A. Life Insur. M.Dir. America. - Transactions of the Association of life Insurance Medical Directors of America.
Tr. A. Resid. & ex-Resid. Physicians Mayo-Clin. - Transactions of the Association of the Resident and Ex-resident Physicians of the Mayo Clinic.
Tr. Acad. Med. Ireland - Transactions of the Academy of Medicine of Ireland.
Tr. Acad. Med. (Toronto) - Transactions of the Academy of Medicine. (Toronto).
Tr. Alumnae Woman's Coll. Penn. -
Tr. Am. A.Genito-Urin, Surgeons - Transactions of the American Association of Genito-Urinary Surgeons. (St. Paul, Minn.).
Tr. Am. A. Obst. - Transactions of the American Association of Obstetricians and Gynecologists.
Tr. Am. A. Obst. Gynec. - Transactions of the American Association of Obstetrics, Gynecology and Abdominal surgery.
Tr. Am. A. Study Goiter 1938 - Transactions of the American Association for the study of Goiter. (See: Tr. Third Internat. Goiter Conf. & Am. A. Study Goiter.)
Tr. Am. Acad. Ophth. - Transactions of the American Academy of Ophthalmology and Otolaryngology.
Tr. Am. Acad. Optometry - Transactions of the American Academy of Optometry.

Tr. Am. Acad. Pediat. - Transactions of the American Academy of Pediatrics.
Tr. Am. Bronchosc. Soc. - Transactions of the American Bronchoscopic Society.
Tr. Am. Child Health A. - Transactions of the American Child Health Association.
Tr. Am. Child Hyg. A. - Transactions of the American Child Hygiene Association.
Tr. Am. Clin. & Climatol. A. - Transactions of the American Clinical and climatological Association. (Saranac Lake, N.Y.).
Tr. Am. Coll. Proct. - Transactions of the American College of Proctology.
Tr. Am. Dent. A. - Transactions of the American Dental Association.
Tr. Am. Gastroenter. A. - Transactions of the American Gastroenterological Association.
Tr. Am. Gynec. Soc. - Transactions of the American Gynecological Society. (S. Louis).
Tr. Am. Hosp. A. - Transactions of the American Hospital Association. (Chicago).
Tr. Am. Inst. Homoeop. - Transactions of the american institute of homoeopthy.
Tr. Am. Laryng. A. - Transactions of the American Laryngological Association. (Philadelphia).
Tr. Am. Laryng., Rhin. & Otol. Soc. - Transactions of the American Laryngological, Rhinological and otological Society. (Boston).
Tr. Am. M. A. - Transactions of the American Medical Association. (Chicago).
Tr. Am. M.A. Philadelphia. - Transactions of the American Medical Association of Philadelphia
Tr. Am. Micr. Soc. - Transactions of the American Microscopical Society. (Menaska, Wis.).
Tr. Am. Neurol. A. - Transactions of the American Neurological Association. (New York).
Tr. Am. Ophth. Soc. - Transactions of the American Ophthalmological Society. (New York).
Tr. Am. Otol. Soc. - Transactions of the American Otological Society. (St. Louis).
Tr. Am. Pediat. Soc. - Transactions of the American Pediatric Society. - (Chicago).
Tr. Am. Proct. Soc. - Transactions of the American Protologic Society. (Philadelphia).
Tr. Am. Soc. Heat. Ventil. Engin. - Transactions of the American Society of Heating and Ventilating Engineers.
Tr. Am. Soc. Plastic & Reconstructive Surg. - Transactions American Society of Plastic and Reconstructive Surgery.
Tr. Am. Soc. Region. Anesth. - Transactions of the American Society of Regional Anesthesia.
Tr. Am. Soc. trop. M. - Transactions of the American Society of Tropical Medicine.
Tr. Am. Surg. A. - Transactions of the American Surgical Association. (Philadelphia).
Tr. Am. Therap. Soc. - Transactions of the American Therapeutic Society. (New York).
Tr. Am. Urol. A. - Transactions of the American Urological Association.
Tr.Arizona M. A. - Transactions of the Arizona Medical Association.
Tr. Arkansas M. Soc. - Transactions of the Arkansas Medical Society.
Tr. Assur. M. Soc.,(Lond.) - Transactions of the Assurance Medical Society. (London).
Tr. Australas. M. Congr. - Transactions of the Australasian Medical Congress.
Tr. Bibliogr. Soc. (Lond.) - Transactions of the Bibliographical Society. (London).
Tr. Bristol Med. - Chir. Soc. - Transactions of the Bristol Medico-Chirurgical Society.
Tr. Calcutta M. Soc. - Transactions of the Calcutta Medical Society.
Tr. Canad. Soc. Dis. Child. - Transactions of the Canadian Society for the Study of Diseases of Children. (Toronto).
Tr. Canada M. A. - Transactions of Canada Medical Association.
Tr. Cent. States Pediat. Soc. - Transactions of the Central States Pediatric Society.
Tr. Chicago Path. Soc. - Transactions of the Chicago Pathological Society.
Tr. Chicago Urol. Soc. - Transactions of the Chicago Urological Society.
Tr. Clin. Soc. - Transactions of the Clinical Society.
Tr. Clin.Soc. London - Transactions of the Clinical Society of London.
Tr. Clin. Soc. Univ. Michigan - Transactions of the Clinical Society of the University of Michigan.
Tr. Coll. Phys. Philadelphia - Transactions of the College of Physicians of Philadelphia.
Tr. Colorado M. Soc. - Transactions of the Colorado Medical Society.
Tr. Conf. State Terr. Health Off. - Transactions of the annual conference of State and Territorial Health Officers with the United States Public Health Service.
Tr. Congr. Am. Physicians - Transactions of the Congress of American Physicians to Surgeons.
Tr. Dent. Soc. State N. York. - Transactions of the Dental Society of the State of New York.
Tr. Edinburgh Obst. Soc. - Published in Edinburgh Medical Journal.
Tr. Far East. A. Trop. Med. - Transactions of the Far Eastern Association of Tropical Medicine.
Tr. Glasgow Obst. & Gynaec. Soc. - Transactions of the Glasgow Obstetrical and Gynaecological Society.
Tr. Glasgow Path. & Clin. Soc. - Transactions of the Glasgow Pathological and Clinical Society.
Tr. Grant Coll. M. Soc. - Transactions of the Grant College of the Medical Society.
Tr. Gynaec. Soc. Boston - Transactions of the Gynaecological Society of Boston.
Tr. Hawaii Territor. M. A. - Transactions of the Hawaii Territorial Medical Association. (Honolulu).
Tr. Highl. Agric. Soc. Scotl. - Transactions of the Highland and Agricultural Society of Scotland. (Edinburgh).
Tr. Homoeop. M. Soc. - Transactions of the Homeopatic Medical Society.
Tr. Hunterian Soc. - Transactions of the Hunterian Society.
Tr. Indiana Acad. Ophth. & Otolaryng. - Transactions of the Indiana Academy of Ophthalmology and Otolaryngology. (Indianapolis).
Tr. Indiana M. Soc. - Transactions of the Indiana Medical Society.
Tr. Inst. Civil Engin. Ireland - Transactions of the Institution of Civil Engineers of Ireland.
Tr. Internat. Coll. Surgeons - Transactions of the international college of surgeons. (Chicago). (Continued as J. Internat. Coll. Surgeons).
Tr. Internat. M. Cong. - Transactions of the International Medical Congress.
Tr. Internat. Opth. Congr. - Transactions of the International Opthalmologie Congress.
Tr. Internat. Union Tuberc. - Transactions of the International Union against Tuberculosis.
Tr. Iowa M. Soc. - Transactions of the Iowa Medical Society.
Tr. Ital. M. Soc. (N.Y.) - Transactions and annual reports (at head of tp.: Italian Medical Society). (New York).
Tr. Jap. Path. Soc. - Transactions of the Japanese Pathologic Society.
Tr. Kansas Acad. Sc. - Transactions of the Kansas Academy of Science. (Lawrence, Kan.).
Tr. Kansas City. Acad. Med. - Transaction of the Kansas City Academy of Medicine. (Kansas City, Mo.).
Tr. Lehigh Valley M. A. - Transactions of the Lehigh Valley Medical Association.
Tr. Luzerne Co. M. Soc. - Transactions of the Luzerne county medical Society. (Welkes-Barre,Pa.).
Tr. M. A. - Transactions of the Medical Association.
Tr. M. A. Alabama - Transactions of the Medical Association of Alabama. (Birmingham, Ala.).
Tr. M. A. Georgia - Transactions of the Medical Association of Georgia.
Tr. M. A. Missouri - Transactions of the Medical Association of Missouri.
Tr. M. A. St. Louis - Transactions of the Medical Association of St. Louis.

Tr. M. Chir. Fac. Maryland - Transactions of the Medical and Chirurgical Faculty of the State of Maryland. (Baltimore).
Tr. M. & Phys. Soc. Bombay - Transactions of the Medical and Physical Society of Bombay.
Tr. M. & Phys. Soc. Calcutta - Transactions of the Medical and Physical Society of Calcutta.
Tr. M. Soc. - Transactions of the Medical Society.
Tr. M. Soc. Arkansas - Transactions of the Medical Society of Arkansas.
Tr. M. Soc. California - Transactions Medical Society of California.
Tr. M. Soc. City Hosp. Alumni,(St. Louis)- Transactions of the Medical Society City Hospital Alumni,(St. Louis).
Tr. M. Soc. County Albany - Transactions of the Medical Society County Albany.
Tr. M. Soc. Dist. Columbia - Transactions of the Medical Society of the District of Columbia.
Tr. M. Soc. Hawaii - Transactions of the annual meeting of the Medical Society of Hawaii. (Honolulu).
Tr. M. Soc. Kansa Lawrence - Transactions of the Medical Society Kansa Lawrence.
Tr. M. Soc. London - Transactions of the Medical Society of London. (London).
Tr. M. Soc. New Jersey - Transactions of the Medical Society of New Jersey.
Tr. M. Soc. New York - Transactions of the Medical Society of New York.
Tr. M. Soc. North Carolina - Transactions of the Medical Society of North Carolina.
Tr. M. Soc. Pennsylvania - Transactions of the Medical Society of Pennsylvania.
Tr. M. Soc. Sacramento - Transactions of the Medical Society of Sacramento.
Tr. M. Soc. Tennessee - Transactions of the Medical Society of Tennessee.
Tr. M. Soc. Virginia - Transactions of the Medical Society of Virginia.
Tr. M. Soc. Washington - Transactions of the Medical Society of Washington.
Tr. M. Soc. West Virginia - Transactions of the Medical Society of West Virginia.
Tr. Maimonides M. Soc. - Transactions;Maimonides Medical Society. (Detroit).
Tr. Maine M. A. - Transactions of the Maine Medical Association.
Tr. Massachusetts Med.-Leg. Soc.- Transactions of the Massachusetts Medico-Legal Society. (Boston, Mass.).
Tr. Med.-Chir. Soc.-Transactions of the Society medico-chirurgical.
Tr. Med.-Chir. Soc. Edinburgh - Transactions of the medico-chirurgical society of Edinburgh. (Edinburgh).
Tr. Med.-Chir. Soc. Glasgow- Transactions of Medico-Chirurgical Society of Glasgow.
Tr. Med.-Leg.Soc. (Lond.) - Transactions of the Medico-legal Society. (London).
Tr. méd. Paris - Transactions médicales,(Paris).
Tr. Michigan M. Soc.- Transactions of the Michigan Medical Society.
Tr. Minnesota M. Soc. St. Paul. - Transactions of the Minnesota Medical Society St. Paul.
Tr. Mississippi M. A. - Transactions of the Mississippi Medical Association.
Tr. N. Hampshire M. Soc. - Transactions of the New Hampshire Medical Society. (Concord,N.H.).
Tr. Nat. A. Prev. Tuberc. - Transactions of the National Association for the Prevention of Tuberculosis. (London).
Tr. Nat. Dent. A. - Transactions of the National Dental Association. (Philadelphia).
Tr. Nat. Eclect. M. A. - Transactions of the national eclectic medical association. (Rochester).
Tr. Nat.Safety Counc. - Transactions of the National Safety Council. (Chicago).
Tr. Nat. Soc. Electrother.- Transactions of the National Society of Electrotherapeutists. (New York).
Tr. Nat. Tuberc. A. - See: Nat. Tuberc. A. Tr.
Tr. New England Obst. & Gynec. Soc. - Transactions of the New England Obstetrical and Gynecological Society.
Tr. New England S. Soc. - Transactions of the New England Surgical Society. (Boston, Mass.).
Tr. New York Acad. Sc. - Transactions of the New York Academy of Sciences.
Tr. New York M. A. - Transactions of the New York Medical Association.
Tr. New York & New England A. Railw. Surgeons- Transactions of the New York and New England Association of Railway Surgeons.
Tr. New York Obst. Soc.- Transactions of the New York Obstetrical Society.
Tr. New York path. Soc. - Transactions of the New York Pathological Society.
Tr. New York Surg. Soc. - Transactions of the New York Surgical Society.
Tr. Nippon Dent. A. - Transactions of the Nippon Dental Association. (Tokyo).
Tr. North Central Am. Urol. A. - Transactions of the North Central Branch of the American Urological Association. (Cleveland).
Tr. Obst. Soc. (London)- Transactions of the Obstetrical Society,(London.).
Tr. Odont. Soc. Great Britain - Transactions of the odontological society of Great Britain.
Tr. Ohio M. Soc. - Transactions of the Ohio Medical Society.
Tr. Ophth. Soc. Australia- Transactions of the Ophthalmological Society of Australia.
Tr. Ophth. Soc. U. Kingdom. - Transactions of the ophthalmological Society of the United Kingdom.
Tr. Pacific Coast Oto-Ophth. Soc.- Transactions of the Pacific Coast Oto-ophthalmological Society.
Tr. Pacific Coast S. A. - Transactions of the Pacific Coast surgical Association.
Tr. Pacific Coast Soc. Obst.- Transaction of the Pacific Coast Society of Obstetrics and gynecology.
Tr. Pacific Homoeop. M. Soc. California- Transactions of Pacific Homoeopathic Medical Society of the State of California.
Tr. Pan. Am. M. Congr.- Transactions of the Pan-American Medical Congress.
Tr. Panama Pacific Dent. Congr.- Transactions of the Panama-Pacific DentalCongress.
Tr. Path. Soc. London - Transactions of the Pathological Society of London.
Tr. Path. Soc. Philadelphia- Transactions of the Pathological Society of Philadelphia.
Tr. Philadelphia Acad. Surg. - Transactions of the Philadelphia Academy of Surgery (Philadelphia.)
Tr. Philadelphia Obst. Soc.- Transactions of the Philadelphia Obstetrical Society.
Tr. Prov. M. & S. A. - Transactions of the Provincial Medical and Surgical Association.(Lond.).
Tr. Rhode Island M. Soc.- Transactions of the Rhode Island Medical Society.
Tr. Roy. Acad. Med. Ireland - Transactions of the Royal Academy of Medicine in Ireland (Dublin).
Tr. Roy. Irish Acad. Soc.- Transactions of the Royal Irish Academy of Science.
Tr. Roy. med.-Chir. Soc. Glasgow- Transactions of the royal medico-chirurgical society of Glasgow. (Glasgow). (Published in Glasgow Medical Journal).
Tr. Roy. Soc. Canada (Sect.V.Biol.Sc.) - Transactions of the Royal Society of Canada. Section V. Biological Sciences. (Ottawa).
Tr. Roy. Soc. Edinburgh - Transactions of the Royal Society of Edinburgh. (Edinburgh).
Tr. Roy. Soc. Trop. Med. & Hyg. - Transactions of the Royal Society of Tropical Medicine and Hygiene. (London).
Tr. Scient. Chem.-Pharm. Inst.,(Moskva) - Transactions of the Scientific Chemical-pharmaceutical Institute.(Moskva).
Tr. Sect. Dermat. & Syph. A. M. A. - Transactions section on dermatology and syphilology; american medical Association.

Tr. Sect. Gynec. Coll. Phys. Philadelphia - Transactions of the section on Gynecology College of Physicians of Philadelphia.
Tr. Sect. Laryng.,Otol. &Rhin.,A.M.A. - Transactions of the Section on Laryngology, Otology and Rhinology of the American Medical Association.
Tr. Sect. Obst. Gynec. & Abd. Surg.,A.M.A. - Transactions section on obstetrics, gynecology and abdominal surgery. American medical Association. (Ceased publication).
Tr. Sect. Ophth.,A. M. A. - Transactions of the Section on Ophthalmology of the American Medical Association.
Tr. Sect. Pediat. A. M. A. - Transactions; section on pediatrics american medical association. (Ceased publication).
Tr. Sect. Pharmacol. Ther. A.M.A. - Transactions of the Section on Pharmacology and Therapeutics of the American Medical Association.
Tr. Sect. Practice Med., A.M.A.- Transactions of the section on practice of medicine; American medical Association. (Ceased publication).
Tr. Sect. Surg.,Gen. & Abd., A.M.A. - Transactions of the section on surgery, general and abdominal of the american medical association. (Ceased publication).
Tr.Sect. -Urol. A. M. A. - Transactions of the section on urology American medical association. (Ceased publication).
Tr.Soc. Alumni Bellevue Hosp. - Transactions of the Society of the Alumni Bellevue Hospital.
Tr. Soc. biol. Barcelona - Treballs; societat du biologia (Barcelona).
Tr. Soc. path. jap. - Transactions Societatis pathologicae japonicae. (Tokyo).
Tr. South Carolina M. A. - Transactions of the South Carolina Medical Association.
Tr.South Indian Branch Brit. M. A. - Transactions of the South Indian Branch of the British Medical Association.
Tr. South. S. A. - Transactions of the Southern Surgical Association. (Philadelphia).
Tr.South. Surg. & Gynec. - Transactions of the Southern Surgery and Gynecology Association.
Tr. & Stud., Coll. Physicians, Philadelphia - Transactions and Studies of the College of Physicians of Philadelphia.
Tr. Texas M. A. - Transactions of the Texas Medical Association.
Tr. Third Intern. Goiter Conference - Transactions of the Third International Goiter Conference.
Tr. Ulster M. Soc.- Transactions of the Ulster Medical Society. (Belfast, Ireland).
Tr. Univ. Michigan Pediat. Infect. Dis. Soc.- Transactions of the University of Michigan Pediatric and Infectious Disease Society.
Tr. Vermont M. Soc. - Transactions of the Vermont Medical Society.
Tr.Wasn. Obst. & Gynec. Soc. - Transactions of the Washington Obstetrical and Gynecological Society.
Tr. West S. A. - Transactions of the Western Surgical Association. (St. Paul).
Tr.West. S. & Gynec. A. - Transactions of the Western Surgical and Gynecological Association.
Tr.West. Sect. Am. Urol. A. - Transactions of the Western Section of the American Urological Association.
Tr. Wisconsin M. Soc. - Transactions of the Wisconsin Medical Society.
Trab. Cáted. hist. crit. med.,(Madr.) - Trabajos de la Cátedra de historia critica de la medicina (Madrid).
Trab. Cated. de semiol. quir. Asunción -
Trab. Clin. Esucdero, B. Air. - Trabajos y publicaciones de la Clinica del professor Pedro Escudero. (Buenos Aires).
Trab. Inst. fisiol. Barcelona - Trabajos; Instituto de fisiologia: Universidad de Barcelone; Facultad de medicine (Barcelona).
Trab. Inst. med. social,(Lima)- Trabajos del Instituto de medicina social. (Lima).
Trab. d. lab. di inst. bacter. Camaro Pestana, (Lisbon)- Trabajos de laboratorio di instituto bacteriologico Camera Pestana. (Lisbon.)
Trab. d. lab. de Investig. Univ. de Madrid - Trabajos d. laboratorio de investigaciones biologicas; Universidad de Madrid.
Trab. Lab. pat. vet.,(Lisb.) - Trabalhos (Repostiorio de) do Laboratorio de patologia veterineria. (Lisboa).
Trained Nurse - Trained nurse and hospital review. (East Stroudsburg, Pa.).
Training School Bull. - Training school bulletin. (Veneland, N.J.).
Traité de chir. clin. et opér. (Le Dentu et Delbet Par.) -
Traité méd. inf. - Traité de médecine infantile. (Paris).
Transvaal M. J. (Johannesburg) - Transvaal medical journal (Johannesburg).
Transylvania J. Med. - Transylvania Journal of Medicine and the associate sciences (Lexington).
Trav. de chir. anat.-clin.-
Trav. Inst. d'hyg. pub. de l'État tchécoslovaque - Les travaux de l'institut d'hygiène publique de l'État tchécoslovaque. (Praha).
Trav. Inst. Rech. Physiol. (Moscou)-
Trav. Inst. thér.(Brux.) - Travaux de l'Institut de thérapeutique. (Bruxelles).
Trav. Lab. physiol. Inst. Solvay - Travaux de Laboratoire de physiologie (at head of tp.) Instituts Solvay. (Bruxelles).
Trav. Membres Soc. Chim. biol. - Travaux des membres de la société de chimie biologique. (Paris).
Trav. et publ. inst. prophylac. - Travaux et publications de l'institut prophylactique (Paris).
Trav. scient. Clin. inf. Univ. Varsovie - Travaux scientifiques de la Clinique infantile de l'Université de Varsovie. (Warszaws).
Trav. scient. Univ. Rennes - Travaux scientifiques de l'Université de Rennes. (Rennes).
Treas. Human Inher. - The Treasury of Human Inheritance.
Treba. Soc. biol. Barcel. - Treballs de la Societat de biologia. (Barcelona).
Tribuna méd. - Tribuna médica (Buenos Aires).
Tribuna méd. - Tribuna médica (Habana).
Tribuna méd. - Tribuna médica (Milan).
Tribuna méd. - Tribuna médica (Paris).
Tribuna méd. - Tribuna médica (Rio de Janeiro).
Tribuna méd. - Tribuna médica (Santiago de Chile).
Tri-State M. J. - Tri-State Medical Journal. (Shreveport, La.).
Trop. Dis. Bull. - Tropical Diseases Bulletin. (London).
Trop. med. vet.(Moskva)- Tropicheskaia meditsina i veterinaria. (Moskva).
Trop. natuur. - Tropische natuur. (Batavia).
Trop. Vet. Bull. (Lond.) - Tropical veterinary bulletin. (London).
Trudi Azerbaid. inst. mikrob. - Trudi Azerbaidzhanskovo instituta mikrobiology i gigieny. (Baku).
Trudi Inst. eksp. vet. med.(Moskva)- Trudi Gossudarsstvennovo instituta eksperimentalnoi veterinary i meditsiny. (Moskva).
Trudi Sev.-kavkaz. ass. nauch. issled. inst.- Trudi Severo-kavkazkoi assossiazy nauchno issledovatelskykh institutov.
Trudi Sezda bakt. epidem. san vrach. - Trudi sezda bakteriologov, epidemiologov,i sanitarnykh vrachei.
Trudi Sezda detsk. vrach. - Trudi Sezda detskykh vrachei.
Trudi Sezda fizioter.- Trudi Sezda fizioterapevtov.
Trudi Sovet. tuberk. Inst. (Moskva)- Trudi Pervovo sovetskovo tuberkuleznovo instituta. (Moskva).
Trudi Vseross. sezda glazn. vrach. - Trudi Pervovo vserossyskovo sezda glaznykh vrachei.
Trudi Vsesoiuz. sezda fizioter.- Trudi----Vsesoiuznovo sezda fizioterapevtov.
Trudy Fiziol. lab. Pavlova - Trudy Fiziologicheskikh laboratory akademika I.P. Pavlova.(Leningrad).

Trudy Inst. Genet. - Trudy Institut genetiki; Akademia nauk S.S.S.R. (Leningrad).
Trudy Inst. Méd. exper. Ukr. -
Trudy lab. eksper. biol. Moskovsk. zooparka - Trudy; laboratoria eksperimental'noi biologie Moskovskogo zooparka. (Moscow).
Trudy naucno-izsledov. Inst. Fiziol. - Trudy; Nauchno-issledovatel'skii institut fiziologii.
Trudy Obsh. dietsk. vrach. - Trudy Obschchestvo dietskikh vrachei v Moskva.
Trudy obsh. nevropat. (Saratov) - Trudy Obshchestva nevropatologov i psikhiatrov Saratovskovo Universiteta. (Saratov).
Trudy Obsh. Patol. v. S.-Peterb. - Trudy obshchestvo patologov v St.-Peterburgie. (Kharkov).
Trudy Obsh. Russk. vrach. v. Mosk. - Trudy Obshchestvo russkikh vrachei v Moskvie.
Trudy Odessk. g. boln. - Trudy Odesskaia gorodskaia bol'nitsa. (Odessa).
Trudy i Pratok. imp. Kavazk. med. Obsh.,Tiflis-
Trudy v. syezda Obsh. russk. vrach. v. pamyat Pirogova - Trudy IX Pirogovskago siezda; Obshchestvo russkikh vrachei v pamiat N. I. Pirogova.
Tsentr. med. J. - Tsentralny meditsinsky jurnal. (Moskva).
Tuberc. Abstr.,(Newark, N.J.). Tuberculosis abstracts. (Newark, N.J.).
Tubercle-Tubercle. (Chicago)
Tubercle-Tubercle. (London).
Tubercolosi - Tubercolosi. (Rome).
Tuberculology - Tuberculology. (Denver). (Continuation of Bull. Acad. Tuberc. Physicians).
Tuberk. - Biblioth. - Tuberkulose-Bibliothek. (Beihefte zur Ztschr. f. Tuberk. (Leipzig).
Tuberkulose, (Münch.) - Die Tuberkulose. (München).
Tumori - Tumori. (Milano).
Tung-Chi med. Monatschr. - Tung-Chi medizinische Monatschrift. (Shanghai).
Tunisie méd. - La Tunisie médicale, (Tunis).
Türk tib. cem. mec. - Türk tib cemiyeti mecmuasi. (Istanbul).
Twentieth Cent. Pract. - Twentieth Century Practitioner.
Tygodnik lek. -
Tzentr. M. J. -
U. S. Dept. Int. Fish and Wildlife Service - United States Department of the Interior Fish and Wildlife Service.
U. S. M. Invest. - United States medical investigator. (Chicago).
U. S. Nav. M. Bull. - United States naval medical bulletin. (Washington).
U. S. Vet. Bur. M. Bull. - See:M. Bull. Vet. Admin.
Ucheb. detsk. bolez - Uchebnik detskykh boleznei. (Moskva).
Uchenye Zapiski Saratov. Univ. - Uchenye zapiski, Saratov universitet (Saratov).
Ugesk. f. laeger - Ugeskrift for laeger. Den alm. danske laegeforening. (København).
Ujabb gyogyszer. és gyógy-mód. - Ujabb gyógyszerek és gyógymodok. (Budapest).
Ukrain. med. arkh. - Ukrainsky medichny arkhiv. (Kharkov).
Ukrain. med. vist. - Ukrainski medichnil vistnik. (Kiev).
Ulster M. J. - The Ulster Medical Journal. (Belfast).
Umbria med. - Umbria medica. (Terni).
Umschau- Umschau. (Frankfurt a. M.).
Ung. f. Arch. med. - Ungarisches archiv für medizin (Wiesbaden).
Ung. med. Presse - Ungarische medizinische presse. (Budapest).
Union méd. du Canada - L'union médicale du Canada. (Montréal).
Unión méd. (Caracas) - Unión médica (Caracas).
Unión méd.,(Lérida) - Union médica (Lérida).
Union méd. (Paris) - Union médicale; journal des intérêts scientifiques et pratiques, moraux et professionnels du corps médical. (Paris).
Union méd. scient. nord-est. - Union médicale et scientifique du Nord-est. (Reims).
Union méd. de la Seine-Inf.(Rouen)- Union médicale de la Seine-Inférieure. (Rouen).
United Fruit Co.,Med.Dept. - United Fruit Company Medical Department.
United Nations Compend. Czechoslovak M.A. in Great Britain - United Nations Compendium of the Czechoslovak Medical Association in Great Britain.
Univ. Buenos Aires. Mision estud. pat. reg. argent. - Universidad de Buenos Aires Mision de estudios de patologia regional argentina.(Jujuy.)
Univ. California Publ., Anat. - University of California Publications in Anatomy. (Berkeley).
Univ. California Publ.,Entomol. - University of California publications in Entomology. (Berkeley).
Univ. California Publ. Microbiol. - University of California Publications in Microbiology. (Berkeley).
Univ. California Publ.,Pharmacol.-University of California Publications in Pharmacology. (Berkeley).
Univ. California Publ.,Physiol. - University of California Publications in Physiology. (Berkeley).
Univ. California Pub., Pub. Health - University of California Publications in Public Health. (Berkeley).
Univ. California Publ.,Zoöl. - University of California Publications in Zoölogy. (Berkeley).
Univ. Cincinnati Rec. - University of Cincinnati record. (Cincinnati).
Univ. Colorado M. Bull. - University of Colorado Medical Bulletin.
Univ. Durham Coll. M. Gaz. - University of Durham College Medical Gazette. (Newcastle-upon-Tyne).
Univ. Hosp. Bull.(Ann Arbor) - University Hospital Bulletin. (Ann Arbor).
Univ. Illinois Bull. - University of Illinois bulletin. (Urbana).
Univ. Iowa Monogr. - University of Iowa monographs. (Iowa City).
Univ. Iowa Stud. - University of Iowa studies. (Iowa City).
Univ. Izviesk.,(Kiev) - Universitetskiia izviestiia (Kiev).
Univ. M. Mag. - University Medical Magazine.
Univ. M. Rec. - University Medical Record.
Univ. Med. (Galveston) - University of Medicine, (Galveston).
Univ. of Missour. Agricult. Exper. Station Res. Bull. - University of Missouri Agricultural Experimental Station Research Bulletin
Univ. Nebraska Stud. - University of Nebraska studies (Lincoln, Nebr.).
Univ. Oregon Pub. - University of Oregon publication. (Eugene, Oreg.).
Univ. Pennsylvania Lect. - University of Pennsylvania lectures. (Philadelphia).
Univ. Pennsylvania M. Bull. - University of Pennsylvania Medical Bulletin.
Univ. Pittsburgh Bull. School. Med. - University of Pittsburgh bulletin. School of medicine. (Pittsburgh).
Univ. Toronto. M. J. - University of Toronto Medical Journal. (Toronto).
Univ. Toronto Stud. - University of Toronto studies. (Toronto).
Univ. Washington Publ. biol. - University of Washington publications in biology. (Seattle, Washington).
Univ. West. Ontario M. J. - University of Western Ontario Medical Journal.
Univ. Wisconsin,Symposium on Blood - University of Wisconsin,Symposium on Blood and Blood-forming Organs.
Untersuch. z. Naturl. d. Mensch. u. d. Thiere- Untersuchungen zur naturlehre des menschen und der Thiere (Frankfurt a.M.).

Untersuch. a. d. physiol. Lab. in Bonn - Untersuchungen aus dem physiologischen Laboratorium in Bonn.
Upsala läkaref. förh. - Upsala läkareförenings förhandlingar. (Upsala).
Urol. & Cutan. Rev. - Urologie and Cutaneous Review. (St. Louis).
Urologia - Urologia. (Budapest).
Urologia - Urologia. Rassegna trimestrale di urologia medico chirurgica. (Belluno, Venezia, Italy).
Urologia, (Moskva) - Urologia. (Moskva).
Usp. sovrem. biol. - Uspekhi sovremennoi biologii. (Moscow).
Utah State M. J. - Utah state medical journal (Salt Lake City) (Continued as Rocky Mountain M. J.).
Uzhny' med. J. -Uzhny meditsinsky jurnal. (Odessa).
Valsalva - Il valsalva. (Roma).
Ven. Dis. Inform. - Venereal Disease Information. (Washington).
Vener. derm. (Moskva) - Venerologia i dermatologia. (Moskva).
Vereinsbl. d. pfälz. Aerzte - Vereinsblatt der pfälzischen ärzte. (Frankenthal).
Vererb. & Geschlleben - Vererbung und Geschlechtsleben. (Dresden).
Verhandel. Akad. wet. Amsterdam. - Verhandelingen der K. Akademie van wetenschappen te Amsterdam.
Verhandel. - uitgeg. d. de Holland Monatsch. d. Weetensch. te Haarlem -
Verhandl. d. Anat. Ges. zu Jena - Verhandlungen der anatomische gesellschaft (Jena).
Verhandl. d. Berlin. Gesellsch. f. Anthrop. - Verhandlungen der Berliner gesellschaft für anthropologie ethnologie und urgeschichte.
Verhandl. d. Berlin. med. Gesellsch. - Verhandlungen der Berliner medizinische gesellschaft. (Leipzig).
Verhandl. Deutsch. Dermat. Gesellsch. - Verhandlungen der Deutschen dermatologischen Gesellschaft. (Berlin).
Verhandl. deutsch. Gesellsch. f. Chir. - Verhandlungen d. Deutsche gesellschaft für chirurgie. (Berlin).
Verhandl. Deutsch. Gesellsch. gerichtl. Med. - Verhandlungen der Deutschen Gesellschaft für gerichtliche und soziale Medizin.
Verhandl. deutsch Gesellsch. f. Gynäk. - Verhandlungen deutschen gesellschaft für gynäkologie. (Leipzig).
Verhandl. d. deutsch. Gesellsch. f. inn. Med. - Verhandlungen der deutschen Gesellschaft für innere Medizin. (München).
Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. - Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. (Dresden, Leipzig).
Verhandl. Deutsch. Gesellsch. f. Unfallh. - Verhandlungen der Deutschen Gesellschaft für Unfallheilkunde, Versicherungs-und Versorgungsmedizin.
Verhandl. d. deutsch. Gesellsch. f. Urol. - Verhandlungen d. deutsche gesellschaft für urologie. (Berlin).
Verhandl. Deutsche. orthop. Gesellsch. - Verhandlungen der Deutschen Orthopädischen Gesellschaft. (Stuttgart).
Verhandl. d. deutsch. path. Gesellsch. - Verhandlungen d. deutsche pathologische gesellschaft. (Jena).
Verhandl. Deutsch. Röntg.-Gesellsch. - Verhandlungen der Deutschen Röntgen-Gesellschaft. (Hamburg).
Verhandl. d. deutsch. zool. Gesellsch. - Verhandlungen d. deutsche zoologische gesellschaft. (Leipzig, Berlin).
Verhandl. Gesellsch. deutsch. Hals & c. Aerzte - Verhandlungen der Gesellschaft deutscher Hals-, Nasen- und Ohrenärzte.
Verhandl. d. Gesellsch. deutsch. Naturforsch. u. Ärzte - Verhandlungen d. gesellschaft deutscher naturforscher und aerzte (Berlin, Leipzig).
Verhandl. d. Gesellsch. f. Geburtsh. u. Gynäk. in Berlin - Verhandlungen d. gesellschaft für geburtshülfe und gynäkologie (Berlin).
Verhandl. d. Gesellsch. f. Geburtsh. u. Gynäk. zu Leipzig - Verhandlungen d. gesellschaft für geburtshülfe und gynäkologie. (Leipzig).
Verhandl. Gesellsch. f. phys. Anthrop. - Verhandlungen der Gesellschaft für physische Anthropologie. (Stuttgart).
Verhandl. Gesellsch. f. Verdauungskrank. - Verhandlungen der Gesellschaft für Verdauungs- und Stoffwechselkrankheiten.
Verhandl. d. internat. Kongr. f. Geburtsh. -
Verhandl. Internat. Kongr. Sexforsch. - Verhandlungen des Internationalen Kongresses für Sexualforschung.
Verhandl. d. X internat. med. Cong. -
Verhandl. Jap. chir. Gesellsch. - Verhandlung der Japanischen chirurgischen Gesellschaft. (Tokyo).
Verhandl. Jap. path. gesellsch. - Verhandlungen der Japanischen pathologischen Gesellschaft. (Tokyo).
Verhandl. Naturhist.-med. Verein. Heidelberg - Verhandlung des Naturhistorisch-medizinischen Vereins zu Heidelberg. (Heidelberg).
Verhandl. Nord. Kongr. inn. Med. - Verhandlungen des Nordischen Kongresses für innere Medizin.
Verhandl. Ophth. Ges., (Berl.) - Verhandlungen der ausserordenlichen Tagung der Ophthalmologischen Gesellschaft. (Berlin).
Verhandl. d. phys.-med. Gesellsch. - Verhandlungen d. physikalisch-medicinische gesellschaft (Würzburg). (Continued as Ber. d. phys. -med. Gesellsch. zu Würzburg.).
Verhandl. Schweiz. naturforsch. Ges. - Verhandlungen; Schweizerische naturforschende gesellschaft. (Geneva).
Verhandl. Schweiz. Physiol. -
Verhandl. ungar. ärztl. Gesellsch. - Verhandlungen der ungarischen ärztlichen Gesellschaften. (Budapest).
Verhandl. d. Ver. deutsch. Laryngolog. - Verhandlungen der deutscher laryngologen (Berlin).
Verhandl. d. Ver. pfälz. Aerzte - Verhandlungen d. verein pfälzischer aerzte.
Verm. Abhandl. (v. einer Gesellsch. pract. Aerzte zu St. Petersberg) (Leipzig). Vermischte abhandlungen aus dem gebiete der heilkunde. (Gesellschaft praktischer aerzte zu St. Petersburg).
Vermont. M. Month. - Vermont Medical Monthly (Burlington).
Veröff. Medverwalt. - Veröffentlichungen aus dem Gebiete der Medizinalverwaltung. (Berlin).
Veröffentl. Deut. Gesellsch. Rheumabekämpf. - Veröffentlichenung der Deutschen Gesellschaft für Rheumabekämpfung. (Berlin).
Veröffentl. Heer. San. - Veröffentlichungen aus dem Gebiete des Heeressanitätswesens. (Berlin).
Veröffentl. a. d. Geb. Kriegs Konstpath. - Veröffentlichungen aus dem Gebiete der Kriegs- und Konstitutionspathologie (Jena).
Veröffentl. a. d. Geb. Marine San. - Veröffentlichungen aus dem Gebiete des Marine-Sanitätswesens. (Berlin).
Veröffentl. a. d. Geb. d. Med.-Verwalt - Veröffentlichungen aus dem Gebiet der Medizinischen Verwaltung.
Veröffentl. a. d. Geb. Mil. San.- Veröffentlichungen aud dem Gebiete des Militärsanitätswesens. (Berlin).
Veröffentl. a. d. Geb. d. Volksgesundhdienstes - Veröffentlichungen aus dem Gebiete des Volks gesundheitsdienstes. (Berlin).
Veröffentl. a. d. Gewerbepath. - Veröffentlichungen aus der Gewerbe- und Konstitutionspathologie. (Jena).
Veröffentl. d. Hufeland. Gesellsch. in Berl. Balneol Gesellsch. - Veröffentlichungen d. Hufelandsche gesellschaft in Berlin, Balneologische gesellschaft. (Berlin).

Veröffentl. Reichsgesundhamt.- Veröffentlichungen des Reichsgesundheitsamts. (Berlin).
Veröffentl. Tierärzte Preussens- Veröffentlichungen aus den Jahres-Veterinärberichten der beamteten Tierärzte Preussens (Berlin).
Veröffentl. Volksgesundhamt. (Wien)- Veröffentlichungen des Volksgesundheitsamtes im Deutsch-österreichischen Staatsamt für soziale Verwaltung (Wien).
Versl. d. Koninkl. Akad. v. Wetensch.- Werslagen d. Koninkl. K. Akademie van wetenschappen, (Amsterdam).
Versl. volksgezondh.- Verslagen en mededeelingen betreffende de volksgezondheid's Gravenhage.
Vestnik cesk. lek.- Vestnik ceskoslovesnkych lekaru (Praha).
Vestnik khir.- Vestnik khirurgii (Leningrad).
Vestnik mikr., epidemiol. i parazitol.- Vestnik mikrobiologii, epidemiologii i parazitologii (Saratov).
Vestnik obsh. gig. subed. i prakt. med.- Vestnik obshchestvennoi gigieny, sudebnoi i prakticheskoi meditsiny (Petrograd).
Vestnik oftal.- Vestnik oftalmologii (Moscow).
Vestnik rentg.- Vestnik rentgenology i radiology (Leningrad).
Vestnik sovet. oto-rino-lar.- Vestnik sovetskoi oto-rino-laringology (Moskva).
Vestnik subed. med.- Viestnik sudebnoi meditsiny i obshchestvennoi gigieny (St- Petersburg).
Vet. Bull (Lond.)- Veterinary bulletin (London).
Vet. Bull. (Wash.)- Veterinary bulletin (Washington).
Vet. hist. Jahrb.- Veterinärhistorisches Jahrbuch (Leipzig).
Vet. hist. Mitt.- Veterinärhistorische Mitteilungen (Hannover).
Vet. J. - Veterinary Journal (London).
Vet. Med.- Veterinary Medicine (Chicago).
Vet. Pract. (Evanston)- Veterinary practice (Evanston, Ill).
Vet. Rec.- Veterinary Record (London).
Vet. Rev. (Edinb.)- Veterinary review (Edinburgh).
Victorian Yearb.- Victorian yearbook (Melbourne).
Vida nueva- Vida nueva (Habana).
Vie méd.- La vie médicale (Paris).
Villaclara méd.- Villaclara médica (Santa Clara, Cuba).
Virchows Arch. f. path. Anat.- Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin (Berlin).
Virginia Clin. Rec.- Virginia Clinical Record (Richmond).
Virginia Health Bull.- Virginia health bulletin (Richmond, Va).
Virginia M. Monthly- Virginia Medical Monthly. (Richmond).
Virginia M. Semi-Month.- Virginia Medical Semi-Monthly (Richmond).
Visual Educ.- Visual education (Chicago).
Vitamine und Hormone- Vitamine und Hormone.
Vitamins & Hormones- Vitamins and Hormones.
Vjschr. f. gerichtl. Med.- Vierteljahrsschrift für gerichtliche Medizin und öffentliches Sanitätswesen (Berlin).
Vjschr. f. Zahnheilk.- Vierteljahrsschrift für zahnheilkunde (Berlin).
Vocat. Summary- Vocational summary (Washington).
Voenno med. J. (Moskva)- Voenno-meditsinski jurnal (Moskva).
Voenno-med. Z. (St. Petersb.)- Voenno-meditsinskii zhurnal (St. Petersburg).
Voenno-san. delo- Voenno-sanitarnoe delo (Moskva).
Voj. rozhl.- Vojenske rozhledy (Praha).
Voj.-san. glasnik.- Vojno-sanitetski glasnik (Belgrade).
Voj. zdrav. listy- Vojenske zdravotnicke listy (Praha).
Voks Bull.- Voks Bulletin.
Volk & Rasse- Volk und Rasse (München).
Volkskragte- (See: Manpower).
Volkswohlfahrt- Volkswohlfahrt (Berlin).
Volta Rev.- Volta review (Washington).
Vopr. genet. reflex.- Voprosi geneticheskoi reflexology i pedology mladenchestva. (Leningrad).
Vopr. neurokhir.- Voprosy neurokhirurgii (Moscow).
Vopr. Onkol.- Voprosy onkologii (Kharkov; Kiev).
Vopr. pediat.- Voprosi pediatry, pedology i okhrany materinstva i detstva (Leningrad).
Vopr. pedol.- Voprosi pedology i detskoi psikhonevrology (Moskva).
Vopr. tuberk.- Voprosi tuberkulosa (Moskva).
Vorschr. sächs. Vet.- Vorschriften für das Sächsische Veterinärwesen (Dresden).
Vorschr. Vet. Bayern- Vorschriften für das Veterinärwesen in Bayern (München).
Vox (Berl.)- Vox; Internationales Zentralblatt für experimentelle Phonetik (Berlin).
Vox med.- Vox medicorum (Utrecht)
Vrach. delo.- Vrachebnoe delo, nauchnyĭ meditsinskii zhurnal (Kharkov).
Vrach. gaz.- Vrachebnae gazeta (Leningrad).
Vrach. Gaz. - Vrachebnaia gazeta (St.Petersburg).
Vrach. Viedom.- Vrachebnyia vîedomosti.
Vrtljschr. f. d. prakt. Heilk.- Vierteljahrsschrift für die praktische heilkunde (Prague, Leipzig).
War Doctor.- The War Doctor.
War. Med.- War Medicine (Paris).
Warszaw. Czas. lek.- Warszawskie czasopismo lekarskie (Warsaw).
Washington Bull.- The Washington Bulletin.
Washington M. Ann.- Washington Medical Annals (Washington).
Washington Univ. M. Alumni Quart.- The Washington University Medical Alumni Quarterly.
Water Bodem Lucht- Water, Bodem, Lucht (Amsterdam).
Water Supply Papers- Water supply papers of the (U.S.) Geological Survey (Washington).
Wchnbl. d. k. k. Gesellsch. d. Aerzte in Wien- Wochenblatt d. K. K. Gesellschaft der aerzte in Wien (Anzeiger).
Wchnschr. f. d. ges. Heilk.- Wochenschrift für die gesammte heilkunde (Berlin).
Wchnschr. f. Tierh. u. Viehzucht- Wochenschrift für tierheilkunde und viehzucht.
Wchnschr. f. Ther. Hyg. Auges- Wochenschrift für Therapie und Hygiene des Auges (Dresden).
Weekly Bull. Bd Health California- Weekly bulletin of the State Board of Health of California (Sacramento).
Weekly Bull. California Dep. Pub. Health- Weekly bulletin; California Department of Public Health. (Sacramento, Calif.).
Weekly Bull. Chicago Dep. Health - Weekly bulletin; Chicago Department of Health (Chicago).
Weekly Bull. Dep. Health City N. York- Weekly bulletin of the Department of Health, City of N. York. (New York).
Weekly Bull. Jackson Co. M. Soc.- Weekly bulletin of the Jackson County Medical Society (Kansas, City).
Weekly Bull. St. Louis M. Soc.- Weekly Bulletin of the St. Louis Medical Society.
Weekly Health Index- Weekly health index of the (U.S.) Bureau of Cenzus (Washington).
Weekly M. Rev.- Weekly Medical Review (St. Louis).
Weekly Pub. Health Rep. (Wash.)- Weekly public health reports (Washington, D. C.).
Weekly Roster (Phila.)- Weekly roster and medical digest (Philadelphia).
Welf. Bull. (Springf.)- Welfare bulletin (Springfield, Ill.).
Welf. Mag. (Pontiac)- Welfare magazine (Pontiac,, Ill.).
Werk. u. h. Genootsch. ti Bevard. d. Nat., Geneesen Heelk. to Amsterdam.-
West African M. J.- West African medical journal (Lagos) (Ceased publication).
West. Hosp. Rev.- Western hospital review (San Francisco).
West. J. Med.- Western Journal of Medicine (Indianapolis).
West. J. Med. & Surg.- Western Journal of Medicine and Surgery (Louisville, Ky.)
West. J. Surg.- The Western Journal of Surgery, Obstetrics and Gynecology (Portland, Ore).
West. Lancet San Francisco- Western Lancet of San Francisco.
West London M. J.- West London Medical Journal (London).

West M. Rep.- Western Medical Reporter (Chicago, N.Y.)
West. M. Rev.- Western Medical Review (Lincoln; Omaha, Neb.)
West. M. Times.- Western Medical Times (Denver).
West. Med.-Chir. J.- Western Medico-Chirurgical Journal (Keokuk).
West. Reserve M. J.- Western Reserve Medical Journal (Cleveland).
West Virginia M. J.- West Virginia Medical Journal (Charlestown).
Westdeut. Aerzte Ztg.- Westdeutsche Aerzte-Zeitung für Standesfragen und soziale Medizin (Frankfurt a.M.).
Westminster Hosp. Rep.- Westminster Hospital Report (London).
Wiadom. weteryn.- Wiadomosci weterynaryjne (Warsaw).
Wien. Arch. f. inn. Med.- Wiener Archiv für innere Medizin (Wien).
Wien. Beitr. z. prakt. Arznk.-
Wien. klin. Rundschau- Wiener klinische Rundschau (Vienna).
Wien. klin. Wchnschr.- Wiener klinische Wochenschrift (Wien).
Wien. med. Bl.- Wiener medizinische blätter.
Wien. Med.-Halle- Wiener medizinal-halle (Vienna).
Wien. med. Presse- Wiener medizinische presse (Vienna).
Wien. med. Wchnschr.- Wiener medizinische Wochenschrift (Wien).
Wien. tierärztl. Monatschr.- Wiener tierärztliche monatsschrift (Wien).
Wilhelm Roux' Archiv- Wilhelm Roux' archiv für entwicklungsmechanik der organismen (Leipzig).
Wisconsin M. J.- Wisconsin Medical Journal (Milwaukee).
Wissensch. Ber. d. Moskauer Staatsuniv.-
Without the Camp (Lond.)- Without the camp (London).
Women in Med.- Women in Medicine (Oak Park, Ill.).
Women's M. J.- Women's Medical Journal.
Woodlawn Hosp. Clin. Quart.- Woodlawn Hospital clinical quarterly (Chicago, Ill.).
World Health (Par.)- World's health (Paris).
World Peace Found. Pamphl.- World Peace Foundation pamphlets (Boston, Mass.).
Württemb. med. Korresp. bl.- Medizinisches korrespondenzblatt für Württemberg.
Würzburg. Abhandl.- Würzburger abhandlungen aus dem gesamtgebiete der praktischen medizin (Würzburg).
Würzburg. Abhandl. Med.- Würzburger Abhandlungen aus dem Gesamtgebiet der Medizin (Leipzig).
Würzburg. med. Ztschr.- Würzburger medicinische zeitschrift. (Würzburg).
Würzburg. naturwiss. Ztschr.- Würzburger Naturwissenschaftliche Zeitschrift (Würzburg).
Wyadomosci lek.-
Yale J. Biol. & Med.- Yale Journal of Biology and Medicine (New Haven).
Yale Rev.- The Yale Review (New Haven, Conn.).
Yearb. Am. philos. Soc.- The Yearbook of the American Philosophical Society (Philadelphia).
Yearb. M. A. Gr. New York- Yearbook, Medical Association of Greater City of New York (New York).
Yearb. New York N. England A. Railw.- Yearbook of the New York and New England Association fo Railway Surgeons.
Yearb. U. S. Dep. Agr.- Yearbook of the (U.S.) department of Agriculture (Washington).
Yuzhno-russk. med. gaz.-
Z. Akus.- Zhurnal akusherstva i zhenskikh boleznei.
Z. sovrem. khir.- Zhurnal sovremennoi khirurgii(Moscow)
Zacchai (Rome)- Zacchia; rivista di medicina legale e delle assicurazione.
Zahnärztl. Rdsch.- Zahnaerztliche rundschau (Berlin).
Zellstimulationsforschungen- Zellstimulationsforschungen (Berlin).
Zentr.-Bl. f. d. ...Aerzte Oest.-Ungarn's Wien.-
Zentr. org. ges. Chir.- Zentralorgan für die gesamte Chirurgie und iher Grenzgebiete (Berlin).
Zentralbl. f. allg. Path. u. Path. Anat.- Zentralblatt für allgemeine Pathologie und pathologische Anatomie (Jena; Würzburg).
Zentralbl. f. Bakt.- Zentralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten (Jena).
Zentralbl. f. Biochem.- Zentralblatt für Biochemie und Biophysik mit Einschluss der theoretischen Immunitätsforschung (Leipzig).
Zentralbl. f. Chir.- Zentralblatt für Chirurgie (Leipzig).
Zentralbl. f. d. ges. Hyg.- Zentralblatt für die gesamte Hygiene (Berlin).
Zentralbl. f. d. ges. Kinderh.- Zentralblatt für die gesamte Kinderheilkunde (Berlin).
Zentralbl. f. d. ges. Neurol. u. Psychiat.- Zentralblatt für die gesamte neurologie und Psychiatrie (Berlin).
Zentralbl. f. d. ges. Ophth.- Zentralblatt für die gesamte Ophthalmologie und ihre Grenzgebiete (Berlin).
Zentralbl. f. d. ges. Radiol.- Zentralblatt für die gesamte Radiologie (Berlin).
Zentralbl. f. d. ges. Therap.- Zentralblatt für die gesamte therapie (Vienna; Berlin).
Zentralbl. f. d. ges. Tuberk.-Forsch.- Zentralblatt für die gesamte Tuberkuloseforschung (Berlin; Würzburg).
Zentralbl. f. Gewerbehyg.- Zentralblatt für Gewerbehygiene und Unfallverhütung (Berlin).
Zentralbl. f. d. Grenzgeb. d. Med. u. Chir.- Zentralblatt für die grenzgebiete der medizin und chirurgie (Jena).
Zentralbl. f. Gynäk.- Zentralblatt für Gynäkologie (Leipzig).
Zentralbl. f. Hals-,Nasen- u. Ohrenh.- Zentralblatt für Hals-, Nasen- und Ohrenheilkunde sowie deren Grenzgebiete (Berlin).
Zentralbl. f. Haut- und Geschlechtskr.- Zentralblatt für Haut- und Geschlechtskrankheiten sowie deren Grenzgebiete (Berlin).
Zentralbl. f. Herz- u. Gefässkr.- (See: Ztschr. f. Kreislaufforschung).
Zentralbl. f. inn. Med.- Zentralblatt für innere Medizin (Leipzig).
Zentralbl. f. d. med. Wissensch.- Zentralblatt für die medizinischen wissenschaften (Berlin).
Zentralbl. f. Neurochir.- Zentralblatt für Neurochirurgie (Leipzig).
Zentralbl. f. Path.- (See: Zentralbl. f. allg. Path. u. path. Anat.)
Zentralbl. f. Physiol. (Wien)- Zentralblatt für Physiologie (Wien).
Zentralbl. f. Psychotherap.- Zentralblatt für Psychotherapie und ihre Grenzgebiete einschliesslich der medizinischen Psychologie und psychischen Hygiene (Leipzig).
Zentralbl. States M. Monit.-
Zhur. nevropat. psykhiat.- Zhurnal nevropatologii i psikhiatrii.
Zhur. teor. prakt. med.- Zhurnal teoreticheskai i prakticheskoi meditsiny.
Zhur. ush., nos. i gorl. bolez.- Zhurnal ushnykh, nosovykh i gorlovykh bolezney (Kharkov).
Ziekenhuis- Ziekenhuis (Amsterdam).
Zodiacus med.-gall.- Zodiacus medico-gallicus (Geneva).
Zool. Ann. (Würzb.)- Zoologische Annalen (Würzburg).
Zool. Anz.- Zoologischer anzeiger (Leipzig).
Zool. Jahrb. Abt. f. allg. Zool.- Zoologische jahrbücher Abt. für allgemeine zoologie und physiologie der tiere (Jena).
Zool. Jahrb., Abt. f. Anat.- Zoologische jahrbücher Abt. für anatomie und ontogenie der tiere (Jena).
Zoologica- Zoologica (Cassel; Stuttgart).
Zoologica (N.Y.)- Zoologica (New York).
Ztschr. f. allg. Physiol.- Zeitschrift für allgemeine Physiologie (Jena).
Ztschr. f. Altersforsch.- Zeitschrift für Altersforschung (Dresden; Leipzig).
Ztschr. f. Anat. u. Entwcklngsgesch.- Zeitschrift für Anatomie und Entwicklungsgeschichte (Munich; Berlin).
Ztschr. f. angew. Anat. u. Konstitutionsl.- Zeitschrift für angewandte Anatomie und Konstitutionslehre (Berlin).

Ztschr. f. Angew. Chem.- Zeitschrift für angewandte Chemie.
Ztschr. angew. Entom.- Zeitschrift für angewandte Entomologie (Berlin).
Ztschr. angew. Psychol.- Zeitschrift für angewandte Psychologie und Charakterkunde (Leipzig).
Ztschr. f. ärztl. Fortbild.- Zeitschrift für ärztliche Fortbildung (Jena).
Ztschr. f. Augenh.- Continued as Ophthalmologica.
Ztschr. f. Bahnärzte- Zeitschrift für Bahnärzte (Leipzig).
Ztschr. f. Behandl. Anomal.- Zeitschrift für die Behandlung Anomaler (Halle a.S.).
Ztschr. f. Behandl. Schwachsinn.- Zeitschrift für die Behandlung Schwachsinninger (Halle a.S.).
Ztschr. f. Bekämpf. Geschlkr.- Zeitschrift für Bekämpfung der Geschlechtskrankheiten (Leipzig).
Ztschr. f. Bevölkpolit.- Zeitschrift für Bevölkerungspolitik und Säuglingsfürsorge (Leipzig).
Ztschr. f. Biol.- Zeitschrift für Biologie (Munich; Berlin).
Ztschr. f. Desinfekt.- Zeitschrift für Desinfektions- und Gesundheitswesen (Dresden).
Ztschr. d. deutsch Chir. Ver.-
Ztschr. f. diatet. u. physik. Therap.- Zeitschrift für diatetische und physikalische therapie.
Ztschr. f. Endokrinol.- Zeitschrift für Endokrinologie.
Ztschr. f. d. Erforsch. u. Behandl. d. jugendl. Schwachsinns.- Zeitschrift für die erforschung und behandlung des jugendlichen schwachsinns auf wissenschaftlicher grundlage (Jena).
Ztschr. f. Ernährung- Zeitschrift für Ernährung (Leipzig).
Ztschr. f. Ethnol.- Zeitschrift für ethnologie (Berlin).
Ztschr. f. exp. Path. Ther.- Zeitschrift für experimentelle Pathologie und Therapie (Berlin).
Ztschr. f. Fleisch Milchhyg.- Zeitschrift für Fleisch- und Milchhygiene (Berlin).
Ztschr. f. Geburtsh. u. Frauenkr.- Zeitschrift für geburtshülfe und frauenkrankheiten (Stuttgart).
Ztschr. f. Geburtsh. u. Gynäk.- Zeitschrift für Geburtshülfe und Gynäkologie (Stuttgart).
Ztschr. f. d. Ges. Anat.- Zeitschrift für die gesamte anatomie (Munich; Berlin).
Ztschr. f. d. ges. exper. Med.- Zeitschrift für die gesamte experimentelle Medizin (Berlin).
Ztschr. f. d. ges. Krankenhausw.- Zeitschrift für das gesamte Krankenhauswesen. (Berlin).
Ztschr. f. d. ges. Med.- Zeitschrift für die gesamte medicin (Hamburg).
Ztschr. f. d. ges. Neurol. u. Psychiat.- Zeitschrift für die gesamte Neurologie und Psychiatrie (Munich, Breslau, Berlin).
Ztschr. f. d. ges. phys. Therap.- Zeitschrift für die gesamte physikalische therapie (Leipzig, Berlin).
Ztschr. d. k. k. Gesellsch. d. Aerzte zu Wien- Zeitschrift der K. K. Gesellschaft der aerzte in Wien (Anzeiger).
Ztschr. d. Gesundhfürs.- Zeitschrift der Gesundheitsfürsorge (etc) (Berlin).
Ztschr. f. Gesundhtechn.- Zeitschrift für Gesundheitstechnik und Städtehygiene. (Dresden).
Ztschr. f. Gesundhverwalt.- Zeitschrift für Gesundheitsverwaltung und Gesundheitsfürsorge (Berlin).
Ztschr. f. Gewerbehyg. (Wien).- Zeitschrift für Gewerbehygiene und Unfallverhütung (Wien).
Ztschr. f. gynäk. Urol.- Zeitschrift für gynäkologische Urologie (Leipzig).
Ztschr. f. Hals-, Nasen- u. Ohrenh.- Zeitschrift für Hals-, Nasen- und Ohrenheilkunde (Berlin, Jena).
Ztschr. f. Heilk.- Zeitschrift für heilkunde (Prague; Vienna; Berlin).
Ztschr. f. Heilpädag. (Wien)- Zeitschrift für Heilpädagogik (Wien).
Ztschr. f. Hyg. u. Infektionskr.- Zeitschrift für Hygiene und Infektionskrankehiten (Berlin).
Ztschr. f. hyg. Zool.- Zeitschrift für hygienische Zoologie und Schädlingsbekämpfung (Berlin).
Ztschr. f. Immunitätsforsch. u. exper. Therap.- Seitschrift für Immunitätsforschung und experimentelle Therapie (Jena).
Ztschr. f. induk. Abst. u. Vererbungsl.- Zeitschrift für induktive abstammungs- und vererbungslehre (Berlin).
Ztschr. f. indukt. Abst. u. Vererbungsl.- Zeitschrift für induktive Abstammungs- und Vererbungslehre (Leipzig).
Ztschr. f. Infektionskr.- Zeitschrift für Infektionskrankheiten, parasitäre Krankheiten und Hygiene der Haustiere (Berlin).
Ztschr. f. Kinderforsch.- Zeitschrift für Kinderforschung (Berlin).
Ztschr. f. Kinderh.- Zeitschrift für Kinderheilkunde (Berlin).
Ztschr. f. Kinderpsychiat.- Zeitschrift für Kinderpsychiatrie (Basel).
Ztschr. f. Kinderschutz, (Wien)- Zeitschrift für Kinderschutz, Familien und Berufsfürsorge (Wien).
Ztschr. f. klin. Med.- Zeitschrift für klinische Medizin (Berlin).
Ztschr. f. Konstitutionsl.- Zeitschrift für Konstitutionslehre.
Ztschr. f. Krankenanst.- Zeitschrift für Krankenanstalten (Leipzig).
Ztschr. f. Krankenpfl.- Zeitschrift für Krankenpflege. (Berlin).
Ztschr. f. Krabsforsch.- Zeitschrift für Krabsforschung. (Berlin).
Ztschr. f. Kreislaufforsch.- Zeitschrift für Kreislaufforschung zugleich Fortsetzung von Zentralblatt für Herz- und Gefasskrankheiten. (Vienna; Dresden; Leipzig).
Ztschr. f. Kristallogr.- Zeitschrift für kristallographie, mineralogie und petrographie (Leipzig).
Ztschr. f. Krüppelfürsorge- Zeitschrift für Krüppelfürsorge (Hamburg; Leipzig).
Ztschr. f. Laryng., Rhin., Otol.- Continued as Hals-, Nasen- u. Ohrenarzt, Teil 1: Originale.
Ztschr. f. Med.-Beamte- Zeitschrift für medizinalbeamte (Berlin; Breslau).
Ztschr. f. Med.-Beamte- Zeitschrift für Medizinalbeamte (Leipzig).
Ztschr. f. Med., Chir. u. Geburtsh.- Zeitschrift für medicin, chirurgie und geburtshülfe (Magdeburg; Leipzig).
Ztschr. d. med. Gesellsch. zu Tokyo- Zeitschrift der medicinische gesellschaft zu Tokyo.
Ztschr. f. menschl. Vererb.-u. Konstitutionslehre- Zeitschrift für menschliche Vererbungs- und Konstitutionslehre (Munich; Berlin).
Ztschr. f. mikr.- anat. Forsch.- Zeitschrift für mikroskopisch-anatomische Forschung (Leipzig).
Ztschr. f. Militärärzte (Tokyo)- Zeitschrift für Militärärzte (Tokyo).
Ztschr. f. Morphol. u. Anthropol.- Zeitschrift für Morphologie und Anthropologie (Stuttgart).
Ztschr. f. Naturwiss.- Zeitschrift für naturwissenschaften (Halle).
Ztschr. f. Neur.- Zeitschrift für Neurologie.
Ztschr. f. Ohrenh.- Zeitschrift für Ohrenheilkunde und für die Krankheiten der Luftwege (Wiesbaden).
Ztschr. f. ophth. Optik.- Zeitschrift für ophthalmologische Optik mit Einschluss der Instrumentenkunde (Berlin).
Ztschr. f. Orthop.- Zeitschrift für Orthopädie und ihre Grenzgebiete (Stuttgart; Berlin).
Ztschr. f. orthop. Chir.- Zeitschrift für orthopädische Chirurgie einschliesslich der Heilgymnastik und Massage (Stuttgart).
Ztschr. f. Oto-rino-lar. (Tokyo)- Zeitschrift für Oto-Rhino-und Laryngologie (Tokyo).
Ztschr. f. pädag. Psychol.- Zeitschrift für pädagogische Psychologie, experimentelle Pädagogik (Leipzig).
Ztschr. f. Parapsychol.- Zeitschrift für Parapsychologie (Leipzig).
Ztschr. f. Parasitenk.- Zeitschrift für Parasitenkunde (Berlin).
Ztschr. f. Pflanzenkr.- Zeitschrift für Pflanzenkrankheiten und Pflanzenschutz. (Stuttgart).

Ztschr. f. physikal. Chem.- Zeitschrift für physikalische chemie (Leipzig; Berlin).
Ztschr. f. physiol. Chem.- Hoppe-Seyler's Zeitschrift für physiologische Chemie (Berlin).
Ztschr. f. physiol. Chem.- Zeitschrift für physiologische Chemie (Hoppe-Seylers) (Leipzig).
Ztschr. f. phys. u. diätet. Therap.- Zeitschrift für physikolische und diätetische therapie (Leipzig).
Ztschr. f. pract. Heilk. u. Med.-Wes.- Zeitschrift für praktische heilkunde und medicinalwesen (Hanover).
Ztschr. f. prakt. Ärzte.- Zeitschrift für praktische aerzte (Frankfurt a.M.; Leipzig).
Ztschr. Preuss. Statist. Landamt.- Zeitschrift des Preussischen statistischen Landesamts (Berlin).
Ztschr. f. psych. Hyg.- See: Allg. Ztschr. f. Psychiat.
Ztschr. f. Psychol.- Zeitschrift für Psychologie.
Ztschr. f. Psychol. u. Physiol. d. Sinnesorg. Abt. I- Ztschr. f. Psychol.; Abt. II- Ztschr. f. Sinnesphysiol.- Zeitschrift für psychologie und physiologie der sinnesorgane Abt. I- Zeitschrift für psychologie: Abt. II- Zeitschrift für sinnesphysiologie (Hamburg, Leipzig).
Ztschr. f. Psychother.- Zeitschrift für Psychotherapie und medizinische psychologie (Stuttgart).
Ztschr. f. Rassenphysiol.- Zeitschrift für Rassenphysiologie (Munich).
Ztschr. f. ration. Med.- Zeitschrift für rationelle medicin (Zurich, Heidelberg; Leipzig).
Ztschr. f. Rheumaforsch.- Zeitschrift für Rheumaforschung (Dresden; Leipzig).
Ztschr. f. Röntgenkde u. Radiumforsch.- Zeitschrift für Röntgenkunde und Radiumforschung.
Ztschr. f. Schädlingsbekämpf.- Zeitschrift für Schädlingsbekämpfung (Berlin).
Ztschr. f. Schulgesundh.- Zeitschrift für Schulgesundheitspflege und soziale Hygiene (Hamburg).
Ztschr. f. Sexualwissensch.- Zeitschrift für sexualwissenschaft (Leipzig, Berlin).
Ztschr. f. Sinnesphysiol.- Zeitschrift für Sinnesphysiolgie.
Ztschr. f. Stomatol.- Zeitschrift für Stomatologia. (Vienna, Berlin).
Ztschr. Tierzüchtung- Zeitschrift für Tierzüchtung und züchtungsbiologie (Berlin).
Ztschr. f. Tuberk.- Zeitschrift für Tuberkulose (Leipzig).
Ztschr. f. Untersuch. d. Lebensmitt.- Zeitschrift für Untersuchung der Lebensmittel (Berlin).
Ztschr. f. Untersuch. d. Nahrungsmitt.- Zeitschrift für Untersuchung der Nahrungs- und Genussmittel (Berlin).
Ztschr. f. Urol.- Zeitschrift für Urologie (Berlin; Leipzig).
Ztschr. f. Urol. Chir. u. Gynäk.- Zeitschrift für urologische Chirurgie und Gynäkologie (Berlin).
Ztschr. Verd. u. Stoffwechselkrankheiten-
Ztschr. f. vergl. Physiol.- Zeitschrift für vergleichende physiologie (Berlin).
Ztschr. f. Vitaminforsch.- Zeitschrift für Vitaminforschung zugleich Zentralblatt für Vitaminologie und verwandte Ernährungsprobleme.
Ztschr. f. Völkerpsychol.- Zeitschrift für Völkerpsychologie und Soziologie (Berlin).
Ztschr. f. Wissensch. Bäderk.- Zeitschrift für wissenschaftliche Bäderkunde (Berlin).
Ztschr. wissensch. Biol.- Zeitschrift für wissenschaftliche Biologie (Berlin).
Ztschr. wissensch. Insektb.- Zeitschrift für wissenschaftliche Insektenbiologie (Berlin).
Ztschr. f. wissensch. Mikr.- Zeitschrift für wissenschaftliche Mikroskopie und für mikroskopische Technik (Leipzig).
Ztschr. f. Wissensch. Zool.- Zeitschrift für wissenschaftliche Zoologie (Leipzig).
Ztschr. f. Wundärzte und Geburtsh.- Zeitschrift für wundärzte und geburtshelfer (Fellbach, Stuttgart).
Ztschr. f. Zellforsch. u. mikr. Anat.- Zeitschrift für Zellforschung und mikroskopischen Anatomie (Berlin).
Ztschr. f. Zellforsch. u. Gewebel.- Zeitschrift für zellforschung und gewebelehre.
Ztschr. Zool.- Zeitschrift für zoologie und vergleichende anatomie.
Züchtung.- Züchtungskunde (Göttingen).
Zymologica (Bologna)- Zymologica, chimica dei colloidi e degli zuccheri (Bologna).

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