Review

THE OSLO STUDY OF THE NATURAL HISTORY OF UNTREATED SYPHILIS

An Epidemiologic Investigation Based on a Restudy of the Boeck-Bruusgaard Material

A Review and Appraisal

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INTRODUCTION

GJESTLAND has recently completed in monographic form[1] a retrospective follow-up study of Boeck's famous collection of untreated syphilitics. This recent investigation is an outstanding example of the application of modern epidemiologic methods[2,3] to the natural history of chronic disease. It is, moreover, a convincing illustration of international cooperation in the field of medical science. This cooperation has included two national departments of health (United States Public Health Service and the Norwegian Public Health Service); three universities (the Universities of Oslo and Bergen in Norway and Columbia University in New York); and a number of physicians and statisticians on both sides of the Atlantic.

The basis for the present investigation is the well-known Boeck material, first described in 1929 by Boeck's successor, E. Bruusgaard.[4] It has now been re-studied in the department of Bruusgaard's successor, Niels Danbolt. Forty to sixty years ago (1890-1910), Boeck, then Professor of Venereology and Dermatology, hospitalized approximately 2,000 patients with primary and secondary syphilis until the lesions healed without specific treatment. These lesions were carefully described on admission to the hospital and their regression and time of disappearance noted in well-kept records. Bruusgaard, in 1925, began a follow-up of these patients in order to show "how syphilis progresses when little or no treatment is given and the patient's defense mechanism is allowed to combat the disease alone."[4] His study led to the famous and internationally quoted "Bruusgaard material," which has formed the basis for prognostic statements concerning both treated and untreated syphilis for more than 25 years. Gjestland's carefully planned and executed epidemiologic re-study of this unique

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clinical material has been presented as a dissertation to the University of Oslo. The results should be of interest to epidemiologists and to the large group of physicians concerned with the natural course of syphilis in particular and of chronic disease in general.

The re-study, supported by the Research Grants Division of the National Institutes of Health, United States Public Health Service, owes its origin to the continued interest in Bruusgaard's work by many persons, particularly Moore of Johns Hopkins University, and those associated with him as staff and students. The actual investigation came as a result of discussions both here and abroad among Moore, Danbolt, Guthe (now of WHO, then a postgraduate student at the Johns Hopkins School of Hygiene and Public Health) and Heller, then Chief of the Venereal Disease Division of the United States Public Health Service. Following a visit in 1947 by Moore to Oslo to examine the basic data, funds were made available and the detailed study was undertaken in 1948 by Gjestland, also a graduate of the Johns Hopkins School of Hygiene and Public Health. The facilities of Danbolt's department in Oslo were placed at his disposal. After a period of careful planning and two years of data collection, Gjestland spent the major part of the academic year 1951-1952 as a research associate in epidemiology at the Columbia University School of Public Health, during which time a great part of the analyses were made.

The objectives of the present paper are: (a) to review and appraise this important contribution; (b) to present some of the details of the planning and execution of the investigation as an excellent example of the epidemiologic method; (c) to provide a brief résumé of the results of the study for the American reader; and (d) to emphasize the significance of this investigation for the natural history of chronic disease.

Arising from basic scientific principles (exact observation, correct interpretation, rational explanation, and scientific construction) and developing as a result of studies of epidemics and of infectious diseases, the epidemiologic approach to the investigation of the natural history of disease is an orderly scientific method of study comprising a continuum of several well-defined steps. Gjestland's study adhered to a plan of five steps: (1) definition of the nature, extent, and significance of the problem and clarification of objectives; (2) appraisal of existing information; (3) formulation of hypotheses; (4) testing of hypotheses; and (5) conclusions and practical application.

I. DEFINITION OF NATURE, EXTENT, AND SIGNIFICANCE OF THE PROBLEM AND CLARIFICATION OF OBJECTIVES

This initial phase began in 1948 with the original suggestions of Moore, Danbolt, Guthe, and others. These suggestions were incorporated by Gjestland into a plan which provided clear definition of the nature, extent, and significance of this problem, a clarification of the objectives, and a proposal of important questions which might be answered by a re-study of this material.

Gjestland introduced the discussion of the nature of the over-all problem with a quotation from Stokes[6]: "No one who has had even a limited experience in answering the questions on which students and physicians seek information in their practical contacts with the disease can fail to realize that the great ailment of modern syphilological practice is a lack of comprehension of the why and wherefore, rather than the what to do." Comprehension of the "why and wherefore" lay in a better understanding of the prognosis of untreated syphilis. The beneficial effects of treatment in modifying the biologic course of syphilis infection is well known. What was lacking was quantitative information on what happens to those who go untreated. The reason for this lack lay in the absence of studies of large groups of untreated patients, thoroughly diagnosed and observed over sufficient periods of time. The Boeck material provided such a large group of patients. Boeck's conviction as to the prognosis of syphilis is summarized by Bruusgaard[4*]: "The immune mechanisms of the body are the most important factors in combating this disease. The specific drugs must be considered as adjuvants only; they are not potent enough to exterminate the disease completely—the antibody formation is disrupted; the course of the disease becomes atypical and serious complications may result. Specific drugs should be used only in cases where the body does not seem able, itself, to overcome the disease—they should then be used in great quantities and over a long period of time. You are at the mercy of the drugs." Thus, mercury was seldom administered in Boeck's department and potassium iodide became the nonspecific drug of choice in all cases where the clinical course indicated its use. This policy of management was firmly established by January, 1891, and was followed in all cases until late 1910, when the first injection of 606 was given. This attitude of Boeck provided approximately 2,000 patients who were untreated for primary and secondary syphilis. These patients were hospitalized until all evidence of primary and secondary syphilis disappeared and received no treatment during this period, with the exception of potassium iodide in some instances. Since other syphilologists in Norway did not share Boeck's opinion as to the efficacy of mercury, it is possible that some of these patients were treated after discharge from the University Hospital. To what extent this was the case could only be clarified by follow-up information. All that could be said at the outset was that this was a group of patients untreated for primary and secondary syphilis, but unknown as to subsequent therapy.

Further significance of the problem of prognosis is emphasized by the reliance of modern syphilologists upon the results of Bruusgaard's investigation of a small sample of Boeck's patients in 1925-1927. Bruusgaard located a total of 473 patients; some he actually examined; on others he recorded information obtained through records of clinic or hospital visits, autopsy records, and death certificates. This gave Bruusgaard information on patients who had had syphilis for intervals ranging from 3 to 40 years. No mention is made as to antisyphilitic treatment during these intervening years. By combining his data on the 309 living and the 164 dead persons on whom there was information from 3 to 40 years after discharge from the hospital, it has been estimated in authoritative works of

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*Referring, of course, to the pre-arsenical-bismuth-antibiotic era.

reference that the probable outcomes of untreated syphilis are as shown in Table I. This table suggests that approximately two-thirds of patients with untreated syphilis will experience no disabling effects of the disease.

TABLE I.   SUMMARY OF BRUUSGAARD'S DATA AS TO ULTIMATE OUTCOME OF
UNTREATED EARLY SYPHILIS

PATIENTS SHOWING AT RE-EXAMINATION OR DEATH	PER CENT OF TOTAL NUMBER (473 PATIENTS)
Neurosyphilis	9.5
Cardiovascular syphilis	12.8
Benign late syphilis	12.2
Latent syphilis (no clinical evidence, blood serologic test positive)	14.1
Spontaneous "cure" (no clinical evidence, blood serologic test negative)	27.9
Died of syphilis other than cardiovascular or central nervous system	0.8
Died of some other cause (cancer, tuberculosis scattering)	22.6

From Moore, J. E.: The Modern Treatment of Syphilis, ed. 2, Baltimore, 1943, Charles C Thomas, p. 40.

As these estimates of prognosis have passed from textbook to textbook and from one scientific paper to another, they have taken on a significance entirely unwarranted by the nature of Bruusgaard's data. Bruusgaard himself warned that acceptance of his data should be made "with the reservation which the nature of the material makes necessary."[4] Nevertheless, most of the existing hypotheses on the outcome of untreated syphilis are based upon Bruusgaard's study. Critical reviews and appraisals of the Bruusgaard material by Harrison[6-8] and Sowder[9] have shown that Bruusgaard's sample was highly selected, not being representative either of the Boeck material or of untreated syphilis as a whole. Gjestland discusses these factors of selection and adds to them the following observations on the Bruusgaard data: there is no information on treatment subsequent to 1910; information on many of the patients came from hospital records of admissions to the Municipal Hospital for a variety of diseases; information on some patients came from interviews rather than physical examinations; only a few had spinal fluid examinations; only 40 patients had been autopsied. Each of these factors adds to the highly selective nature of the Bruusgaard data. Despite their own warnings as to interpretations, authors of papers on the prognosis of untreated syphilis and authors of the leading textbooks of syphilology have presented these data as the most reliable material on the prognosis of untreated syphilis. Some authors have used these figures as a basis of comparison of the efficacy of treatment. Therefore, it is important that an effort be made to clarify the issue by a more complete study of the material.

    The significance of the problem of untreated syphilis in current American practice is further emphasized by the fact that more than one-half of the persons (in the United States in the past decade) who acquire syphilis do not reach medical attention until after the early lesions have disappeared, some many years afterward, others not at all. American literature contains many statements lamenting this fact and pointing out that the golden opportunity for therapy in these

patients has been lost. It has been estimated by the U. S. Public Health Service that, as of Dec. 31, 1954, in the United States, there were approximately 2,000,000 persons whose blood, if tested, would be reactive for syphilis. Some of these have false positive tests but for those with untreated syphilis, some indication of their fate may come from this study. It is important, also, that although an estimated 86,800 United States civilians acquired syphilis in fiscal 1954, less than 10 per cent of these (7,688) were reported and treated for primary and secondary syphilis.[10] Every year more persons in the United States are diagnosed as having early latent syphilis than are diagnosed as having primary and secondary syphilis, and each year this ratio is increasing, meaning that relatively more each year remain untreated for primary and secondary syphilis. In 1954 the ratio of early latent (24,999 reported cases) to primary and secondary (7,688 reported cases) was approximately 3.5 to 1; in 1946 it was 1 to 1.

Another important fact in the significance of this problem is the evidence, both by clinical observation on man and laboratory experiments on animals, that syphilis in some way affects morbidity and mortality, aside from the late effects of the disease itself.[11] Thus, there appears to be considerably greater morbidity among untreated syphilitics and, in addition, life is shortened appreciably due to other conditions than manifestations of late syphilis.

Of prime importance in determining the potential contribution of this investigation was to examine the diagnostic criteria of those times and analyze the validity of the diagnoses made in Boeck's department. These diagnoses were based entirely on clinical examination and subsequent observation (because neither darkfield nor serologic tests for syphilis were employed in Oslo before 1910). A large sample of the hospital records have been examined carefully by the authors of this review (E.G.C. and N.D.) and in their opinions there is no doubt that a great majority of these patients had early syphilis. The potential margin of error of conventional clinical admission diagnoses was reduced significantly by observations on the daily course of the untreated disease over periods of months in all patients. These patients were hospitalized from their first tentative admission diagnosis until all signs and symptoms disappeared (an average of 3.6 months, Table II), many of them (42.6 per cent of males and 20.5 per cent of females) having primary and secondary syphilis on admission or developing secondaries after primary lesions had disappeared. One-half of the males and three-fourths of the females were observed with secondary syphilis only (see Fig. 1). Furthermore, Boeck was an expert of international reputation and his deputies were experienced dermatosyphilologists, all trained in the highly developed art of clinical description of the times. The necessity for accurate diagnosis was further increased by the requirements of a good teaching hospital.

Table II shows the length of stay of patients in the hospital, 39 of the patients remaining in the hospital for as long as 10 to 12 months. The mean stay in months for males was 2.7 and for females 3.9. Of interest is the considerably longer hospitalization of the females than of the males. Whether this means that the lesions of females persist longer than those of males or whether for the control of infectiousness, it seemed better to hospitalize the females longer,

cannot be determined, but it is possible that this is an early indication of the difference in the response of males and females to this infection. This lengthy hospitalization of both sexes illustrates the long duration of early syphilis lesions and emphasizes the potential dangers of untreated syphilis in a population.

TABLE II. STUDY GROUP—NUMBER OF MONTHS IN HOSPITAL AND
MEAN HOSPITAL STAY ACCORDING TO SEX

MONTHS	MALE	FEMALE	TOTAL
3 and under	280	379	659
4 to 6	142	435	577
7 to 9	19	110	129
10 to 12	5	34	39
			1,404
Mean stay in months	2.7	3.9	3.6

Adapted from Gjestland, Chapter III.

Fig. 1* shows the distribution of the patients in the study group† by stage of disease and sex. The diagnoses are those confirmed at discharge, after the patients had been under observation throughout the period of hospitalization. In only seven instances is the diagnosis limited to primary syphilis. Of these, three did not develop secondary syphilis while in the hospital and four were discharged against advice before their lesions were healed. The classification "primary *and* secondary syphilis" includes those who were admitted with primary lesions and developed secondary syphilis while in the hospital, together with those who were admitted with primary and secondary lesions. The largest group were those with secondary syphilis, having been admitted in this stage. The primary *and* secondary group comprised a higher percentage of males than females (42.6 versus 20.5), a proportion in accordance with the general experience of later diagnosis of early syphilis in females. The largest proportion of females was in the secondary syphilis group, the diagnosis having been made after the disappearance of primary syphilis, or in some instances without a history of primary syphilis at all. Approximately 5 per cent of the patients were admitted in clinical secondary relapse. This group represents patients previously observed elsewhere for secondary syphilis, with or without treatment, whose symptoms and signs had disappeared only to reappear with manifestations characteristic of secondary relapse.

The aims of Gjestland's study were stated as follows: "Based upon the concept of disease as a process, an attempt will be made to show the natural course of syphilis according to as many indices as the material will allow, and thereby contribute to a better understanding of the prognosis and perhaps establish a base line for the interpretation of the huge mass of information we

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*Figs. 1-13 have been constructed by one of us (E. G. C.) from the detailed tabular material provided by Gjestland.

†See page 319 for description of study group.

already possess."[1]   The immediate objectives for reaching these aims were formulated as follows: "1.   To trace as many patients as possible to an 'end point,' defined as the last observation, living or dead; 2. To collect the maximum amount of clinical data (including data on treatment) on each patient from the date of his original discharge from Boeck's department all through the interim period and up to the 'end point'; 3. To determine the causes of death through a study of post-mortem examinations, hospitalizations, death certificates, etc., with the maximum amount of accuracy; 4. To examine at the Rikshospitalet as many living patients as possible and to employ as complete examinations for syphilis as circumstances will permit and to have examined elsewhere according to the same principles those patients who, for some reason or other, could not be brought to the Rikshospitalet."[1]   The question asked from the beginning was: What is the final outcome in terms of late syphilis, duration of life, and cause of death in persons who are untreated for symptomatic early syphilis?
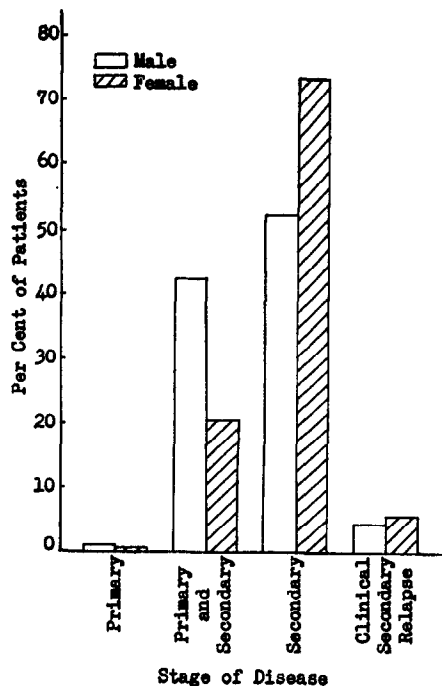

Fig. 1.—Distribution by stage and sex of the study group (1,404 Norwegian residents of Oslo). (See page 319 for description.)

II. APPRAISAL OF THE EXISTING INFORMATION BEARING ON THE SUBJECT

A critique of all of the pertinent literature obviously could not be made, because a subject so broad as the natural course of syphilis infection would require reference to practically the entire field of syphilology.   Appraisals were limited to: (a) classification and critical evaluation of other investigations on the outcome of untreated syphilis, and (b) well-known authoritative reports dealing with the various aspects of syphilitic infection: secondary relapse, benign

late syphilis, cardiovascular syphilis, neurosyphilis, etc. Gjestland's evaluations of the literature on these specific aspects of syphilis infection in relation to his own data are among the worthwhile contributions of this investigation, particularly the presentation and evaluation of the essential items to consider when comparisons between studies are attempted. So frequently the results of one study are compared with the results of another, and because of similarities of numbers they are considered to support each other. This is often done without a consideration of the factors that go to make up the study material. Gjestland's monograph provides an excellent lesson in comparative analyses.

Most of the studies of untreated syphilis are based upon series of patients who are self-selected, either because of no knowledge of being infected or because of recalcitrance in following medical advice. Gjestland was able, from a search of the literature, to find only two groups who were denied treatment deliberately and these were left untreated for two totally different reasons: (a) the Boeck group, untreated because of a scientific conviction as to noneffectiveness of mercurial treatment, and (b) the "Alabama" group, left untreated for the purpose of comparing health and longevity of an untreated syphilitic population with an otherwise similar but nonsyphilitic population.[11-15]

There are at least four methods or techniques by which information on the outcome of untreated syphilis has been acquired: (a) from anamnestic data, obtained from patients seen for the first time in latency or in the late symptomatic stages of the disease; (b) from autopsy studies, such as those of Rosahn[17,18]; (c) from prospective "no treatment" studies, such as the "Alabama" series (loc. cit.); (d) from specific groups of patients known to have been denied treatment in the past (e.g., Bruusgaard study of the Boeck patients).

"Each of these four techniques is fraught with sources of potential bias and these should be carefully considered in making statements about the prognosis of untreated syphilis. The shortcomings of the first technique, which, incidentally, is more frequently used than any of the others, are quite apparent. The patients are highly selected and the groups studied rarely include patients whose courses were so benign as to require no medical attention."[1] None of the anamnestic studies is critically appraised by Gjestland, but evaluations of the other three types are made in considerable detail. These details will not be presented in the present review, except to point out the similarity between the figures of Rosahn and those of Bruusgaard, despite the fact that the basic data are not comparable in any respect. Rosahn's patients were drawn from a hospital population of several types of patients, whereas the Bruusgaard group came from a hospitalized syphilitic population. Bruusgaard's included both the living and the dead, whereas Rosahn's comprised only those examined at autopsy. Only 8.5 per cent of the Bruusgaard group came to autopsy. The Bruusgaard material comprised 64 per cent females, whereas the Rosahn material was 35 per cent females. The findings were not expressed on a sex specific basis. The Bruusgaard material included several forms of late central nervous system syphilis and benign late syphilis, whereas the Rosahn material included neither benign late syphilis of the skin, mucous membranes, or bones, nor general paresis. The presentation of facts such as these, so critical for valid comparisons, illustrates another important contribution of the Gjestland monograph.

III.   FORMULATION OF HYPOTHESES

Following an appraisal of the most pertinent literature, a careful study of the Boeck records, and a detailed and critical appraisal of Bruusgaard's results, the next step was to consider the specific questions for which the Boeck data might provide answers as follows: among patients untreated for secondary syphilis and with no, some, or unknown subsequent treatment: (1)   What are the frequencies of secondary relapse, of benign late syphilis, of late symptomatic syphilis, of life long latency, and of spontaneous cure?   (2)   What are the effects on longevity, on causes of death, and on mortality over that of nonsyphilitics?   (3)   Does age at time of infection influence outcome?   (4)   Does sex influence outcome?   (5)   What are the effects on the outcome of pregnancy at varying intervals following infection?   (6)   Is morbidity from conditions other than syphilis greater than among nonsyphilitics?

"None of these questions have been omitted from consideration during the course of tracing and in the analysis of the data, but as the study progressed it became obvious that answers could not be provided for each and every one of them.   The reasons for this lie in the material itself and in the extent to which complementary data could be obtained."[1]

On the basis of these questions and on the appraisal of pertinent literature, the study was designed to provide support or denial of the following hypotheses: (1)   Syphilis, untreated in its primary and secondary stages, has a favorable outcome in a majority of instances.   (2)   Serious results are more frequent in males than in females.   (3)   Untreated syphilis prolongs the period of community danger of infection.   (4)   There is no way to predict the outcome in individual cases.   (5)   Syphilitics have a higher morbidity and mortality from other conditions than do nonsyphilitics.

It seemed reasonable at the outset that these five hypotheses were testable directly or indirectly with the Boeck patients, if a sufficient proportion could be traced and information secured on their clinical outcome.   There was some doubt that sufficient information would be obtained to verify hypothesis number five; this proved to be partially true.

IV.   TESTING OF HYPOTHESES

This step in the continuum of the epidemiologic method is the actual planning and execution of the design of the field investigation.   It includes: the selection of the study group; the listing of possible sources of information; a plan for orderly tracing; a decision as to the method of collecting and recording data; a consideration of possible controls; and the actual collection and analysis of data.

Design of Investigation.—The study group finally decided upon comprised 1,404 individuals drawn from Boeck's original series of hospitalized patients. It may be recalled that the Bruusgaard study related to 473 persons of a total of 2,181 patients.   On examination of the original records it was found that only 1,978 patients, rather than 2,181, were admitted between Jan. 1, 1891, and Dec. 31, 1910.   This discrepancy is explained on the basis of duplicate entries and the possible inclusion of other stages and doubtful diagnosis in the registry

from which Bruusgaard's count was made. It is possible also that Bruusgaard's list included a few patients discharged during the year 1890. The 1,978 was reduced to 1,404 by the elimination of 574 Norwegian nonresidents of Oslo and non-Norwegians. It was believed that limiting the tracing to Norwegian residents of Oslo would not bias the over-all study and at the same time would simplify tracing and aid in the selection of controls. The decision to eliminate the 574 persons was made after a careful field study of a random 20 per cent sample of Boeck's original patients.

The remaining 1,404 Norwegian residents of Oslo came from the underprivileged section of society which at that time lived in the east zone of the city. Approximately 62 per cent were referred by the Bureau of Indigents, approximately a third by the Venereal Disease Division of the Oslo City Health Department, and a very small proportion came of their own accord to Boeck's clinic. A great majority (68 per cent) was admitted during the period 1891-1900. Only 10 per cent of the total group were admitted during the last five years of the period under study (1906-1910). The decreasing admissions to Boeck's clinic, year by year from 1891 to 1910, is parallel to the downward trend of actual notified cases in the city of Oslo, indicating that the smaller proportions admitted in the later years are the reflection of the declining syphilis problem, rather than a specific selection of the group coming to medical care.

Fig. 2 illustrates the sex and age distribution of the study group. There were twice as many females as males, perhaps due to the relative numbers of male and female beds on the dermatology service. The ratio of males to females among notified cases in the city of Oslo was 2 to 1. The sex differences made it essential that all of the analyses throughout the entire study be made on a sex specific basis. Among both males and females the highest proportions were among the 15-24 age groups (46.7 per cent and 61.7 per cent, respectively) and the next highest among those 25-39 years of age (38.3 and 28.0 per cent). The mean age for the total group is 24.8 years with a mean of 25.6 and 24.3 years for males and females, respectively. The patients under the age of 15 acquired syphilis in the home, usually from another member of the family. They were often admitted to the hospital together with their mothers or fathers, or both, and occasionally together with one or more brothers or sisters. In many instances the whole family group suffered from secondary syphilis. The stage of disease by sex was shown in Fig. 1.

Careful examinations of the original records were made in order to determine the exact amount of treatment, that these patients received before, during, or *immediately** after discharge by Boeck. The vast majority of the patients (96.4 per cent) received no specific treatment whatever during the early stages of the disease and there are no appreciable differences between the sexes in this respect. The 3.6 per cent who received mercury in one form or another (inunctions, mercury pills, and mercury baths) received minimal amounts, only six men and nine women receiving more than 30 inunctions. Of the 50 patients who received mercury in one form or another, only three were treated by Boeck himself, the remainder having been treated before admission to Boeck's department, or immediately after discharge from it.

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*Treatment received in later years is shown in Tables IV and V.

The complete plan of investigation cannot be given in detail here, but the thoroughness with which this plan was considered and undertaken and the method of search and identification is a model example of thoroughness. Two essential preliminary requirements for retrospective studies of this kind are the establishment of a "search order" and a system of identification of name and recorded data. A "search order" is a listing of possible sources of information in prearranged order which will assure a minimum of duplication of effort and, if followed routinely, will add a considerable degree of accuracy to the identifying process. Every name should be searched through the entire list even when it appears to have been located in the first source searched. Similarities of name and other identifying data make this necessary. Identity can be established objectively only by comparing a number of personal, geographic and clinical characteristics each time new information is found.
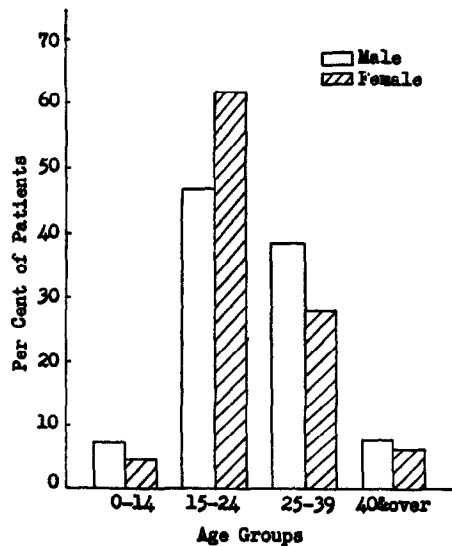

Fig. 2.—Distribution by age and sex of the study group (446 males and 958 females).
Mean age: males, 25.6 years; females, 24.3 years.

Initial explorations were made on small samples of the total group in an attempt to discover the various sources where information might be obtained and the order in which the search should be made. Furthermore, a plan was devised whereby the identifying information found in one record could be checked objectively with that of another record by use of a special form and by following a fixed pattern. Every new record found in the tracing process presented problems of identity.

A list of the sources of identifying and clinical information, arranged in the order in which they were searched, is given here. This is the "Search Order" through which each name was taken. Only minor exceptions were made in this orderly and objective plan.

THE "SEARCH ORDER"

Chief Sources of Information and Order of Search *

1. Death registers.
2. The Department of Dermatology and Venereology of the Rikshospitalet.
3. The Oslo Bureau of Indigents.
4.† Bureaus of Indigents elsewhere.
5. The Central Bureau of Statistics' Marriage Registry for Oslo (women only).
6. The Oslo Population Register.
7. The Oslo City Health Department, Venereal Disease Division.
8. The Municipal Hospital at Oslo, Venereal Disease Division.
9.† Parish minister, sheriff, or local Population Register at patient's place of birth.
10.† Parish minister, sheriff, or local Population Register at patient's place of residence prior to his settling in the City of Oslo.
11.† Individual sources, especially relatives of the patient, but also many others not specified.
12. The Oslo City Health Department and the Central Bureau of Statistics (for transcription of death certificates).
13. Mental hospitals, psychiatric wards, neurological and other hospital wards (private practitioners as indicated).

In addition to the small exploratory samples noted above, a 20 per cent representative sample of the 1,978 original patients, obtained by the use of random sampling numbers, was chosen and carefully investigated to test the record system and tracing procedures and to determine the practicality of studying the entire material. An analysis of this sample by Gjestland and a special committee‡ led to a decision to follow the entire study group along the same lines established through experience with the sample. The decision to include only those who were Norwegian residents of Oslo in 1890-1910 was supported by the evaluation of the sample.

It would have been interesting, and perhaps useful as well, to have traced as "controls" a similar group of nonsyphilitics and one of presumably adequately treated syphilitics. This was not done because an adequately treated group was not available and because it did not seem that the hypotheses being tested required such "control" groups. Considered as possible controls was a sample of contemporary nonsyphilitic, clinic or hospital patients, or a sample of contemporary admitting agency clientele. The decision against this was based upon the premise that only questions relating to cause and effect would absolutely require controls. Furthermore, there was the practical consideration of the availability of records and of time and resources to search them. The control which seemed most feasible under the circumstances was a comparison of the life experience of the untreated syphilitics with that of the local population from

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*Adapted from Gjestland. Recheck sources omitted.

†These are supplemental sources.

‡The collected data on the sample was brought to this country by Danbolt and Gjestland in 1950 and reviewed by a committee composed of J. E. Moore, Niels Danbolt, Margaret Merrill (Associate Professor of Biostatistics, Johns Hopkins University), A. P. Iskrant (Chief Statistician, U. S. Public Health Service), Geraldine A. Gleeson (Statistician, U. S. Public Health Service), and E. Gurney Clark.

which they came. The study group was limited largely to patients residing in the eastern districts of the city of Oslo. There are official mortality records in Oslo by district so that it was possible to compare the mortality experience of untreated syphilitics with that of a population of the same socioeconomic status. For the details of the selection and study of the control group, reference must be made to the original monograph.

Collection of Data.—With a limited staff (Gjestland, a nurse-secretary, and a filing secretary), the tracing procedure began in 1949. From time to time the operation required and received the cooperation of various hospital staffs and many persons employed in the official record bureaus of the country. The magnitude of the job to be done did not detract from the attention to essential details. Every bit of information found on every patient was checked according to the identification plan, and all records (hospital and others) were recorded in toto in the master record folder. The record system, organized before the tracing began, comprised: (a) an index card file which served as a key to the other files and an index of the current status of tracing on each patient; (b) a master folder which contained the transcribed records from hospitals, admitting agencies, and physicians' offices; and (c) a summary record devised to permit analysis of the material as efficiently as possible in terms of the proposed questions and to give information on the natural course of syphilis infection.

At the close of the investigation in August, 1951, some usable information had been obtained on about 80 per cent of the study group of 1,404 persons. This corresponds very closely with the estimates of the 20 per cent sample and justified the use of the exploratory sample. In Table III and Fig. 3 are the results of the tracing efforts.

TABLE III. STUDY GROUP—TRACING STATUS, 1951, BY SEX "KNOWN,"
PARTIALLY "KNOWN," AND "UNKNOWN"*

TRACING STATUS	MALE		FEMALE		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
"KNOWN" LIVING	72	16.1	187	19.5	259	18.4
"KNOWN" DEAD	259	58.1	435	45.4	694	49.4
Subtotal	331	74.2	622	64.9	953	67.9
"PARTIALLY KNOWN"	43	9.6	151	15.8	194	13.8
Subtotal	374	83.9	773	80.7	1,147	81.7
"UNKNOWN"	72	16.1	185	19.3	257	18.3
TOTAL	446	100.0	958	100 0	1,404	100.0

From Gjestland, Chapter V.
*Defined in text.

The "known" group comprises those on whom a diagnosis could be established at a classifiable "end point." They were alive and examined during the investigation period; or, if dead, the time and status at death could be determined.

"Partially known" refers to those with one or more observations during the years following discharge from Boeck's department, but not to the same clear-cut "end points" of diagnosis as those of the "knowns." "Unknown" means no information following discharge from Boeck's department. For 83.9 per cent of the males and for 80.7 per cent of the females there was some significant information. Still alive in 1951 were 16.1 per cent of males and 19.5 of females. No follow-up information was available on 16.1 per cent and 19.3 per cent respectively. This is a high and probably unique degree of success in tracing a population group some 40 to 60 years after the original event. It is even more remarkable when one considers the mobility of the class of population from which these patients came, and the fact pointed out by Harrison[6] that during the period 1891-1920 there were 351,915 Norwegians (80 per cent of whom were in the ages 16-35) who migrated to the United States. The population of Norway in 1900 was 2,242,995.
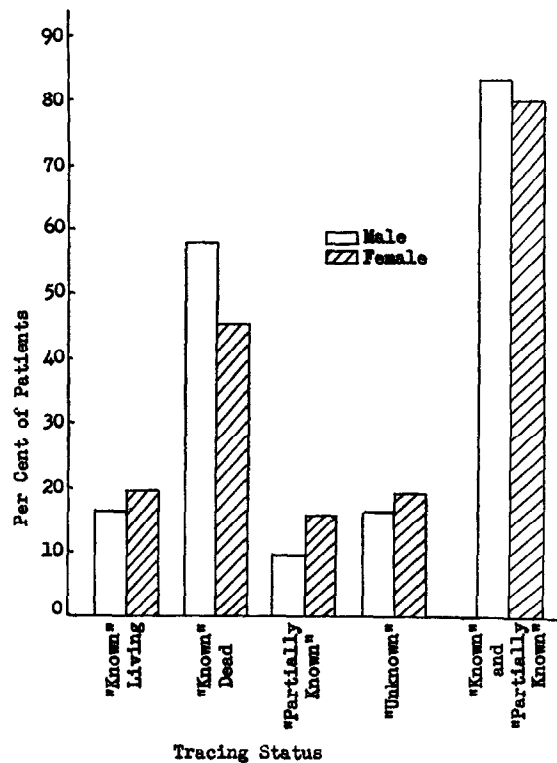

Fig. 3.—Tracing status in 1951 by sex.

The quantity and the quality of the information obtained on the "knowns" and "partially knowns" may be judged in part from the number of recorded observations and from an analysis of the sources of information at or just before death. On the 953 persons classed as "known" there were 3,584 recorded observations (an average of 3.8 per person), and on the 194 "partially known" 523

observations (2.7 per person), the over-all average being 3.6 observations. Of the "knowns" 259 were still alive (Table III) and of these 83.4 per cent were examined in Norway or elsewhere during or shortly prior to the period of investigation (1949-1951). For the remaining 16.4 per cent (43 persons) information was obtained directly or indirectly as to their health status. None were seriously ill, but complete examinations are not available. Information on the dead (694 persons) came from physical examinations immediately prior to death in approximately 29 per cent, from autopsy examinations in 30 per cent, from physical examinations a short time prior to death in 15 per cent, and from death certificates or other sources in 26 per cent.

A comparison of the 953 "known" and the 194 "partially known" with the total study group (1,404) according to original diagnosis, sex, and age groups and mean age revealed such similarity that it can be concluded that the "knowns" and "partially knowns" combined are definitely representative of the total as regards these variables.

An analysis of the amount, type, and time of treatment received by these patients during the 40 to 60 years since their discharge is important if valid information is to be forthcoming about the natural course of untreated syphilis. However, lack of complete information about treatment would not detract entirely from the practical value of this investigation. It is certain that no treatment was received for *early* syphilis by these patients, and what happens to such patients regardless of subsequent therapy is a subject of great interest. This is the situation which obtains for a large number of persons who annually pass untreated through early syphilis infection and who are candidates for discovery and varying amounts of treatment during the years that follow. An estimate of the possible outcomes in such persons with no or varying amounts of treatment is a major contribution of this study. This does not mean that the findings of the study have universal application to all similar situations, but no one will deny that the report provides useful information which does not exist elsewhere.

From the information available, Gjestland carefully analyzed the possible effect of treatment on the course of the disease in these patients. It was not possible to determine the exact treatment history for the majority, but it was possible to introduce a chain of circumstances which provide evidence that any treatment received was highly inadequate as judged by acceptable standards. "This evidence, both circumstantial and factual, is convincing and consists of two parts: (a) the historical development of *available* adequate treatment; and (b) the actual amount of treatment known to have been received by our patients."[1]

Two tables adapted from those of the monograph are presented here. Table IV shows the possibilities for specific treatment in Norway from 1891 to the present. These are the treatment schemes for "fresh" syphilis rather than for later stages. Before 1920, patients with latent or late syphilis were usually treated symptomatically and rarely, if ever, given as much treatment as is described in Table IV. Beginning about 1930, when Boeck's patients had had syphilis for 20 to 40 years, the practice in Norway (and elsewhere) changed and more extensive treatment was given at all stages of the disease.

TABLE IV.   POSSIBILITIES FOR SPECIFIC TREATMENT IN NORWAY 1891 TO PRESENT

DATES	TYPE	COMMENT
1891–1910	Mercury alone	Rubs, pills, baths; amount based on clinical response
1911–1920	Arsenicals and mercury	Alone or combined, 3-6 injections, rarely more
1921–1930	Arsenic, mercury, bismuth	Combinations, courses 12-15 injections as plus 80-100 Hg. Bi infrequent
1931–1946	Arsenic, mercury, bismuth	Courses 16 As, 16 Bi, repeated 2 or more times, serologic control
1947–	Arsenic, bismuth, penicillin	Penicillin first in 1947, combined with As and Bi until 1950, then alone

Adapted from Gjestland, Chapter V.

The amounts of treatment known to have been received are shown in Table V. In 83.4 per cent there was no treatment or no information as to treatment. Of those whose treatment histories were adequate, 15 patients (10 per cent of the treated, less than 1 per cent of the total) received 40 or more treatments; 86 (50 per cent of the treated, 6 per cent of the total) received less than 10 treatments (1 bismuth unit equals 6 mercury inunctions). In the majority of instances the treatment was received irregularly over periods of many years. "To what

TABLE V.   INFORMATION ON ACTUAL TREATMENT RECEIVED FROM ONSET OF
DISEASE TO "END POINT" BY SEX AND AMOUNT

STATUS	MALE		FEMALE		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
No information as to treatment, or no treatment	276	83.4	519	83.5	795	83.4
Patients found to have received treatment No. of As and/or Bi Units						
40 and over	4		11		15	
20–39	9		15		24	
10–19	14		19		33	
Subtotal	27	8.2	45	7.2	72	7.6
1– 9	28	8.4	58	9.3	86	9.0
TOTAL	331	100.0	622	100.0	953	100.0

From Gjestland, Chapter V.

extent the treatment given has affected the end results, however, is close to impossible to determine, but the problems will be dealt with in considerably more detail in the following sections on the various complications."[1]

V. CONCLUSIONS AND PRACTICAL APPLICATIONS

In conformity with the requirements of this final step, the collected and analyzed data are presented to show the extent to which the questions have been answered and the hypotheses verified for practical use.   The results are given and discussed under the following chapter headings in the monograph: Clinical Secondary Relapse; "Benign" Tertiary Syphilis; Cardiovascular Syphilis; Neurosyphilis; Other Late Syphilis; Mortality; The Prognostic Significance of Clinical Secondary Relapse and "Benign" Tertiary Syphilis; and Spontaneous Cure. A consistent pattern is followed by the author in each chapter: excerpts and comments from the pertinent literature; the findings of the present study; and comparisons and discussions.   In addition, there are ten annexes of tables, charts, analyses, discussions of a technical and explanatory nature, and exhibits. Only brief and incomplete presentations of these results can be made in this paper.   For details reference must be made to the monograph itself or to the abbreviated version which will be available eventually.
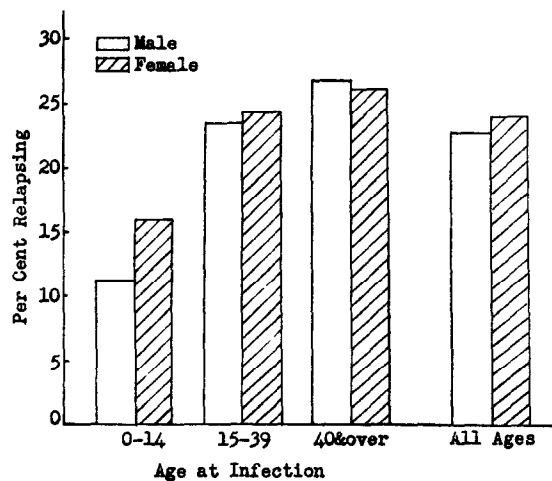

Fig. 4.—Clinical Secondary Relapse.   Occurrence among 1,035 "knowns"
and "partially knowns" by age at infection and sex.

Clinical Secondary Relapse.—This is one of the most significant of the analytical sections, contributing much to knowledge of the natural course of syphilis, so much, in fact, that the entire concept of relapse may be modified as a result of these findings.   Although the opinion is not universal, much of the modern literature states that clinical secondary relapse is a phenomenon related only to inadequate treatment of early syphilis or must be regarded as progression. On the other hand, Meirowsky and Pinkus,[19] quoted by Gjestland, subscribe to Fournier's idea and emphasize the rhythmic course of syphilis infection unrelated to treatment.   The Oslo study shows conclusively that clinical secondary relapse occurs in the absence of treatment.   Approximately 25 per cent of these subjects experienced this phenomenon, and of these about one-fourth had multiple episodes.   Figs. 4, 5, and 6 give data on the frequency and probability of secondary

relapse. Figs. 4 and 6 include the "known" and "partially known" of Table III (374 males and 773 females) from which have been removed those originally admitted *in* secondary relapse (Fig. 1) and those known to have received any kind of specific treatment before, during, or immediately after hospitalization by Boeck.

Fig. 4 shows the occurrence of *observed* clinical secondary relapse according to sex and age. None of these patients had received any treatment prior to the relapse. There are no differences between the sexes, and the lower proportion in the 0-14 age group is well within chance variation. Among the 244 patients (23.6 per cent of 1,035) who developed relapse, 46 (18.9 per cent) experienced two, 8 (3.3 per cent) three, and 1 (0.4 per cent) four, outbreaks; i.e., multiple outbreaks occurred in 22.5 per cent. Furthermore, both from the clinical and public health standpoint it is important to note that in 85 per cent of instances the relapsing lesions involved the mouth, throat, or anogenital regions.
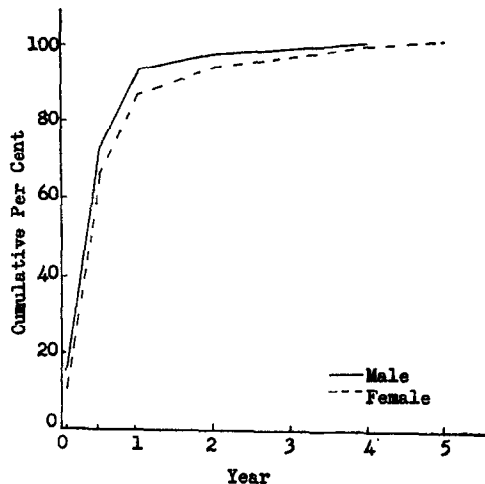

Fig. 5.—Clinical Secondary Relapse. Cumulative per cent by sex of those relapsing according to time interval between healing and observed relapse.

Fig. 5 shows graphs by sex of the cumulative percentages of those developing infectious relapse by time interval from healing of secondaries to first observed relapse. These results are similar to those presented by the Clinical Cooperative Group for inadequately treated patients. More than two-thirds of the relapsers had relapsed by the end of six months (males 72.3 per cent, females 65.1 per cent); by the end of a year, 92.3 per cent and 86.6 per cent; at two years, 96.9 per cent and 93.3 per cent; and by the end of five years, 100 per cent.

Fig. 6 shows the cumulative probability of developing the first outbreak of clinical secondary relapse among the Boeck patients. There is no appreciable difference between males and females, the probability being 22.5 per cent and 21.3 per cent by the end of the first year, and 24.3 and 24.8 per cent by the end of the fifth year.

The following quotation summarizes the author's conclusions: "It has been shown that symptoms and signs in untreated *secondary syphilis** disappear after a period of a few weeks to twelve months. This is then followed by a period of clinical latency, which in a minimum of 25 per cent of the cases is interrupted by new demonstrable lesions, or symptoms and signs of clinical secondary relapse. Of these patients again, a little more than one-fifth will experience from one to three additional outbreaks, likewise occurring after periods of clinical latency. *This development, therefore, must be considered as part of the natural course of the disease.** It has been held that the reaction of the skin and the mucosal membranes (and probably also of the eye, the bones, etc.) is dependent upon the multiplication of the spirochaetes at any given time, the rate of which is in turn determined by the status of the struggle between the immune forces of the body and the invading organisms. In our relapsers, the immune forces presumably have not been able to subdue the multiplication of the spirochaetes sufficiently to prevent a new crop of lesions from developing, the majority of which are infectious or potentially infectious. In other words, the theory held by so many
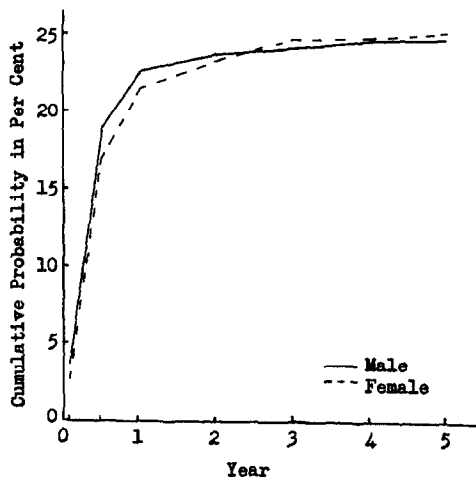

Fig. 6.—Clinical Secondary Relapse. Cumulative probability of developing in per cent, by sex, after healing.

modern syphilologists, that clinical secondary relapse is in itself mainly caused by inadequate or irregular treatment which interrupts the natural development of 'immunity,' has not been confirmed. If unsuccessful treatment of *secondary syphilis** results in the development of a certain percentage of relapses, it could better be put this way: The treatment has not been sufficiently adequate to prevent the natural course of the disease as expressed by the occurrence of clinical secondary relapse. Whether irregular or inadequate treatment during the secondary stage may result in a greater frequency of secondary relapse is a different matter, but so far there is no evidence pointing in this direction. On the contrary, it seems that under these circumstances even inadequate treatment is able to prevent secondary relapse to a certain extent."[1]

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*Italics are Gjestland's.

Benign Tertiary Syphilis.—"The development of 'benign' tertiary lesions [benign late syphilis] is in general thought to be related to an upset in the parasite-host relationship resulting from reactivation of remaining treponemes in a sensitized host. That such a reaction in a sensitized host can result from treponemes introduced from sources outside the host is suggested by superinfection experiments in the laboratory and on man and by the observations of Grin[20] on endemic syphilis in Yugoslavia."[1] This statement introduces the section on benign late syphilis, defined as tertiary manifestations of the skin, mucous membranes, bones, and joints (exclusive of Charcot's joints). Gumma of the brain is classified under neurosyphilis and gumma of the liver under visceral syphilis.
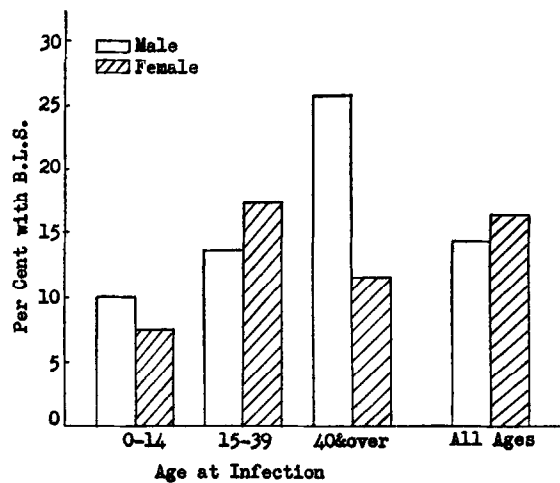

Fig. 7.—Benign Late Syphilis. Per cent occurrence according to age at infection and sex

Figs. 7 and 8 and Table VI show the frequency and probability of "benign" tertiary syphilis. Fig. 7 gives the proportions developing this manifestation according to sex and age at time of infection. No statistically significant differences between the two sexes can be demonstrated, the males being higher in the 0-14 and the 40 and over age bands and the females higher in the 15-39 and in all ages (males 14.4 per cent and females 16.7 per cent). There is a tendency toward increasing proportions with age, but the differences are well within chance variation. Of those observed with benign late syphilis, 25 per cent of the males and 34.7 per cent of the females had from two to seven episodes of this manifestation, showing again a rhythmic feature of this disease. Solitary (single structure) lesions were more common (90 per cent) than multiple structure involvement; 70 per cent were skin, 9.6 per cent skeletal, and 10.3 per cent mucous membrane lesions. In the remaining 10 per cent which were multiple structure lesions, the skin was one of the structures involved in more than half of the instances.

Fig. 8 shows for 42 males and 115 females the cumulative percentages according to time interval since the healing of secondaries and the discovery of

benign late lesions. Lesions developed from the first to the forty-sixth year, the majority developing by the end of the fifteenth year, and the mean duration of infection was 12.8 years in males and 11.2 years in females.

When the probabilities were calculated (Table VI), males and females showed significant differences at 15, 30, and 35 years, females being higher in each instance. This may indicate that the female agent-host equilibrium is disturbed earlier than that of males, and furthermore, may indicate actually a greater frequency of benign late syphilis in females, a finding not in keeping with what appears to be the case with later manifestations of this disease.
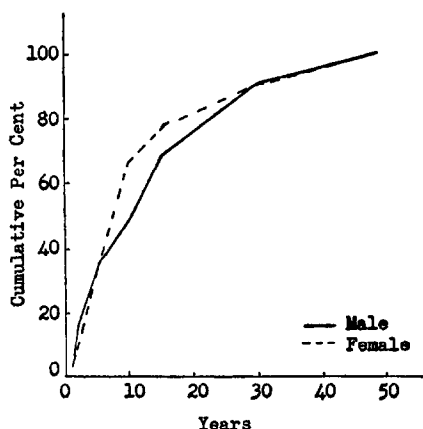

Fig. 8.—Benign Late Syphilis. Cumulative per cent by sex of those developing Benign Late Syphilis according to time interval from healing to observed lesions. Mean duration of infection, males 12.8; females 11.2 years.

TABLE VI. OUTCOME—BENIGN LATE SYPHILIS. PROBABILITY OF DEVELOPING B.L.S. CUMULATIVE, PER CENT, BY SEX

BY END OF	MALE	FEMALE
15 years	10.9	15.9
30 years	15.7	19.8
35 years	16.4	21.4

Adapted from Gjestland, Chapter VII.

Cardiovascular Syphilis.—It is not possible to present all of the details of this elaborate chapter of the monograph. Gjestland discusses many of the controversial and accepted features of this manifestation of syphilis, relating them to the data derived from his study. Of particular interest are those features having to do with diagnosis, duration of infection at time of diagnosis, sex differences, prognosis, and the relationship to occupation.

Only two tables (Tables VII and VIII) and two figures (Figs. 9 and 10) are presented here to illustrate some of the important features of this section. Fig. 9 gives the per cent of each age group and of all ages of the "known" 953 who were discovered to have developed some type of cardiovascular involve-

ment. Of particular interest is the fact that *none* of those infected before the age of 15 was found to have this type of late syphilis and, as expected in each age group, the proportions of males were significantly higher than those of females, the total rates for males being almost twice that for females, 13.6 per cent and 7.6 per cent, respectively. There was autopsy verification in 60 per cent, uncomplicated aortitis being discovered at autopsy in 22 of the 25 instances.

Fig. 9.—Cardiovascular Syphilis. Occurrence among 953 "knowns" by age at infection and sex.

Table VII gives the proportion of "knows" by sex and type (under age 15 excluded), who were observed to have developed cardiovascular syphilis, and the ratio of males to females for each type. Except for uncomplicated aortitis, where the ratio was 1 to 1, the ratio of males to females was 2 to 1 or greater.

TABLE VII. OUTCOME—CARDIOVASCULAR SYPHILIS. PROPORTION OF "KNOWNS" OBSERVED TO HAVE DEVELOPED CARDIOVASCULAR SYPHILIS BY FORM AND BY SEX (UNDER 15 REMOVED)

	303 MALES	584 FEMALES	887 TOTAL	RATIO M/F
Uncomplicated aortitis	2.6	2.9	2.8	1/1
Aortic insufficiency	7.3	3.3	4.6	2.2/1
Saccular aneurysm	3.6	1.5	2.3	2.4/1
Ostial stenosis	0.7	0.3	0.5	2.3/1
Aortitis—found at death	0.7	0.0	0.2	
Total complicated	12.3	5.1	7.6	2.4/1
TOTAL	14.9	8.0	10.4	1.9/1

Adapted from Gjestland, Chapter IX.

In Table VIII an attempt is made to give some suggestion as to possible minimum and maximum frequencies of cardiovascular syphilis by comparing the total "known" group with the autopsied population. Thus, it was suggested by Gjestland that the actual occurrence of uncomplicated aortitis among

TABLE VIII. OUTCOME—CARDIOVASCULAR SYPHILIS. COMPARISON OF
"KNOWN" STUDY GROUP WITH AUTOPSIED PATIENTS

FORM OF CARDIOVASCULAR SYPHILIS	PER CENT IN STUDY GROUP	PER CENT IN AUTOPSIED GROUP
Uncomplicated Aortitis		
Males	2.6	9.3
Females	2.9	11.2
Complicated Forms		
Males	12.2	25.3
Females	5.1	10.4

Adapted from Gjestland, Chapter IX.

males may lie between 2.6 per cent and 9.3 per cent, and among females between 2.9 per cent and 11.2 per cent. The actual occurrence of the complicated forms may lie between 12.2 per cent and 25.3 per cent among males and between 5.1 per cent and 10.4 per cent among females. It was suggested further that the higher figure is the more likely one for the occurrence of uncomplicated aortitis, but that this is probably not the case in the complicated forms. These points can be clarified somewhat by a quotation as follows:

"It is obvious, for instance, that figures arrived at through the study of autopsy populations are not comparable with those found in ordinary follow-up studies. Any atuopsy population will necessarily be more or less heavily weighted with serious cases as compared with the hospital population from which it is drawn, and even more so as compared with the original 'syphilis universe.' This phenomenon was clearly demonstrated in our series, where the autopsied patients showed a considerably higher frequency of cardiovascular lesions than the study group as a whole. Moreover, if we consider the dead, the fact that about 66 per cent of those with cardiovascular involvement were found to have been autopsied, as compared with about 30 per cent of the total, shows that persons who had developed such complications ended up in hospitals *and** were submitted to autopsies to a far greater extent than were the others. When it comes to hospital populations, including a varying number of dead and living patients, materials selected from such groups also tend to become biased in the direction of more serious cases, because diseases brought the patient to the hospital, and thus figures arrived at in studies of this nature cannot be directly compared with those arrived at in follow-up studies. Finally, this is probably true as well of figures found in the studies of patients picked from hospitals *and** clinics (or outpatient departments), although not quite to the same degree as in the first two instances mentioned.

"Since the present investigation has all the characteristics of a follow-up study, it is hardly advisable to compare our quantitative data in respect to cardiovascular syphilis with those arrived at through the various other methods of approach just mentioned. As a matter of principle, therefore, we are in-

*Italics by Gjestland.

clined to consider it a prerequisite for such comparisons that the figures in question stem from a similar type of study. But this in itself is not a sufficient guarantee for comparability since methods of tracing, identification, and collection of clinical data may vary from one follow-up study to another according to geographical area, population groups involved, the investigator's attitude toward the problems, and other factors, all of which may have a considerable bearing on the end results. A critical evaluation of these factors and how they may have influenced the findings undoubtedly forms another requirement for eventual comparisons. The point is exemplified in our discussion of Aggerbeck's (1949) and Nielsen's (1950) Danish studies as well as in the analysis of our own data. Thus, only after having evaluated the basic epidemiologic methods employed in establishing the materials in question is it, in our opinion, worthwhile to proceed to a discussion of the many other factors involved, the most important of which are going to be considered in the following."[1]
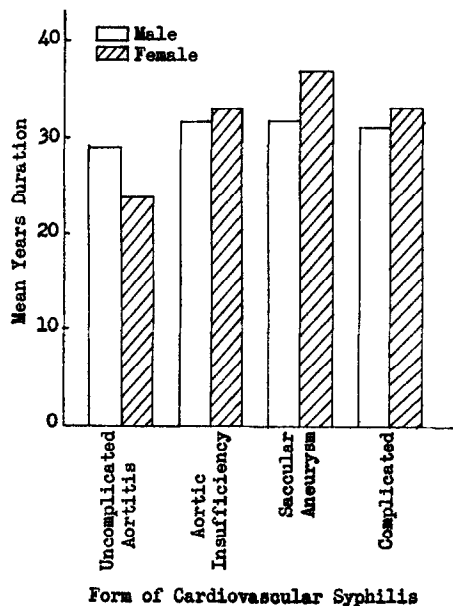

Fig. 10.—Cardiovascular Syphilis. Duration of infection at discovery, in mean years, by form and by sex.

Fig. 10 is constructed to show the duration of infection at the time of diagnosis of cardiovascular syphilis (not the onset of symptoms). In all forms except uncomplicated aortitis the diagnoses were made on the average in the fourth decade of infection. The numbers are small and the differences slight.

Neurosyphilis.—In this section of the monograph the data are presented as before with a consideration of the pertinent literature, the presentation of the data of this investigation, and a discussion of his own data as they relate to other information in the medical literature. The precautions to be observed in making comparisons of one set of figures with another is repeatedly emphasized. Figs. 11 and 12 and Table IX briefly review some of the information in this section.

Fig. 11 gives the proportion of each age and sex group and of all ages observed to have developed neurosyphilis by age at time of infection. Of the 62 persons who developed neurosyphilis, 31 were males and 31 females, whereas of the total "known" group the population of females was twice that of males. Neurosyphilis was observed in 9.4 per cent of the males and 5.0 per cent of the females. It is of interest here to note that neurosyphilis *did* develop among those infected under the age of 15. Of this age group 6.1 per cent developed neurosyphilis, with a male to female ratio of approximately 4 to 1. None of the 28 males over 40 at infection developed neurosyphilis, whereas 2 of 45 females did. It is to be noted also that this analysis includes only symptomatic forms; no asymptomatic neurosyphilis is included.
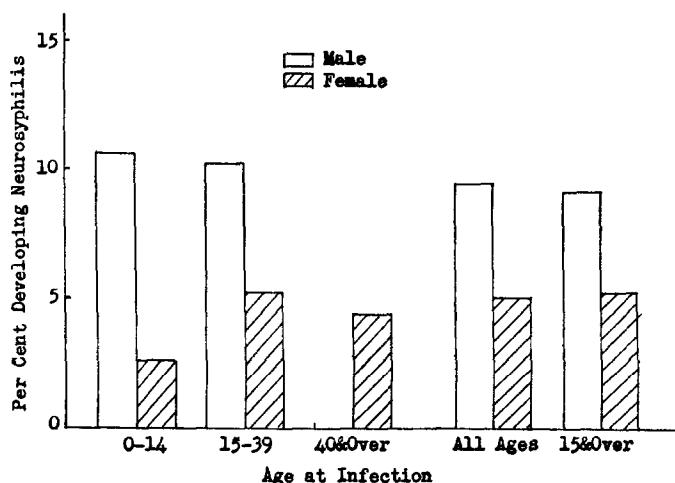

Fig. 11.—Neurosyphilis. Occurrence among 953 "knowns" by age at infection and sex.

Table IX shows the forms of neurosyphilis and the proportions of the "knowns" (of all ages) who developed each form. Also given is the ratio of males to females, and it can be seen that in each category the ratio is about the same, approximately 2 to 1. Of the 62 persons with neurosyphilis, 18 were alive and examined during the period of the investigation, these being equally divided among males and females. Of the dead, neurosyphilis was recorded as the primary cause of death in two-thirds of the instances. In the other third, neurosyphilis was present but unrelated to the causes of death.

TABLE IX. OUTCOME—NEUROSYPHILIS. PROPORTIONS OF "KNOWNS" OBSERVED TO HAVE DEVELOPED NEUROSYPHILIS BY FORM AND BY SEX—ALL AGES

	331 MALES	622 FEMALES	953 TOTAL	RATIO M/F
Diffuse meningovascular	3.6	1.7	2 3	1.9/1
General paresis	3.0	1.7	2 1	1 8/1
Tabes dorsalis	2.5	1.4	1 9	1.7/1
Gumma of brain	0.3	0.2	0 2	1 5/1
TOTAL	9.4	5 0	6 5	1.8/1

Adapted from Gjestland, Chapter VIII.

The duration of infection at the time of diagnosis is shown in Fig. 12, according to form and by sex. There is little difference between the sexes, except in general paresis where, on the average, the duration of the infection was less in females. The duration is shorter than that of cardiovascular syphilis and is in keeping with what is known about the natural course of this disease.
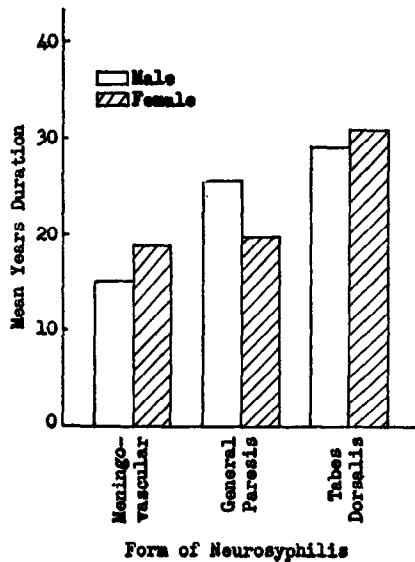

Fig. 12.—Neurosyphilis. Duration of infection at discovery, in mean years, by form and by sex.

Other Late Syphilis.—Out of 953 patients classified as "known," only two were found to have other types of late syphilis. Two females had gummas of the liver, one found at autopsy and one diagnosed clinically. In each instance the manifestation was considered to be the primary cause of death.

Mortality.—Two theories have been advanced to explain the excess mortality among syphilitics above that expected as a result of the late effects of the disease itself: (a) Syphilitics by and large come from a segment of the population characterized by high mortality rates from many causes as a result of low socioeconomic status; (b) syphilis as a generalized systemic disease exerts an adverse and nonspecific effect on most of the organ systems of the body.[11,13,14,21] The mortality of this series of patients was studied by Gjestland from three viewpoints: (a) the actual causes of death; (b) the probabilities of dying primarily as a result of syphilis infection; and (c) the excess mortality of syphilitics as compared with a control series.

Table X shows the primary causes of death among the 694 known dead. Syphilis was the primary cause of death in 15.1 per cent of the males and 8.3 per cent of the females, a ratio of 1.8 to 1. Among males, syphilis ranked second, and among females, fifth, as a cause of death. In each group tuberculosis led the causes of death, and in females more died of cancer and diseases of the circulatory and respiratory systems than of syphilis. Thus, among a 100 per cent syphilitic population 84.9 per cent of males and 91.7 per cent of females died of other causes.

TABLE X.   PRIMARY CAUSES OF DEATH BY SEX AMONG 694 KNOWN DEAD

PRIMARY CAUSES OF DEATH	MALES			FEMALES		
	NO.	PER CENT	RANK	NO.	PER CENT	RANK
Tuberculosis	45	17.4	1st	74	17.0	1st
Syphilis	39	15.1	2nd	36	8.3	5th
Cancer and other tumors	32	12.4	3rd	71	16.3	3rd
Diseases of circulatory system*	28	10.8	4th	72	16.6	2nd
Diseases of respiratory system*	25	9.7	5th	42	9.7	4th
Sudden—Unknown, Unspecified	20	7.7	6th	18	4.1	8th
Diseases of urinary and genital tract	16	6.2	7th	16	3.7	9th
Diseases of nervous system and sense organs*	14	5.4	8th	34	7.8	6th
Accidental deaths	11	4.2	9th	9	2.1	12th
Diseases of digestive system	7	2.7	10th	24	5.5	7th
ALL OTHERS	22	8.7		39	8.9	

Adapted from Gjestland, Chapter XII.
*Syphilis excluded.

The cumulative probability of dying directly as a result of syphilis was 17.1 per hundred in males and 8 per hundred in females by the end of 40 years of infection among this group of patients.

In order to study possible cause and effect relationships for the excess mortality of syphilitics over nonsyphilitics, a control group was chosen from the population of the city of Oslo for comparison with the mortality experience of Boeck's patients.   It was found that most of his patients came from the eastern parishes of the city and their mortality experience could be compared by age, sex, and cause, and by decade with the population from which they came.   This was studied in considerable detail and will be reported in a separate publication.[22] The findings reported in the monograph are shown in Table XI.

TABLE XI.   MORTALITY.   EXCESS IN SYPHILITICS AS COMPARED TO THAT EXPECTED ON BASIS OF EXPERIENCE OF RESIDENTS OF EASTERN PARISHES OF OSLO BY AGE AND SEX FROM 1890-1940*

AGE	MALES			FEMALES		
	EXPECTED DEATHS	OBSERVED DEATHS	EXCESS PER CENT	EXPECTED DEATHS	OBSERVED DEATHS	EXCESS PER CENT
10–19	2.3	1	0	4.4	5	14
20–29	13.7	15	9	29.4	42	43
30–39	21.5	33	53	43.1	84	95
40–49	24.8	55	122	36.8	69	88
50–59	30.5	48	57	38.3	60	57
60–69	28.4	41	44	26.6	41	54
70 and over	18.9	21	11	25.3	31	23
ALL AGES	140.1	214*	53	203.9	332*	63

Adapted from Gjestland, Chapter XII.
    *Deaths after 1940 excluded.   Decade included German occupation of Norway which influenced Norwegian population and mortality statistics.

This table shows that these untreated syphilitics had an excess in mortality over that expected of 53 per cent in males and 63 per cent in females (all ages), and there was some degree of excess in every age group except males 10-19. The excess was most pronounced in males 40-49 and in females 30-39. A similar picture of excess mortality was found when the mortality experiences of the eastern and western parishes were compared according to age, sex, and decade; the eastern group with lower economic status showed excess mortality over that of the west in practically every category of comparison. The average excess mortality of the east over the west (all ages) was 16 to 27 per cent among males and 25 to 38 per cent among females.

Gjestland concludes this section by expressing an opinion that although these results appear to lend confirmatory evidence to the nonspecific unidentified effect of syphilis infection on mortality, he does not believe that this is true. Additional quant:tative support will doubtless be offered in the detailed study of mortality to be published later.[22] In the monograph he states that if these results are to be explained on the basis of this unknown factor, it must be assumed that it exerts its influence at all ages and at all durations, that its influence varies in different age groups, and that it exerts its effects through a number of other diseases in various organ systems. He cannot conceive of a mechanism that could work in this manner. He explains the excess mortality purely on a basis of lower socioeconomic status; and this seems reasonable in view of the similarity in the pattern of excess mortality when west is compared with east and the eastern population is compared with the Boeck patients. With decreasing socioeconomic status there are increasing risks of mortality from many diseases, and even within the lower strata there are perhaps some groups at greater risks than others.

Summary of Data on Outcome.—Fig. 13 gives a summary of the outcomes among the living and dead according to sex and shows that in this series of patients, as in many other series that have been reported, serious outcomes are more frequent among males than among females. The proportion of infectious relapses are about the same. A higher proportion of females than males developed benign late syphilis, but for cardiovascular and neurosyphilis the ratio of males to females is approximately 2 to 1. Similarly, syphilis as a primary cause of death gives a male:female ratio of 2 to 1. The varying numbers of patients upon which these proportions are based can be better understood by reference to Table III. Infectious relapse is based upon both the "known" and "partially known" group, less those treated and those seen originally in infectious relapse. Benign late includes the entire "known" and "partially known" groups. Cardiovascular and neurosyphilis are based upon the "knowns" only and the cause of death based on those in Table III known to be dead.

The Prognostic Significance of Clinical Secondary Relpase and "Benign" Tertiary Syphilis.—The prognostic significance of clinical secondary relapse was examined by dividing the patients by sex into two groups, those who were observed to have clinical secondary relapse and those who were not observed to have clinical secondary relapse. The occurrence of benign late syphilis,

cardiovascular, and neurosyphilis was calculated for each of these two groups (table not shown here). There was considerable variation in both directions and in females there seemed to be a slight tendency toward more benign late syphilis and more neurosyphilis in the relapsers as compared with the nonrelapsers. This was not marked in males nor in the group as a whole (of relapsers 43 per cent had late syphilis, of nonrelapsers 39 per cent), and none of the differences were found to be statistically significant. Thus, from these data, there is no indication that the occurrence of clinical secondary relapse per se influenced the ultimate outcome of the disease among these patients untreated during primary and secondary syphilis.
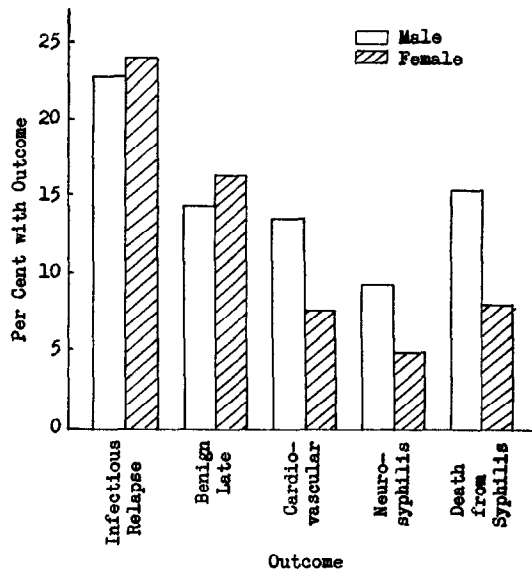
Fig. 13.—Summary of outcomes by sex.

Because of numerous references in the literature to the protective influence of benign late syphilis, Gjestland examined the prognostic significance of benign late syphilis from three standpoints: (a) concomitant benign late and other late syphilis; (b) the extent to which benign late preceded other late syphilis; and (c) the final outcome among those observed to develop benign late and those who did not.

Among his patients, concomitant or simultaneous benign late syphilis and cardiovascular syphilis occurred in 2 of 92 instances; benign late and neurosyphilis in 5 of 62 instances. This is what one would expect in view of the fact that the mean ages of development of these complications are so different. The extent to which cardiovascular and neurosyphilis were preceded by benign late syphilis was found to be no greater than the proportion of benign late syphilis in the study group as a whole (17 per cent of late syphilis had benign late, 16 per cent of the study group). The final outcome among those who had previously developed benign late syphilis and those who had not did not differ significantly in this series of patients (late syphilis was observed in approximately 21 per cent of those who had had benign late and in 16 per cent of those who

did not). "As the figures stand, therefore, and with the reservations made necessary by the small numbers involved, it is probably safe to state that the findings in the present series do not provide evidence for the concept that lesions of the skin, mucous membrane, and the bones in themselves exert a protective influence against serious late manifestations."[1]

Spontaneous Cure.—There are many statements in the literature about the frequency of spontaneous cure, but very little evidence is available to support the estimates. One of the barriers to an understanding of this problem is the strictness of definitions of spontaneous cure made by various authors. For the purposes of examining this problem in the Oslo material, a definition of spontaneous cure suggested by Moore in a personal communication to Gjestland and slightly modified by him was used. By this definition a diagnosis of spontaneous cure would have to be limited to those in a group of originally untreated syphilitics who (a) had shown no symptoms of syphilis after the early outbreak; (b) had received no specific treatment for latent syphilis during the interim period; (c) had been examined before death, with normal physical findings as far as syphilis was concerned and who then had a negative serologic test and normal spinal fluid; (d) had at autopsy shown no evidence of syphilis. It is safe to say that no representative group of patients satisfies these rigid criteria. The present study is no exception. The shortcomings in this respect of the Bruusgaard series and that of Rosahn are discussed thoroughly by Gjestland and, furthermore, details are given to show that the present data do not lend themselves to an analysis of this kind. It is doubtful that any material will ever become available which will satisfy these criteria. From a practical standpoint, however, in so far as individual patients are concerned, the important question is: To what extent does a group of untreated or highly inadequately treated syphilitics pass through life with little or no inconvenience as a result of the disease? The following quotation indicates an answer derived from the study of this material. "Out of every 100 patients 13 were found to have developed 'benign' tertiary alone, 15 were found to have developed cardiovascular and/or neurosyphilis, either alone or in various combinations; that is, a total of 28 were found to have developed some type of late manifestations. In other words, some 72 patients out of every 100 were found *not* to have developed any late lesions. In this connection it must be emphasized that our figures on the various complications to a certain extent were considered to be minimum. Therefore, the above figure of 72 out of every 100 patients is probably not representative. As mentioned previously, it is connected with considerable difficulties (sic) to estimate to what extent our figures for the various complications were minimum, but if we assume that somewhere between 60 and 70 (probably closer to 60 than to 70) out of every 100 untreated syphilitics in the present series went through life with little or no inconvenience as a result of the disease we are probably not too far from the truth."[1] It should be noted that 30 out of every 100 males were found to have developed some type of late lesions (including benign late syphilis) and 26 out of every 100 females developed such lesions.

These figures (60 to 70 per cent not inconvenienced by untreated syphilitic infection) appear to confirm the estimates based upon Bruusgaard's material (Table I). From an epidemiologic point of view, however, the similarity of the figures is fortuitous since Bruusgaard's are based on an inadequate sample (about 20 per cent of the total) followed for relatively brief periods of time (many for less than 10 years and some of these unexamined) and not sex specific. The present study, on the other hand, involves an 80 per cent sample and a follow-up period of 40 to 60 years and analyzed on a sex-specific basis. While Bruusgaard limited himself to the presentation of his basic facts and drew no inferences therefrom, many subsequent workers did draw such inferences as to the prognosis of untreated syphilis based on their own and Bruusgaard's work. In spite of the fact that, as Harrison,[6-8] Sowder,[9] and now Gjestland[1] have shown, such inferences were unjustified, those who drew them are perhaps lucky to have so little to retract, since Gjestland's data thoroughly justify the prognostic estimates based upon the Bruusgaard material, despite the selected nature of his sample.

SUMMARY

Nowhere in the world is there a more unique opportunity to learn what happens when early syphilis goes untreated than from the files of Boeck of Oslo, Norway. His scientific conviction as to the inadequacies of the specific treatment of the day led him to withhold treatment from approximately 2,000 patients with primary and secondary syphilis during the twenty-year period, 1891-1910. Community protection from infection was aided by the hospitalization of these patients until all traces of the disease had disappeared (from 1 to 12 months, average 3.6 months). In 1929, his successor, E. Bruusgaard, reported on a follow-up study of 473 of these patients and provided information on the outcome of untreated syphilis, which has formed the basis for prognostic statements on syphilis for more than twenty-five years. Now, in the department of Bruusgaard's successor, Danbolt, the entire material has been restudied successfully by Gjestland.

This restudy represents a striking example of the application of the modern epidemiologic approach. In addition to the scientific contribution of this investigation, an outstanding illustration of international scientific cooperation has been demonstrated.

The remarkable degree of success in obtaining significant information on approximately 80 per cent of the study group, 1,404 Norwegian residents of Oslo of 1891-1910, was undoubtedly due to the careful planning which preceded the tracing efforts. This planning included: (a) a consideration of the nature, extent, and significance of the problem of untreated syphilis; (b) an appraisal of existing information on the subject; (c) the setting up of hypotheses to be tested and questions to be answered; and (d) a detailed outline for a practical experiment design. The pretracing experiment design comprised: the selection of the study group; the listing of possible sources of information; a plan for orderly tracing; a provision for the collection and recording of information; plans for "controls"; and an outline for the analysis of data. Of particular

importance is that these features of detailed planning preceded actual data collection. This characteristic of the epidemiologic method is well illustrated by this study.

The study was undertaken with the ultimate objective of providing information on the ". . . natural course of syphilis according to as many indices as the material will allow. . . ."[1] The questions originally asked of the material were: Among patients untreated for secondary syphilis and with no, some, or unknown subsequent treatment: 1. What are the frequencies of secondary relapse, of benign late syphilis, of late symptomatic syphilis, of life-long latency, and of spontaneous cure? 2. What are the effects on longevity, on causes of death and on mortality over that of nonsyphilitics? 3. Does age at time of infection influence outcome? 4. Does sex influence outcome? 5. What are the effects on the outcome of pregnancy at varying intervals following infection? 6. Is morbidity from conditions other than syphilis greater than among nonsyphilitics?

Analysis of this material provides useful information in reference to questions 1 to 4. Unfortunately, it was impossible to collect significant data for question 5 and the matter of congenital syphilis was postponed for future investigation on a more limited scale. Data relating to question 6 will be introduced in a subsequent publication[22] if satisfactory inferences can be drawn about morbidity from an extensive mortality study. The data relating to the remaining four questions are summarized in the following paragraphs.

One of the significant contributions of this investigation is the information obtained on clinical secondary relapse: 23.6 per cent of these patients experienced this manifestation within five years of discharge from the hospital (males 22.7 per cent, females 24.0 per cent) and of these approximately one-fourth had multiple episodes.

Benign late syphilis occurred in 14.4 per cent of males and 16.7 per cent of females. It was observed as early as the first year after discharge and as late as the forty-sixth year, the majority developing by the fifteenth year. There was some evidence of earlier appearance in females than in males and some suggestion that the probability of development is greater among females.

Cardiovascular syphilis was observed to have developed in 13.6 per cent of males and 7.6 per cent of females, no cases occurring in those infected before the age of 15.

Neurosyphilis did develop in patients who were infected before the age of 15 but not in males infected after the age of 40. In neurosyphilis there was a 2 to 1 ratio of males to females (males 9.4 per cent and females 5.0 per cent).

The mortality from syphilis among males was twice that of females, but in neither sex was it an important cause of death. It was second as a cause of death in males and fifth in females, but approximately 90 per cent of deaths were from other causes. There was a definite excess mortality among these syphilitics as compared to the population group from which they came.

No evidence was found to support the idea of the prognostic importance of either clinical secondary relapse or benign late syphilis.

The best definition of spontaneous cure is too rigid to permit quantitative evaluation. More practical is a consideration of the extent of disability during the lifetime of the persons involved. It was estimated that between 60 and 70 out of every 100 of these patients went through life with a minimum of inconvenience despite no treatment for early syphilis. This gives no encouragement to withhold treatment because the final outcome in any individual cannot be predicted, and, too, syphilis is still a transmissible disease when untreated and can cause serious difficulties among 30 to 40 out of each 100 who remain untreated.

This is probably the most comprehensive study of untreated syphilis that has yet been made, and the great mass of data that has been collected will provide the basis for additional contributions to our knowledge of syphilis infection. This brief review cannot do justice to this monumental piece of work comprising a monograph of some 500 pages, with 83 tables and 12 figures, and an annex of 70 pages with 30 tables and 2 figures. Gjestland's contribution will stand as a model of carefully planned and successfully executed field research and will provide the medical literature with the long awaited restudy of the Boeck-Bruusgaard material.

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