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A HANDBOOK OF CLINICAL CHEMICAL PATHOLOGY

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PREFACE

THE following chapters are based on a course of lectures on clinical chemical pathology given to senior students of the Leeds University Medical School. In presenting them in the present form it is hoped that they will serve as a short text-book on the subject which may be of use not only to medical students but to house surgeons and house physicians and to general practitioners.

It might be urged, with some reason, that anything in the nature of a text-book on this subject is premature. The greater part of the subject is of very recent development, and it is as yet too early to assess correctly the value of many of the chemical methods which have been introduced as aids to diagnosis. Nevertheless there are strong reasons in favour of the course I have adopted. In the first place, the fact that present-day students are expected to be acquainted with the modern applications of chemistry to clinical work appears to me to justify the appearance of such a book. In the second place, many of the methods described have passed beyond the stage of trial and are now recognised to be of considerable value. They therefore deserve to be more widely known and more generally used. Further, the fact that the value of many proposed methods is as yet uncertain seems to me to be an argument in favour of greater publicity concerning them, for only by their extended use can their true value become known. But if the application of such methods is to be of any value from this point of view, it is necessary that they shall be carried out with a clear appreciation of the principles underlying them as well as with exact knowledge of the practical details involved. Hence it appears advisable to present those principles and practical details in a readily available form.

The application of chemistry to clinical medicine is not entirely restricted to questions of diagnosis. Many subjects essentially chemical have a close bearing on clinical work, apart from this sphere. For this reason I have included certain subjects which, while having no close connection with diagnostic methods, nevertheless seem to me to be of considerable importance.

The book is not in any sense a handbook for laboratory workers. Hence no attempt is made to describe methods of chemical analysis. The plan already adopted in most of our hospitals, namely, the concentration of actual laboratory procedures in the hands of those specially trained in this work, is firmly established, and, besides being an object of doubtful value, it appears to me to be a waste of effort to attempt to persuade each clinician to be his own chemist. What is of importance is that the clinician should have a clear knowledge of the help he may obtain from laboratory tests, of their limitations and of the conditions to be observed in order to get the best results from them. In other words, he should know when to have tests made, how to obtain the necessary specimens and how to interpret the results. It is with the object of offering information on these points that the book has primarily been written. Actual chemical work may be left in the hands of the laboratory expert. Already laboratory services are available to most medical men. Where this is not the case such services will become available if a sufficient demand for them arises.

As this book is not intended to be a guide for research workers no attempt has been made to give anything like a complete bibliography of the subject. Only a few references have been given, chiefly to recently published work.

F. S. F.

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FOREWORD

THE application of chemistry to the problems which arise in clinical medicine and surgery has undergone great and very rapid development in recent years, and the subject is now so large that it is difficult for the clinical teacher or even the clinical text-book to deal adequately with it. Many of the medical schools now have teachers who pay special attention to this subject. Printed instruction is to be found principally in the standard works on physiological chemistry or pathology or in books which deal with certain aspects from the clinical and chemical standpoint. There are, however, not a few reasons which appear to make it desirable to treat clinical chemical pathology as a separate subject, not because it is to be considered as something apart from pathology, physiology or clinical medicine—in fact its proper understanding is dependent on a wide knowledge of all three—but because certain general principles apply throughout the whole subject binding the different parts into a fairly coherent whole. Such parts are therefore best studied consecutively, so that these principles may be kept in mind throughout, and the same mental attitude maintained towards them. Moreover, the subject is now of such dimensions that it can best be dealt with along these lines.

In the rather formidable curriculum of the modern medical student increasing attention is now being paid, and must increasingly be paid, to the subject. It is therefore desirable to offer him a book in which the information he requires is collected together in logical order and is comprehensive yet concise. The increasing use of laboratory procedures in hospitals and elsewhere makes it desirable that resident

officers should have an accessible and reliable source to which they can turn for knowledge of principles and practice.

Dr. Fowweather has almost entirely omitted to give details of purely chemical processes. Every medical man should understand the application of laboratory methods to problems of diagnosis, and should be able to take advantage of such methods. But every medical man cannot be an expert chemist. Indeed, training in purely chemical procedures should be reserved for those specially interested in this study, and the services of these trained workers, who have experience not only in chemical analysis, but in the application of chemical methods to clinical problems, will become increasingly available as the demand for them grows.

This delegation of a part of the work involved in the application of laboratory tests from the clinician to a second person is perhaps unfortunate, but it is surely made inevitable by the growth of the subject. It has already been abused, and a system has to some extent grown up which has been rightly ridiculed as "penny-in-the-slot diagnosis." Here the clinician sends a specimen to the laboratory and expects to receive in return, not merely the result of the analysis, but also a brief diagnosis of his case. This abuse is due to the fact that the clinician has not sufficient knowledge to give him confidence to interpret for himself the results of chemical analysis and to incorporate them, along with the information he has gained from clinical examination of the patient, into a composite picture. The duty and the pleasurable task of making a diagnosis rests finally with the clinician and never with the laboratory worker. It is with a desire to help the clinician to take advantage of laboratory methods in this way that the book has been written.

Books dealing with clinical chemical pathology on these lines are at present few. This volume meets, in my judgment, a real need. I cordially commend it to my colleagues.

BERKELEY MOYNIHAN

FOWWEATHER'S PATHOLOGY

CHAPTER I

INTRODUCTORY

PATHOLOGY has been defined as the science of disease, or the study of disease by scientific methods. Chemical pathology is that part of the subject which employs chemical methods and chemical knowledge in the study of disease. Clinical chemical pathology is the application of the results gained by the study of disease in this way to clinical medicine.

In other words, it is the application of our knowledge of the chemistry of disease to the study of the condition of individual patients. Its purpose is to give us information which may assist us in diagnosing and treating disease in our patients and in arriving at a true idea of its progress and prognosis.

Amongst these functions, that of assisting diagnosis is one which has received considerable attention during recent years. Indeed, the attention paid to this branch of the subject is such that there is some danger of losing sight of the fact that chemical tests are not the sole nor even the principal means to be employed for the purpose of diagnosis. The clinical laboratory should never be regarded as an institution which of itself is capable of supplying a diagnosis. It is a means of obtaining additional information about a patient, where it is felt that further information is needed, to add to that already obtained by careful and complete clinical examination. A diagnosis must then be made in the

light of all the evidence available. But sound clinical observation is, and must remain, the principal means of arriving at a correct diagnosis.

Not only must chemical evidence be regarded as secondary to clinical evidence in the great majority of cases, but in the absence of the latter chemical evidence may be useless or even misleading. Many of the chemical changes known to occur in disease are common to a number of conditions. If then a given test shows that a certain chemical change has occurred, *e.g.*, a pathological increase or decrease of some blood constituent, all we learn from the test alone is that one of a number of conditions is present. The application of clinical evidence will then frequently enable us to differentiate between the conditions indicated by the chemical test. On the other hand, if clinical evidence fails to allow us to differentiate convincingly between conditions which are known to give different results with certain chemical tests the application of those tests will generally remove our difficulties, and in some cases where evidence obtained by purely clinical means is lacking in some important particular, the deficiency may be made good by the application of chemical methods, and so our picture is made more complete.

The correct attitude of the clinician to laboratory work is that if in any case, after using all the available clinical means at his disposal, he is not thoroughly satisfied concerning the matter in hand, whether it be one of diagnosis, prognosis or treatment, then he should consider in what way laboratory information may help him, whether to throw further light on a doubtful case, to confirm or negative a probable diagnosis, to decide between alternative views, or in any way to make more certain his knowledge of the matter in hand. This procedure involves the intelligent consideration of the relation of laboratory work to each individual case, and is the reverse of the method of routine application of numerous laboratory tests before a serious attempt is made to consider a case from the clinical standpoint.

As a distinction has been made between clinical examination and laboratory tests, it should be pointed out that the simpler tests on urine, *e.g.*, tests for albumin and sugar, are to be included in the clinical examination. They are a necessary part of the routine examination of a patient, and should be used as freely and unconsciously as the most obvious physical methods of examination. They should certainly be done before the advisability of undertaking other laboratory tests is considered. And with these should be included, where indicated, tests for acetone bodies in the urine.

The chemical pathologist makes analyses of various materials from the patient—blood, urine, fæces, etc.—and compares the results with the results which are known to be obtained from similar materials from healthy people and from people known to be suffering from certain diseases. To interpret the results correctly two things are necessary, in addition to a complete clinical examination of the patient. These are, firstly, a knowledge of the normal variations of certain constituents of the material analysed, and, secondly, a knowledge of the way in which in certain diseases the chemical composition of these materials is altered. Hence it is only in those conditions which are accompanied by significant chemical changes capable of recognition by the analyst, and known to be abnormal, that laboratory tests can be of any assistance. Even in conditions where definite chemical changes are known to occur, the application of that knowledge to clinical medicine depends largely on the methods we possess for recognising and estimating those changes. Methods which are very laborious and require a high degree of technical skill and an elaborate equipment, or which cause considerable discomfort to the patient, can never have more than a very restricted use. Fortunately the efforts of recent years have been successful in devising methods which are comparatively simple and mostly free from the undesirable features just mentioned.

Certain limitations have to be borne in mind in attempting the interpretation of laboratory results. In the first place, what are considered normal values of certain chemical constituents of body fluids, etc., cover a fairly wide range, and it is usually impossible to attach much significance to an analytical result which falls within this range. Yet in certain individuals a change from a value near one end of the range to a value near the other end of the range may be a change of appreciable magnitude and possibly due to some pathological condition which we are seeking to recognise.

Another considerable limitation lies in the fact that we often attempt to ascertain the presence or absence of disease in an organ by ascertaining by chemical methods if its functional capacity is normal or impaired. But the presence of disease in or damage to an organ and impairment of its functional capacity are not necessarily co-existent. Frequently an organ can function normally, at any rate so far as our present tests can indicate, although it is the seat of considerable disease. Hence a negative result of such a test must be recognised simply for what it is, namely, that functional capacity, so far as the particular test is concerned, appears normal. It must not be made to bear the added significance that the organ in question is necessarily perfectly sound and healthy. This limitation would appear at first sight to render much of our work valueless, and while it must be admitted that it does narrow the usefulness of laboratory tests considerably, yet by using all our available experience of such tests and taking into account all the information about our case that we can gather by other means, we are frequently able to arrive at a much clearer understanding of our patient than we could have done in the absence of these laboratory tests.

The presence of these inherent limitations to the application of our results makes it all the more necessary that we should guard strongly against any fallacies that are preventable. That means that we must have a perfectly clear con-

ception of what we are trying to find out—a firm grasp of the principle underlying the test. To interpret the result of a test wrongly is worse than to omit the test altogether, for it is definitely misleading. One has to consider not merely the result of an analysis but all the circumstances attending the taking of the sample. Probably no test has been more abused in its interpretation than the testing of urine for sugar. For example, too often has it been asserted confidently that a patient is not suffering from diabetes because a test on a sample of urine taken haphazard from him has yielded a negative result. This is, of course, owing to a failure to appreciate the relation of glycosuria to glycæmia, and the relation of the latter to the intake of carbohydrate food by the patient. In other words, it is impossible to interpret correctly the result of such a test unless the time relation between the passing of the urine by the patient and his last carbohydrate meal is known.

In the same way, many other tests can only be interpreted correctly in the light of exact knowledge regarding the patient's diet. Other factors, too, demand careful attention. In making certain urine tests, for example, the information we are seeking can only be correctly obtained from an analysis of the twenty-four hours' output, whereas for other tests we require a single specimen taken under certain definite conditions.

In general, most tests should be carried out before any treatment of the patient is undertaken. If in any case treatment is begun before a desired test is made the possible effect of the treatment on the results of the test must be carefully considered, and where there is any likelihood of the treatment interfering with or obscuring the results of the test, treatment must be suspended for a few days before the contemplated test is carried out.

Taking Specimens.—If the clinician is making an analysis or examination of a specimen himself he will, of course, have made himself quite familiar with all the conditions govern-

ing the method he has selected. But if the specimen is to be dealt with by someone else the clinician should not fail to obtain beforehand information as to the quantity of material required: if blood, whether it should be allowed to clot or prevented from clotting, and so on. It is of considerable advantage if he understands something of the principles underlying the different analytical methods used, but even so it may be necessary to ascertain from the pathologist what are his requirements in any given case, for there are frequently alternative methods available, for which individual pathologists have their own preferences. The pathologist will be anxious to give any guidance he can, so that the results obtained shall be of real value and not misleading. Further, there is the patient's point of view. It must be held as a cardinal principle that the patient must not be caused to suffer more than the minimum of trouble in giving specimens for analysis. Frequently a patient has to suffer repeated venipunctures or lumbar punctures, or other procedures, when only one should have been necessary, because specimens have been taken in ignorance of the true requirements of the case and therefore found to be useless. True the majority of the usual methods of obtaining specimens are not very severe ordeals for the patient. Still he has usually a strong dislike to them, and no clinician will be popular with him if he multiplies these procedures unnecessarily through his own ignorance.

It is obvious that one must become familiar with the technique of the different methods of taking specimens. The usual procedures are described in text-books of clinical methods, and there is therefore no need to describe them fully here. One or two points, however, may be referred to. Blood samples are most usually obtained by means of a needle and syringe from one of the superficial veins in front of the elbow. In fat people and in children these veins may not be visible or even palpable. Unless a vein can be definitely located either by sight or touch no attempt to

obtain blood at this site should be made. The practice of pushing a needle through a patient's skin in the hope that it will enter a vein is not a successful one, and is unpopular with patients. If there appears to be no reasonable prospect of success at the usual site other sites should be examined. Sometimes the veins at the wrist can be used, or a vein at the ankle, the dorsum of the foot, or other site may be easily accessible. Students often have difficulty with patients who have lost flesh. The veins are quite visible, but owing to the flabby skin and loss of supporting tissue the veins are very mobile and the needle tends to push them aside instead of entering them. The difficulty can be overcome by holding the vein in position by tightening the skin over it, provided that the skin is not drawn so tightly that the vein becomes completely flattened out.

In children I have sometimes found it convenient to use the external jugular vein. The patient's head should be turned to the side opposite to the selected vein so that the latter becomes stretched out over the sterno-mastoid muscle, which forms a firm bed for the vein during the operation. In infants blood may be obtained from the superior longitudinal sinus by puncture through the anterior fontanelle.

The syringe should always be as dry as possible, and care should be taken that all containers are dry.

If whole blood is to be examined it must be prevented from clotting. Potassium oxalate is usually used for this purpose, and it is important to avoid excess: 20 mgm. are adequate for 10 c.c of blood. The oxalate should be obtained in very fine powder form and placed in the receptacle intended to hold the blood. The blood and oxalate should be shaken together as soon as possible after the blood is withdrawn from the patient. It should be remembered that potassium oxalate must not be used if the blood is to be examined for calcium or potassium content. In these cases sodium citrate is used.

It is always advisable to send the specimen to the labora-

tory as soon as possible. Most specimens deteriorate on standing, and delay in dealing with them may render the results of analysis misleading. Where delay is unavoidable, storage in the ice-chest helps to preserve samples. If they are to be sent through the post, samples of blood may be preserved by adding sodium fluoride. This, besides being a preservative, is an anti-coagulant. Hence it cannot be used to preserve samples of blood which are required to clot. For whole-blood samples or where plasma is to be used in analysis it may take the place of potassium oxalate, or mixtures of equal parts of sodium fluoride and potassium oxalate may be used. Like potassium oxalate, it must not be used for blood in which calcium is to be determined, and obviously it must not be used if sodium is to be determined.

If urine has to be preserved, as, for example, in collecting a twenty-four-hour specimen, it is best to keep the urine in a refrigerator or ice-chest. If such is not available, the next best procedure is to add 2 per cent. of toluene. If the urine is required for chemical tests alone, chloroform is a sufficiently good preservative, added in such a quantity that one or two drops remain undissolved at the bottom of the vessel. It does not preserve the formed elements, for which formalin may be used, though the latter interferes with certain chemical tests.

The same remarks apply to cerebro-spinal fluid as to urine.

It should also be remembered that preservation is very considerably favoured if specimens are taken under sterile conditions and placed in sterile containers.

There are certain obvious advantages to be gained by the clinician who carries out laboratory tests himself, particularly if there is no pathologist readily available. But comparatively few men engaged in clinical work have the time, aptitude and skill for laboratory work. To the private practitioner the expense of equipment and maintenance of a laboratory is also a factor to be considered, and cheap

makeshift arrangements are generally unsatisfactory. Hence the practice followed in most hospitals, namely, to concentrate this work in the hands of persons specially trained for it and in laboratories specially equipped for the purpose, is a necessity. Similar laboratory services are available to most practitioners. Consequently it is not necessary for the clinician to carry out all analyses himself in order to obtain the help which is offered by the application of chemical methods to clinical work. Hence no attempt will be made in this book to deal with the technical details of chemical analysis. These are to be found in many text-books of practical physiological chemistry. In subsequent chapters an attempt will be made to discuss certain aspects of chemical pathology and their bearing on clinical work, and in particular to explain the principles underlying various chemical tests, together with the points to be observed in each case with regard to obtaining the necessary specimens. It is hoped that the reader will thus be able to obtain sufficient knowledge to enable him to decide when he should have certain tests carried out and how to interpret their results. If he gains a clear knowledge of how these tests may help him, then, if he is not prepared to carry them out himself, he will get into touch with someone who has the necessary equipment and skill to do the analyses for him. If this involves sending specimens some distance, by post or otherwise, he must use whatever methods are available for preventing any change in the specimen during transit, and, above all, he must do everything possible to see that the time which elapses between taking a specimen from a patient and its arrival at the laboratory is the absolute minimum possible.

Finally, a specimen should never be sent to a pathologist for examination or analysis unless accompanied by information concerning the salient features of the case in hand. He may be an expert analyst, but he is much more than that. He has probably a considerable fund of experience which is

at the disposal of the clinician, provided the facts of the case are known to him. Where necessary the clinician should consult with him as to the interpretation of his results in any given case.

The greatest value of the application of laboratory tests in clinical work can only be obtained by the closest co-operation between the clinician and the laboratory worker.

CHAPTER II

THE ACID-BASE BALANCE OF THE BLOOD

THERE are certain physical conditions of the body which must be maintained very nearly constant. Any considerable deviation from the normal level for such conditions is incompatible with life. The most familiar example of such a condition is body temperature. Another whose maintenance is equally important is the reaction of the blood, and the body fluids which depend on it.

The reaction of any fluid may be roughly described as acid, alkaline or neutral. But acidity and alkalinity are descriptive terms which are only of precise significance when we can express the qualities they represent in quantitative terms. Hence, before discussing the reaction of the blood it will be advisable to recall to mind briefly the modern notation which is used to express reaction in a quantitative way. Acid or alkaline properties of a solution are due not so much to the substances which have been dissolved in a solvent but to the hydrogen ions or hydroxyl ions which have been produced by the process of solution. If there is an excess of hydrogen ions over hydroxyl ions the solution has acid properties, whereas an excess of hydroxyl ions over hydrogen ions gives rise to alkaline properties. In any solution the product of the concentration of hydrogen ions and of hydroxyl ions is a constant. Pure water is our standard of neutrality, and hence hydrogen and hydroxyl ions are present in equal numbers. The quantity of hydrogen ions in this case is

$$\frac{1}{10{,}000{,}000} = \frac{1}{10^7} = 10^{-7} \text{ of a gram in 1 litre.}$$

We write this as

$$cH = 10^{-7}$$

Now since the product of hydrogen and hydroxyl ions is a constant, then in any solution in which the hydrogen ions exceed the hydroxyl ions cH will exceed 10^{-7}, and in any solution in which hydroxyl ions are in excess cH will be less than 10^{-7}. Hence it is only necessary to refer to the hydrogen ion concentration in any case and compare it with that of water to decide whether it is acid or alkaline, and to note what degree of acidity or akalinity is present.

For a decinormal solution of hydrochloric acid which contains one-tenth of a gram of hydrogen per litre, we have (assuming that at this dilution the acid is completely ionised)

$$cH = \frac{1}{10} = 10^{-1}.$$

It is the custom now to leave out both the 10 and the negative sign in representing the reaction of solutions and to call the remaining figure, viz. the index, the pH.

Thus we have for pure water,

$$pH = 7,$$

and for decinormal hydrochloric acid,

$$pH = 1,$$

that is, the greater the acidity the lower the number represented as the pH. Hence it will be seen that all substances which are alkaline have a pH over 7, and the greater the alkalinity the greater is the pH, though the relation is not, of course, a simple arithmetical one.

Using the notation just described, it may be stated that normally the pH of arterial blood ranges from 7·3 to 7·5, while venous blood gives slightly less values. That is, the normal reaction of the blood is slightly on the alkaline side of neutrality. In disease the pH of blood very rarely falls

below 7 or rises above 7·8. When these values are compared with the *p*H which has just been given for decinormal hydrochloric acid it will be realised to what a very small extent the reaction of the blood approaches the condition of acidity or alkalinity as ordinarily understood, even under conditions of greatest variation from normal. Further, when one considers how the supply of acid substances to the body and the production of acids within the body vary, it will be realised that there must be a very delicate mechanism controlling the reaction of the blood and carefully regulating excretion of acid and alkaline substances, in order to maintain the blood reaction at so constant a level under such varying conditions.

Since excretion and intake are not by any means simultaneous, there must first be an immediate control of reaction, pending the final control by excretion of either acid or alkaline substances not required for the maintenance of normal conditions. It will be convenient to deal mainly with conditions tending to increase acidity and to refer more briefly to the opposite conditions.

The first action which occurs on the addition of acid substances to the blood is one of "damping down" the acidity due to the added materials. This is accomplished by substances present in the blood which are known as buffers. The chief of these is sodium bicarbonate. Next in importance are the phosphates, chiefly those of sodium; and finally the proteins.

Imagine an acid, *e.g.*, hydrochloric acid coming into contact with sodium bicarbonate. We get the following reaction:

$$HCl + NaHCO_3 = NaCl + H_2O + CO_2,$$

i.e., instead of a molecule of a strong acid we now have a molecule of a neutral salt and a molecule of CO_2, which is very much less acid than hydrochloric acid.

If a strong acid comes into contact with a mixture of

mono- and di-sodium phosphate, such as is present in blood, it reacts with the di-sodium salt as follows :

$$HCl + Na_2HPO_4 = NaCl + NaH_2PO_4.$$

In this case the free acid is replaced by a salt of low acidity. (Alkali, on the other hand, would react with the mono-sodium salt, giving, for example :

$$NaOH + NaH_2PO_4 = Na_2HPO_4 + H_2O,$$

i.e., the alkali would be replaced by a salt which is practically neutral.)

Proteins are capable of forming salts with both acids and alkalis, and so reducing the reaction of either.

Following this damping down of the reaction there comes excretion. The CO_2 formed by the reaction of acid bodies with sodium bicarbonate is excreted *viâ* the lungs. The salts of the acid bodies with sodium (and also with other bases, *e.g.*, potassium, calcium and magnesium) are excreted into the urine. Elimination of acid bodies by the kidney is almost entirely in the form of salts ; even in conditions in which large amounts of acid bodies are excreted only a relatively small porportion of such bodies succeeds in passing into the urine as free acid. Further, in addition to the excretion of the salts of added acid bodies, we have the excretion of acid phosphates. While both Na_2HPO_4 and NaH_2PO_4 are present in the blood the greater portion of the phosphate is present in the form of Na_2HPO_4. The kidney eliminates some of this in the form of NaH_2PO_4, leaving a residue of base free to combine with the CO_2 present in the blood and so raise the bicarbonate content while reducing the CO_2. The end result of the process may be represented as—

$$Na_2HPO_4 + H_2O + CO_2 = NaHCO_3 + NaH_2PO_4 \text{ (excreted)}.$$

As a result of the neutralisation and excretion of acids then, we have two important processes, viz. :—

1. Reduction of the bicarbonate and other buffer salts.

2. Loss of bases, chiefly sodium, but also potassium, calcium, etc. from the body.

Under normal conditions the ordinary processes occurring in the body (*e.g.*, absorption of bases from the alimentary canal) are capable of making good this diminution of buffer salts and loss of bases, so that their amount in the blood remains fairly constant. But when the amount of acids to be dealt with is large, it may be beyond the power of the body to replace the loss, and then serious consequences may follow.

The materials in the blood, *i.e.*, the buffers, capable of behaving as alkalis, in that they neutralise the action of acids, are known collectively as the alkali reserve. The condition in which the acids dealt with by the blood are in such quantity that the alkali reserve becomes diminished is usually called acidosis. The opposite condition, viz., increase of the alkali reserve, is usually called alkalosis. As will be shown later, this definition of acidosis does not cover all cases in which there is a tendency to a more acid condition of the blood, but it is the most generally accepted definition and covers the majority of cases. It is important to note carefully that acidosis does not mean acidity of the blood; it indicates a tendency in that direction. Actually, the *p*H of the blood very rarely falls below 7, and acidosis may be present without any alteration in the *p*H.

Of the buffer salts, sodium bicarbonate is present in greatest quantity and is the most important. We will therefore consider acidosis a little more closely from the point of view of changes in this substance. As we have seen, the addition to it of acids results in the production of CO_2, which itself is a weak acid. We have to deal then with the presence of the acidic substance, CO_2, and the alkaline substance $NaHCO_3$. In order to maintain a constant blood reaction the ratio between these two must remain constant. If the bicarbonate becomes reduced, this tends to alter the reaction, *i.e.*, to lower the *p*H. But the respiratory centre in the brain is extremely sensitive to changes in *p*H, and this change affects the respiratory centre in such a way that

ncreased pulmonary ventilation occurs, by which the CO_2 in the blood becomes reduced so that the ratio $CO_2 : NaHCO_3$ is brought to its former value. Thus with decreased bicarbonate in the blood we now have a decreased CO_2 content, and this will be reflected in the composition of the alveolar air. Excretion of acid phosphate by the kidneys by the mechanism already described also helps to bring about this adjustment, but this mechanism is less rapid than the pulmonary one. If, although we have reduction of the alkali reserve, the mechanisms described (together with certain others, of less importance) succeed in maintaining the *pH* of the blood at a constant level, the acidosis is spoken of as compensated, whereas if the condition is such that failure to prevent a change in blood *p*H occurs, the acidosis is called an uncompensated one. In the same way we may have compensated and uncompensated alkalosis.

In addition to these changes, certain other results of acidosis must be noticed. As already mentioned, the loss of bases from the body, if beyond its capacity to replace them from the usual sources, is a very serious matter. So urgent is the need for a sufficient quantity of bases in the blood that the supplies of base present in the bones may be drawn upon. It has been shown experimentally that prolonged administration of acid leads to a diminution of the calcium carbonate content of bone. Pritchard put forward the view that acidosis is the essential cause of the bone changes in rickets, and I have put forward the view that in a similar way acidosis is the cause of the bone changes in osteomalacia.

There is a mechanism which has not yet been mentioned, by which an attempt is made by the body to conserve its bases. This mechanism is believed to have its seat in the kidney, and is one by which a portion of the urea normally excreted in the urine is converted to ammonia, so that acids may be excreted as ammonium salts instead of salts of the fixed bases, in order that the latter may be retained in the body. Hence in states of acidosis the proportion of the nitrogen in the

urine which is present as ammonia is often very considerably increased.

The Causes of Acidosis

Acidosis is not a disease, but a condition which arises in the course of many diseases. There must be two main causes of the condition, viz. :—

1. Excessive production of acids within the body.
2. Defective elimination of acids normally produced.

When the former occurs, depletion of the alkali reserve by direct neutralisation of acids is excessive, and when the latter occurs, the mechanisms by which reaction is adjusted through excretion are interfered with.

Excessive Production of Acid within the Body.—This is due to certain metabolic disorders in which the normal oxidation of fats is incomplete. Instead of proceeding to the stage in which CO_2 and H_2O are the final products of oxidation, the process stops short at the stage at which diacetic acid, β-oxybutyric acid and acetone are formed. This abnormal fat oxidation occurs in conditions in which there is defective carbohydrate oxidation, for it is found that fats cannot be completely oxidised in the absence of adequate and complete oxidation of carbohydrates. It therefore occurs in conditions in which there is a defect in the body's power to deal with carbohydrates, and therefore typically, and to its greatest extent, in diabetes. It also occurs in conditions of starvation, in which, though the power to metabolise carbohydrates is unimpaired, the actual supply of carbohydrates for oxidation is insufficient to ensure complete oxidation of fats. Under the heading of starvation must be included not merely abstinence from food or limitation of carbohydrate intake, but also those conditions which prevent absorption of food, such as the pernicious vomiting of pregnancy, the cyclical vomiting of childhood, and certain conditions of defective absorption of carbohydrate by the intestinal tract.

The condition in which there is excessive production of

acetone, diacetic acid, etc.—the so-called ketone bodies—is often referred to as ketosis.

On examination, we find in acidosis of the type just described excretion of increased amounts of acid phosphate, the presence of ketone bodies and increased amounts of ammonia in the urine. In the blood there is diminution of the plasma bicarbonate, and in the alveolar air a reduced CO_2 content. There is increased pulmonary ventilation which may give rise to hyperpnœa.

Theoretically acidosis should also result from increased intake of acids, and such an acidosis has been produced under experimental conditions. Under all other conditions, except perhaps in poisoning by acids or in grossly altered intake resulting from perverted taste, the body is capable of dealing with variations in acid intake without allowing acidosis to occur.

Acidosis occurs in certain other conditions than those mentioned, but the mechanism of its production is as yet imperfectly understood. In some children, for instance, symptoms of acidosis frequently arise. They are often accompanied by ketonuria, and are relieved by the administration of sodium bicarbonate. Reduction of the fat of the diet has a very favourable effect. The cause of the acidosis would therefore appear to lie in some metabolic disturbance. Possibly there is a state of fat metabolism in which disturbances are caused by demands which in the normal child can be well tolerated.

Acidosis also occurs as a result of administration of the volatile anæsthetics. It is frequently associated with decreased plasma bicarbonate and ketonuria, and is therefore probably dependent on some interference with normal metabolism.

Van Slyke has shown that there is a tendency to acidosis in pregnancy.

Defective Elimination of Acid.—Cases in which this condition occurs fall into two groups :—

(*a*) *Retention of Phosphoric Acid due to Defective Elimination by the Kidneys.*—This occurs in certain types of renal disease, particularly those characterised by marked nitrogen retention, and is seen in its most typical form in late stages of uræmia. There is generally reduced plasma bicarbonate and increased pulmonary ventilation, with low CO_2 content of the alveolar air. There is, however, no ketosis. There is also a relatively low ammonia content of the urine, possibly due to the fact that with much damage to the kidneys the power to make ammonia available for the excretion of acid bodies is lost.

(*b*) *Retention of Carbonic Acid.*—This occurs in conditions of defective blood circulation. Owing to poor supply of blood to the lungs efficient aeration and removal of CO_2 does not occur. Such a state of affairs may arise in uncompensated heart disease. A similar occurrence also results in pulmonary conditions, where the state of the lungs is such that efficient ventilation does not take place. Hence it may accompany such conditions as emphysema.

It should be noted that in conditions of carbonic acid retention an attempt to preserve a constant reaction of the blood, *i.e.*, a constant ratio between CO_2 and $NaHCO_3$, will result in an *increase* of plasma bicarbonate to balance the increased CO_2. We have, therefore, increased alkali reserve, though the general tendency of the conditions present is to reduce the *p*H. It is in such cases where the usual definition of acidosis as a decrease in alkali reserve appears to be inadequate.

Alkalosis

Alkalosis as a clinical condition has received much less attention than acidosis. Though it is of much less frequent occurrence than acidosis, it is nevertheless of sufficient importance to warrant attention.

Examining it in the way in which we have examined acidosis, we find that a tendency to increased alkalinity of

the blood may result either from increasing bicarbonate or from withdrawing acid.

Alkalosis due to increased bicarbonate may occur in patients to whom excessive quantities of bicarbonate have been administered. On the other hand, withdrawal of acid, leaving a relatively increased proportion of alkali, may occur in cases of hyperpnœa, where the increased pulmonary ventilation washes out excessive quantities of CO_2 from the blood. It is met with, for instance, in carbon-monoxide poisoning and in patients exposed to low oxygen pressures. It also follows prolonged immersion in a hot bath, due again to hyperpnœa, which results from the efforts to keep down the body temperature under such conditions. Withdrawal of acid may also occur in cases of vomiting, where great loss of hydrochloric acid occurs from the stomach. The acid stomach contents being lost, there is no call to use up the alkali of the pancreatic juice for neutralisation purposes. This represents a balance of alkali to the body beyond what it would have normally. It has previously been shown that vomiting, by tending to bring about a condition of starvation, may cause an acidosis. By saying that vomiting may also cause alkalosis would seem to introduce considerable confusion. The matter will be clearer if attention is paid to the type of vomiting and to its results. In the vomiting which has been mentioned as causing acidosis there appears to be a condition in which the stomach exhibits an intolerance to food, so that the latter is rejected soon after it enters the stomach, and before much acid secretion has taken place into it. The effect of starvation greatly overshadows any loss of HCl that may occur. In the type causing alkalosis, shown particularly in pyloric obstruction, the food is only vomited after remaining for some time in the stomach, and when acid secretion is more or less completed. But in these cases, if pyloric obstruction is such that very little food passes onwards to the intestine, starvation results and a tendency to acidosis will arise which will oppose the condition resulting

from excessive loss of HCl, so far as the reaction of the blood is concerned.

The findings in urine, blood and alveolar air in alkalosis will be practically the opposite of those seen in acidosis from opposite causes. Thus in overdosage by sodium bicarbonate and in excessive loss of fixed acid (HCl) we shall find bicarbonate in the urine and also diminished quantities of ammonia and phosphate. In the blood there is increased bicarbonate, and increased CO_2 in the alveolar air. We may, perhaps, have a ketosis, the acid "ketone bodies" apparently resulting from an attempt by the body to find increased acid to balance the increased alkali which is present.

In alkalosis due to relative deficiency of CO_2 we may find diminished bicarbonate in the blood, with diminished CO_2 in the alveolar air. The urine will exhibit changes similar to those found in the previous type, since in both there is an attempt to excrete alkali to compensate for the causal condition.

The typical symptoms of alkalosis are those usually associated with tetany, early symptoms being numbness of the extremities and facial rigidity. These may be followed by the typical spasm of feet and hands.

Laboratory Methods of Investigating Acidosis and Alkalosis

1. The most useful single test for determining the presence or the severity of acidosis or alkalosis is the determination of the carbon-dioxide combining power of the blood, which represents the amount of bicarbonate present therein. This may be done either by a gasometric method or a titration-method. Much the most usual method is the gasometric method of Van Slyke. The result is stated in centimetres of CO_2 bound as bicarbonate in 100 c.c. of plasma. The normal range is from about 55 to 70 c.c. In moderately severe cases of acidosis the value is found to lie between 40 and 50 c.c., while in comatose patients values as low as 15 c.c may be

found. According to Van Slyke, definite symptoms due to acidosis occur when the CO_2 values fall below 30 c.c.

Some figures by Myers and Killian in alkalosis show values up to 125 c.c.

For the method it is advisable to take about 5 c.c. of blood from a vein. The blood should not be taken under conditions of stasis, so that if a bandage is used to facilitate the finding of the vein and entry of the needle into it, the bandage should be removed to allow the blood to flow freely for a few moments before blood is drawn into the syringe. The blood is transferred at once to a centrifuge tube containing a little potassium oxalate, and then a few drops of liquid paraffin are added to prevent gaseous exchange between the blood and surrounding air. The blood should be sent as soon as possible to the laboratory for analysis.

2. **Determination of Alveolar Carbon-dioxide.**—The simplest method for clinical purposes is that devised by Fridericia.

The normal value for men is about 5·5 volumes per cent. In women and children it is somewhat lower. According to Poulton, a value of 2 per cent. indicates the onset of coma within twenty four hours, while a value of 3 to 4 per cent. suggests the probability of coma coming on within three or four days. Samples are taken directly into the Fridericia apparatus at the bedside.

In connection with these two tests it is to be remembered that similar findings may be obtained in quite different conditions, *e.g.*, low plasma bicarbonate and low alveolar CO_2 in oxygen want, and also in acidosis of the diabetic or nephritic type. Usually there should be no difficulty in interpreting the results, as the clinical history will indicate the meaning of any variation from normal which we may find. So far as laboratory tests alone are concerned, differentiation between the two can be made from an analysis of the urine. For in the former condition there is diminished ammonia excretion, with excretion also of bicarbonate, while in the latter there

is increased ammonia excretion, and increased excretion of acid phosphate.

3. **Determination of the *p*H of the Blood.**—While this is frequently used in certain investigations, it is not much used as a routine clinical test.

4. **Determination of the Ammonia Coefficient of the Urine.**—To decide if ammonia excretion is increased or diminished it is not usual to consider the actual amount of ammonia in the urine. We determine what proportion of the total nitrogen in the urine is present in the form of ammonia. Normally this value is about 5 per cent. In certain conditions of acidosis, particularly in diabetes, values as high as 50 per cent. may be found.

While high values are quite conclusive, it is difficult to attach much significance to comparatively slight variations from the normal.

If the results are to have any value, samples should be examined fresh; or if that is not possible, precautions to avoid fermentation must be taken, as urine normally undergoes a fermentation on standing, due to certain bacteria, by which ammonia is produced. Ammoniacal fermentation may take place also within the bladder, in certain cases of cystitis for example. The possibility of this should be excluded, therefore, before carrying out this test.

5. **Tests for Ketone Bodies in the Urine.**—The tests most commonly used are the ferric chloride test (Gerhardt's test) and the nitroprusside test (Rothera's test). The latter is much more sensitive than the former. Hence a positive result with the ferric chloride test indicates a severer degree of acidosis than a positive result with the nitroprusside test only.

CHAPTER III

GLYCOSURIA AND DIABETES

One generally associates the disease diabetes with the presence of sugar in the urine, a fact which was demonstrated by a Liverpool physician, Matthew Dobson, in 1775. Until recently the symptom glycosuria has been the one which had received most attention, its degree being taken to represent the severity of the case and its variations as indicating the course and progress of the disease. Glycosuria, however, is now recognised to be a symptom which may be a manifestation common to different conditions, not all of them definitely pathological.

The presence of sugar in the urine indicates loss of sugar from the circulating blood, and in order to understand the meaning of glycosuria attention must be directed to the concentration of sugar in the blood, and its variations.

Let us recall briefly the chief stages in carbohydrate metabolism. Carbohydrates are broken down, or hydrolysed, in part by the ptyalin of the saliva, but mainly by the amylase of pancreatic juice into maltose, which is finally converted to glucose by the succus entericus. This is absorbed in the intestine, whence it passes by the portal circulation to the liver, where it is stored as animal starch or glycogen. From the store of glycogen in the liver it is reconverted into glucose as and when required by the tissues as a supply of energy, and in the tissues it is oxidised to CO_2 and H_2O.

Sugar is thus constantly circulating in the blood in order that the tissues may receive their necessary supply, but nevertheless it is normally absent from the urine.

If, however, the concentration of sugar in the blood rises above a certain value, viz., about 0·18 per cent., then some of it is excreted by the kidney, and we find glycosuria. We express this by saying that the kidney has a threshold value for sugar—a threshold value being that concentration of a substance in the blood below which there is no passage of the substance from blood to urine. Now in normal individuals the renal threshold value for sugar is only rarely exceeded, *i.e.*, absence of glycosuria is the rule in normal people. Even very large doses of sugar by mouth are generally unable to cause the blood sugar concentration to exceed the threshold value. Alimentary glycosuria, as a condition occurring in normal individuals having a normal renal threshold for sugar, and due simply to excessive intake of carbohydrates, is not so frequent as is often supposed, particularly in people below middle age. Further reference to this subject will be made later. In certain diseased conditions, including diabetes, the normal renal threshold is frequently exceeded, *i.e.*, the blood sugar concentration exceeds the normal maximum. This is known as hyperglycæmia, and if we have hyperglycæmia in the presence of a normal renal threshold for sugar, glycosuria results. This is the most frequent cause of glycosuria.

While the renal threshold is fairly constant, it is not absolutely so. Certain individuals are met with who have normal blood sugar concentrations, but have a lowered renal threshold. Now in such individuals glycosuria will occur without hyperglycæmia, simply because the normal sugar concentration is higher than their renal threshold value. Here what error there is lies in the kidney, and not in the mechanisms controlling blood sugar concentration. Such a condition is known as renal glycosuria. and is of itself, so far as we know, quite a harmless condition. It is sometimes found to co-exist with a definite hyperglycæmia, but in such cases there is probably no causal relationship between the two.

Lowering of the renal threshold is sometimes found to occur during pregnancy. This is important, and should always be borne in mind when glycosuria arises in the course of pregnancy. Generally the normal threshold is regained after delivery, but it appears probable that in certain cases of glycosuria arising during pregnancy, the condition subsequently passes into true diabetes. There is room for much

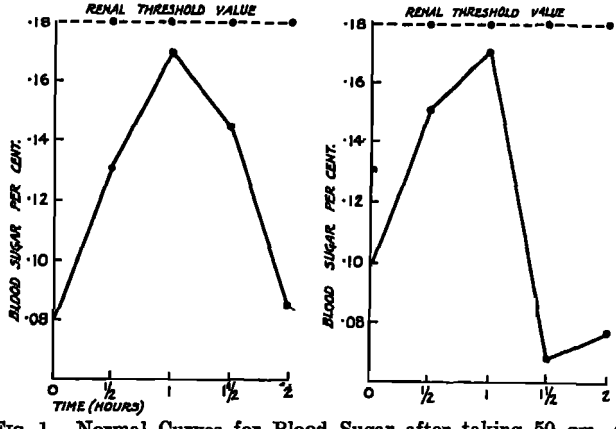


FIG. 1.—Normal Curves for Blood Sugar after taking 50 gm. of Glucose. Threshold value normal.

more definite information on this subject than we possess at present.

There is another possibility to be borne in mind. In addition to lowering of the renal threshold, persons are sometimes found in whom it is raised. Such a raising of the threshold is most frequently found in long-standing cases of diabetes, and in persons whose kidneys are the seat of certain degenerative changes. Such people may have a definite hyperglycæmia, but unless the blood sugar concentration exceeds this raised threshold value there will be no glycosuria. Summing up, then, *glycosuria may be present with or without hyperglycæmia, and hyperglycæmia may be present without glycosuria.*

Now in diabetes it is not glycosuria itself that matters. The important feature is the hyperglycæmia which occurs. Moreover, glycosuria is not necessarily a constant symptom. It may be present at one hour and absent the next. For a further understanding of this and of the subject of hyperglycæmia, we must consider the way in which variations occur in the blood sugar concentration.

If a normal healthy person takes, say, 50 gm. of glucose, it is found that his blood sugar concentration begins to rise

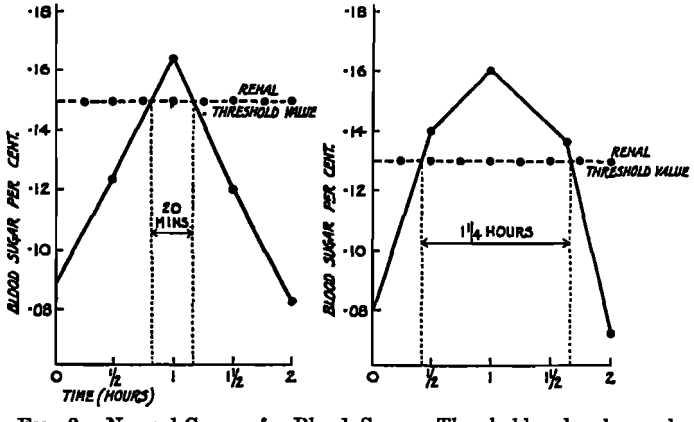


FIG. 2.—Normal Curves for Blood Sugar. Threshold value lowered. Threshold values exceeded for different lengths of time according to extent by which threshold is lowered.

almost immediately, and reaches its maximum in from thirty to sixty minutes. This maximum is usually between 0·16 and 0·18 per cent. The concentration then begins to fall with equal rapidity, so that it reaches the starting value, or sometimes even lower, within two hours from his taking the glucose (Fig. 1). Since the renal threshold value is not exceeded, there is no glycosuria. If, however, the threshold is lower than normal, the blood sugar concentration may be above the threshold value for a length of time, depending on the extent to which the threshold is lowered (Fig. 2). This time may in some cases be only a few minutes, in

others it may be much longer. In the same way, in conditions in which there is true hyperglycæmia there is still variation in the blood sugar concentration following the ingestion of glucose, and though there are certain differences from the course just described the general plan is the same, namely, a rise followed by a fall. It is only in fairly considerable degrees of hyperglycæmia that the values always lie above the threshold value. In other cases, therefore, there are times when the blood sugar concentration is below the threshold and consequently no glycosuria occurs. Thus in cases showing renal glycosuria and also in those showing true hyperglycæmia glycosuria may not be a constant symptom. This shows the fallacy of deciding as to the existence of glycosuria from the result of testing a single specimen of urine taken haphazard, without ascertaining the time relation between the taking of the specimen and the patient's last meal, for the ordinary carbohydrates of food cause blood sugar concentration changes similar to those caused by taking glucose. It explains, for instance, why patients sometimes report that glycosuria has been found by one medical man while another reports it absent.

I have dealt with glycosuria at some length, because even now, in spite of all the teaching on the subject, mistakes are still frequently made through failure to attend to the points just mentioned.

Let us now consider in greater detail the behaviour of blood sugar concentration after taking glucose—the blood sugar curve, as it is called. The most striking feature is the sudden fall, following the rapid rise. This occurs when there is still much sugar in the stomach, and so cannot be due to sudden cessation of absorption. It is mainly due to the operation of the process previously mentioned, namely, the storage of sugar in the liver as glycogen, and its consequent removal from the circulation. This storage mechanism is evidently brought into play with considerable intensity when the blood sugar concentration approaches the normal

renal threshold, and thereafter continues in such a way that more sugar is now stored than is added to the blood by absorption, so that the blood sugar concentration is quickly brought to the starting level. From that point until the ingestion of the next meal, it remains approximately constant. In addition to the operation of the storage mechanism, the fall of the sugar concentration is aided to some extent by utilisation of sugar by the tissues.

If hyperglycæmia occurs, it must then be due to the following causes .—

1 The storage mechanism may not act effectively (and by effectively I mean in such a way that the blood sugar concentration begins to be reduced) until a blood sugar concentration higher than normal is reached, but when it does so act it operates in the normal way, causing the usual rapid return to the resting level. We get a curve which is normal in type, except that its peak is higher than usual, and thus generally exceeds the threshold value. Such a type of curve has been called a "lag" type, as there appears to be a lag in the operation of storage, which, however, once in full operation, appears to be quite efficient. Such patients generally show glycosuria for a short time, as shown in Fig 3. Apart from this they appear to be symptomless, and it is probable that the condition has no great pathological significance Probably many patients showing intermittent slight glycosuria about an hour after meals, and otherwise quite healthy, are of this

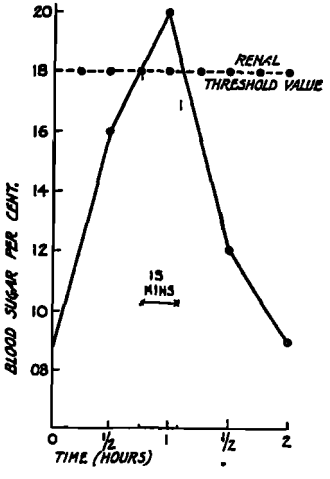


FIG. 3 —"Lag" type of blood sugar curve, threshold value normal

type, and are amongst those cases frequently labelled as alimentary glycosuria.

2. Inefficiency of the storage mechanism.

3. Inefficient utilisation by the tissues of the sugar circulating in the blood which is intended for their use.

The greater portion of the pathological hyperglycæmias show both (2) and (3), *i.e.*, defective storage and defective utilisation of carbohydrates. So far as cases usually classed as diabetes are concerned it is a debatable point whether there are some in whom there is a storage defect only. This will be referred to later. In certain other types of case which will be mentioned it does appear that a storage defect alone is the cause of the hyperglycæmia.

The majority of cases showing persistent hyperglycæmia, including those showing it to the greatest extent, are cases of diabetes. Not all cases when first met with show an obvious hyperglycæmia, for it may be absent in the earlier stages of the disease, but on careful examination some defect will be found in their capacity to deal with carbohydrates. This is expressed in another way by saying that their tolerance for sugar is lowered. And as the disease tends to be progressive, these cases will sooner or later show a definite hyperglycæmia, if they remain untreated.

It has been abundantly proved now that in true diabetes mellitus the lesion is in the pancreas, and is due to degeneration of, or possibly in some cases functional disturbances of, the cells of the islets of Langerhans. These cells are responsible for the internal secretion now known as insulin, which has a remarkable power of controlling carbohydrate metabolism. It is unnecessary to discuss here the actual mechanism of the action of insulin. It will be sufficient to say that where it is deficient storage of glycogen by the liver is deficient. In severe diabetes, for instance, the liver is almost entirely denuded of this material. Consequently abnormal amounts of sugar remain circulating in the blood. But this is not the only result of deficiency in insulin supply.

In spite of the excessive amount of sugar in the blood supplying the tissues, the latter are unable to utilise it in the normal way. Thus deficiency of insulin results in deficient storage and deficient oxidation of carbohydrates.

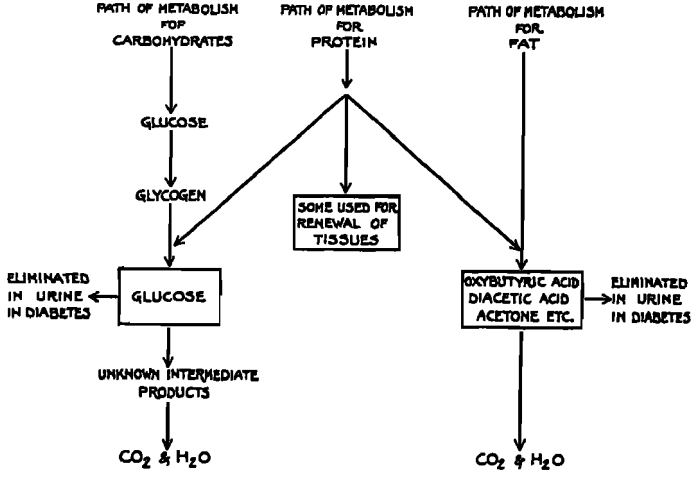
Insulin, however, must not be regarded as the sole regulator of carbohydrate metabolism. Other internal secretions, *e.g.*, that of the pituitary and the adrenals, exert an effect which in some respects appears to be opposite to that of insulin, and it appears probable that the prime need of a sufficient supply of insulin is to preserve the correct balance between the internal secretions on which normal carbohydrate metabolism depends. It follows that disturbances in the production of other internal secretions should be able to produce alterations from the normal carbohydrate metabolism. As will be shown later, such disturbances do occur, but not, so far as we know, with the same regularity, frequency or degree as shown by disturbances in insulin production.

The deficient oxidation of carbohydrate which has been referred to has certain important sequels, which are responsible for some of the more severe and alarming symptoms found in diabetes. Since sufficient energy cannot be derived from carbohydrates, both fats and proteins are called upon, but in the absence of complete oxidation of carbohydrates the metabolism of these does not seem able to proceed normally to completion, but stops short at stages which normally are so transient as to be hardly recognisable. Thus from fats are obtained oxybutyric acid and diacetic acid, and from the latter, by loss of CO_2, acetone is produced. Here oxidation stops short, and instead of it proceeding to CO_2 and H_2O, these "ketone bodies" accumulate in the blood, and give rise to the acidosis which has been described in the previous chapter. The process is well indicated in the diagram given overleaf, taken from Maclean [1].

The most dreaded, and often fatal, event in diabetes is the

[1] H. Maclean. "Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes." 1924. Constable & Co., Ltd., London.

onset of coma, and this event is closely associated with the acidosis just mentioned. Though the exact relationship between acidosis and diabetic coma is not understood, it is known that the latter does not occur in the absence of the former, and the tendency for coma to occur is roughly proportional to the degree of acidosis present. Consequently the investigation of acidosis may be of considerable value in certain cases, for not only does it give an indication of the



severity of the condition, but it also supplies an indication of the probability of the onset of coma. The methods to be used in this investigation have been dealt with in the previous chapter.

Let us now consider the practical investigation of the problems raised by glycosuria and disturbances in carbohydrate metabolism. What we really want to know concerning any case is the patient's capacity for dealing with carbohydrates, and the level of his renal threshold value for sugar. His capacity for dealing with carbohydrates is indicated by his blood sugar curve. If, therefore, we carry

out a test to enable us to construct such a curve, and at the same time obtain corresponding values for blood sugar concentration and urine sugar concentration, we shall generally have all the information we require concerning sugar tolerance and renal threshold value. Such a test is known as a Glucose Tolerance Test, and is carried out as follows :—

The patient is first instructed to empty the bladder. About an hour afterwards a specimen of blood is taken from him, and at the same time a specimen of urine. The patient then drinks a solution of 50 gm. of glucose in 100 to 150 c.c. of water. From the time when the glucose is taken, further specimens of blood are withdrawn from the patient at half-hourly intervals for two hours. Further urine specimens are taken hourly over the same period. The sugar concentration of all the specimens of blood and urine is then determined.

The test should be arranged so that the first specimen of blood is taken from the patient at least three hours from the time of his previous meal. In certain cases to be described, it is advisable to carry out the test in the early morning, after an all-night fast. On this account it is now the practice in this hospital to carry out all glucose tolerance tests in the early morning.

The maximum value shown by the curve is not always the highest value actually reached, for the blood sugar concentration may only remain at its maximum for a very short time, and it is probable that by taking specimens half-hourly we miss the true maximum in a large number of cases. Nevertheless, the values we do obtain are quite sufficient for practical purposes.

The curve we obtain in any given case gives us a picture of the variations in the blood sugar concentration during the two hours of the test. When we also examine the three specimens of urine we are able to see something of the relation between blood sugar concentration and urine sugar

concentration. The connection between the two is not a very close one. The first specimen of urine shows approximately the concentration of sugar in the urine, corresponding to the first blood sugar concentration. The second specimen of urine represents the urinary secretion throughout the first hour of the test, and the third, secretion throughout the second hour. From consideration of these results it is generally possible to obtain a good idea as to the position of the renal threshold value. More exact knowledge could be obtained if required by taking urine specimens more frequently, *e.g.*, every half-hour.

The type of curve obtained in glucose tolerance tests on normal young and middle-aged persons has already been described, and is illustrated in Figs. 1 and 2, which show a maximum blood sugar concentration below 0·18 per cent. and a return to the starting value, which generally lies between 0·08 per cent. and 0·11 per cent., within two hours. Tests on the urine specimens taken during the test show absence of glycosuria.

Porter and Langley [2] recently brought forward evidence showing that in older patients the resting value for blood sugar concentration tends to be higher than in young subjects. The actual rise caused by taking glucose is the same in extent, so that the maximum value is higher, and the return to the resting value again is delayed, with increasing age. They state that these changes begin to be apparent first in the decade thirty to forty, while later on the rise in the maximum is such that the value exceeds that of the normal renal threshold in a certain proportion of cases, and consequently there is some glycosuria during the period when the blood sugar is at or near the maximum. It is well to bear this in mind when interpreting the results of tests on older patients.

In the normal individual, other sugars behave similarly to glucose in their effect on the blood sugar concentration,

[2] *Lancet*, November 6th, 1926.

except lævulose and galactose. These two sugars, however, cause hardly any rise at all in the blood sugar concentration following their ingestion. The ordinary starchy foods also behave similarly to glucose when taken in proportionate amounts. When present in an ordinary mixed meal, however, their digestion and absorption may be somewhat delayed, so that their effect on the blood sugar concentration may not come to an end until about three hours after the meal. It is for this reason that glucose tolerance tests should not be commenced within three hours after a meal, for it is advisable that the starting value for blood sugar concentration should also be the resting value.

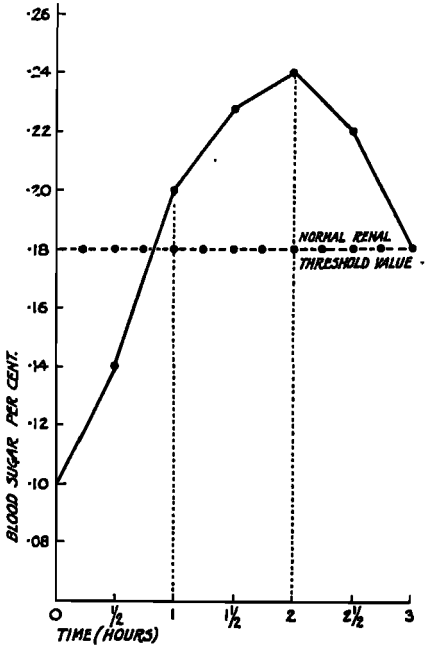


FIG. 4.—Blood sugar curve in severe diabetes.

Let us now consider the results of glucose tolerance tests in marked cases of diabetes. The salient features will be at once apparent from Fig. 4. They are :—

1. The rise to the maximum blood sugar concentration takes a much longer time than in the normal subject.
2. The maximum value is much higher than the normal.
3. The fall in blood sugar concentration is not so abrupt.
4. The return to the starting value takes a longer time.

I.e., the curve is high and long drawn out. Complete

return to the resting value in such a case may occupy a few hours. If the test is commenced before the resting value is quite reached, following a previous meal, the curve is similar to the one shown except that it occupies a higher level throughout, the increased height depending on the increased value of the blood concentration of the first specimen of the test. It will be seen that in such a case the blood sugar concentration, three hours after a meal, is considerably higher than the normal resting value. If at that time a glucose tolerance test is begun, the additional rise in blood sugar concentration caused by the ingestion of 50 gm. of glucose may produce a maximum value which is dangerous to the patient. For this reason it is advisable to carry out glucose tolerance tests on patients in whom sugar tolerance is suspected or known to be impaired, only after fasting overnight, when their blood sugar concentration will be in the neighbourhood of the normal resting value.

Fig. 4 also shows that a considerable portion of the blood sugar curve lies above the renal threshold value, so that glycosuria occurs over a considerable period. In the case actually represented, the first specimen of urine is sugar-free, the specimen secreted over the first hour of the test contains only a small quantity of sugar (about 0·2 per cent.) since the blood sugar concentration only exceeds the threshold value by a small amount and for a short time, while the specimen of urine secreted over the second hour of the test contains 3 to 4 per cent. of sugar. The volumes of the urine specimens are also found to be larger than in normal cases, owing to the polyuria present in such cases.

In many cases the fall in blood sugar concentration as far as the renal threshold occupies a longer period than normally elapses between meals. Hence patients showing a curve of such character will under ordinary circumstances show glycosuria as a constant symptom.

When we consider mild cases of diabetes we find that the maximum blood sugar concentration disclosed by the

glucose tolerance test may be very little above the normal. Consequently there may be little or no glycosuria. But there is seen to be a delay or inefficiency in storage, for return to the resting value is delayed, and the curve, though not much raised, is definitely drawn out, as compared with the normal. (See Fig. 5.) Thus the character of the curve rather than the magnitude of its maximum value is the chief feature in helping us to decide on its interpretation.

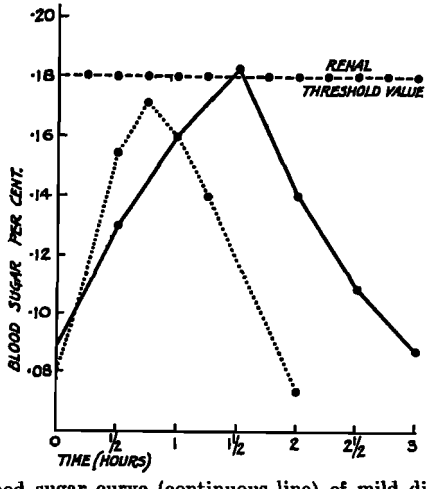


FIG. 5.—Blood sugar curve (continuous line) of mild diabetes, compared with normal (dotted line) curve.

Hence the condition of all patients whose blood sugar concentration shows a definite delay in returning to the normal resting value after the ingestion of glucose should be regarded with suspicion.

There are certain cases, found mostly amongst elderly subjects, in whom glycosuria is the main feature and in whom there appears to be little or no ketosis, though hyperglycæmia is usually present. In many of them little or no evidence of disturbed oxidation can be obtained. It is believed by some workers on the subject that such cases

represent simply a condition in which there is deficient storage, without the disturbances consequent on deficient oxidation, and these workers would place this "senile diabetes" in a different category from true diabetes. Others, however, do not believe that these cases are essentially different from the true diabetes of earlier life. It seems to me to be very probable that the cases referred to include two separate conditions, namely, cases in whom the changes shown by Porter and Langley to occur with advancing age are somewhat more marked than in the average case, *i.e.*, patients whose hyperglycæmia and glycosuria may be said to be somewhat exaggerated expressions of the physiological results of advancing age, and cases in whom there is true diabetes, but of a milder and less rapidly progressive type than is met with in young subjects.

Let us now consider briefly some other conditions in which there is disturbance of carbohydrate metabolism. Amongst these are certain endocrine disorders.

Thyroid Conditions.—In the milder forms of Graves' disease there is frequently no alteration in sugar tolerance, but a decrease in tolerance is a fairly constant finding in severe cases. The blood sugar curve then closely resembles that found in mild or moderately severe diabetes. The defect appears to be one of storage only, for oxidation instead of being deficient is excessive in this condition. Administration of thyroid extract may cause the development of the same type of curve.

In cretinism sugar tolerance is found to be increased, *i.e.*, the resting blood sugar concentration is low, and carbohydrates are unable to produce a rise in blood sugar of the same degree as occurs in normal individuals. In myxœdema it is said that the tolerance for sugar may be found to be increased or diminished, but there is usually a raised renal threshold.

Adrenal Conditions.—The injection of adrenalin causes a rise in the blood sugar concentration, and increase of

adrenalin production within the body, such as occurs in over-function of the adrenal glands, causes a decrease in sugar tolerance. It is believed that in conditions like Addison's disease the sugar tolerance is increased.

Pituitary Conditions.—Hyperglycæmia and glycosuria are usually present in acromegaly. In Fröhlich's disease the majority of cases show a markedly increased tolerance, though in a few cases tolerance has been found to be diminished. In some cases of pituitary tumours increased tolerance has been found.

In general, it may be taken that over-function of the thyroid, adrenal or posterior lobe of the pituitary may cause a decreased sugar tolerance.

Other causes of hyperglycæmia and glycosuria are :—

1. Cerebral injuries, hæmorrhage and tumours.

The classic example of hyperglycæmia from such a cause is that following Claude Bernard's *piqûre*. In such cases it is said that the hyperglycæmia may occur through stimulation of the splanchnic nerves causing over-production of adrenalin.

2. Emotional disturbances.

Hyperglycæmia from such a cause is temporary. This, too, has been attributed to stimulation of the adrenal glands.

3. Alcoholism.

4. Certain infective conditions.

The glycosuria accompanying boils and carbuncles is fairly frequently met with. It usually clears up after removal of the infective focus.

In this connection it will be recalled that infective conditions exert a very unfavourable influence on the condition of true diabetics.

Routine Investigations.—Let us now consider the procedure to be adoped in investigating the conditions which have already been discussed. The need for investigation commonly arises in connection with patients showing :—

1. Glycosuria.

2. Other classic symptoms of diabetes, *e.g.*, thirst, polyuria, weakness and wasting.

It will be obvious from what has been said that the true state of affairs will, in most cases, be made clear by the result of a glucose tolerance test. Some difficulty may arise in those cases showing a moderate reduction of sugar tolerance, when, on laboratory evidence alone, differentiation between diabetes mellitus and certain endocrine disturbances cannot be made. In such cases the clinical evidence will usually indicate what type of case we are dealing with. In cases of suspected thyroid disturbance, additional useful evidence may be obtained from a determination of the basal metabolic rate (see Chapter X.).

But it is by no means necessary in all cases of suspected disturbance of sugar tolerance to carry out a complete sugar tolerance test as described. It is frequently possible to simplify the procedure and still get all the evidence necessary in a given case.

If glycosuria and other diabetic symptoms are present, the presumption is strongly in favour of a diagnosis of diabetes mellitus. Here, all that is necessary, at any rate in the first instance, is to determine the blood sugar concentration in a specimen of blood taken three hours after a moderate mixed meal. A result which is definitely higher than the normal resting value for a patient of similar age will be confirmation of the diagnosis of diabetes. In addition to diagnosis, treatment has to be considered, and for this it is advisable to know something about the renal threshold, if the effect of treatment is to be judged and controlled by its effect on glycosuria, and not by frequent blood sugar estimations. I have personally met with two or three cases in which true diabetes and marked renal glycosuria were co-existent, and other cases have been reported. In such cases, attempts to abolish glycosuria, in ignorance of the low threshold which is present, may result in causing the patient's blood sugar concentration to fall to a dangerously low level,

and in any case an erroneous idea of the effect of treatment will be formed, unless the true state of affairs is realised. (Incidentally, this point illustrates the advantage of controlling treatment by blood sugar tests over the method of control by observations on glycosuria.)

It is advisable, therefore, when making the first blood sugar test to make an estimation of sugar in a corresponding specimen of urine. The bladder should be emptied immediately before taking the blood specimen, and then a specimen of urine should be obtained as early as possible after taking the blood. A consideration of the two values, viz., blood sugar concentration and urine sugar concentration, may serve to indicate sufficiently clearly the position of the renal threshold.

Cases in which glycosuria is the only symptom complained of frequently call for investigation. These are often found in the course of routine examination, *e.g.*, for life insurance. Again, a blood sugar and urine sugar determination three hours after a meal will show us the true state of affairs in the majority of cases. It will indicate a reduction in sugar tolerance, for instance, if the blood sugar is definitely higher than the normal resting value. If the blood sugar is low and at the same time sugar is present in the urine, we have clear evidence of renal glycosuria, whereas if both blood and urine show normal results, then the glycosuria originally found must be due either to renal glycosuria in which the threshold, though lowered, is not reduced to the normal resting blood sugar concentration, or to the condition of abnormal rise in blood sugar, with rapid fall, which gives rise to the lag type of curve. To decide between these a full tolerance test is advisable.

Where we have symptoms like polyuria and wasting in the absence of glycosuria the diagnosis generally rests between diabetes with raised renal threshold, diabetes insipidus and chronic interstitial nephritis. Here again a blood sugar estimation three hours after a meal will generally serve to indicate whether the case is one of true diabetes or not.

In all cases of doubt, or where the simpler tests do not offer all the information that is desired, a full glucose tolerance test should be carried out. In suspected endocrine disorders a knowledge of the state of sugar tolerance is often of considerable value.

The information obtained in the laboratory in diabetic and allied conditions is in general more clear cut, more decisive and more capable of supplying a diagnosis by itself than in any other conditons.

As regards actual specimens great differences are found between the requirements of different methods. In general, whole blood is used. In this country, Maclean's method of blood sugar determination has been largely adopted. It has the advantage that it does not require a colorimeter, which is a somewhat expensive instrument. The quantity of blood required for each determination is 0·2 c.c. Other methods have been devised in which as little as 0·1 c.c. of blood is required. Such methods are of considerable value in dealing with young children, especially where a full tolerance test is desired. The blood is taken from a prick in the finger or ear into a special graduated pipette, from which it is at once transferred to a vessel containing a fixed volume of a special reagent. Where large numbers of tests are constantly being done, or where it is necessary to send specimens away for analysis, the method of Folin and Wu is preferable. This is a colorimetric method, and requires 2 c.c. of blood, which are taken from a vein and treated with potassium oxalate, or with sodium fluoride if preservation is required. It should be added that while resting blood sugar concentrations in venous and arterial (*e.g.*, finger-prick) blood are practically identical; the concentrations under other circumstances usually show certain differences, namely, that the concentration in venous blood is lower than in arterial blood. In certain cases, the difference may amount to as much as 0·03 or 0·04 per cent.

Before closing this account of diabetes two other subjects

require brief mention. One of these is hypoglycæmia. Its importance was largely academic before the introduction of insulin treatment. As with body temperature, the *p*H of the blood, etc., so with blood sugar concentration, any considerable deviation from the normal *in either direction* is provocative of symptoms and possibly death. A blood sugar concentration much below the normal resting value may result from over-dosage by insulin, and has to be carefully guarded against. A full consideration of the subject really belongs to text-books on treatment, where it is generally to be found.

The other subject to be noted is diabetes insipidus in order that we might clearly differentiate it from true diabetes or diabetes mellitus. The polyuria in this condition is extremely marked, and decidedly greater than in the average case of diabetes mellitus. The urine, unlike that in diabetes mellitus, has a low specific gravity and does not contain sugar. The condition is not usually associated with an alteration in sugar tolerance.

CHAPTER IV

RENAL FUNCTION TESTS

DIRECT and unequivocal signs of renal disease, except in really acute conditions, are often very few. Hence, where renal disease is suspected, or where it is advisable to ascertain as accurately as possible the state of the kidneys, as before contemplated operations, it is customary to submit the patient concerned to certain tests intended to show whether his renal apparatus is functioning normally or otherwise.

The number of renal function tests proposed or actually in use is very great—a sufficient indication that not one is wholly satisfactory. Nevertheless, some at any rate are capable of affording very useful help in the consideration of a large proportion of cases.

In considering the scientific basis of these tests it is advisable to bring to mind what are the main functions of the kidney. They are, briefly, as follows :—

1. Excretion of water.
2. Removal of certain waste products of nitrogenous metabolism.
3. Removal of acid products from the body.
4. Maintenance of the optimum concentration of the various salts of the body fluids and tissues.
5. Excretion of many toxic materials, formed within the body, or of foreign materials, toxic and otherwise, artificially introduced.

Some, if not all, of these functions are shared with other organs of the body, but the share taken in them by the kidney is such that serious results are likely to follow if the kidney becomes inefficient in the performance of these functions.

It is to be remembered that inefficiency on the part of the kidney is not shown by failure of one function only. All may be, and probably are, involved, though certain effects may be more prominent than others, and more easily demonstrated by chemical tests. The general result, however, is that an alteration occurs in the concentration of various substances in the blood and the urine, frequently accompanied by alteration in the volume of urine produced by the kidney.

Besides causing failure of function demonstrable as altered concentrations of various substances in blood and urine (the term failure is, of course, used relatively; death results in most cases long before absolute failure occurs), disease of the kidney produces certain other results, namely, the passage of substances into the urine from the blood that are not normally allowed to pass. These substances are the proteins, whose presence in the urine is described by the term albuminuria. In addition, acute inflammations of the kidney may, of course, show their presence by the appearance of blood and pus in the urine, while these and other substances not present in normal urine may make their appearance therein, in many pathological conditions of the urinary tract.

Albuminuria has, until comparatively recently, been largely regarded as synonymous with renal disease. It is now regarded as a symptom only, which though it may have its source in the kidney may yet exist in patients whose kidneys appear perfectly normal in all other respects. Further, albuminuria may be absent though renal disease is present, possibly in a considerable degree. Moreover, it is still too often forgotten, in routine examinations, that there are many extra-renal sources of albumin (or protein) which ultimately appears in the urine, and an attempt should always be made to exclude such sources, before it is decided that the kidney is the cause of the symptom. This can often be done quite easily if appeal is made to the centrifuge and the catheter, and the former should be as universal an instrument as the latter.

Blood, pus, spermatozoa, urethral and vaginal secretions may all be extra-renal causes of albuminuria. Of these, blood, pus and spermatozoa may easily be recognised by microscopic examination of the centrifugalised deposit. Vaginal secretions may be excluded by examining a catheter specimen. Urethral secretions may, perhaps, be excluded if we collect the first portion of urine obtained in one vessel and then the later portion in a separate vessel. For the first portion will wash out from the catheter any albuminous secretion with which it may have become contaminated during its passage along the urethra, while the second should be relatively free from such contamination. In the same way, comparison of catheter with non-catheter specimens may suggest the source of any pus or blood we may find.

The centrifugalised deposit offers other useful information. It may show, for instance, that a reddish deposit which to the naked eye suggests the presence of blood may in reality be only due to urate crystals. It may reveal the presence of triple phosphate crystals due to ammoniacal decomposition in the bladder, thus indicating the probable presence of cystitis, and further confirmation of this view is obtained if pus cells and large numbers of desquamated cells from the bladder are also seen in the deposit. Or examination of the deposit may reveal the presence of casts.

The source of red blood corpuscles and pus cells in a urinary deposit is often indicated by their accompaniments. Most renal lesions of an inflammatory nature which are sufficiently acute to cause the appearance of large numbers of such cells in the urine also cause the appearance there of cellular casts, whereas in affections of the lower part of the urinary tract, and particularly the bladder, the blood and pus which appear in the urine are accompanied by much epithelial débris, while casts are absent.

But even when the source of the protein is definitely traceable to the kidney, albuminuria is not an infallible sign of renal disease. For example, albuminuria in the absence

of any other sign of disease of the kidneys is frequently found in young people, and is generally known as functional or physiological albuminuria. It is also called orthostatic albuminuria owing to the fact that it is frequently absent during rest but reappears when the patient resumes his activities. It would, therefore, appear to be dependent on mechanical conditions of the circulation. In many cases it disappears in later years, and observations on the condition show that it is a harmless one.

A temporary albuminuria is sometimes found as the result of prolonged and severe exercise, after cold bathing and after taking certain drugs.

It will therefore be apparent that in many cases showing renal albuminuria the true significance of the symptom can only be arrived at by careful examination and enquiry into the true state of the kidneys, and for this purpose the functional tests to be described later are often called for.

Let us return now to a consideration of the excretory functions of the kidney, and examine the changes which occur as a consequence of impairment of these functions.

The nitrogenous waste products eliminated by the kidney, which for practical purposes are considered as non-threshold bodies, include urea, uric acid, creatinin, small amounts of amino-acids and certain other mostly unrecognised substances, the nitrogen of the whole being included in the term "total non-protein nitrogen." If we examine the concentrations of urea, uric acid and creatinin in the blood and in the urine we find that normally each is present in much greater concentration in the urine than in the blood, *i.e.*, the kidney exerts a considerable concentrating power with respect to these substances in passing them from blood to urine. The actual figures are :—

	Blood Concentration	Concentrating Power
Urea .	20–40 mg. per 100 c.c.	.. 60–80 times.
Uric acid .	2–3 ,, ,,	.. 30–40 ,,
Creatinin .	1–2 ,, ,,	.. 40–50 ,,

Some of the most striking effects of failure of function on the part of the kidney appear to be due to impairment in this concentrating power, and the most widely used methods of investigating renal function are based on the examination of this capacity for concentration. Hence it is important to examine the sequence of events which may follow on failure of this function.

The first effect of failure to concentrate is an attempt at compensation. To achieve this, *i.e.*, to maintain the blood concentrations at a normal level, an increased volume of urine is produced, for the waste products to be got rid of must be excreted in more dilute solution than usual, since normal concentration is not possible. Hence there occurs polyuria, the urine having a lowered specific gravity. There is also a more uniform concentration amongst different specimens of urine, since the kidney has lost to some extent its ready adaptability of function to the changing concentrations of various materials in the blood. This compensation is usually seen in early chronic nephritis.

But compensation may fail, so that, even with increased excretion of fluid, the maintenance of normal blood concentrations is not achieved. Consequently increased concentration of certain substances in the blood occurs. This is found in more advanced chronic nephritis.

On the other hand, compensation may not have been possible at the outset, for it implies a capacity to excrete large quantities of water. This capacity may be lost due either to primary failure on the part of the kidney, or to retention of fluid by the tissues. Under such conditions retention of substances in the blood will be found to occur, without any polyuria. We may, in fact, have oliguria, as seen in acute nephritis.

When we turn our attention to the threshold bodies, *i.e.*, substances of great value to the body, like sodium chloride, which are not excreted unless their concentration in the blood reaches a certain definite value, we find rather different condi-

tions obtaining. Their excretion is not so uniform as that of the nitrogenous waste products, since it is dependent not only on renal conditions but on the needs of the body generally. Hence it is usually impossible under ordinary conditions to draw the same sort of conclusions from chloride concentration of urine, for instance, as from urea concentration. In conditions like lobar pneumonia, for example, in which exudation of chloride-rich material into the lung causes loss of chloride from the blood, absence of chloride from the urine may really be evidence of an intact regulating function rather than a kidney defect. Moreover, the concentration of chloride in the blood is not subject to the same degree of variation as urea. Sodium chloride is the salt mainly responsible for the maintenance of suitable osmotic conditions in the body fluids. As osmotic conditions must not vary greatly, retention of chloride involves retention of water, and *vice versâ*. The question as to whether renal œdema is due primarily to retention of chloride by the kidney, causing retention of fluid, or whether it is due primarily to retention of fluid by the tissues and consequent retention of chloride is not definitely settled. But whatever the actual mechanism, chloride retention and œdema are closely associated with certain renal conditions, and often in such conditions nitrogen excretion appears to be unaffected. On the other hand, cases are found in which chloride excretion is normal, while nitrogen excretion is much impaired. This apparent dissociation between chloride and nitrogen excreting functions is seen typically in chronic nephritis. Hence it is customary to divide chronic nephritis into two types, namely, the azotæmic type, in which the chief feature is nitrogen retention, and the hydræmic type, in which the chief feature is chloride and water retention. The former corresponds generally to what is known as chronic Bright's disease or chronic interstitial nephritis, and is much the commonest type, while the latter corresponds to what is usually described as chronic parenchymatous nephritis, and

is relatively rare. Many cases, however, are mixed, *i.e.*, they show evidence of defect in both chloride and nitrogen excretion in varying proportions.

This conception of two separate mechanisms in the kidney, the one concerned with nitrogen and the other with chloride excretion, is quite useful from the practical point of view, but is probably not a correct representation of the real facts. De Wesselow,[1] for example, has recently shown that in cases showing failure to concentrate the nitrogenous bodies a roughly parallel degree of failure to concentrate chloride can also be demonstrated. He also pointed out that in cases of well-developed chronic parenchymatous nephritis, characterised by œdema, effusion into serous cavities, marked albuminuria and oliguria, but showing little or no failure to concentrate the nitrogenous bodies, the fact that little or no chloride is passed in the urine does not necessarily indicate a dissociation between the concentrating power of the kidney for urea, etc., and for chloride; for on examining the cases further there is found to be a low plasma chloride content with a high chloride concentration in effusion fluids. Hence the disappearance of chloride from the urine is dependent on impoverishment of the blood caused by accumulation of chloride in tissue fluids, and is not due to renal defect. He deduces therefore that the œdema is of extra-renal rather than of renal origin, and results from a general alteration in the capillary permeability of the body. If these conclusions are correct, then in azotæmic nephritis we have failure of concentration not limited to the nitrogenous bodies, while in hydræmic nephritis we have little or no failure of concentration but retention of chloride by the body owing to its withdrawal from the blood into other fluids and tissues. To call the œdema extra-renal may not be strictly correct; for it has been suggested that the œdema may be due to the fact that loss of protein through the damaged renal epithelium leads to such a diminution in the protein of the plasma, and so

Lancet, September 18th, 1926.

alters the osmotic relationships between plasma and tissue fluids, that water and chloride leave the blood and enter the tissues. If such is the case the œdema will be renal in origin, in the sense that its cause lies in the defect in the kidney which allows this excessive loss of protein.

Another result of failure on the part of the kidney to carry out its normal functions is that sooner or later acidosis will occur, since the kidney is such an important organ with respect to the maintenance of the normal reaction of the blood. This subject has already been dealt with in Chapter II., so that little need be said of it here, but it should be remembered that the acidosis of renal disease is not accompanied by ketosis, nor by any change in the ammonia coefficient of the urine. The dyspnœa resulting from the acidosis is the condition known as renal asthma, frequently seen in advanced cases of renal disease.

Certain failures on the part of the kidney to excrete toxic and foreign materials are of some significance. Thus diseases which produce a condition of toxæmia are always of graver import in patients with damaged kidneys. Also in patients who are the subjects of renal disease care must be exercised in the administration of certain powerful drugs, whose principal channel of excretion is normally the kidney. Methods involving the administration of certain dyes and the determination of their rate of excretion, in some well-known tests of renal efficiency, are really investigations of this particular function.

Lastly, certain other findings in failure of renal function may be mentioned. These are :—

(*a*) Increase of blood phosphate and sulphate, due probably to the same mechanism that is concerned in retention of nitrogen. The increase in phosphate is not usually apparent to any great extent in the early stages of renal disease, and when blood phosphate is much raised, a bad prognosis is indicated. Comparatively little work has been done on the retention of sulphate.

(*b*) Decrease in blood calcium. In azotæmic nephritis the variations in the blood calcium appear to bear an inverse relationship to those of phosphate. The precise connection has not been worked out.

We can now pass on to a consideration of the findings in certain kidney diseases, and of the help to be gained in these conditions from laboratory tests.

Acute Nephritis.—(*a*) *Urine.*—The quantity is diminished at first, then increased as recovery takes place. Much protein is present and also blood. There are also casts, epithelial and blood casts being the most characteristic. Both chloride and urea content are usually diminished; in severe cases chloride may be absent.

(*b*) *Blood.*—Except in the mildest cases there is nitrogen retention.

It is not usually necessary to resort to laboratory tests for purposes of diagnosis in acute nephritis. The chief value of tests in this condition is in respect to the help they may afford in estimating the severity of the condition, its progress and prognosis. Sometimes the clinical condition of the patient suggests a more serious condition than the chemical findings indicate. It is generally found in such cases that the patient ultimately does better than the clinical findings would have suggested. Chemical findings are generally a truer reflex of the patient's progress than the clinical condition. In protracted acute and subacute cases a persistent increase in the blood urea, for example, indicates a very grave prognosis, whereas the outlook is always good, however severe the symptoms appear to be, if the blood urea falls steadily. It will generally be possible by means of our tests to determine whether complete recovery is taking place or whether the acute condition is passing into a chronic one.

Maclean [2] urges that in acute nephritis tests for chlorides

[2] "Modern Methods in the Diagnosis and Treatment of Renal Disease." 1924. Constable & Co., Ltd., London.

in the urine should always be carried out, since the return or increase of chlorides in the urine is one of the best and earliest indications of improvement in severe cases.

Chronic Nephritis.—As already pointed out, these cases are generally subdivided into azotæmic and hydræmic types, but it must not be forgotten that a large number of cases are mixed and exhibit features of both types.

Azotæmic Type of Chronic Nephritis.—(*a*) *Urine.*—There is generally polyuria, with low specific gravity, and with diminished urea concentration. Protein is small in quantity, and may be absent. Under ordinary circumstances there are no characteristic changes in the amount of chloride excreted. Casts are generally but not always present; they are usually of the granular and hyaline varieties.

(*b*) *Blood.*—In early cases there may be no increase in blood urea, etc., but in the majority of cases nitrogen retention is a definite feature, and may be present to a very high degree.

Hydræmic Type of Chronic Nephritis.—(*a*) *Urine.*—This is usually reduced in amount. Urea concentration is usually normal or nearly so, but chloride is much diminished. Protein is present in considerable quantity. Casts are also fairly constantly present—epithelial, granular and hyaline.

(*b*) *Blood.*—There is usually little, if any, nitrogen retention, but a fairly constant and striking feature is an increase in the blood cholesterol.

The value of laboratory tests in the diagnosis of chronic renal disease has often been questioned. So far as the diagnosis of the pure hydræmic type is concerned, evidence other than clinical evidence is rarely called for, apart from the routine examination of the urine for protein, casts, etc., owing to the constancy of such symptoms as œdema and ascites. If help is required one may utilise the blood cholesterol estimation, the chloride concentration test of de Wesselow or Calvert's test. Most of the cases we meet with are of the azotæmic type or have the azotæmic features most

prominent, and it is principally in reference to these that the value of tests has been questioned. It is sometimes said that laboratory evidence only becomes conclusive when the clinical condition is such that it alone renders the diagnosis obvious. While this may be true of many cases it is not true of all. I have often seen cases in which, from clinical evidence alone, there was little to warrant a diagnosis of chronic nephritis, and in some there was little even to suggest it, yet its presence has been proved beyond reasonable doubt by the results of certain tests. But in conditions of possible mild degree of chronic nephritis, or conditions in which it is desirable to exclude this condition, our tests do often fail to give us the precise and clear-cut lead that we desire.

In severer cases it may be taken that the gravity of the condition is roughly indicated by the laboratory results, provided we keep in mind the liability of chronic cases to have acute exacerbations, when the laboratory results will be subject to corresponding changes. Hence if such an acute phase is at all likely to be present when tests are made, further tests at intervals should be made, to obtain anything like a correct estimate of the true state of affairs. By repeated tests we are able to form some opinion of the rate of progress of the condition, and from the point of view of prognosis this is generally of greater value than the actual findings at any one time.

On comparing the findings in acute and chronic conditions we notice that recovery frequently occurs in acute nephritis following degrees of nitrogen retention, which in chronic nephritis would indicate a very grave outlook indeed.

Surgical Conditions.—The presence of renal disease always increases the risk in surgical operations, and may be a definite contra-indication to such procedures. Renal efficiency tests are of value therefore in attempting to assess the efficiency of the kidneys when information on this subject is felt to be desirable in considering the advisability of operation. In unilateral renal disease the results of ordinary tests may

disclose no functional impairment, since one sound kidney is capable of carrying out urinary excretion satisfactorily. An indication as to which kidney is diseased is often obtained by comparing the chemical composition (*e.g.*, percentage of urea and chlorides) of two specimens of urine taken at the same time, one from each ureter.

In cases of obstruction to the outflow of urine, as with enlarged prostate, kidney function always becomes impaired if the obstruction continues for any length of time, and hence the operative risk under such conditions may be a serious one. Unlike the renal impairment of most other conditions, that due to obstruction frequently disappears very largely after the obstruction is removed. Consequently it has become a routine procedure in such conditions to estimate renal function before proceeding to serious operative measures. If it is found to be impaired, a comparatively simple procedure for relief of obstruction and establishment of free drainage is first carried out, *e.g.*, by suprapubic cystotomy. Thereafter improvement of renal function frequently occurs and can be closely followed by repeated tests, and the time ascertained when it is safe to undertake a more radical cure, as by prostatectomy.

A description of the actual tests employed may now be given.

Renal Function Tests

Apart from examination of urine for albumin, casts, etc., the tests most frequently used are the determination of the nitrogenous waste bodies in the blood, and the determination of the urea concentration of the urine. Determinations of urea, uric acid, creatinin and non-protein nitrogen of the blood have all been used for the estimation of renal function. Of these only non-protein nitrogen and urea need be considered here. Except in eclampsia and certain liver diseases these bear a fairly constant relationship to one another, the urea nitrogen being approximately one-half of the non-

protein nitrogen. Hence in renal conditions practically the same significance may be attached to variations in either of them. For simplicity, therefore, as well as from the fact that urea determinations are in most general use, I shall deal only with the blood urea. In this connection it should be pointed out that two ways of expressing results relating to blood urea are in use. In one, commonest in America, results are expressed in terms of urea-nitrogen, while in the other, actual urea is given. The latter figure is 2·14 times the former. Following the practice in this hospital, I shall refer throughout to urea-nitrogen.

The normal range of blood urea-nitrogen is from 10 to 20 mgm. per 100 c.c. of blood. In general, young persons tend to approximate to the lower figure and old people to the upper one. It has been stated that old people may have values up to about 30 mgm. and still exhibit efficient renal function. Though this is true of many cases it is not true of all. Recently I collected all the results of urea-nitrogen determinations carried out in this hospital on patients between 60 and 70 years of age. The number of figures below 20 mgm. was found to be so great as to indicate that it is unwise to accept any value above 20 as normal, without some other confirmatory evidence. This has an obvious bearing in considering urea determinations as evidence of the state of renal function in patients with enlarged prostate.

Urea determinations alone have certainly considerable usefulness. They will distinguish between patients who have nitrogen retention and those who have not. Determinations of blood urea on the same patient at intervals give valuable information as to the progress of his condition, provided he remains throughout under fairly constant conditions as to diet, etc., but as a true index of renal function blood urea values must be considered in the light of the following facts :—

(*a*) There may be renal inefficiency which is compensated

by polyuria, etc., so that no appreciable increase in the blood urea occurs.

(*b*) If the diet of a patient with renal inefficiency has a very low protein content, the amount of nitrogenous products to be eliminated is less than if he were receiving a normal diet. Under these conditions his kidneys may be able to excrete the smaller amount of urea to be got rid of, without allowing any increase in blood concentration, whereas on a normal diet urea retention may occur. In the same way, by appropriate dieting it is possible to reduce the blood urea of patients with renal disease, but the reduction is not an indication of improvement in the renal condition.

(*c*) Blood urea may be raised owing to extra-renal causes. Amongst these are :—

(i.) Physiological causes, *e.g.*, abstention from fluid for a short time, more particularly in hot weather; or excessive protein intake.

(ii.) Pathological causes. Amongst the factors concerned here are, firstly, conditions interfering with the absorption of fluid and tending therefore to produce oliguria; secondly, conditions resulting in excessive protein metabolism; and, thirdly, conditions in which there are circulatory defects.

To the first of these classes belong excessive vomiting or excessive diarrhœa. I can recall one case in which a uræmic condition resulted from a malignant growth of the duodenum, the obstruction due to the growth or the vomiting caused by it being such that the amount of fluid absorbed was so small that a condition of almost complete anuria resulted. To the same class belong conditions like empyema, where effusions cause the withdrawal of fluid from the blood. An additional factor is probably depression of function due to an accompanying toxæmia. The same causes are probably responsible for the raised blood urea often found in patients suffering from acute or subacute intestinal obstruction.

To the second class of conditions, viz., those resulting in

excessive protein metabolism, belong cases suffering from febrile diseases. Here, too, toxæmia may be a factor.

To the third class belong cases of cardiac disease.

In addition to the conditions mentioned, I have frequently noticed an increased blood urea in patients with cystitis, in whom tests have shown that the renal function is quite efficient.

In the large majority of cases, the rise in blood urea produced by extra-renal causes is not of very high degree, the blood urea rarely exceeding 50 mgm. of urea-nitrogen per 100 c.c. of blood.

On account of these facts it is often necessary to carry out some other test to supplement and correct the findings suggested by a blood urea determination. The one which is generally used is **Maclean's Urea Concentration Test.** In its original form, this consists in giving to the patient 15 gm. of urea dissolved in about 100 c.c. of water, and determining the concentration of urea in a specimen of urine passed one hour, and another passed two hours, after the urea has been taken. The test has been modified in this hospital, so that our routine "Renal Efficiency Test" is as follows :—

The patient is not allowed any food over night and only the minimum quantity of fluid; this procedure is to limit any possible diuresis which may be caused by giving urea. At a suitable time in the morning the patient empties his bladder and the urine is discarded. One hour afterwards a specimen of blood is taken, and a specimen of urine at about the same time. This urine specimen is labelled A. Fifteen grams of urea are then given in about 100 c.c. of water, and at one hour, and again at two hours afterwards, the bladder is emptied, the urine specimens so obtained being labelled B and C respectively. The urea-nitrogen content of the blood is determined, and the percentage of urea in each of the three specimens of urine.

It is best to consider the results under two heads :—

1. **Blood Urea-Nitrogen Normal.**—If any of the three specimens of urine shows a urea concentration exceeding 2 per cent. renal function is considered to be efficient. If all urea concentrations are appreciably below 2 per cent., some inefficiency is indicated. If the maximum value found amongst the three specimens approaches 2 per cent., regard is paid to the difference between the maximum and minimum values. If the difference is comparatively small, *e.g.*, below about 0·6, some inefficiency is probably present, whereas if the difference is great, renal function is probably satisfactory.

2. **Blood Urea-Nitrogen Raised.**—If the urea concentration of none of the urine specimens exceeds 2 per cent., some renal inefficiency is indicated. If, however, a considerably increased urea concentration is found in any of the specimens, the inference is that, although there is some accumulation of nitrogenous bodies in the blood, the power of the kidney to concentrate urea is unimpaired, and hence the raised blood urea is due to some extra-renal cause.

When we come to consider actual figures, however, some difficulties arise. Maclean says, "If the test shows a concentration of 2·5 per cent. or so, it is quite certain that the kidneys are acting very efficiently." This rather hard and fast rule appears to me to be untenable. A kidney with moderately impaired concentrating power has not lost all its power of response to varying concentrations of urea in the blood, and therefore it can hardly be assumed that it is incapable under all circumstances of producing urine containing as much as 2·5 per cent. of urea. For suppose we have a kidney with a concentrating power of 30 instead of the normal 60 to 80. When the blood contains 20 mgm. of urea-nitrogen per 100 c.c. the urine would contain 1·3 per cent. of urea, a value definitely below normal. But with the the same concentrating power and with the blood containing 50 mgm. of urea-nitrogen per 100 c.c. the urine would contain 3·2 per cent. of urea, a result which in Maclean's view

would justify the diagnosis of efficient function. Thus, while agreeing in a general way with Maclean's view, it seems to me that actual blood urea concentration should be considered as well as urine concentration in deciding whether renal function is fully efficient or not. I will quote three examples to illustrate this point :—

	Blood Urea-Nitrogen (mgm. per 100 c.c.)	Urine Urea (%) and Urine Volume. A	B	C
1. Eliz. McC.	50·2	2·0 98 c.c.	2·1 57 c.c.	2·5 85 c.c.
Urine contained many granular casts.				
2. Lawrence, H.	27·6	2·6 62 c.c.	3·0 94 c.c.	3·7 67 c.c.
Urine contained no casts.				
3. Richard B.	44·1	4·0 16 c.c.	4·4 20 c.c.	4·5 28 c.c.

In cases 2 and 3 the rise in urine concentration is roughly proportional to the increase in the blood concentration, and it is obvious that concentrating power is being well maintained. The volumes of urine in case 3 are small, so that it seems probable that the increase in blood urea may be due to some condition causing oliguria. The volumes of urine in cases 1 and 2 are on the whole very similar, so that the differences between the results are not explained by simple diuresis. But while the urine concentrations in cases 2 and 3 show an increase corresponding to the rise in blood urea, the maximum concentration in case 1 is hardly as high as might be expected from an efficient kidney when the blood urea is two and a half times the normal maximum. Hence I regard with suspicion, from the point of view of renal function, cases of raised blood urea without a roughly proportional increase in the urine urea concentration.

It is, of course, quite possible that in some cases raised blood urea may be due to both renal and extra-renal causes.

In some of these, the actual impairment of renal function may be temporary and due to some condition like toxæmia which accompanies the condition giving rise to the extra-renal nitrogenous retention. This point can usually be decided by a subsequent test after the extra-renal cause of retention has been discovered and dealt with.

Calvert's [3] Range of Urea Concentration Test or Range of Function Test.—This test, which has been found to be of considerable value, has for its object the estimation of renal function by determining the power of response of the kidney to widely different conditions. Calvert points out what has already been referred to above, namely, that the range of action of diseased kidneys in excreting urine of high and low concentration must be less than normal. Hence, he says, not only should the maximum concentration be determined, but also the minimum. Moreover, a test of this kind reveals defect of function in both types of nephritis. In hydræmic nephritis the failure is to diuresis; in the azotæmic type, to concentration. Concentration usually takes place to the greatest extent during sleep, while ability to form a dilute urine is best determined during the waking hours when the kidneys are most sensitive to diuretics. His description of the test is as follows :—

The taking of fluid during the five to six hours preceding the test is forbidden. Thus little fluid is taken at tea-time (5 o'clock) and none with the evening meal (7 to 8 o'clock). At, say, 10 p.m. the patient (an adult) drinks the following 3 oz. dose :—

Urea	ʒiv
Tr. aurant	ʒss.
Aq. ad.	℥iij

An hour later the bladder is emptied and the urine discarded. The patient is then kept warm in bed and encouraged to sleep.

[3] *British Medical Journal*, January 10th, 1925.

All the urine is collected from 11 p.m. to 7 a.m., the bladder being completely emptied at the latter hour. This urine is labelled A.

At 7 a.m. plenty of fluid is given. Thus between 7 and 7.45 a.m. the patient *sips* two large cups of weak tea, containing little or no sugar, followed by a pint of water, that is, about 30 oz. in all. The urine is collected from 7 to 9 a.m. This is labelled B.

A gives the maximum concentration of urea. B the minimum. (The urine is discarded up to one hour after the giving of the dose of urea to allow any diuretic effects to pass off.) Calvert gives the following as typical of the results of such a test :—

	Percentage of Urea in Urines.		
	Normal	Marked Chronic Interstitial Nephritis.	Marked Chronic Parenchymatous Nephritis.
A	3·82	1·32	2·60
B	0·40	1·12	2·40

It will be seen that the range between maximum and minimum in chronic interstitial nephritis is much less than normal, and in the worst cases may be nil. In chronic parenchymatous nephritis the range may be equally limited, but at a higher level, maximum and minimum figures being practically always above 2 per cent. In general, the lower the maximum concentration and the more restricted the range, the worse is the prognosis.

Urea concentration tests with blood urea estimations will in most cases give us all the information required or obtainable. For certain special types of cases, and sometimes where additional information is sought, other tests are carried out. Some of these are as follows :—

De Wesselow's Chloride Concentration Test.—Four grams of potassium chloride and 200 c.c. of water are given, urine being collected hourly afterwards, for three hours. No restrictions are placed on the previous intake of food or

drink, the test being started two hours after a self-chosen breakfast. In normal individuals the maximum chloride concentration reached generally exceeds 0·8 per cent. In cases of chronic interstitial nephritis (azotæmic type) much lower values are obtained, and a tendency to fixity of concentration is noticed, little difference in chloride concentration before and after the test being found. In marked cases, values of the order of 0·2 per cent. were found. In well-developed chronic parenchymatous nephritis extremely low values of chloride concentration are seen. An example quoted by de Wesselow shows values of 0·015, 0·017 and 0·005 per cent.

Of tests based on the introduction of dyestuffs into the circulation and subsequently noting their rate of excretion, only one is of sufficient value to merit description, namely, the

Phenol Sulphone Phthalein Test.—Phenol sulphone phthalein, or phenol red, is a dye which gives an intense brilliant red colour in alkaline solution. It is quickly excreted in the urine without change if the kidneys are healthy, but much more slowly if they are diseased. Moreover, it is non-toxic. It is supplied in sealed ampoules as a solution in saline containing 6 mgm. per cubic centimetre.

Twenty to thirty minutes before the test the patient is given 300 c.c. of water to drink. The bladder is now emptied and 1 c.c. of the dye solution is injected, generally intramuscularly. Excretion of the dye usually commences within ten minutes. This point may be noticed by employing a catheter and allowing the urine to drip into a vessel containing a dilute solution of caustic soda. The dye makes its presence evident by the appearance of a red colour as the urine becomes alkaline. From the point when dye excretion commences, the urine is collected during the first hour into one vessel, and during the second into another. It is not necessary to use the catheter throughout unless it is felt that complete emptying of the bladder at the end of the two hourly periods would not otherwise be obtained. The

whole of the two specimens of urine are now sent to the laboratory, where their dye content is ascertained colorimetrically.

In normal cases about 50 per cent. of the injected dye is excreted in one hour, and about 70 per cent. in the two hours. Anything much below 60 per cent. for the two hours or 40 per cent. for the first hour is considered as evidence of impaired renal function.

This test has been mainly used in surgical cases, and is believed to give valuable indications as to the suitability for operation in such cases (*e.g.*, enlarged prostate). It is particularly useful in determining the functional value of the individual kidneys by examining the separated urines obtained by ureteral catheters.

Three other tests deserve mention, viz., the determination of the inorganic phosphorus of the blood, the blood cholesterol, and the urinary diastase.

Phosphate estimations have been chiefly used as a guide to prognosis in recognised cases of chronic nephritis. The normal plasma or serum phosphate averages about 3·7 mgm. of inorganic phosphorus per 100 c.c. in adults (about 5 mgm. in children). Any figures above 10 mgm. indicates almost invariably a hopeless prognosis.

The rise in blood cholesterol in cases of hydræmic nephritis has already been described. From the work of MacAdam and Shiskin[4] cholesterol estimations appear to be of considerable value with regard to treatment of cases of urinary obstruction due to prostatic enlargement.

They point out that in such cases one has to consider not merely the state of renal function but also the capacity of the patient to resist the spread of sepsis to the upper urinary tract, since a cystitis of greater or less degree is usually present. They suggest that a low blood cholesterol in a case of acute or chronic retention due to prostatic enlargement is significant of a low capacity for antibody formation, and

[4] *British Journal of Surgery*, XII., 435. 1925.

points to the case being a bad operative risk as regards prostatectomy. Thus while a high blood urea alone is not necessarily serious as to ultimate prognosis, since such cases with normal or high cholesterol usually acquire a normal blood urea after suprapubic drainage, the combination of high blood urea and low cholesterol is of very serious import, and points to an undoubtedly bad surgical risk.

The determination of urinary diastase has often been referred to in works on renal function. The excretion of diastase is, like that of many other substances, considerably reduced in certain cases of renal disease. Normally the values for urinary diastase are found to lie between 6 and 30 units. In renal conditions values below 6, frequently as low as 1 or 2 units, may be found. The test should be performed on the twenty-four-hours' urine, since there may be considerable variation between individual samples passed at different times of the day. This test is of very little value by itself, but may be of some use in conjunction with other tests.

Practical Points.—*Urine.*—The conditions under which urine samples should be taken are laid down in the description of the various tests. Generally it is advisable to send the whole of the specimens to the laboratory, though it will be sufficient in many cases to send 20 to 30 c.c. only, provided the actual volume of each specimen is measured and noted at the bedside.

Blood.—For urea, non-protein nitrogen and uric acid whole blood is used. Potassium oxalate is the usual anticoagulant. Care must be taken to avoid excess, as it interferes with the preparation of a protein-free filtrate. About 5 c.c. of blood should be obtained.

For inorganic phosphorus, plasma or serum may be used, and for cholesterol, plasma. About 4 c.c. of blood (oxalated when plasma is required) should be obtained in each case.

Before leaving the subject of renal function, a few words are required concerning certain renal symptoms.

Uræmia.—Though the clinical condition described as

uræmia is the characteristic termination of chronic interstitial nephritis, and is therefore generally accompanied by marked nitrogen retention, patients showing uræmic symptoms are sometimes met with whose blood shows very little increase in urea content. The explanation, chiefly due to Volhard, appears to be that there are two types of uræmia, the one called true uræmia, in which there is marked retention of nitrogenous products and phosphates with diminution of the alkali reserve and of calcium, and the other called by Volhard eclamptic pseudo-uræmia, in which, beyond dilution of the blood, little change in chemical composition is shown by analysis. In the latter type lumbar puncture shows that the cerebro-spinal fluid is under increased pressure, and the cause of the symptoms appears to be related to œdema of the brain and increased intra-cranial pressure, associated with rise in blood pressure.

The immediate cause of true uræmia is not known. Though accompanied by retention of various substances, a study of the toxic properties and effects of such bodies as urea, uric acid, creatinin and phosphates shows that the whole clinical picture shown by uræmia is hardly likely to be due to retention of any of them. Neither can all the symptoms be explained by the reduction in alkali reserve or in calcium, though to the former may be attributed the dyspnœa, and it is probable that the latter may be responsible for certain nervous symptoms (see Chapter XIII.). Various substances, generally nitrogenous, and believed to be retained along with the well-known nitrogenous waste products, have been suggested from time to time as the cause of true uræmia, but no explanation so far offered has received general acceptance.

It should be pointed out that though two types of uræmia may exist, corresponding roughly to the two types of chronic nephritis, azotæmic and hydræmic, both may exist together in the same patient, and probably do so in a large number of cases.

Oxaluria.—Oxalic acid is a constituent of normal urine, about 15 to 20 mgm. being eliminated in twenty-four hours. Under ordinary conditions it all remains in solution. When oxalic acid appears as a solid in the urine in the form of calcium oxalate crystals, which can be recognised in the urinary deposit, the patient is said to be suffering from oxaluria.

A deposit of oxalate may occur under the following conditions :—

1. Certain physical changes in the urine may cause the precipitation of oxalate which is present in the urine in normal amount. Certain changes in reaction, for instance, may bring this about.

2. Ingestion of large amounts of oxalic acid-containing foods (especially tomatoes, spinach, rhubarb) may increase the excretion of oxalates beyond the amount capable of being kept in solution.

3. Certain alterations of metabolism appear to result in excretion of increased amounts of oxalates, *e.g.*, in diabetes mellitus, certain organic diseases of the liver and certain conditions in which oxidation seems to be impaired (as in some lung and heart diseases).

The point which concerns us here is that oxaluria is not evidence of renal disease, as has sometimes been supposed. It is possible that the presence of oxalate crystals in the urine does give rise to symptoms referable to the urinary tract, such as pain on micturition, for I have frequently been asked to investigate renal function in patients suspected of having some renal disease, and have been able to find no abnormality beyond the presence of oxalate crystals in the urine.

Phosphaturia.—Phosphaturia, *i.e.*, the condition in which phosphates are found as sediment in the urine, is nearly always due, not to increased excretion of phosphate, but to a change in the reaction of the urine towards alkalinity. It may be caused by the ingestion of alkalis, it may accom-

pany certain metabolic disorders, or it may result from fermentation of the urine by organisms which produce alkalinity in the urine. It is said to occur frequently in neurasthenic individuals. It has no relation to renal disease.

In examining for oxalates or phosphates in urine only fresh specimens should be accepted, for in urine which is allowed to stand, changes may occur which would cause the presence of these substances in a deposit which did not contain them when the urine was passed by the patient.

When oxaluria or phosphaturia is found in a patient it should be dealt with, if possible, to avoid the tendency to calculus formation which arises if either condition is allowed to persist (see Chapter XIV.).

CHAPTER V

LIVER FUNCTION TESTS

CHEMICAL tests for the recognition of impairment of liver function are subject to many limitations, and have given rise to many disappointments. Frequently they fail to give the clinician the much-needed help he sometimes hopes for, in the consideration of certain conditions which clinically are obscure. The number of tests which have been suggested is very large, but the ideal liver function test is still being sought for.

The difficulties of the subject will be appreciated when one recalls the multitudinous activities carried on by the liver. It is the one organ of the whole body which most deserves the title of general chemical laboratory. Moreover, when disease attacks this organ and its activities begin to fail, the different functions carried on there do not apparently begin to fail in any constant order. If so it would be a comparatively simple matter to determine that order, to find out which function is most easily disturbed by disease, and base our test in any particular case on a study of this one function. But it has been often noted that in one case, for example, there is evidence of failure of certain metabolic functions while pigmentary functions appear to be efficient, and in another case pigmentary functions appear normal, though there is evidence of inefficiency in certain metabolic functions. This confusion is probably due in part to the fact that many functions for which the liver is largely responsible are not entirely carried on by that organ, so that a moderate degree of failure on the part of the liver with respect to certain functions may be accentuated or masked according to the condition of certain other organs.

It does not follow, however, that in view of what has just been said, all liver function tests are entirely useless. On occasion certain tests have proved of very considerable value to the clinician, and in many cases their help is not to be despised, provided that they are carefully carried out and intelligently interpreted.

Before proceeding to a consideration of liver function tests, it will be advisable to summarise the principal functions of the liver. They are as follows :—

1. **Metabolic Functions.**—The liver is concerned in the metabolism of all three classes of foodstuffs. The storage within it of carbohydrate as glycogen has already been referred to. Deamination of amino-acids and formation of urea also take place there.

2. **Pigmentary Functions.**—The liver is concerned in the formation of bile pigment which it excretes in the bile, along with the bile salts and cholesterol. It also excretes urobilin which has been absorbed from the intestine.

3. **Excretory Functions.**—Many foreign chemical substances, including certain dyes, are excreted by the liver in the bile. Bacteria, too, may be dealt with in the same way.

4. **Antitoxic Functions.**—The liver destroys certain toxic substances entirely, or in some cases combines them with other substances, forming non-toxic bodies which are excreted.

5. **Hæmopoietic Functions.**—In addition to the formation of bile pigment from hæmoglobin, the liver has other relations with the blood. It is concerned, for instance, in the formation of fibrinogen, and hence has an influence on blood coagulation.

This is not by any means a complete list covering all the activities of the liver. There are others (*e.g.*, the part played by the liver in the metabolism of iron) about which little is known, but those above-mentioned have all been used as bases for many tests of hepatic function, some of which will now be discussed.

Many attempts have been made to detect impairment of hepatic function by examining for alterations in protein metabolism. These depend on the assumption that failure of deamination of amino-acids will lead to an increase in the concentration of amino-acid nitrogen in the blood and therefore in the urine. There will also be a decrease in the formation of urea, and therefore reduced concentrations of urea in blood and in urine. Such alterations have, in fact, been found, but only to a convincing degree in cases in which disease of the liver is very extensive or severe. The normal range of amino-acid nitrogen in the blood is from 4 to 9 mgm. per 100 c.c. Values above 9 mgm. are not often found except in acute yellow atrophy or eclampsia, and even in these conditions the increase is not always very great. In a recent case I obtained a value of about 11 mgm. in a patient who died from acute yellow atrophy the following day and in whom the post-mortem examination revealed a typical and very intense lesion of the liver.

Low values for blood urea are rarely found, probably due in part to the fact that the hepatic lesions concerned are frequently accompanied by functional disturbances of the kidneys, which cause urea retention.

Since urea-nitrogen of the blood tends to be decreased, and amino-acid nitrogen tends to rise, the ratio of the urea-nitrogen to the total non-protein nitrogen of the blood includes both effects. The determination of this ratio is of greater value than either amino-acid nitrogen or urea nitrogen determinations taken alone. Normally this ratio is 50 per cent., but in certain cases of liver disease, values of about 30 per cent. are sometimes found. This ratio is also found to be reduced in certain cases of eclampsia. The same ratio has been examined with respect to the urine, where normally it amounts to 80 to 90 per cent., and values down to 50 per cent. have been obtained in some cases of liver disease.

In conditions of gross liver derangement the amino-acids

leucine and tyrosine may be found in the urine. Their identification with certainty is frequently a matter of some difficulty, and they are only present with any constancy in severe diseases like acute yellow atrophy.

Though the liver plays an important part in fat metabolism, much of its work in this direction is as yet very imperfectly understood, so that this function has not been used as a basis for clinical tests of liver efficiency. A study of carbohydrate metabolism has, however, given us two tests. The first of these is the lævulose tolerance test. We have already seen that when a normal person takes lævulose by mouth, little or no rise results in the blood sugar concentration. In other words, the blood sugar curve, following the ingestion of lævulose, is practically a horizontal straight line. In diseases of the liver, however, the capacity to store the lævulose sufficiently rapidly to prevent an increase in blood sugar concentration becomes impaired. Consequently, the blood sugar concentration rises and we obtain a blood sugar curve similar to that which is obtained following the ingestion of glucose. The actual test is carried out in a manner exactly similar to that of the glucose tolerance test, a resting blood sugar concentration being obtained, followed by blood sugar values half-hourly for two hours after lævulose has been taken. Some workers vary the dose of lævulose according to the weight of the patient. My own practice is to give the same quantity of lævulose for this test as the quantity of glucose used in the glucose tolerance test, viz., 50 gm. for adults, with suitable reduction for children. It is important that the lævulose used should be free from glucose. A maximum blood sugar concentration of 0·14 per cent. or over, or a rise of over 0·03 per cent. above the resting value, is to be considered as an indication of impairment of hepatic function.

Many workers have claimed good results from this test. Others have met with disappointment, and hence claimed that it is valueless. The latter claim is certainly overstated. It is true that, according to the limits just mentioned, many

cases of liver disease show a negative result, but positive results according to this standard can usually be relied on as evidence of some hepatic disease.

The lævulose tolerance test is of no value in the investigation of hepatic disease in diabetics, for in uncomplicated diabetes a rise in blood sugar concentration always follows the ingestion of lævulose.

The second test related to carbohydrate metabolism is the galactose tolerance test. The technique and implications are similar to the lævulose tolerance test, but the dose of galactose recommended is 40 gm. This test is said to give positive results in diseases affecting the liver parenchyma, but is negative in hæmolytic and obstructive jaundice. Up to the present it has been mainly used in America and on the Continent, but not much in this country.

Investigations based on the pigmentary functions of the liver are, perhaps, more widely used than any others, since in the main they are intended to throw light on the origin of the symptom of jaundice. Hence, before proceeding to an account of actual tests, it will be advisable to recall to mind the modern theory of jaundice.

The principal bile pigments are bilirubin and biliverdin, and in man the former is considerably in excess of the latter. In considering the production of jaundice, therefore, it is sufficient to confine our attention to bilirubin. This pigment is formed from hæmoglobin by the cells of the reticulo-endothelial system. In the liver these are represented by the Kupffer cells lining the venous capillaries, but similar cells are present in the spleen and elsewhere. The bilirubin so formed normally passes through the polygonal cells of the liver into the bile capillaries, and in its passage through these polygonal cells it undergoes a change. There are different views as to the chemical nature of the change, but the most important fact seems to be that the pigment is changed from a colloid to a crystalloid. There are thus two varieties of bilirubin, namely, the bilirubin which is formed by the

reticulo-endothelial cells, which we will call A, and the bilirubin which has been subjected to change by the polygonal cells of the liver, which we will call B. Jaundice is the result of the presence of bile pigment in the blood in quantities greater than are normally present, and it may obviously occur in the following ways :—

1. In excessive blood destruction more bilirubin may be formed than the polygonal cells can deal with. Hence some of it is forced back into the general circulation, and this will be bilirubin A.

2. Normally formed pigment, passed normally through the polygonal cells, and therefore changed to bilirubin B, may be obstructed in some part of the bile tract and thus become reabsorbed into the blood stream.

3. The polygonal cells of the liver may be damaged, so that they lose their power to pass all the bile pigment through, some of it (the unchanged A) being forced back into the *circulation*.

4. We may have combinations of the above conditions, *e.g.*, damage to polygonal cells, together with some obstruction, as in cholangitis and sometimes in cirrhosis.

On this basis, jaundice is classified as follows :—

(*a*) **Hæmolytic Jaundice.**—Found in certain hæmolytic conditions, such as acholuric jaundice and pernicious anæmia. The pigment in excess in the blood is bilirubin A, which being colloidal has difficulty in passing through the kidney. Hence the presence of bile pigment in the urine is not a feature of these conditions.

(*b*) **Obstructive Hepatic Jaundice.**—Seen typically in obstruction of the hepatic duct or the common bile duct by stones. Here the pigment in excess in the blood is bilirubin B. This may pass into the urine, provided its concentration in the blood exceeds the renal threshold value (about 4 units).

(*c*) **Toxic and Infective Hepatic Jaundice,** in which the principal lesion is damage to the liver parenchyma. Many

conditions come under this heading and are usually sub divided according to the nature of the toxin responsible, whether chemical and introduced from outside the body (*e.g.*, salvarsan, phosphorus, chloroform) or formed within the body (as in pyæmia and septicæmia, the toxæmias of pregnancy, etc.). The pigment in excess in the blood may be wholly bilirubin A, or associated obstructive conditions may cause some bilirubin B to be retained also.

(*d*) **Combinations of the Above Forms,** as in catarrhal jaundice, where there is usually a hepatitis, interfering with the functions of the liver cells, together with obstruction in the bile ducts due to cholangitis. The relative effects of these two factors in causing jaundice and retention in the blood of the two forms of bilirubin varies in different cases, and throughout the course of individual cases.

The normal amount of bilirubin in the blood is 0·1 to 0·3 mgm. per 100 c.c. of serum, or 0·2 to 0·6 unit (where one unit is 1 part in 200,000). The renal threshold for bilirubin is 4 units, while clinical jaundice (*i.e.*, jaundice which can be recognised by the appearance of a yellow colour in the sclerotics and skin), is said to occur only when the blood concentration approaches 20 units. Hence there may be degrees of increase of bilirubin in the blood appreciably beyond the normal, but not sufficient to indicate its presence in the appearance of the patient or in his urine. Such a condition is known as latent jaundice. Tests for bile pigment in blood have therefore two aims, one being to recognise jaundice in its early stages, while it is still latent, and the other to determine if possible the type of jaundice we are dealing with. The test which most nearly fulfils these aims is the van den Bergh test, which depends on the production of a purplish red colour by the interaction of bilirubin and the van den Bergh reagent. In the first of these aims it is quite successful, though it often fails in the second. That it ever succeeds in differentiating the type of jaundice is due to the fact that it differentiates between the two types of bilirubin. This

(and the next two tests to be described) is usually carried out on blood serum, though plasma may also be used. Now, the A type of bilirubin, when in untreated serum, does not react at all with the van den Bergh reagent, or only does so after a considerable interval. The B type, however, reacts with it promptly. If the serum is treated with alcohol and the proteins thereby precipitated are removed, any bilirubin in the remaining solution will react with the reagent, whether the pigment is of the A or B type.

Hence the van den Bergh test comprises two distinct reactions, namely, what is known as the direct reaction, which is the reaction with untreated serum, and the indirect reaction, which is carried out on serum from which proteins have been removed by first precipitating with alcohol. A prompt direct reaction is one in which colour development begins in about 30 seconds and reaches its maximum in about two minutes. A delayed direct reaction is one in which the colour begins to appear after thirty seconds have elapsed, and develops slowly, while a negative direct reaction is one in which no colour develops within thirty minutes. A reaction to the direct test, known as the biphasic reaction, is usually described. This is one in which a red colour promptly makes its appearance and then slowly changes to the more typical purplish hue. Personally, I have very rarely got a convincing biphasic reaction, even where it is most to be expected, and prefer to leave it out of consideration.

The indirect reaction has no subdivisions. It is positive if the maximum colour developed exceeds in intensity that obtained under identical conditions with normal sera. Since both types of pigment react equally well in the indirect reaction, it is obvious that sera giving direct reactions (prompt or delayed) will also give positive indirect reactions, and, moreover, it is this test which is used for the quantitative estimation of bile pigment in blood in all types of jaundice, for this reaction in its more recent modifications enables one to obtain quantitative results with reasonable

ease and accuracy, so that by it the actual degree of jaundice can be determined and changes in degree noted throughout the progress of individual cases.

Now let us consider certain types of result.

The prompt direct reaction is obtained typically in obstructive jaundice. The delayed or negative direct reaction, with positive indirect reaction, is obtained in non-obstructive hepatic jaundice, or hæmolytic jaundice. This broad separation between obstructive and non-obstructive cases is useful, but limited in its application to exact diagnosis in that it does not of itself enable us to separate cases due to obstruction alone, and those with some obstruction, together with damage to the liver parenchyma. Cases of catarrhal jaundice, for instance, vary in response to the test, sometimes giving a prompt direct reaction and sometimes only a delayed or negative one. Cases of cirrhosis of the liver with jaundice, in which, in addition to damage to liver cells, there may be obstruction to the outflow of bile due to fibrosis and contraction, usually fail to give a prompt direct reaction, though this is not a constant finding. Other tests sometimes help us in our difficulty. Thus a failure of the normal amount of bile to reach the intestine is often indicated by an increased amount of unabsorbed, split fat in the stools. This does not occur as a rule in hæmolytic jaundice, but is often found, for instance, in cirrhosis of the liver. The subject will be further dealt with in discussing certain intestinal conditions (see Chapter VIII.).

Two other tests are used for the recognition of bile pigment in serum. One of these is Fouchet's reaction. This is not so sensitive as the van den Bergh reaction, makes no attempt at distinguishing the type of pigment present, and is not quantitative. The other is the determination of the icteric index. This is simply a comparison of the colour of blood serum against an arbitrary standard consisting of a 1 in 10,000 aqueous solution of potassium bichromate. The normal range is given as 4 to 6 units (*i.e.*, 4 to 6 times the standard). Cases

of latent jaundice show 7 to 16 units and clinical jaundice 17 units and upwards. As a quantitative test this is much inferior to the van den Bergh test, for other pigments besides the bile pigments may be present in serum and lead to false results. Hæmolysis will also make the results inaccurate.

Another test depending on the pigmentary functions of the liver is the test for urobilin in the urine. Bilirubin, after passing into the intestine, becomes transformed by reduction into urobilin or its precursor urobilinogen. This is absorbed to some extent, taken to the liver, where it is reconverted to bilirubin and re-excreted in the bile. In disease of the liver this capacity for dealing with absorbed urobilin and re-excreting it may become impaired, so that instead of being transformed and excreted in the bile, this substance becomes absorbed into the circulation and excreted in the urine. The presence of an excess of urobilin (or urobilinogen) in the urine may therefore be an indication of impaired hepatic function. Positive results to the test are also given in fevers, and in hæmolytic jaundice as well as in lesions confined to the liver. With regard to the other important constituents of bile, namely, the bile salts and cholesterol, little information has so far been obtained which throws any light on the functions of the liver. It has been ascertained that they are related to one another in chemical constitution, but the formation of bile salts from cholesterol, or *vice versâ*, within the body has not been demonstrated. The formation of cholesterol within the body has been a matter of some doubt, but recent evidence tends to show that this does take place. Investigation of variations in bile salt concentration in body fluids has been held up from lack of a satisfactory method for the quantitative determination of these substances, but work on this subject is now proceeding, though it is as yet too early to assess the value of the results. It will be evident from previous references to the subject that blood cholesterol estimations are amongst the usual procedures carried out in a pathological laboratory,

but practically the only positive value of such estimations, so far as diseases associated with the liver are concerned, lies in the fact that increased blood cholesterol concentration is sometimes found in patients with gall-stones. The proportion of cases with high blood cholesterol has been variously stated by different workers, but may be taken as approximately 60 per cent. A positive finding is therefore valuable confirmatory evidence in cases where other evidence suggests the presence of gall-stones. It appears highly probable that the raised blood cholesterol is indicative of a present or recent attack of the process responsible for the formation of stones, which is in the majority of cases cholecystitis.[1] (See also Chapter XIV.)

Tests based on investigation of the excretory functions of the liver depend on the fact that certain dyes are excreted almost entirely by the liver into the bile. Among the dyes which have been used for this purpose are phenoltetrachlorphthalein and rose bengal. In both tests a quantity of dye is injected into the circulation and its rate of disappearance from the blood is noted. Any decrease in this rate of disappearance, compared with what is known to be the normal rate, is regarded as evidence of hepatic inefficiency.

In the phenoltetrachlorphthalein test [2] the dose is 5 mgm. for each kilo of body weight. A solution of the dye containing 5 mgm. per 0·1 c.c. may be obtained in ampoules. The required quantity of this solution is added to 100 c.c. of sterile normal saline solution, which is then injected into the patient intravenously, the needle being then washed out into the vein with a further small quantity of normal saline solution. Fifteen minutes and one hour after the injection specimens of blood are removed from the patient (about 5 c.c. in each case), allowed to clot and the amount of dye in the serum is determined colorimetrically. In normal

[1] See Fowweather and Collinson. *British Journal of Surgery*, XIV., 583. 1927.

[2] See Rosenthal. *J. Pharmacol. and Expl. Therapeutics*, XXIII., 385. 1924.

cases 2 to 6 per cent. of the amount of dye injected remains in the circulation after fifteen minutes, and none after an hour. The presence of an appreciable amount of dye in the blood at the end of an hour indicates some hepatic disorder. In the rose bengal test,[3] 10 c.c. of a 1 per cent. solution of the dye in normal saline is injected intravenously and the needle washed through slowly with 5 to 10 c.c. of saline, held ready in a fresh syringe. The needle is left in the vein, and at exactly two minutes after the injection of the dye a sample of blood (10 c.c.) is withdrawn from the needle into a clean syringe and added to a centrifuge tube containing a little potassium oxalate, the tube then being inverted two or three times. The needle is again washed through with saline solution, to prevent clotting within its lumen, and at eight and sixteen minutes from the time of injection samples of blood are withdrawn as before. The amount of dye in the eight and sixteen-minute samples is then compared with that in the two-minute sample, which is taken to represent the maximum concentration of the dye in the blood. In normal individuals the eight-minute sample shows from 40 to 60 per cent. of the dye retained in the blood, and the sixteen-minute sample shows 23 to 30 per cent. Cases of obstructive jaundice, catarrhal jaundice and arsphenamine jaundice are said to show definite delay in eliminating the dye, the delay being greatest in obstructive jaundice. In cirrhosis of the liver the result seems to be in direct ratio to the amount of liver involvement, marked delay in excretion being shown in advanced cases. Diffuse replacement of the liver tissue by carcinoma also produces definite retention, and acute hepatic infections, too, show marked impairment as judged by this test. Chronic passive congestion of the liver, nephritic toxæmias of pregnancy and certain types of ascites, other than those associated with cirrhosis, have given negative results.

[3] See Epstein, Delprat and Kerr. *Journ. American Med. Association*, May 21st, 1927.

A method of investigating certain liver conditions based on the same principle as the above tests, is the method of cholecystography. As this is not a method requiring the assistance of the laboratory, but is a radiographic method, I shall only describe it very briefly. The dye used at the present time is tetraiodophenolphthalein, and this is opaque to X-rays. Hence instead of determining its rate of disappearance from the blood by chemical methods, its excretion into the gall-bladder is noted by taking radiographs of the gall-bladder region at intervals after the entry of the dye into the circulation. At first the dye was injected intravenously, but owing to the occasional occurrence of unpleasant and sometimes dangerous reactions the oral route is now favoured. The dose is 5 gr. per 10 lb. of body weight, and is contained in keratin-coated capsules, containing 5 gr. each. The capsules are taken at night (9 p.m. or 10 p.m.) and the total dose of ten or more capsules should be spread over an hour or more, a liberal supply of water being taken with them. A radiograph is taken twelve hours and again sixteen or seventeen hours after the dye was taken, the patient having no food during this period. A meal is then given to the patient and a further radiograph taken an hour afterwards.

In normal individuals the radiographs show a shadow of the gall-bladder, uniform in intensity, and increasing at first, then decreasing, in size and density. The abnormal results obtained are :—

1. No shadow obtained. This may be due to considerable impairment of the liver so that very little of the dye has been excreted, to obstruction of the cystic duct preventing the dye from entering the gall-bladder, or, with the oral method of administration, failure of absorption of the dye into the circulation.

2. Delay in filling or emptying, due to impaired excretion of the liver or to obstructive causes impeding but not wholly preventing the entry of bile into the gall-bladder or outflow from it.

3. Distorted or mottled shadows seen.

The latter indicates usually the presence of stones, while the former suggests structural changes in the gall-bladder, adhesions, etc.

Tetraiodophenolphthalein cannot be used in the same way as phenoltetrachlorphthalein for determination of the rate of its disappearance from the blood stream, as its detection and determination in blood plasma by chemical means cannot be satisfactorily carried out. On the other hand, phenoltetrachlorphthalein is transparent to X-rays, and so cannot be used for cholecystography. It has been claimed, however,[4] that phenoltetraiodophthalein (sodium salt) can be used simultaneously for cholecystography and for hepatic function tests. The dose of the dye is 40 mgm. per kilo of body weight, except that the dose need in no case exceed 2·5 gm. It is freshly prepared in 8 per cent. solution for each case, by dissolving the dye in freshly distilled water, filtering through fine filter paper and sterilising for fifteen minutes in a boiling water bath. The solution is injected intravenously and is followed by the injection of a few cubic centimetres of normal saline to prevent leakage of the dye from the vein wall or through the needle.

For liver function tests blood specimens are collected one half-hour and again one hour after injection, and estimation of the dye contained in the serum of these specimens is made. A retention of less than 15 per cent. of the dye in the blood serum one half-hour after injection and less than 4 per cent. one hour after is considered normal.

For cholecystography, radiographs are taken four, eight and twenty-four hours after injection of the dye, no food being given to the patient between the injection and the radiographs.

This dye is as yet very expensive, and little work appears

[4] See Graham, Cole, Copher and Moore. *Journ. Amer. Med. Association*, 86, 467 and 1899. 1926.

to have been done on this test apart from that carried out by its authors.

Of tests based on the antitoxic powers of the liver two will be described. The first, Roger's reaction, depends on the function of the liver by which certain substances are combined with glycuronic acid and excreted in this combination in the urine. In hepatic disease this function is lost, so that glycuronic acid does not appear in the urine. The substances used are sodium salicylate or aspirin, of which 5 gr. are given by mouth, or camphor of which a solution of 5 gr. in olive oil is injected subcutaneously. Following administration of the drug, the urine is collected during the subsequent twenty-four hours and is tested for glycuronic acid. If this substance is absent, impairment of hepatic function is indicated.

The second test is that of Roch and Schiff, recently modified by Thiers.[5] Thiers claims that a normal adult passes no sodium salicylate whatever into the urine after taking a dose of 0·04 gm., the substance being destroyed by the liver. In cases of liver damage, however, following this dose, salicylic acid appears in the urine during the second to the seventh hour after its ingestion. Accordingly, he carries out his test as follows :—

The dose of 0·04 gm. (0·6 gr.) of sodium salicylate is given in aqueous solution at 8 a.m. The urine is then collected from 9 a.m. until 1 p.m. or, if necessary, to obtain sufficient urine for the test until 4 p.m. Fifty or 100 c.c. of urine are used for the chemical test for the presence of salicylic acid, which he describes in detail, including a quantitative modification. He states that the test should not be employed during a period of profuse diuresis.

A number of tests based on the relations of the liver with the blood have been devised. One to which much attention has recently been paid is Widal's test. This depends on the fact that following a meal a leucocytosis occurs, whereas in the presence of a damaged liver, either no rise in the leucocyte

[5] *Lyon Medical*, May 15th, 1927.

count occurs, or even a leucopenia. The test is carried out by making a leucocyte count on the patient before his breakfast, then giving him 7 oz. of milk to drink and repeating the count at intervals of twenty and forty minutes following this meal. Whereas normally the count shows an increase at one or other of the periods after the meal of up to 3,000 over that obtained before the meal, in cases of hepatic derangement, the count remains constant, or falls. Considerable claims have been made for this test by some writers, while others have raised considerable doubts as to its value.

Two other tests depend on the fact that in hepatic inefficiency the fibrinogen content of the blood is decreased. One test utilises the actual determination of fibrinogen. This is normally 0·3 to 0·4 gm. per 100 c.c. of plasma, whereas considerable reduction below this occurs in hepatic diseases. The other test is a determination of the coagulation time of the blood. This determination is not a laboratory test; it must be performed at the bedside. Many different methods have been used, and none appears to have succeeded in gaining any notable pre-eminence over the rest. The normal coagulation time depends entirely on the method used, so that no general figure can be given. The interpretation depends on the coagulation time found, compared with the normal for the method employed, an increase in coagulation time being considered as an indication of hepatic derangement.

A survey of the number of tests used and the different principles involved is sufficient indication of the difficulty of the subject, and the absence of any one test of outstanding merit. In investigating a particular case, choice of tests should depend on the nature of the case. It is extremely difficult to assess the true value of most of the methods in use. Few if any pathologists or clinicians have sufficient experience in the use of all these tests to enable them to make a critical comparison of their value. Many of them are of

very recent introduction. With regard to most of them very conflicting results have been reported by different workers. But the need for tests which shall add to the knowledge obtainable by ordinary clinical methods concerning the liver is very great. It is therefore desirable that extended use should be made of such tests as appear to have any merit, so that a considerable body of experience may be accumulated, to enable us to arrive at a true estimate of their value.

Practical Points

Urine.—The actual quantities of urine required for the various tests mentioned varies somewhat according to the methods of analysis employed. For determination of the ratio of urea-nitrogen to total (non-protein) nitrogen, and for tests for urobilin and bile pigments, about 20 c.c. should be sent to the laboratory in each case. For examination for the presence of leucine and tyrosine 100 c.c. should be sent. It is not necessary in these cases to wait for a twenty-four-hours' specimen.

Blood.—The requirements for non-protein nitrogen, urea and cholesterol determinations are given in Chapter IV. For amino-acid nitrogen whole blood is used. Three to four cubic centimetres should be obtained, and treated with potassium oxalate. For the lævulose and galactose tolerance tests the determinations are the usual blood sugar determinations mentioned in Chapter III. In the van den Bergh and Fouchet reactions serum is used. About 5 c.c. of blood should be obtained and transferred to a clean, dry centrifuge tube in which the blood is allowed to clot. Fibrinogen determinations require 3 to 4 c.c. of blood which has been oxalated (Wu's method). The requirements of other tests have been indicated in the description of the tests concerned.

CHAPTER VI

THE TOXÆMIAS OF PREGNANCY

SOME account of the laboratory findings in the toxæmias of pregnancy follows naturally after dealing with functional tests on the kidney and the liver, for in a certain proportion of cases that are examined post-mortem definite lesions are found in both organs, and during life evidence is sometimes found of disturbed function of these organs. It would be difficult even to mention all the theories which have been put forward to account for these conditions. They fall mainly into two groups, viz., " maternal " theories and " ovular " theories.

To the former group belong those views which attribute the conditions included under the above term to some changes in the maternal metabolism during pregnancy. One view suggests that the cause is a toxin produced in the intestine ; another that it results from a disturbance in the secretion of the ductless glands ; still another that it is due to an exaggeration of the alterations in metabolism which normally occur in pregnancy ; and yet another that it depends on a pre-existing renal lesion, harmless enough under normal circumstances and frequently unrecognisable then, but such as to render the kidneys incapable of bearing the added strain due to pregnancy, so that toxic products normally eliminated are now retained.

To the " ovular " group belong those views which believe the conditions to be due to some cause having its origin in the fœtus or its appendages ; for example, that the proteins of the fœtus or placenta behave as foreign proteins in the maternal circulation ; or that the fœtus or placenta elaborate

toxic substances which find their way into the mother's blood; or that the mother absorbs poisonous autolytic products from the placenta.

In spite of all these theories and the tremendous volume of work which has been done on the subject, no theory is at all completely satisfactory or has received anything approaching general acceptance. In view of this uncertainty as to the cause of the conditions with which we have to deal, it is not surprising that such laboratory tests as have been used have not given uniform results.

It is not my present purpose to discuss the use of biochemical tests in investigating the cause of the toxæmias of pregnancy. I shall merely indicate what tests are likely to be of value where help is required in regard to diagnosis or treatment.

Symptoms which may early give rise to concern in pregnancy are excessive vomiting and albuminuria, and each may or may not be indicative of the presence of a toxæmia. Hence it is important to determine, if possible, the nature of the condition underlying the symptom. The majority of cases of excessive vomiting in pregnancy are neurotic in origin, and most of such cases can be dealt with successfully by appropriate treatment, without the necessity of terminating the pregnancy, though it is possible that even this may be advisable in the worst cases. But in true toxæmic or pernicious vomiting, a somewhat rare condition, termination of the pregnancy must be undertaken, the earlier the better. Attempts have been made to distinguish pernicious vomiting from other types by determining the degree of acidosis; but while we may have an acidosis due to the effect of toxins on hepatic metabolic processes or on tissue metabolism in general, we have some degree of acidosis in all cases of excessive vomiting due to the state of starvation or semi-starvation which results. Moreover, in normal pregnancy there is always a tendency towards a depletion of the alkali reserve. Hence definite signs of acidosis do not point defi-

nitely to toxæmia as a cause of the condition. True, in a general way, the degree of acidosis is of some help; the more severe the degree, the more likely are we to be dealing with the graver condition. Of actual tests, the ammonia coefficient has been most used, and any figure over 80 per cent. suggests the presence of toxæmia. In addition, any evidence of marked renal or hepatic derangement may be taken as evidence of toxæmia. In such cases the urine is much diminished in quantity, contains blood and casts and much albumin, and may contain bile pigment.

The liver function tests already described have been much used in investigating this and other forms of pregnancy toxæmias. It is claimed that in a certain proportion of pregnant women without any clinical signs of hepatic impairment positive results are found. Hence, such tests are of little use for exact differentiation. The position can be summed up by saying that definitely positive results, especially if obtained with more than one kind of test, are, on the whole, in favour of the presence of toxæmia, while negative results are of little or no value. With regard to pernicious vomiting, it is hardly necessary to point out that clinical observations regarding the degree and rate of wasting, the temperature, blood pressure, etc., are of the utmost importance.

Albuminuria of renal origin may occur during pregnancy, without any other abnormal signs or symptoms, but in view of its almost general association with serious conditions, it can never be regarded lightly; an attempt must always be made to ascertain its significance. As we have already seen, a number of people show albuminuria without any other signs of renal disease, and no doubt a proportion of cases in which albuminuria is noticed during pregnancy belong to this class. In others it can be definitely shown that the albuminuria has only arisen during the pregnancy. Of these, some may be cases of very slight toxæmia in which albuminuria is the only recognisable symptom. In others, mechani-

cal causes operating by pressure on the ureters or renal veins may be responsible. This type is said to be more common in twin pregnancies and where hydraminos is present. Albuminuria also occurs in cases with accidental hæmorrhage and vesicular mole.

Albuminuria of much greater significance is associated with two large groups of cases, viz., pre-eclamptic toxæmia and nephritic toxæmia; as well as with eclampsia itself. Pre-eclamptic toxæmia is the condition, due to pregnancy, which shows the type of renal functional failure and other symptoms, including, sometimes, those of hepatic failure, which are known to precede eclampsia. All cases, however, do not pass into eclampsia.

Nephritic toxæmia is the condition in which nephritic symptoms, chiefly of the azotæmic type, predominate, and is not due to pregnancy itself, but to the effect of pregnancy on a pre-existing renal lesion.

It is important both as regards prognosis and treatment to distinguish between the two wherever possible. Many cases cannot be definitely diagnosed on clinical grounds alone. Of these, the nature of many can be ascertained by laboratory tests, while a few can only be definitely identified by ascertaining the state of renal function some time after the pregnancy has been concluded. In pre-eclamptic toxæmia the kidneys usually recover their function completely after pregnancy is terminated, whereas the tendency in nephritic toxæmia is for the renal function to be further impaired as a result of the effect of pregnancy.

Some general points of difference are :—

In pre-eclamptic toxæmia, albuminuria and œdema usually occur during the latter half of pregnancy, eye changes are due mainly to œdema and are temporary. Cardio-vascular changes are absent. A rise in systolic blood pressure is a constant symptom, but disappears with recovery. The condition does not necessarily recur in another pregnancy. It is more common in primiparæ than in multiparæ.

In nephritic toxæmia albuminuria and œdema are usually early symptoms, albuminuric retinitis may be present, and also arterio-sclerosis and cardiac hypertrophy. The blood pressure may be either normal or raised, but if raised the rise persists after delivery. Abortion or death of the fœtus *in utero* frequently occurs. The condition is likely to recur with increasing severity in future pregnancies.

The findings shown by laboratory tests in the two classes of cases are as follows :—

Urine.—In pre-eclamptic toxæmia the quantity of urine may be small, with high specific gravity, much albumin and reduced chloride concentration, whereas in nephritic toxæmia the quantity, specific gravity and chloride concentration of the urine may be normal, and the amount of albumin small. For the urea concentration test de Wesselow [1] recommends that urine specimens should always be taken one, two and three hours after giving the usual dose of urea, and if any diuresis that occurs has not passed off by the third hour (*i.e.*, if the volumes of the second and third specimens exceed 100 c.c.) no definite conclusions should be drawn. With the test as thus described, cases of pre-eclamptic toxæmia may show urea concentrations of 3 per cent. or more, and frequently give values between 2 and 3 per cent. Values below 2 per cent. are characteristic of nephritic toxæmia.

Another test frequently applied is the determination of the diastatic index of the urine. A portion of the twenty-four-hours' specimen should be used. In pre-eclamptic toxæmia the value may be raised (above 30 units), though it is very frequently normal, whereas in nephritic toxæmia this value is never raised, and may be definitely low (less than 5 units).

Blood.—In considering the question of nitrogen retention we have to remember that the normal blood urea concentration in pregnancy is lower than that found in non-pregnant women, and is usually not more than 10 mgm. of urea-nitrogen

[1] "Modern Views on the Toxæmias of Pregnancy." 1924. London: Constable & Co.

per 100 c.c. of blood, in the later months. Judged by this standard, there is some nitrogen retention in most cases of pre-eclamptic toxæmia, but this is not usually of any large degree, the urea-nitrogen being generally not much more than 20 mgm. In nephritic toxæmia nitrogen retention may be marked, and the urea nitrogen is frequently higher than 20 mgm. In general, the higher the blood urea concentration the more definite is the indication of a nephritic toxæmia.

In pre-eclamptic toxæmia, liver function tests *may* show positive results; in nephritic toxæmia they generally give negative results.

In a general way it may be stated that pre-eclamptic toxæmia resembles more or less, so far as renal function is concerned, the hydræmic type of nephritis, to which may be added in some cases evidence of impaired hepatic function, whereas nephritic toxæmia tends to resemble more the azotæmic or mixed type of nephritis.

The use of tests should not be confined merely to diagnosis. The decision to terminate pregnancy or to allow it to proceed to its natural termination frequently depends on the response of the condition to treatment, and in determining that response laboratory tests may be of some assistance.

Eclampsia.—If convulsions and coma supervenc in a patient in whom symptoms of pre-eclamptic toxæmia have already been noted, there is no difficulty on arriving at a diagnosis of eclampsia. If, however, a patient is first seen in convulsions, other possible causes have to be thought of. Of these perhaps epilepsy is the commonest. Hysteria and meningitis are other possible causes. It will usually not be difficult if the case is one of eclampsia to obtain evidence which will justify treatment of the patient as an eclamptic. Thus the quantity of urine will generally be found to be very much diminished. If a specimen is obtainable it will be found to contain a large quantity of albumin. The ammonia-coefficient will probably be high, and ketone bodies may be present. The diastatic value may be raised and the chlorides

reduced. Blood pressure and cerebro-spinal fluid pressure will be considerably raised.

Finally, in all cases which have shown marked renal symptoms during pregnancy or immediately subsequent to it, renal function tests should be carried out at intervals following recovery, for on the residual state of renal function must depend our advice to the patient regarding subsequent pregnancies.

Practical Points.—The requirements of the tests which have been mentioned have been indicated in the two preceding chapters.

CHAPTER VII

TESTS OF GASTRIC FUNCTION. FRACTIONAL TEST MEALS

THE symptoms of gastric disease are frequently of an inconclusive nature, and the problems in differential diagnosis presented to us in patients complaining of these symptoms are often very difficult ones. Hence attempts have been made to obtain further information regarding such cases by chemical examination of the stomach contents. Such examinations are now amongst the routine procedures of most large hospitals.

The points on which information is sought in these tests are :—

1. The state of gastric secretion—whether normal, increased or diminished.

2. The motility of the stomach, particularly as regards its rate of emptying.

3. The presence of abnormal products in the stomach.

In addition to conditions dependent on known gastric lesions, there are one or two other conditions, *e.g.*, pernicious anæmia, which have well-recognised connection with certain abnormalities of gastric secretion, and in which, therefore, examination of gastric contents may sometimes be of assistance in diagnosis.

Until recently it was the practice to examine the gastric contents withdrawn from the patient one hour after he had been given a special test meal. This has now been largely superseded by the fractional test, in which specimens are withdrawn at fifteen-minute intervals over a period of about three hours, following a special meal. Although the in-

formation to be obtained by the fractional test is more complete than from examinations of single specimens, the latter method is not without value, and may afford useful information in certain cases.

A single specimen may be taken either from the fasting stomach, or following a meal. In the former case it is taken in the morning, before breakfast. The stomach tube is passed and the contents of the stomach removed as completely as possible. Normally the resting juice averages about 50 c.c., and should not exceed 100 c.c. It is of watery consistency and appearance, except that it is sometimes coloured by bile. Volumes over 100 c.c. are probably abnormal, and due either to the presence of some obstruction which delays emptying of the stomach, or to hypersecretion. The presence or absence of food residues will indicate which condition is present. In addition to determination of the volume the juice is examined for blood, pus, certain organisms, and lactic and other organic acids. Small quantities of fresh blood may be due to trauma resulting from the passage of the tube. Apart from this, the presence of blood is evidence of ulceration. In such cases, especially where the ulceration is due to malignancy, the blood is generally altered by the gastric juice and gives a brown colour to the fluid. In deciding on the significance of pus, the possibility of its having been introduced into the stomach by swallowing pus-containing sputum or saliva must be enquired into.

In cases of gross obstruction due to carcinoma the gastric fluid is often exceedingly foul, the smell of organic acids (butyric acid, lactic acid, etc.) can be recognised, and microscopic examination usually reveals the presence of yeasts, sarcinæ, etc. In lesser degrees of obstruction the presence of lactic acid and other acids may be demonstrated by chemical tests.

The chief aim in examining stomach contents withdrawn from a patient after he has taken a meal is to determine the

secretory response of the stomach to the presence of food. In the method which depends on the examination of a single specimen the Ewald test meal is usually given and the stomach contents are withdrawn an hour afterwards. The meal consists of a pint of tea and about half an ounce of toast. In addition to the examination just described for fasting specimens, the specimen taken after the meal is submitted to examination for free hydrochloric acid and for total acidity (which includes acidity due to organic acids and to acid salts as well as to free hydrochloric acid) and quantitative determinations of free and total acidity are often made. From the figures obtained, deductions are made concerning the state of gastric secretion. But it is now recognised that quantitative analysis of single specimens often fails to give a correct idea of the state of gastric secretion. Hence the results of such analysis can only be interpreted in a very general way, if at all, and the only real advantage of such a test over the examinations of the resting stomach contents is that the identification of free hydrochloric acid in this test definitely excludes achlorhydria.

In all methods in which a test meal is employed the nature of the meal usually differs considerably from that of an ordinary mixed meal. Hence the response given by a patient to such a test is not necessarily a very close approximation to what happens when he takes his usual meals, and our standard for comparison must be the response of the healthy individual to identical, somewhat artificial, conditions.

In the Ewald method, in which the ordinary stomach tube is frequently used, various modifications of the meal have been suggested to make it more like an ordinary mixed meal. In the fractional method, since many specimens are obtained throughout the course of the test, the ordinary stomach tube is entirely unsuitable. The fractional test in fact has only been made practicable by the introduction of a much smaller tube, which can be passed fairly easily at the beginning

of the test and can remain *in situ* throughout, without causing the patient much discomfort. The use of a tube of small bore, however, requires a meal which can be drawn through it by moderate suction from a syringe, and which shall, therefore, be free from solid particles of a size likely to choke up the tube, or block the entrance into it, and it is these considerations rather than questions regarding the actual composition of the meal which have determined its nature.

The tube most commonly used is Ryle's modification of the Rehfuss tube. This is a rubber tube whose diameter is about that of a No. 8 catheter. One end is open, while the other terminates in a rounded tip weighted with lead (completely covered by the rubber) and having perforations just above the tip, equal in size to the calibre of the tube. The tube is usually marked at 40 cm. and at 57 cm. from the tip, indicating the distances from the teeth to the cardiac orifice and pylorus respectively.

The meal is prepared by adding 2 pints of water to 2 tablespoonfuls of breakfast oatmeal, and then boiling the mixture down to 1 pint. Is is then strained through coarse muslin, and is ready for use.

The test is carried out in the morning, after the patient has fasted overnight.

Before use the tube is allowed to stand in hot water for a few moments to soften it and thus make it more easy to swallow. The tip may be lubricated with a little glycerol or liquid petroleum. It is gently pushed backwards to the root of the patient's tongue, and he is encouraged to swallow persistently while the tube is slowly fed into the mouth. Some slight discomfort occurs during the passage of the tip through the pharynx and past the level of the cricoid cartilage. If the discomfort or irritation of this stage is extreme, the throat may be painted with a 2 per cent. aqueous solution of cocaine hydrochloride, but this is very rarely necessary. When the tube has entered the stomach, the latter is emptied as completely as possible by aspiration into a

syringe fixed to the free end of the tube, and the whole of the specimen sent later to the laboratory, along with subsequent specimens. After the stomach has thus been emptied, the patient swallows the test meal with the tube still in position, and following this, specimens of about 10 c.c. each are withdrawn by means of the syringe at intervals of fifteen minutes for three hours, or until no more fluid can be obtained, whichever is the shorter period. Occasionally some difficulty in withdrawing specimens arises through obstruction of the tube, but this can usually be overcome by injecting a little air into the tube to clear its lumen and orifices.

All the specimens thus obtained are tested for :—

Mucus : An estimate is made as to whether the amount is normal or increased.

Bile : Naked eye examination is usually sufficient.

Blood : Quantity is noted and whether fresh or altered.

Starch : The disappearance of starch from the specimens is taken to indicate the time of emptying of the stomach, except where achlorhydria or marked hypochlorhydria is found to be present. In such cases the disappearance of starch may be due to the continued action of the ptyalin of the saliva whose action has not been inhibited owing to absence of a sufficient concentration of acid. Hence in such cases sugar is tested for and emptying of the stomach assumed from the time of its disappearance.

Free HCl : The concentration of this in each sample is determined quantitatively.

Total acidity : The concentration of this, too, is obtained quantitatively.

In addition to the above tests on each specimen, the first specimen or fasting juice is submitted to the other tests already described with reference to single specimen tests, *e.g.*, the volume is noted and microscopic and chemical tests for the recognition of abnormal substances are carried out.

The results are noted on a chart, the values for free HCl

and total acidity being indicated in the form of curves. A few charts are shown as illustrations (see Figs. 7–14).

Findings in Normal Cases.—The amount of fasting juice varies considerably, averaging about 50 c.c. Bile is present in about 40 per cent. of cases.

The acidity is also variable, many specimens showing absence of free hydrochloric acid.

The curves representing acid secretion throughout the test conform more or less to a general type, in which secretion

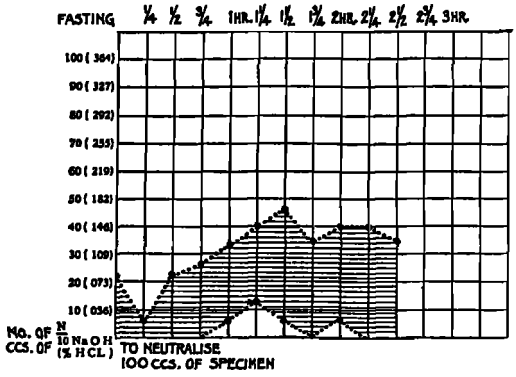
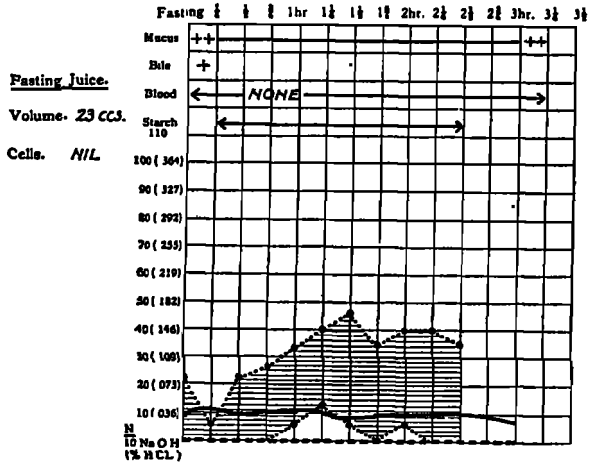


FIG. 6.—The shaded area represents the limits for free hydrochloric acid of 80 per cent. of normal people, as shown by the fractional test meal examination. (Bennett and Ryle.)

is seen to rise to a maximum usually reached in one to one and a half hours, and then to fall gradually. When the fasting juice contains a fair amount of acid the concentration falls when the meal is given, owing to dilution. The height to which the curve rises shows considerable variation. This is best illustrated by the chart of Bennett and Ryle [1] (Fig. 6), showing the limits of secretion of free hydrochloric acid in 80 per cent. of healthy males. An interesting finding is that 4 per cent. of apparently healthy people show no free hydrochloric acid.

[1] *Guy's Hospital Reports*, 71 : 286. 1921.

Bell and Macadam [2] investigated the variations in secretion in a series of twenty tests carried out on consecutive days on the same individual. They found that though considerable variations in absolute figures for both free and total acid are obtained, the same type of curve is seen throughout the series. The lowest acid secretion is seen in the first test, and this is believed to be due to a psychical



The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity.

FIG. 7.—Chart of case of true achlorhydria.

inhibition resulting from the apprehension frequently present on the first occasion of swallowing the tube. They therefore point out that "if a low or normal acid curve is obtained on a first examination when the clinical history of the patient suggests a hyperchlorhydria, the test should be repeated before a high degree of acidity can be eliminated."

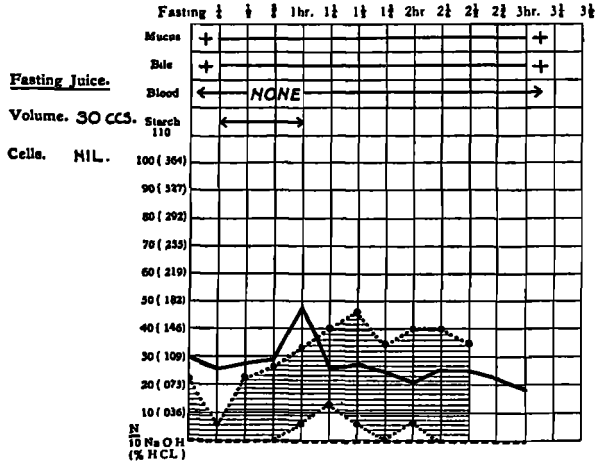
The curve representing acid secretion in this test does not

[2] *Quarterly Journal of Medicine*, 17 : 215. 1924.

actually represent the *amount* of acid secreted, for it has now been definitely shown that regurgitation of alkaline fluid from the intestine into the stomach occurs during normal digestion. Hence it will be seen that the acid curve in this test is influenced by two distinct factors, viz :--

1. Amount of acid secreted.
2. Amount of regurgitation of alkaline fluid from the intestine.

A more correct estimate of the actual amount of acid



The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity.

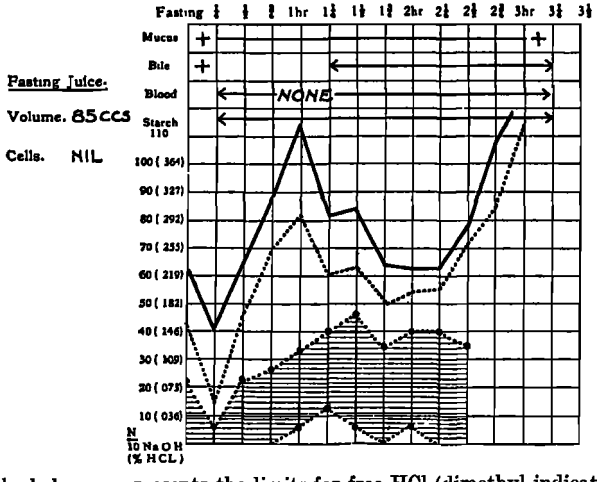
FIG. 8.—Chart of case of apparent achlorhydria.

secreted would be shown by estimation of the total chloride in the specimens, for this will include chloride present as free hydrochloric acid, together with chloride resulting from neutralisation of hydrochloric acid by alkaline duodenal fluid. This point will be referred to later.

The normal rate of emptying has been found to vary con-

siderably, the average rate being 1·9 hours. Emptying in less than one and a quarter hours may be considered as rapid, and in more than two and a half, as delayed.

The Chief Findings in Disease.—In considering variations from the normal results of fractional test meals it is advisable first to consider variations in secretion. These may be of all degrees from complete achlorhydria to extreme hyper-

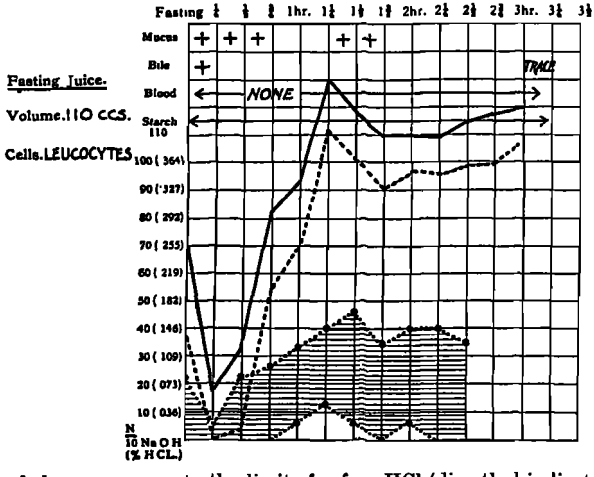


The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity.

FIG. 9.—Chart of case of hyperchlorhydria. "Secondary rise" type of curve.

chlorhydria, and in attempting to explain any result we have always to bear in mind the dual factors responsible for the actual curve obtained, viz., amount of actual secretion, and degree of regurgitation. When we take these into account we realise that achlorhydria, for instance, may be of two kinds, real or apparent. In the former no hydrochloric acid is secreted, while in the latter free acid is secreted, but neutralised by regurgitation, so that no free acid is found

in our specimens. It will be realised also that the presence of bile in the specimens is only evidence of gross regurgitation; regurgitation in lesser degree of alkaline fluid from the duodenum may occur without the appearance of bile in the specimens. The practical distinction of the two types is further complicated by the fact that real achlorhydria may occur along with excessive regurgitation, for the



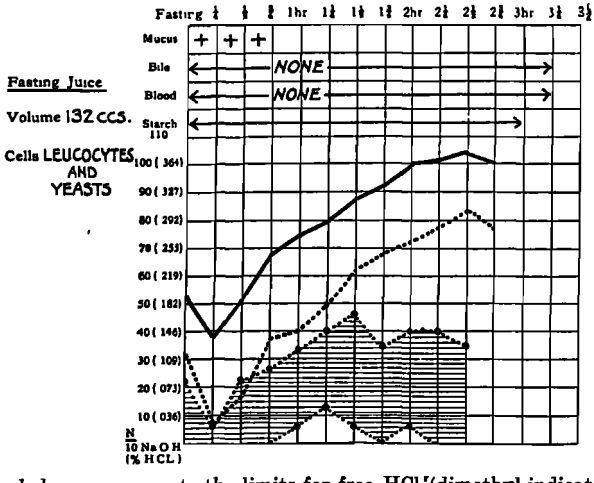
The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity.

FIG. 10.—Chart of case of hyperchlorhydria. "Plateau" type of curve.

absence of acid allows the pylorus to remain relaxed, a condition favourable to the occurrence of regurgitation. We sometimes get help in distinguishing the two types by reference to the curve for total acidity. This is usually very low in true achlorhydria, generally not more than 0·04 per cent., and is practically horizontal (see Fig. 7). In apparent achlorhydria the curve is generally higher and frequently shows a rise at the end of the first hour, suggesting that

there has been some acid secretion, though not enough to show the presence of free hydrochloric acid (see Fig. 8). The presence or absence of bile, as an index of gross regurgitation, is of value, when considered along with the other findings.

The same considerations show that hyperchlorhydria may be, and in fact very often is, due not to an excessive quantity of acid being secreted, but to spasm of the pyloric



The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity

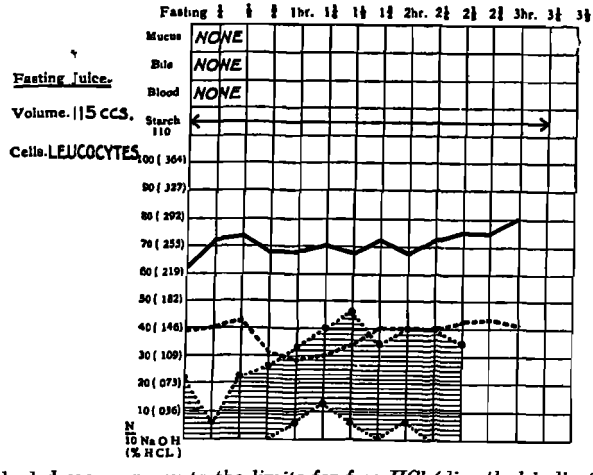
FIG. 11.—Chart of case of hyperchlorhydria. "Climbing" type of curve.

sphincter preventing the normal regurgitation. This spasm may be caused by organic conditions, *e.g.*, by the presence of an ulcer in the neighbourhood of the pylorus, or by reflex stimuli from the central nervous system. Actual stenosis may also be a cause of diminished regurgitation.

Curves showing hyperchlorhydria have been divided into five types, depending on increasing grades of spasm or stenosis or both, viz. :—

1. *The "Secondary Rise" Type.*—In this there is a marked increase in acid concentration in the third hour, due probably to pylorospasm or at least absence of the normal relaxation which takes place at this stage of digestion (Fig. 9).

2. *The Plateau Type.*—So called because the acidity rises



The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity.

FIG. 12.—Chart of case of hyperchlorhydria. "Flat" type of curve.

sharply during the first hour and remains at a high level throughout (Fig. 10).

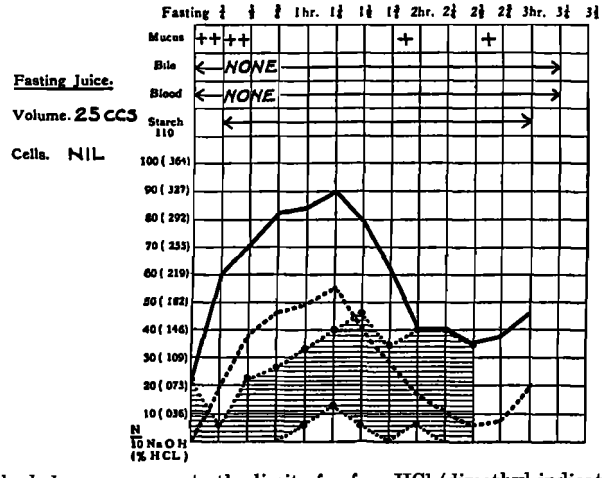
3. *The Climbing Type.*—This is always associated with a marked degree of obstruction at the pylorus. Acid secretion usually begins at a low or normal level and rises slowly but persistently throughout the test (Fig. 11).

4. *The Flat Type.*—This occurs where there is a greater degree of obstruction at the pylorus than that causing the climbing type, and large amounts of food are present in all

the samples, including the fasting juice. The acid curves form two parallel and roughly horizontal lines with a greater distance than usual between the two (Fig. 12).

5. *The "Gastric Ulcer" Type.*—This is an exaggeration of the normal curve, the acid curve rising to a higher level than usual, and showing a somewhat delayed fall (Fig. 13).

Though this type occurs more commonly in gastric ulcer



The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity.

FIG. 13.—Chart of case of hyperchlorhydria. "Gastric ulcer" type of curve.

than in other conditions, it is not of much importance in the diagnosis of this condition, as it only occurs in a small percentage of cases.

When we consider the rate of emptying we find, as would be expected, that in a general way acid secretion and rate of emptying are related. Thus in achlorhydria we often find rapid emptying, while there is a tendency for delay in emptying to be associated with the higher acid curves. In

cases with low acidities, however, we may have delayed emptying due to organic stenosis (especially when of neoplastic origin) or due to atony of the stomach.

The presence of abnormal products has already been referred to in speaking of single tests. Some may be found in the specimens taken throughout the test, as well as in the resting juice. Thus excessive mucus, especially when associated with low acidity, is evidence of chronic gastritis. The presence of blood, when trauma or bleeding from the mouth, etc., can be excluded, is evidence of ulceration. The presence of lactic acid is important with respect to cancer, and will be mentioned under that heading.

We may now consider how different variations from the normal results to our test are associated with certain definite conditions.

Duodenal Ulcer.—In a very large majority of cases definite hyperchlorhydria is found, though occasionally the acid secretion is normal. Any of the types of curve 1 to 4 may be obtained, but those most characteristic of the conditions are types 3 and 4, viz., the "climbing" and the "flat" type. Most cases show definite delay in emptying, and in some this is very marked. In a certain proportion, however, the high acid secretion may be associated with rapid emptying.

Gastric Ulcer.—Any type of acid secretion may be found in patients with gastric ulcer. In about half the cases hyperchlorhydria, frequently associated with delay in emptying, is found. These cases probably include those in which the ulcer is situated near the pylorus. Of the remainder the majority show normal acid secretion, and a few show hypochlorhydria.

The presence of blood is an important finding, since it helps to differentiate ulceration from the following conditions, which so far as acid secretion is concerned show results similar to those given by duodenal and gastric ulcers.

Other Conditions in which Hyperchlorhydria is found.—Eight per cent. of normal men show hyperchlorhydria. The

curves are most frequently of types 1 or 2, and they are not usually associated with delay in emptying.

Certain cases of appendicitis and cholelithiasis show high acid curves, associated with delay in emptying, and thus suggestive, to some extent, of the presence of duodenal ulcer. This suggests that we are dealing with a reflex effect which may be called the pylorospasm syndrome.

In addition, many cases of functional gastric disorder show hyperchlorhydria. This is, in fact, the commonest finding in "dyspepsia."

It will be realised, from what has just been said, that differentiation of all the above-mentioned conditions is frequently impossible from the results of chemical tests only. The value of such tests by themselves in the diagnosis of duodenal ulcer or gastric ulcer, for instance, is frequently very small indeed, and it will be obvious that they must always be considered along with all other information that can be obtained.

Cases with diminished acid secretion are not so common as those with increased secretion, and consequently tests showing marked reduction of acid concentration usually afford us more definite information.

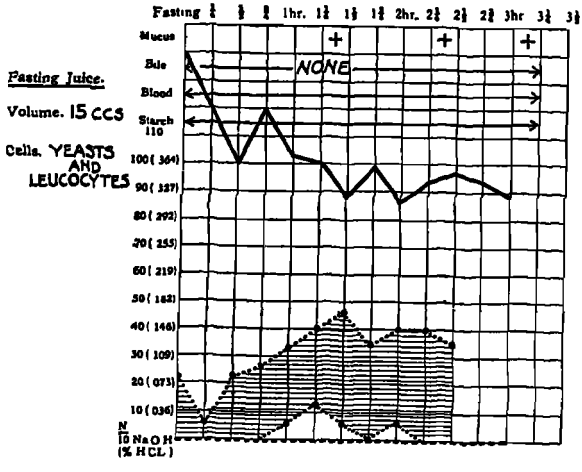
Pernicious Anæmia.—All cases show true achlorhydria, and the curve for total acidity is uniformly low. In most, rapid emptying of the stomach can be demonstrated. Mucus is always present and often excessive. Bile is variable and blood is absent.

Such a picture will be found, if looked for, long before the blood picture is typical of the condition. Its value in early diagnosis will therefore be apparent.

Subacute Combined Degeneration of the Spinal Cord.—In this condition, the findings resulting from gastric analysis are precisely similar to those in pernicious anæmia.

Other types of Anæmia.—Any type of acid secretion curve may be obtained, but the type indicating hypochlorhydria is commonest.

Cancer of the Stomach.—Absence of hydrochloric acid is found in the great majority of cases. In the few cases in which the acid is present it is in relatively small amount, and may be shown to diminish progressively, if repeated tests are made. This absence of free acid does not appear to be due to any excessive regurgitation from the duodenum, but to the direct effect of the cancerous condition in preventing



The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent. of normal people.
.....represents free HCl.
————represents total acidity.

FIG. 14.—Chart from a case of cancer of the stomach.

its secretion. Moreover, along with the absence of hydrochloric acid there can be demonstrated in nearly all cases the presence of lactic acid. It has generally been held that this lactic acid is due to fermentation of stagnating stomach contents. This is a mistaken idea, for it has been shown to be present in cases in which the stomach empties rapidly. Maclean [3] states that if the stomach of a cancer patient is

[3] "Modern Views on Digestion and Gastric Disease." 1925. London: Constable & Co.

thoroughly washed out until the washings contain no lactic acid a test meal given immediately afterwards often reveals the presence of considerable amounts of this acid within half an hour. He therefore stresses the importance of this dual finding—absence of hydrochloric and presence of lactic acid—in the diagnosis of cancer of the stomach. Lactic acid, if present at all in other conditions associated with low or absent hydrochloric acid secretion, is present only in insignificant amounts.

Other results of the fractional test in cancer of the stomach depend on the presence or absence of obstruction. Thus emptying of the stomach is rapid or normal in a few cases. Mucus is excessive, blood is frequently present and bile usually scanty. Cases with much obstruction give characteristic results. All specimens, including the fasting juice, are brownish in colour and of thick consistency. Large amounts of food residues are present even before the test meal is taken. The resting juice has a characteristic appearance and smell, and butyric and other organic acids as well as lactic acid are generally present. The curve for total acidity is exceptionally high (Fig. 14).

Chronic Gastritis.—In this condition the most prominent feature is the presence of an excessive amount of mucus in the specimens withdrawn from the stomach. Free hydrochloric acid is absent, or present only in very small quantity, *i.e.*, we find achlorhydria or marked hypochlorhydria. Lactic acid is absent, a fact which constitutes a useful differentiation between cases of achlorhydria due to gastritis and those due to cancer.

Other Conditions showing Achlorhydria or Hypochlorhydria.—As already mentioned, 4 per cent. of healthy people are found to show no hydrochloric acid secretion after a test meal.

In old people marked diminution in acid secretion is very frequently found, and a considerable proportion show achlorhydria.

Some cases of functional gastric disorder show hypochlorhydria. This is particularly true of the dyspepsias of debility, malnutrition, etc. Hence it is often found in the dyspepsia of phthisis, of neurasthenia, and following such conditions as influenza, pneumonia and other long or severe illnesses. No doubt it is simply an expression of the general lack of tone and lowering of vitality which is known to be present.

Many cases of arthritis are found to be associated with achlorhydria or marked hypochlorhydria, and it is claimed that many such cases benefit by treatment directed to the remedying of this deficiency of secretion.

Achlorhydria is also found in a certain proportion of cases of rosacea.

Other Tests.—*The fact that the concentration of total* chlorides in specimens withdrawn from the stomach is probably a truer index of the actual amount of hydrochloric acid secretion taking place has been already referred to. There are two objections to the determination of total chloride curves as a routine procedure. The first is the considerable labour involved, since for each test about a dozen separate chloride determinations are required. The second is that sufficient work has not yet been done on healthy subjects to give us sufficiently reliable standards for the normal chloride curve. In the majority of cases in which I have made total chloride determinations, any additional information beyond what is obtained from the free and total acid curves has not been worth the trouble taken. The greatest value of the total chloride curve seems to be in the differentiation between true and apparent achlorhydria. In the latter the total chloride curve generally shows a definite, somewhat abrupt rise, while what variations appear in the former are much less in degree, occur less rapidly, and the curve generally is at a lower level than is the case in the latter.

One other test in connection with gastric and duodenal

conditions should be mentioned, viz., the examination for occult blood in the fæces. The presence of blood in the fæces is, of course, simply evidence of bleeding in some part of the alimentary tract. Careful naked eye and microscopic examination as well as chemical examination may help to locate the site of the bleeding. For bleeding having its site in the lower part of the tract will generally result in blood being evident on careful inspection of the specimen, or, if small in amount, red blood corpuscles may be visible on microscopic examination. If " occult " blood is present, *i.e.*, blood which is not evident by these means, but is demonstrable by chemical tests, then the site must be considered as being in the upper part of the tract. Such a finding may be useful confirmatory evidence in suspected cases of gastric or duodenal ulceration. Moreover, bleeding due to simple ulceration is not usually constant; it generally ceases under treatment. Bleeding in malignant disease, however, persists in spite of treatment.

If examination of fæces for occult blood is desired, possible sources of bleeding in the mouth, etc., should be excluded, and if the more delicate chemical tests are to be used, *e.g.*, the benzidine test, meat should be withheld from the patient for two or three days before the test.

Practical Points.—The requirements for test meal examinations have already been sufficiently indicated. For the examination of fæces for blood it is advisable to send the whole of the stool to the laboratory.

CHAPTER VIII

THE INVESTIGATION OF PANCREATIC AND INTESTINAL CONDITIONS

VERY few conditions offer such difficulty to the clinician with regard to diagnosis as those arising from lesions of the pancreas. With the exception of acute pancreatitis and certain cystic conditions giving rise to a palpable tumour, very few cases of pancreatic disease give rise to signs or symptoms which point definitely to the pancreas as their seat of origin. Consequently numerous attempts have been made to obtain information concerning the condition of the gland by the use of laboratory tests. Of the many tests proposed at one time or another, few have been found to be of sufficient value to merit their general acceptance and use, and no attempt will be made to describe tests which have little more than historic interest.

With regard to acute pancreatitis it is generally agreed that the determination of the diastatic index of the urine is of considerable value. As a result of the inflammatory process, the pancreatic ferments escape through the damaged cells and pass into the blood stream in considerable amount, and from the blood they pass into the urine. Hence in such cases a definite and often very considerable increase in urinary diastase can be demonstrated. The normal range for urinary diastase is from 6 to 30 units. In acute pancreatitis values of over 200 units are frequently obtained, but any value over 100 units is strongly suggestive of the condition. The test is extremely useful in the distinction of acute pancreatitis from other acute abdominal conditions.

It would obviously be of no value as a clinical test in such

an acute condition if it were necessary to wait for a twenty-four-hours' specimen of urine. The increase of the diastatic index above the normal is too great for any normal variation throughout the twenty-four hours to have any effect on the significance of the result. Hence the earliest specimen of urine that can be obtained is the best for the test.

With regard to the more chronic lesions, the diastase test is of no value at all. Frequently normal or low values are obtained which have no diagnostic significance. Hence we attempt to assess the function of the pancreas by determining the state of its secretory activity. I am referring here, of course, to the external, digestive secretion. Failure of production of internal secretion—insulin—has already been dealt with.

At best, all we can definitely say, so far as chemical tests alone are concerned, is that the entry of pancreatic secretion into the intestine appears normal, or reduced. We are not able to say whether any reduction or non-entry of ferments into the intestine is due to obstruction or to failure on the part of the pancreas to produce these secretions in normal amount.

The examination of the state of pancreatic secretion may be attempted directly or indirectly, *i.e.*, we may attempt to recognise the presence of the ferments themselves in certain materials, or we may try to assess their presence by determining whether digestion is complete or incomplete.

So far as the direct method is concerned, no information of any assistance in the consideration of pancreatic conditions from the clinical standpoint has yet been obtained from examination as to the presence and amount of ferments in the blood. With the exception of the determination of diastase, in relation to acute pancreatitis, the same may be said of the urine.

Examination of the fæces for the presence of ferments seems an obvious procedure, and has often been attempted. Attention has been directed to trypsin and to diastase (amylase), for it has been found that no value whatever can

be attached to the absence of lipase from the fæces, since it is rapidly destroyed by trypsin. Many methods have been described for the detection of diastase, but the significance of the results is uncertain, and their use, for clinical purposes, has on the whole been disappointing. The same may be said regarding the detection of trypsin. More recently, two other methods of approach have been suggested. One depends on the fact that after a meal regurgitation of fluid from the duodenum into the stomach takes place, and consequently trypsin may often be found in specimens withdrawn from the stomach. The regurgitation takes place most often towards the end of gastric digestion, and especially if much unemulsified fat is introduced into the stomach. On these facts has been based a test in which 200 gm. of olive oil are given with a test meal, and trypsin looked for in specimens subsequently withdrawn from the stomach.

Probably quite as valuable results, with much less discomfort and nausea to the patient, may be obtained from examination of specimens obtained from the stomach, by the ordinary stomach test meal methods. The results are qualitative only, and as regurgitation may possibly not occur in any one particular test, it may be necessary to repeat the test two or three times before much reliance can be placed on the results.

The other method is that of duodenal intubation. In this method a tube similar to Ryle's stomach tube, but longer, is passed into the duodenum, from which specimens of fluid are aspirated by means of a syringe. These specimens are then examined for the presence of lipase or of trypsin. Some idea of the state of pancreatic secretion is thus obtained.

Theoretically the method of duodenal intubation is the soundest we have for investigating pancreatic secretion. The successful passage of the duodenal tube, however, is an operation calling for skill and patience, and requires intelligent co-operation from the patient. Frequently

patients do not tolerate the procedure well. Of this, and of the method depending on duodenal regurgitation, much more experience is required before we can correctly estimate their value as aids in clinical investigations. It may be mentioned here that duodenal intubation is also used for obtaining specimens of bile for the investigation of questions relating to biliary function. In this connection the same remarks apply as those just made respecting the use of the method for investigating pancreatic function.

The indirect tests of pancreatic function depend on the examination of fæces for evidence of incomplete digestion, resulting from absence or diminution of pancreatic ferments. Of many tests suggested, only two are at all widely used at the present time. These are the microscopic examination of the fæces for undigested muscle fibres, and the chemical analysis for fat.

In the normal stool, remnants of meat fibres, yellow or brown in colour due to bile staining, are frequently found. These have rounded ends and show no transverse striations. The presence of pancreatic juice seems necessary for digestion to proceed to the stage at which the transverse striations disappear. Hence if examination reveals the presence of bundles of muscle fibres showing clearly the typical transverse striations, and having sharp, angular ends, incomplete pancreatic digestion may be assumed. In this, as in other methods dependent on determining the state of digestion by examination of the fæces, incomplete pancreatic digestion does not necessarily indicate impairment of pancreatic function, for it must be remembered that while the deficiency may be due to a deficient supply of pancreatic ferments, it may also be due to insufficient time in which the ferments have opportunity to act. Hence evidence of incomplete digestion may be found in any condition in which the food is rapidly passed through the small intestine, *e.g.*, in conditions of irritability of the intestine due to inflammation, the effects of drugs, etc.

In carrying out a test in which the presence of undigested muscle fibres in the fæces is sought for—a condition known as creatorrhœa—it is essential that the patient shall be under certain standard conditions as to diet, etc., for two or three days. All purgatives must be withheld. Coope [1] believes that it is wise to make as little call on the digestive activity as possible during these tests. Hence he places the patient on a light lacto-vegetarian diet, with milk as the main constituent, for two or three days. Then for two days 2 oz. of lightly cooked minced meat are given with the midday meal. Before, during, and after the meal a charcoal biscuit is eaten, so as to mark out the portion of the stool corresponding to the meat diet; by noting the time of the first addition of meat to the diet and that of the passage of the first subsequent stool which is coloured by the charcoal granules, an idea may be gained of the approximate time the meal has taken to pass through the alimentary tract. Examination of the fæces for creatorrhœa should be made as early as possible after the stools have been passed. Coope recommends that, to avoid possible fallacies due to too rapid passage of food residues through, or too prolonged stay in, the gut, only fæces passed in from eighteen to thirty hours after ingestion of the corresponding food should be accepted for examination.

The practice of making as little call as possible on the digestive activity, while favourable to the elicitation of evidence of gross functional disturbance, is contrary to the usual practice in carrying out tests of function. It is well known that organs which are found to be incapable of carrying on their work satisfactorily under normal conditions, may fail to show signs of inefficiency if the work demanded of them is materially lessened. Consequently, while agreeing with his other conditions, I prefer to have the patient on the ordinary hospital diet for two or three days prior to the test,

[1] "The Diagnosis of Pancreatic Disease." 1927. London: Oxford University Press.

and also during the test. With regard to actual findings, only the presence of large numbers of undigested muscle fibres should be taken into account. Moreover, examination should not be limited to a single specimen. The presence of one or two undigested fibres in a film of the fæces or occasional definite creatorrhœa, is of doubtful significance. Only creatorrhœa which is definite in degree, and reasonably constant in appearance, is of any value as evidence of deficient pancreatic digestion.

The test for creatorrhœa may be carried out along with the analysis of the fæces for fat content.

The analysis of the fæces for fat as a test of pancreatic and intestinal conditions has to a considerable extent fallen into disrepute. This is due largely, in my belief, to the fact that unsatisfactory methods of analysis have been used. The most popular clinical method in this country is that of Cammidge. This method has been shown to be unsound on more than one occasion, yet it is still described in modern text-books. In fact, in my view, any method in which the stools are dried by heat before analysis is open to serious objection. Stools are rarely neutral in reaction; many are alkaline. The heating of neutral fat in a finely divided state in the presence of water, and particularly if the reaction of the material is alkaline, would be expected by any chemist to result in hydrolysis or "splitting" of the fat. Hence the neutral fat content of fæces after drying is not always the same as before drying. This is not merely a theoretical objection, but has been shown to occur in practice.[2] Consequently I have used continually during the last three years a method of analysis of fresh, wet stools, and have obtained considerable help from the results. In every case, in order to eliminate the effect on the results of widely differing water content of different specimens, and thus to render the results reasonably comparable with one another, a small

[2] See Fowweather. *British Journal of Experimental Pathology*, VII., 7. 1926.

portion of the stool is dried to constant weight and the weight of dry matter in the stool is calculated. Using this value the fat content of the specimen is calculated as a percentage of the total dry matter present. The method gives the percentage of neutral (or "unsplit") fat, of fatty acids present as soaps, and of free fatty acids, in the stools. For clinical purposes the significance of variations in the relative proportions of free and combined (or soaped) fatty acids is not clear, and the two values are considered together as "split" fat. What is of particular significance with regard to pancreatic conditions is the amount of unsplit fat present, and the proportion this constitutes of the total. By analysis in this way of *fresh* specimens from hospital patients on ordinary hospital diet, who were not suffering, so far as could be ascertained, from any disease of the alimentary tract or its glands, the average of a large number of analyses was found to be as follows :—

	Per cent. of total dry matter.
Total fat	17·5
Soap fat	4·6
Free fatty acid	5·6
Neutral fat	7·3

From a consideration of all the results obtained, the following conclusions have been reached :—

1. Any specimen in which the total fat amounts to more than 25 per cent. of the total dry matter is probably abnormal.

2. Any specimen in which the neutral fat exceeds 11 per cent. of the total dry matter, or 55 per cent. of the total fat, should be suspected of showing evidence of deficient fat-splitting.

3. Any specimen in which the total split fat (*i.e.*, the sum of soap fat and free fatty acid) exceeds 16 per cent. of the total dry matter, or 75 per cent. of the total fat, should be suspected of showing evidence of deficient fat absorption.

These conclusions apply to adults and to children over

about two years of age. The stools of infants have not been thoroughly studied by this method.

It should be pointed out that the fat content of the fæces varies considerably, within certain limits, from day to day, showing perhaps high normal values on one occasion and low normal values on the next. Hence if high values are obtained repeatedly, even if the actual figures may be somewhat within the limits mentioned, some abnormality is to be suspected.

The actual results obtained in pancreatic conditions vary considerably. In chronic pancreatitis, for instance, I have obtained figures for neutral fat between 12 and 24 per cent. of the total dry matter, and, rarely, figures much higher still. The following is an example :—

	Per cent. of total dry matter.
Total fat	42·1
Soap fat	11·9
Free fatty acid	5·8
Neutral fat	24·4

A case of subacute pancreatitis associated with jaundice gave the following result :—

	Per cent. of total dry matter.
Total fat	73·8
Soap fat	12·7
Free fatty acid	15·5
Neutral fat	45·6

This result also shows unmistakable evidence of deficient fat absorption, which is the usual accompaniment of jaundice of an obstructive nature.

Intestinal Conditions

It will be obvious from what has just been said that the determination of the fat in fæces in this way may be used to throw light on certain intestinal conditions, as well as for the

investigation of pancreatic function. Such determinations may, for example, indicate deficiency of fat absorption, as shown in the example just quoted.

Now, satisfactory fat absorption requires not only a properly functioning small intestine, but also an adequate supply of bile salts. Hence deficiency of fat absorption occurs not only in what may be called intestinal conditions proper, but also in conditions of disturbance of the biliary function, especially obstructions in the biliary tract. A consideration of fat absorption will also be found of assistance with respect to certain conditions associated with diarrhœa. If the diarrhœa is simply due to hurrying of food residues through the large intestine, the small intestine being normal, no deficiency of fat absorption will be found. I have analysed a large number of watery stools which have given perfectly normal results so far as fat content is concerned. On the other hand, in conditions of the small intestine which give rise to diarrhœa, fat absorption is interfered with, either by the effect of the conditions (catarrhal inflammation, ulceration, etc.) on the absorptive process itself, or by the hurrying of food residues through the intestine which frequently occurs in these conditions. In cases where such hurrying occurs, there may be some deficiency of fat-splitting also. The following result, from a case of intestinal catarrh, will illustrate these features :—

	Per cent. of total dry matter.
Total fat	47·9
Soap fat	17·0
Free fatty acid	18·0
Neutral fat.	12·9

Here there is obvious deficiency of fat absorption, with at least a suspicion of deficient fat-splitting. This type of result differs clearly from that obtained in uncomplicated pancreatic deficiency, in which excess of neutral fat is the only abnormality. Thus in cases showing excess of neutral

fat, a study of the values for split fat may help to distinguish those cases in which the excess of neutral fat is due to rapid transit of material through the intestine from those in which there is pancreatic disease.

A result of the above type also serves to distinguish inflammatory conditions of the small intestine from those limited entirely to the large intestine, since the latter show normal values for the fat content of the fæces.

The above type of result, showing deficiencies in both fat splitting and fat absorption, closely resembles the type of result obtained in cases in which biliary and pancreatic lesions are associated together. Such association may occur in cirrhotic conditions affecting both liver and pancreas, in inflammatory conditions involving the bile ducts, together with the pancreas or its ducts, or in obstructive conditions which involve both bile and pancreatic ducts.

In obstructive jaundice uncomplicated by disease of the pancreas (or its ducts) analysis indicates deficient absorption with normal fat splitting. The following figures, an average of the results from four cases of gall-stones, are typical of what is found in such cases :—

	Per cent. of total dry matter.
Total fat	50·9
Soap fat	26·8
Free fatty acid	18·1
Neutral fat.	6·0

Similar results have been obtained in catarrhal jaundice, in cirrhosis of the liver, in subacute liver atrophy and in cancer of the head of the pancreas.

I have known of cases in which definite evidence of deficient fat absorption as shown by fæces analysis has been very useful as confirmatory evidence of the presence of obstructive jaundice.

It will be noticed that cancer of the pancreas does not always offer evidence in the stools of pancreatic involvement.

The result will obviously depend on the extent of involvement of the gland itself, and the effect of the growth on the bile and pancreatic ducts. Often the only evidence is that resulting from pressure of the growth on the bile ducts, giving rise to signs of obstructive jaundice.

Some results have been obtained in cases of abdominal tuberculosis in children. These have shown evidence of deficient fat absorption, with, in some cases, some deficiency in fat-splitting.

The results of fæces analysis are of considerable interest in cœliac disease. The following is the result in a somewhat severe case :—

	Per cent.
Total fat	60·5
Soap fat	18·7
Free fatty acid	37·5
Neutral fat.	4·3

This is typical of all cases in its general indications, namely, marked deficiency in fat absorption, with efficient fat-splitting.

Much work has been devoted to cœliac disease, but the cause of the condition is still not clear. The marked deficiency of fat absorption, together with the fact that improvement has been reported in certain cases in which bile salts have been administered by mouth, suggests that some deficiency in the output of bile salts from the liver may be responsible, but this suggestion cannot be thoroughly investigated until we have at our disposal reliable clinical methods for the quantitative determination of bile salts in such materials as blood, fæces, urine, etc.

The stools from a typical case of cœliac disease can be recognised by simple inspection by anyone having experience of the condition. They are bulky, of a characteristic yellowish grey colour, are unformed, and contain much mucus. Analysis, however, is useful to confirm the impression gained

by inspection, to assist in the diagnosis of doubtful cases and as a guide to the progress of individual cases.

Certain other tests are employed in the investigation of intestinal conditions. Of these perhaps the most important is the test for blood in the stools. As already indicated in the previous chapter, the method by which the blood is recognised offers some indication of the source of the bleeding. Blood recognisable by inspection, either with the naked eye or microscope, has its source in the lower part of the alimentary canal. Fresh blood covering a formed stool indicates the rectum as its source, and is frequently due to hæmorrhoids. Bloody mucus suggests dysentery. Blood which is not recognisable by inspection, but demonstrable by chemical tests (" occult " blood), has its source in the upper part of the alimentary tract, except that if bleeding here is considerable it is present in the stools as tarry matter, recognisable as such on inspection. In malignant disease in any part of the alimentary tract small quantities of blood may be continually present. Bleeding from peptic ulcers is usually limited to short periods. Other causes of blood in the stools are typhoid fever, chronic passive congestion, intussusception and volvulus, and, rarely, tuberculous ulceration, and cirrhosis of the liver with portal obstruction.

In testing for occult blood, possible sources of bleeding in the mouth, etc., should be excluded, and if the more delicate tests are used, *e.g.*, the benzidine test, it is advisable to withhold meat from the patient for two or three days before the test.

Chemical tests for mucus are also sometimes made, but are of little value. Simple inspection, however, for increased mucus is always worth while, for, while mucus is always present in normal stools, any mucus which is visible on inspection represents an abnormal increase, and when an increase is present it indicates either a pathological condition of the mucous membrane of the intestine, or a response to some irritation. As with blood, the extent to which the

mucus is mixed with the stool offers some indication of its source. If from the small intestine, the mucus is intimately mixed with the other material present, and is hard to isolate. In very liquid stools it may be seen as small, somewhat gelatinous-looking flakes. Mucus from the large intestine may be seen as a shiny coating, often covering hard fæcal masses, or it may appear in long threads, or as casts of the lumen of the bowel. In some conditions, *e.g.*, mucous colitis, the stools may consist almost entirely of mucus. Mucus is also very evident, as a rule, in the stools from cases of dysentery, rectal diarrhœa and cancer of the rectum.

Another test having some bearing on intestinal conditions is the test for indicanuria. It has been shown that indican arises in great part from intestinal putrefaction. Its presence in increased quantity in the urine is therefore considered as evidence of some condition involving increased putrefaction and stagnation of intestinal contents. The indican of the urine may also be increased in conditions involving much bacterial decomposition in other sites than the intestine, as, for example, in cases of gangrene, or large abscesses.

Practical Points.—In nearly all examinations of fæces specimens should be sent to the laboratory as early as possible. This is particularly true when fat analysis is required, since changes in the fat may occur on standing which would vitiate the results. Though, as a rule, only small quantities of material are actually required for the tests, it is advisable to send the whole of a particular specimen to the laboratory, to allow the pathologist to select for himself the material he requires for his test.

The test for indicanuria requires about 10 c.c. of urine.

CHAPTER IX

TESTS ON THE CEREBRO-SPINAL FLUID

LABORATORY tests on cerebro-spinal fluid are of considerable importance, and frequently afford much help in the diagnosis of diseases of the central nervous system. In a large majority of cases the information afforded by chemical tests is incomplete, and requires to be considered along with the results of a cytological examination, and the Wassermann reaction. The cytological examination is, in fact, the most important single test to which the fluid is subjected. Therefore, although in no sense a chemical subject, an account of the cytological changes which may occur in the cerebro-spinal fluid will be given, since a knowledge of these changes is necessary for a complete and satisfactory consideration of the alterations which the cerebro-spinal fluid may undergo in many pathological conditions.

Normal cerebro-spinal fluid does not contain more than four cells per cubic millimetre. The cells found are principally lymphocytes, with occasional large mononuclear cells. Polymorphonuclear leucocytes are not present in normal fluids, but are found under certain pathological conditions.

The cytological changes which occur in disease may be in number of cells alone, or in number and type. These changes can be conveniently considered in the order given by Greenfield and Carmichael [1] from whose work much of the following account is taken.

1. Changes in number of the mononuclear type of cells (lymphocytes and large mononuclears).

[1] "The Cerebro-Spinal Fluid in Clinical Diagnosis." 1925. London: Macmillan & Co., Ltd.

(*a*) *Slight Pleocytosis* (5 to 10 cells per cubic millimetre).—This change occurs in any form of syphilitic disease of the nervous system after the earlier stages. It is frequently found in the more chronic forms of syphilis, *e.g.*, in tabes and chronic meningeal syphilis. But this change is also associated with many other conditions, and is frequently found in disseminated sclerosis and in encephalitis lethargica. It may also be found in herpes zoster, cerebral abscess, cerebral tumour and some forms of polyneuritis. It also occurs in mumps and whooping-cough.

(*b*) *Moderate Pleocytosis* (10 to 50 cells per cubic millimetre).—This may be found in all the conditions just mentioned. It is common during the onset and progress of syphilitic nervous disease; not very common in disseminated sclerosis and polyneuritis. It may also be found in tuberculous meningitis.

In general diseases, besides mumps and whooping-cough, it occurs in malaria and in trypanosomiasis and spirochætosis ictero-hæmorrhagica.

(*c*) *Severe Pleocytosis* (50 to 250 cells per cubic millimetre).—It is rare to find a mononuclear pleocytosis of this degree, since in cases showing high cell counts some polymorphonuclear cells are nearly always present. Such a mononuclear pleocytosis is, however, occasionally found in the conditions which may give rise to a moderate pleocytosis of the same type.

2. Changes in the number of cells when other types, especially polymorphonuclear cells, are also present.

(*a*) *Slight Pleocytosis* (5 to 10 cells per cubic millimetre).—A count of this magnitude, including mononuclear and polymorphonuclear cells, is very characteristic of brain abscess or of inflammation of the cranial sinuses with involvement of the dura mater. A similar count in which many of the cells are macro-

phages, may occur in cerebral tumour, hæmorrhage or softening.

(*b*) *Moderate Pleocytosis* (10 to 50 cells per cubic millimetre).—This is also found in brain abscess and in tuberculous meningitis, in polio-myelitis and sometimes in syphilitic nervous disease. It is usual in cerebro-spinal meningitis during recovery.

(*c*) *Severe Pleocytosis* (50 to 150 cells per cubic millimetre).—Counts of this nature are found in acute and severe syphilitic nervous disease, in tuberculous meningitis and in polio-myelitis. They may sometimes be found in brain abscess.

(*d*) *Extreme Pleocytosis* (over 250 cells per cubic millimetre).—This is frequently found in cases of tuberculous meningitis and in certain syphilitic conditions, including the severe meningeal involvements which sometimes occur in the secondary stage, in acute and subacute meningeal disease in the tertiary stage, and sometimes in the earlier stages of general paralysis. Greenfield and Carmichael also found it in cases where meningeal symptoms occurred following "influenzal" attacks.

3. Changes in the number of cells when polymorphonuclear cells constitute the majority of the cells present.

A pure polymorphonuclear pleocytosis is very rare, since any increase in these cells is almost always accompanied by a certain proportion of mononuclear cells, usually about 10 per cent. Any pleocytosis in which the polymorphonuclear cells form more than 75 per cent. of the total number of cells present is usually called a polymorphonuclear pleocytosis.

Such a pleocytosis of slight or moderate degree is extremely rare, but may occur in some cases of brain abscess or dural inflammation.

In severe or extreme degree a pleocytosis of this kind is found in all forms of cerebro-spinal meningitis, but a high count of this nature is not always evidence of a generalised

inflammation of the meninges, since it has been sometimes found in localised inflammation of the meninges overlying a cerebral abscess.

Chemical Tests

The Gold Sol Test.—This test depends on the fact that when neutral colloidal gold solutions (or gold sols) are added to normal cerebro-spinal fluid no change in the typical ruby colour of the gold sol occurs, but when such sols are added to certain abnormal fluids aggregation of the colloidal particles of gold takes place, resulting in a change in colour of the gold sol, the amount of change being dependent on the degree of aggregation. The maximum effect is such that the gold becomes completely precipitated, so that a colourless solution results. Lesser degrees of aggregation cause substitution of the ruby colour by blue, in varying amounts. Thus with increasing degrees of aggregation we find changes to purplish red, then lilac, then violet blue, next light blue, and finally colourless. These successive changes, according to the amount of aggregation, are denoted by the numbers 1 to 5, the unchanged colour being represented by 0.

Not only do certain abnormal fluids cause aggregation of the gold particles, but amongst those that do produce this effect, some act in certain dilutions, while others act in other dilutions. In the actual test, ten dilutions are prepared, the first containing one part of the cerebro-spinal fluid in 10 parts of 0·4 per cent. sodium chloride solution, the next, 1 part in 20, and so on until we reach the tenth, in which the dilution is one part in 5,120. Each of these ten dilutions of the fluid is treated with the same quantity of the gold sol. Three distinct types of result are distinguished, as follows :—

1. **The Paretic Type.**—In this the maximum change in the gold sol occurs in the lowest dilution of the fluid. A typical result of this type would be represented as :—

55432 ¦ 10000

where the order of increasing dilution is from left to right. A similar result, showing less intense change would be :—

33210 | 00000

2. **The Luetic Type.**—Here the maximum change is in the third or fourth dilutions, *i.e.*, a little to the left of the middle line as represented above, but not on the extreme left.

Typical results would be :—

23443 | 10000

or 12321 | 00000

3. **The Meningitic Type.**—The maximum change in this type is to the right of the middle line, and may be on the extreme right. The following are examples :—

00001 | 23432

or 00000 | 12343

The paretic type of result is obtained typically in general paralysis. Moreover, it is a constant finding in this condition. Frequently a clear indication of the disease is given by this test when other indications are doubtful.

The luetic type is given by other forms of cerebro-spinal syphilis, including tabes dorsalis. Occasionally these conditions show a paretic type of result, but when that is the case the result tends to become luetic as the case is treated, whereas in general paralysis the type of result remains constant throughout.

Unfortunately syphilitic diseases are not the only ones in which paretic and luetic types of result are obtained, though they are found more constantly in these than in other conditions. In disseminated sclerosis, for instance, roughly half the cases examined give a positive result to the gold sol test, some of the paretic type and some of the luetic type. In encephalitis lethargica positive results are obtained in a considerable proportion of cases—most are luetic in type but a few are paretic. In polio-myelitis somewhat weak results of the luetic type may be found in the first few weeks

of the disease. The result of the Wassermann reaction is a valuable aid to the differentiation of those cases with a paretic or luetic result which are syphilitic from those which are non-syphilitic.

The meningitic type of result is found typically in meningococcal meningitis and in other forms of non-syphilitic meningitis, including tuberculous meningitis. This type is not so constantly found in cases of meningitis as are the luetic and paretic types in cases of syphilis. I have frequently obtained negative results in early meningitis, especially of the tuberculous variety, but the proportion of positive results is high in the later and in the more severe stages of the disease. Weak results of the meningitic type are obtained in some cases of spinal tumour and in some cases associated with localised meningitis.

The preparation of satisfactory gold sols for this test is not a very easy matter. Hence attempts have been made to use other colloidal solutions, amongst them being sols of gamboge, gum mastic and benzoin. Experience has shown, however, that they are not by any means superior to gold sols, and are hardly likely to supplant the latter in general use.

2. **Changes in Protein.**—Increase in protein is the commonest chemical change noticed in the cerebro-spinal fluid.

It has been customary to pay attention only to increase in globulin. As a matter of fact, whenever globulin is increased, albumin is increased also, and in most cases the amount of albumin is very much in excess of that of the globulin. Even in general paralysis in which the increase in globulin is most marked its amount is rarely more than half the amount of albumin present. Hence the truest evidence of protein increase is shown by the total amount of protein present rather than the amount of globulin, and for all ordinary purposes a determination of the total protein is much to be preferred to a test for increased globulin.

The normal protein content of the cerebro-spinal fluid is

15 to 30 mgm. per 100 c.c. Increase of protein may occur with or without increase in cells.

The most characteristic condition in which protein increase is found without increase in cells is compression of the cord, occurring, for instance, in association with tumours. For this reason isolated increase in protein has been frequently referred to as Nonne's compression syndrome, since Nonne pointed out this state of affairs in the cerebro-spinal fluid from a number of cases of tumour of the spinal cord which he examined and described. It is found, however, in certain other conditions, including cerebral tumour, cerebral arteriosclerosis, polyneuritis and the localised spinal meningitis occurring round the cord at the level affected by acute myelitis.

Increase in protein together with increase in cells is the more usual finding. It occurs, for instance, in all forms of meningitis, and also in conditions in which meningeal involvement is secondary to some lesion of the nerve substance itself, as in encephalitis lethargica, poliomyelitis, acute polyneuritis, and many forms of syphilitic disease. In addition it is found in some conditions in which the meninges are not concerned, namely, in tumours or abscesses in relation to the walls of the ventricles, and in disseminated sclerosis.

3. **Changes in Chlorides.**—The chloride content of normal cerebro-spinal fluid is 0·72 to 0·75 per cent. (calculated as NaCl). Knowing already the great importance of sodium chloride in the maintenance of the normal osmotic pressure of the body fluids, we should expect that any alteration from the normal value for the cerebro-spinal fluid would indicate some pathological condition. This is found to be the case.

Increase in chloride (0·8 to 1 per cent.) is frequently found in cases of nephritis. Reduction of chloride is characteristic of meningitis, and serves to distinguish it from conditions like cerebral tumour and polioencephalitis, which may present similar cytological findings. In cerebral abscess, chloride

determinations may serve to indicate whether there is also generalised meningitis or not.

Tuberculous meningitis (especially in children) is the condition in which the greatest reduction of chloride occurs, and a lowering of the chlorides below 0·58 per cent. is considered a certain sign of this condition. In a number of cases I have found values in the neighbourhood of 0·5 per cent.

In other forms of acute meningitis values between 0·65 per cent. and 0·68 per cent. are usually obtained.

It must be remembered, however, that low chloride values may be found in acute lobar pneumonia, in typhoid and typhus fevers.

4. **Changes in Urea.**—The normal urea content of the cerebro-spinal fluid is somewhat less than that of the blood, and alterations in the amount in the fluid occur under the same conditions as those of the blood, but usually lagging a little behind. I have never found any advantage in cerebro-spinal fluid examination over blood examination, so far as investigations of nitrogen retention are concerned. Hence lumbar puncture, for urea determination alone, is not necessary, but the determination may be usefully carried out, when fluid is withdrawn for other tests also.

5. **Changes in Glucose.**—The glucose content of normal cerebro-spinal fluid usually lies between 0·05 and 0·08 per cent. Definite increase above normal is usually a result of increase in the blood sugar, and hence is found under the same conditions as give rise to hyperglycæmia. Reduction in the glucose content is of much more importance from the point of view of diagnosis of nervous conditions, and occurs in cases of acute meningitis. In tuberculous meningitis I have often found values between 0·20 and 0·04 per cent. In acute meningitis due to meningococci, pneumococci and streptococci, glucose may be absent altogether, or present in extremely small quantity.

Meningeal Permeability.—Many substances present in the blood plasma are, under normal conditions, absent from the

cerebro-spinal fluid, or only present in it in small amounts. The same is true of certain substances artificially introduced into the circulation, *e.g.*, certain drugs, dyes, etc. Under certain abnormal conditions, however, particularly in meningitis, these substances are able to pass into the cerebro-spinal fluid in larger amounts, owing to the inflamed or congested condition of the choroid plexus or meningeal vessels. These facts have been made the basis of several tests for meningeal permeability. In these tests, some drug or dye (*e.g.*, Sodium nitrate, in Mestrezat's test, or the dye uranin in Kafka's test) is given by mouth, and subsequently tested for in the cerebro-spinal fluid. These tests have not come into general use, and for purely diagnostic purposes are seldom called for. Hence no further description of them will be attempted.

To sum up, the tests of most general usefulness may be considered to be the following :—

1. Determination of the number and type of cells.
2. Wassermann reaction.
3. Determination of total protein.
4. Gold sol test.
5. Determination of glucose.
6. Determination of chloride.

Having described the tests of greatest clinical value we may now consider their application to some problems of differential diagnosis. Not all the tests mentioned will be applied in every case ; the prominent symptoms will suggest which of them are likely to be of use. Moreover, the value of bacteriological examination of the cerebro-spinal fluid must never be lost sight of, especially in the differentiation of the different varieties of acute meningitis.

Differential diagnosis will be discussed in relation to prominent symptoms.

1. **Acute Meningeal Symptoms.**—Here we have to consider :—

Subarachnoid hæmorrhage.
Epidural or cerebral abscess.

Poliomyelitis or polioencephalitis.
Encephalitis lethargica.
Meningism.
Acute meningitis.

Subarachnoid hæmorrhage is indicated by a fluid which is evenly bloodstained, and which, after removal of cells by centrifugalisation is yellow in colour and shows no other change, apart from an increase in protein.

In the case of abscess, the findings depend on whether the abscess is accompanied by a generalised meningitis or not. If generalised meningitis is not present the cell count is usually not very high—generally below 30 per c.mm., and usually includes some polymorphonuclear cells, which helps to distinguish the condition from encephalitis lethargica. The protein, too, is increased but not to a large extent; usually it is between 30 and 60 mgm. per 100 c.c. Glucose and chlorides are normal and distinguish the condition from meningitis. When the latter supervenes on abscess its onset will be indicated by a fall in chlorides, which will be progressive as the condition advances. When once established, meningitis resulting from abscess may be indistinguishable from meningitis from other causes.

Poliomyelitis and polioencephalitis may be distinguished from encephalitis lethargica in the earlier stages by the fact that polymorphonuclear cells are present in the former but not in the latter. In the later stages these tend to disappear, but there is often considerable increase in protein, frequently to values above 100 mgm. per 100 c.c., and formation of a fibrin coagulum, whereas in encephalitis lethargica protein is rarely much increased beyond about 40 mgm. per 100 c.c., and the formation of a fibrin coagulum does not occur. All these conditions are distinguished from meningitis by the fact that they show no diminution in chloride or glucose. The gold sol test also offers a means of differentiation if a positive result is obtained, since when positive in meningitis it gives the meningitic type of result (except in syphilitic

meningitis), while in encephalitis lethargica any positive result is of the luetic or paretic type, and in poliomyelitis and polioencephalitis it is of the luetic type.

In poliomyelitis and polioencephalitis an increase in cell count in the earliest stages is a constant feature, and polymorphonuclear cells predominate. Later, these tend to disappear, and later still the lymphocytes also diminish in number.

In encephalitis, there is in nearly all cases a moderate increase in cells, which are always of mononuclear type. In many cases no other pathological change is to be found.

In meningism, as distinct from true meningitis, changes in the cerebro-spinal fluid are very small in degree, or absent altogether, except in typhoid fever and pneumonia, in which a definite reduction in chlorides may be found, without any other changes.

The typical findings in meningitis are turbidity or fibrin formation, increase in protein and in cells, decrease in glucose and chlorides, and a positive result of meningitic type to the gold sol test. Not all of these changes are marked in every case or in all stages of the disease. This is true, for instance, as has already been pointed out, with respect to the gold sol test, which frequently fails to give a positive result in early stages of the condition. The cell count in all cases is increased. In tuberculous meningitis figures of 20 to 30 per c.mm. are commonly found in early stages, but later, values over 100 are very frequently obtained. In the higher counts, some polymorphonuclear cells are found, but never predominate, the majority of the cells being always small lymphocytes. In this condition there is always increase in protein, though, as with cells, the increase may not be large. Complete absence of glucose is rare, and the fall at first may be only slight, but increases. Chlorides are diminished progressively and rapidly, but while values below 0·58 per cent. are only found in tuberculous meningitis, such low figures are by no means found in all cases.

The different forms of coccal meningitis all give very much the same results, and can usually only be definitely distinguished from one another by bacteriological examination. The results of the usual tests do differ, however, in certain respects from those typical of tuberculous meningitis. The cell count, for instance, tends to be higher and, moreover, polymorphonuclear cells are in considerable excess. Protein increasc is on the whole greater, glucose reduction is also greater and may be such that this substance is absent altogether, and chloride reduction is not so marked.

In acute syphilitic meningitis the Wassermann reaction is usually, but not always, positive. Other changes resemble those of tuberculous meningitis, except that there is no reduction of chlorides, and the gold sol test gives a result of the luetic, or less frequently the paretic type.

Influenzal meningitis is distinguished from other forms, according to Rivers, by the presence of indol in the cerebrospinal fluid.

In typhoid meningitis the fluid gives a positive Widal reaction.

True meningitis may also occur in connection with mumps, anthrax, typhus, plague, etc.

2. **Acute and Subacute Cerebral Symptoms.**—In this group we must take account of:

Uræmia.
Diabetic coma.
Cerebral abscess.
Cerebral tumour.
Cerebral hæmorrhage or thrombosis.
Extradural or subdural hæmorrhage.
Cerebral syphilis and general paralysis.
Idiopathic epilepsy.
Poliomyelitis and polioencephalitis.
Encephalitis lethargica.

Uræmia and diabetic coma offer little difficulty, the nature

of the case being indicated by blood urea or blood sugar determination, respectively.

In cerebral hæmorrhage the cerebro-spinal fluid may contain much blood, in which case the diagnosis is clear, but if blood does not find access to the ventricles, there may be little change in the fluid beyond a rise in pressure. Many cases show some excess of protein, an accompaniment of cerebral vascular disease associated with high blood pressure.

In thrombosis, slight admixture of the fluid with blood, or the presence of a yellow colour is usual, other changes, apart from slight excess of protein, being absent. In extra-dural or subdural hæmorrhage, changes in the fluid are slight or absent altogether.

The findings in cerebral abscess have already been referred to.

In cerebral tumour the fluid shows no changes in the majority of cases. In other cases there may be increase (usually slight or moderate) in cells, or protein or both, and so far as the cerebro-spinal fluid is concerned, no differentiation may therefore be possible between abscess and tumour in some cases.

For the diagnosis of syphilitic conditions, the Wassermann reaction and the gold sol test are usually required. The fluid in cerebral syphilis, unaccompanied by meningitis, may show no great changes. The gold sol reaction and the Wassermann reaction of the fluid may both be negative, though the Wassermann reaction of the blood is nearly always positive. Where syphilitic meningitis is also present there is a positive Wassermann reaction, and a positive result to the gold sol test in the cerebro-spinal fluid, with considerable increase in cells and protein.

In general paralysis the Wassermann reaction of the fluid is always positive, and the gold sol test gives a paretic type of result. The protein is in most cases increased, but not often to more than 100 mgm. per 100 c.c. The cell count, too, is

increased, usually to a moderate degree, though very high counts are occasionally met with.

The fluid in idiopathic epilepsy shows no alterations from the normal.

The changes in the fluid in poliomyelitis and polio-encephalitis, and in encephalitis lethargica have already been dealt with. In distinguishing the latter from certain forms of syphilis which may show similar cytological changes we have to rely on the Wassermann reaction only.

3. **Spinal Cord Symptoms.**—The conditions here include :—

Syphilitic meningo-myelitis.
Disseminated sclerosis.
Myelitis.
Spinal compression (by tumour, spinal carics and epidural abscess).
Syringomyelia.
Subacute combined degeneration.
Amyotropic lateral sclerosis.

Syphilis as a cause of paraplegia can usually be recognised by a positive Wasscrmann reaction in blood and cerebro-spinal fluid. There is also a raised cell count in this condition.

The results of tests in disseminated sclerosis vary considerably. Some cases can be diagnosed as a result of examination of the fluid alone. In others, no change in the fluid can be demonstrated. The combination of a paretic type of result to the gold sol test with negative Wassermann reaction and little or no change in cell count or protein is clearly indicative of the condition. In many cases, however, the gold sol test is negative or gives a luetic type of result. The protein is slightly increased in some cases. The increase in the cell count, when it does occur, is usually slight, although rarely values in the neighbourhood of 50 cells per cubic millimetre may be encountered.

In acute myelitis there may be found in combination in

the cerebro-spinal fluid, increase in cells, yellow coloration and very considerable increase in protein (over 500 mgm. per 100 c.c.). In later stages the increase in cells disappears while the other changes remain. On the other hand, some cases of myelitis show no alteration in the cerebro-spinal fluid. In a few cases I have obtained weak positive results of meningitic type in the gold sol test.

The combination of yellow coloration, increase in cells (lymphocytosis) and large increase in protein is known as the syndrome of Froin. Besides myelitis, it is found in tumour, spinal caries and epidural abscess, in chronic meningitis (especially syphilitic), and rarely in polyneuritis and Landry's paralysis.

In compression of the cord from any cause, the full syndrome of Froin may be present, as just mentioned, but in many cases it is incomplete. Xanthochromia, for instance, is not constant. Pleocytosis is seldom marked and frequently absent. Increase in protein is the most frequent alteration. It may be small in some cases, but in most cases it is very marked, and in some it exceeds 1,000 mgm. per 100 c.c. Very little help as to the nature of the compression is to be obtained by examination of the fluid. The site of the compression may be determined by injecting Lipiodol into the cisterna magna and the lumbar cul-de-sac and subsequently obtaining radiograms. Lipiodol being opaque to X-rays the level to which the radiogram shows it to have fallen, in the case of the cisternal injection, marks the upper limit of the compression, and the level to which it is found to rise, following the lumbar injection, marks the lower limit.

In other forms of paraplegia no alteration in the cerebro-spinal fluid is found, except perhaps a slight increase in protein.

In subacute combined degeneration, the recognition of complete achlorhydria by means of a gastric test meal is important confirmatory evidence (see Chapter VII.).

4. **Conus Terminalis, Cauda Equina or Bilateral Sciatic Nerve Symptoms.**—Here we may consider :—

Peripheral neuritis.
Tumour
Poliomyelitis.
Syphilitic meningitis.

The findings in tumour in this situation are similar to those already described with respect to tumour of the cord.

In many cases of neuritis the cerebro-spinal fluid shows very little alteration. In some, however, there is definite increase in protein and perhaps slight increase in cells. In certain cases of acute polyneuritis, however, the changes resemble those found in cases of tumour.

The changes in poliomyelitis have already been referred to. In the earlier stages these are sufficient to distinguish the condition from polyneuritis, but in late stages a distinction by examination of the fluid alone may be difficult.

For the detection of syphilitic conditions we must rely mainly on the Wassermann reaction.

Tabes dorsalis cannot properly be included in any of the above four symptom groups, but a few words as to the state of the cerebro-spinal fluid in this condition should be given.

The changes which occur here are usually not very great but are fairly constant. The cell count is increased, figures of 10 to 100 cells per cubic millimetre being commonly found. Values over this are somewhat rare. The cells present are mainly lymphocytes, but a few large mononuclear cells, plasma cells and polymorphonuclear leucocytes may sometimes be seen. The Wassermann reaction of the fluid is positive in about 70 per cent. of cases. Generally the total protein shows little or no increase, but in a few cases moderately high values are found. The gold sol test gives, in the large majority of cases, positive results of the luetic type, but in a few cases the result is of the paretic type.

In the above attempt to indicate how laboratory tests on the cerebro-spinal fluid may assist in the differential diagnosis

of diseases of the nervous system it is not claimed that all possible conditions have been mentioned in which one or more of the tests described may be used.

It will be realised from what has been said that, valuable as laboratory results are in many cases, they can only be applied with success in the light of the information obtained by careful clinical examination of the patient.

Practical Points.—Blood-stained cerebro-spinal fluid is unsatisfactory for many of the tests. Hence it is important that the specimen to be examined should be as free as possible from contamination by blood from any of the tissues through which the needle passes before entering the spinal canal. It is therefore advisable to have two or three suitable containers ready for the collection of the fluid. If the first few drops of fluid are bloodstained these can be rejected and the rest of the specimen collected in a fresh container.

All containers should be perfectly clean, dry and sterile.

The cell count should be made as soon as possible after the fluid is obtained, as the cells tend to disappear rather rapidly. If some delay is unavoidable it is a good plan to mix 1 c.c. of the fluid with 1 c.c. of 10 per cent. formol saline, and reserve this mixture for the cell count, due account being paid, of course, to the degree of dilution thus introduced.

If a number of tests are to be performed on one specimen about 10 c.c. should be obtained. The test for total protein requires up to about 4 c.c. according to the method used. Most other tests require up to 1 or 2 c.c. for each.

CHAPTER X

BASAL METABOLISM

METABOLISM is a general term which comprises all the processes involved in the utilisation of foods, etc., to supply the needs of the body, and so to enable it to carry on its activities. These activities include the growth and repair of tissues, the working of the separate organs of the body and the working of the body as a whole; and in order that all may be carried out a considerable supply of energy is needed. The energy is obtained by the oxidation of foodstuffs and the amount of energy produced will obviously vary considerably according to the state of activity of the body, the amount produced when the body is at rest being much less than when considerable activity (or work) is being undertaken. The amount of energy produced when the body is at rest as completely as possible depends to a large extent on the surface area of the body; but if this is taken into account and the amount of energy produced per unit of surface area per hour is obtained, the value is found to be fairly constant for normal persons of the same age and sex. This value is known as the Basal Metabolic Rate (B.M.R.) and is usually expressed in calories per hour per square metre of body surface.

The most direct way of determining the B.M.R. of a patient is to measure the amount of heat given out by him, when under basal conditions, *i.e.*, when he is at complete mental and physical rest, and at least fifteen hours after taking any food. This method requires a special calorimeter chamber and, owing to the expense, is not a routine clinical method.

The B.M.R. may, however, be determined indirectly;

for since energy is derived from oxidation, by which process H_2O and CO_2 are produced, the amount of oxidation occurring will be directly related to the energy production, and the rate of oxidation will be indicated by the rate at which oxygen is used by the patient (or by the rate at which CO_2 is produced by him). We can therefore ascertain the state of the patient's basal metabolism by comparing his rate of oxygen consumption with what is known to be normal for a patient of the same age and sex, or if we know how much heat is produced by the utilisation of a given quantity of oxygen we can calculate the number of calories corresponding to the oxygen consumption of the patient and thus give his basal metabolism in calories for comparison with standards quoted in similar units.

For the latter purpose it is necessary to know the connection between oxygen consumed and calories produced. This depends on the type of food being oxidised, and for information on this point we must turn to a consideration of the respiratory quotient.

The Respiratory Quotient (R.Q.) is the ratio of CO_2 produced to oxygen absorbed by the body.

If we consider the oxidation of carbohydrates, in which hydrogen and oxygen are present in the same proportion as in water, complete oxidation requires only that amount of oxygen which is needed for the conversion of the carbon present to CO_2. Thus, taking CH_2O as a general formula representing carbohydrates, we have

$$CH_2O + O_2 = CO_2 + H_2O.$$

That is, one volume of CO_2 is produced for each volume of oxygen used, so that the R.Q. is unity.

With fats and proteins, however, the oxygen in the molecules is not sufficient to form H_2O by combining with the hydrogen present. Hence for complete oxidation some oxygen is required for combination with hydrogen as well as with carbon, so that the volume of oxygen required is in

excess of the volume of CO_2 produced, and the R.Q. is therefore less than unity.

For fats it is 0·7 and for proteins 0·82.

The actual heat produced under different conditions of oxidation, that is with R.Q. of different values, has been

Table I.—Calorific Value of One Litre of Oxygen for Various (Non-Protein) Respiratory Quotients.

Respiratory Quotients.	Calories for 1 Litre of Oxygen.	Respiratory Quotients.	Calories for 1 Litre of Oxygen.
0·707	4·686	0·85	4·863
0·71	4·690	0·86	4·875
0·72	4·702	0·87	4·887
0·73	4·714	0·88	4·900
0·74	4·727	0·89	4·912
0·75	4·739	0·90	4·924
0·76	4·752	0·91	4·936
0·77	4·764	0·92	4·948
0·78	4·776	0·93	4·960
0·79	4·789	0·94	4·973
0·80	4·801	0·95	4·985
0·81	4·813	0·96	4·997
0·82	4·825	0·97	5·010
0·83	4·838	0·98	5·022
0·84	4·850	0·99	5·034
		1·00	5·047

From Zuntz and Schumberg. *Studien zu einer Physiologie des Marsches*, Berlin, 1901.

obtained and tables have been constructed from which the calorific value of oxygen used can be read off if the R.Q. is known (Table I). Under basal conditions and for clinical purposes it is generally sufficient to assume an average R.Q. of 0·82, and a corresponding calorific value of oxygen of 4·825 calories per litre.

It will thus be realised that the B.M.R. of a patient can be calculated if we can determine his rate of oxygen consumption under basal conditions.

Two methods are in use. In one the patient, breathing ordinary air, expires into a specially constructed bag and the expired air which is collected in this way over a definite period of time is subjected to analysis in the laboratory. From the results of the analysis the oxygen consumption is calculated. In the other method the patient breathes oxygen from a reservoir contained in a special apparatus. By means of valves the gases he expires return to the same apparatus, where they are deprived of CO_2, after which they pass into the oxygen reservoir again. The decrease in the volume of oxygen in the reservoir represents the amount of oxygen used up by the patient. The apparatus is so arranged that changes in the volume of oxygen in the reservoir are directly recorded on a dial. In this method therefore a single apparatus serves to indicate the rate of oxygen consumption.

Whatever method is used it is important that basal conditions should be obtained and maintained throughout the period of the test. The patient should fast for fifteen hours before the test. He should be advised of the necessity for complete mental and physical rest, and any nervousness or apprehension should be dispelled as far as possible. It is the practice in some hospitals to set aside a special room for the purpose of making these tests, since it is easier to maintain standard conditions in this way than in a large hospital ward. Though desirable, this practice is not absolutely necessary. If the patient is moved from one place to another before the test a wheeled bed or couch should be used to avoid any exertion on the part of the patient.

The first or open method employs the Douglas bag and the Haldane gas analysis apparatus.

The Douglas bag is a canvas-covered gas-tight bag of 100 litres capacity carrying an aluminium three-way cock. To it is attached a flexible corrugated tube carrying a side

tube, a valve box and a mouthpiece. The valve box is constructed so that inspired air is taken from the atmosphere while all expired air passes into the bag (Fig. 15). The bag is first completely emptied by rolling it up. The side tube is closed by a clip and the cock is turned so that the bag is shut off from the rest of the apparatus. The patient then fixes the mouthpiece in position and his nostrils are closed by a clip so that all breathing is carried on through the mouth. When the patient has adjusted himself to these con-

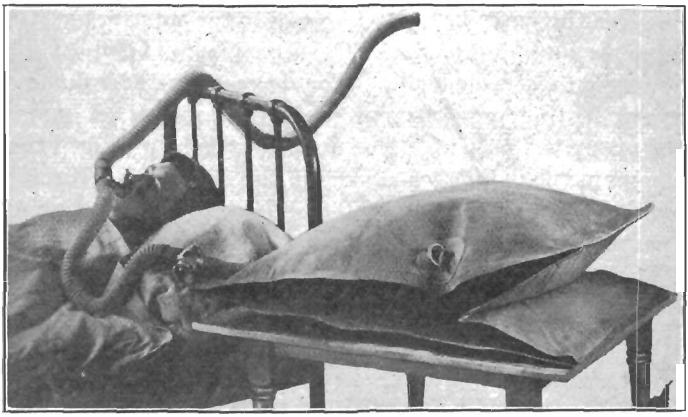
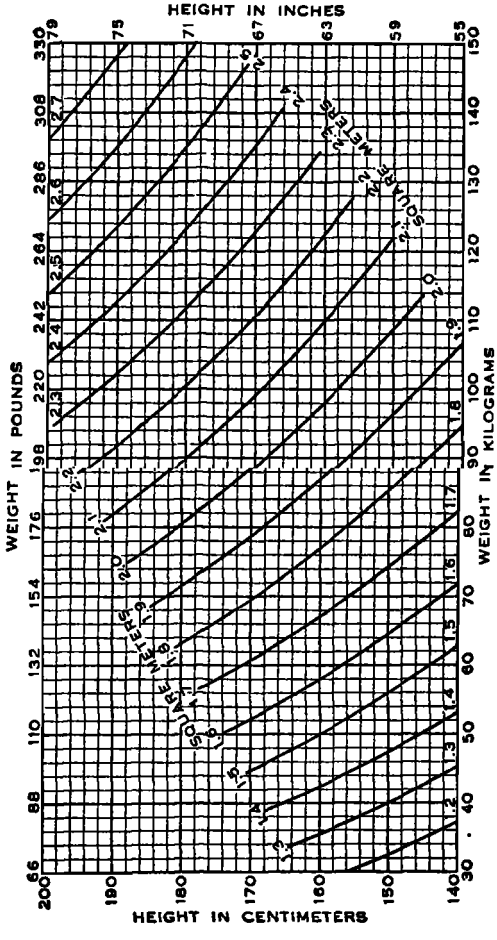


FIG. 15.—Douglas bag in use. (*Siebe, Gorman & Co.*).

ditions and is breathing naturally and regularly the cock is turned so as to allow the expired air to pass into the bag. The time at which this is done is noted. The patient continues to breathe into the bag in this way until it is almost full, when the bag is again shut off from the tubes by turning the cock, the time being again noted. The bag is then taken to the laboratory where the percentages of oxygen and CO_2 in the expired air are obtained by analysis (in the Haldane gas analysis apparatus) of a sample withdrawn through the side tube, while the total volume of expired air is ascertained by using a gas meter.

Table II.

BODY SURFACE CHART



1 lb. = 0·4536 kilo. 1 in. = 2·54 cm.

From "Basal Metabolism," ed. F. B. Sanborn, 1922. Sanborn Co., Boston.

Further data required for the calculation of the B.M.R. are :—

Age and sex of the patient.

Height and weight of the patient. From these, by reference to the Du Bois Height-Weight Chart, the surface area is obtained (Table II.).

Temperature of the meter in which the gas is measured.

Barometric pressure.

From these two a factor for reducing the volume of

Table III.—*Table for Reduction to Dry Air at* 0° *C. and* 760 *mm. of* 100 *Volumes of Air Saturated with Moisture at different Temperatures and Pressures.*

Temperature °C.	Barometric Pressure in Inches or Millimetres.								
	29·13 740	29·33 745	29·53 750	29·72 755	29·92 760	30·12 765	30·31 770	30·51 775	30·71 780
10 .	92·77	93·39	94·04	94·66	95·30	95·93	96·57	97·21	97·84
11 .	92·36	92·98	93·63	94·25	94·89	95·52	96·16	96·79	97·42
12 .	91·95	92·55	93·18	93·80	94·44	95·07	95·70	96·33	96·96
13 .	91·54	92·17	92·80	93·41	94·05	94·68	95·31	95·94	96·57
14 .	91·13	91·76	92·38	93·00	93·62	94·26	94·88	95·51	96·13
15 .	90·71	91·34	91·96	92·57	93·20	93·82	94·44	95·08	95·70
16 .	90·29	90·92	91·54	92·15	92·78	93·40	94·01	94·64	92·26
17 .	89·87	90·50	91·11	91·72	92·35	92·97	93·58	94·21	94·83
18 .	89·45	90·08	90·68	91·30	91·92	92·54	93·15	93·71	94·39
19 .	89·02	89·64	90·25	90·86	91·48	92·09	92·71	93·32	93·94
20 .	88·59	89·21	89·81	90·41	91·04	91·65	92·26	92·88	93·50
21 .	88·18	88·86	89·40	90·01	90·62	91·23	91·84	92·45	93·07
22 .	87·71	88·32	88·90	89·53	90·14	90·75	91·36	91·97	92·60
23 .	87·26	87·87	88·47	89·08	89·69	90·29	90·90	91·51	92·13
24 .	86·61	87·43	88·01	88·62	89·23	89·83	90·44	91·04	91·65
25 .	86·35	86·96	87·57	88·17	88·79	89·38	89·98	90·57	91·17

From Haldane's "Methods of Air Analysis," Griffin, London, 1918.

expired air to its dry volume at 0° C. and 760 mm. can be obtained from a table by Haldane (Table III.).

The method of calculating the B.M.R. from these data may be illustrated by an example, as follows :—

Female, aged nineteen.
Height 60 ins. = 152·4 cm.
Weight 120 lb. = 54·4 kilos.
∴ Surface (Du Bois Chart, Table II.) = 1·5 sq. m.
Duration of test = 10 minutes = $\frac{1}{6}$ hour.
Temperature 17°. Barometer 765 mm.

∴ Factor for reducing to dry volume at 0° and 760 mm. (Haldane Table, Table III.) = 0·930.

Expired air = 85 litres during test = 510 litres per hour.

Analytical results :—

CO_2 = 280 per cent. ∴ Nitrogen = 100 − (2·80 + 17·65)
O_2 = 17·65 per cent. = 79·55 per cent.

We have now to find out how much oxygen was originally present in the inspired air along with this amount of nitrogen. Now the composition of atmospheric air is :—

Nitrogen . . .	79·04	per cent.
Oxygen. . . .	20·93	,,
CO_2	0·03	,,

Hence the oxygen originally present was $\frac{20{\cdot}93}{79{\cdot}04} \times 79{\cdot}55 =$ 21·07 per cent. (The CO_2 in atmospheric air being very small it is not necessary to apply the same calculation, but to assume the CO_2 originally present to be 0·03 per cent.)

∴ Oxygen consumed = 21·07 − 17·65 = 3·42 per cent.
and Co_2 produced = 2·80 − 0·03 = 2·77 ,,

$$\therefore \text{Respiratory Quotient} = \frac{2{\cdot}77}{3{\cdot}42} = 0{\cdot}81.$$

From Table I. the calorific value of oxygen corresponding to this R.Q. is 4·813 calories.

Hence total heat production in 1 hour is

$$510 \times 0{\cdot}930 \times 4{\cdot}813 \times \frac{3{\cdot}42}{100} = 78{\cdot}08 \text{ calories.}$$

∴ B.M.R., or total heat production per sq. meter per hour,

$$= \frac{78{\cdot}08}{1{\cdot}5} = 52{\cdot}0 \text{ calories.}$$

By reference to the table of standards of normal metabolism (Table IV.), we find that the normal for a female of nineteen is 38 calories.

Hence the patient's B.M.R. is $\frac{52 - 38}{38} \times 100 = 37$ per cent. *above normal.*

The above calculation has been given in full because it is more customary to state values referring to metabolism in calories, but if we have a table giving normal oxygen consumption under basal conditions we may shorten the calculation somewhat. The table given (Table VI.) refers to adult men only. Hence we must adjust for age and sex as follows :—

Table IV.—*Standards of Normal Metabolism, Average Calories per hour per square metre of Body Surface* (*Du Bois*).

Age.	Males.	Females.
Years.	Calories.	Calories.
14 to 16	46·0	43·0
16 ,, 18	43·0	40·0
18 ,, 20	41·0	38·0
20 ,, 30	39·5	37·0
30 ,, 40	39·5	36·5
40 ,, 50	38·5	36·0
50 ,, 60	37·5	35·0
60 ,, 70	36·5	34·0
70 ,, 80	35·5	33·0

From Aub and Du Bois, *Arch. Int. Med.*, 1917, xix., 823.

Table V.—Basal Heat Production of Boys and Girls per 24 hours, predicted from Body Weight.

Body Weight (without clothing).	Predicted Heat.		Body Weight (without clothing).	Predicted Heat.	
	Boys.	Girls.		Boys.	Girls.
Kilos.	Cals.	Cals.	Kilos.	Cals.	Cals.
2·5	115	110	20·5	873	818
3·0	150	150	21·0	885	830
3·5	180	185	21·5	898	842
4·0	210	220	22·0	910	855
4·5	240	253	22·5	925	867
5·0	270	285	23·0	940	880
5·5	300	318	23·5	953	890
6·0	330	350	24·0	965	900
6·5	360	377	24·5	978	915
7·0	390	405	25·0	990	930
7·5	418	432	25·5	1,005	940
8·0	445	460	26·0	1,020	950
8·5	470	480	26·5	1,033	962
9·0	495	500	27·0	1,045	975
9·5	520	520	27·5	1,058	987
10·0	545	540	28·0	1,070	1,000
10·5	568	560	28·5	1,080	1,010
11·0	590	580	29·0	1,090	1,020
11·5	607	595	29·5	1,103	1,032
12·0	625	610	30·0	1,115	1,045
12·5	643	625	30·5	1,127	1,058
13·0	660	640	31·0	1,140	1,070
13·5	678	652	31·5	1,150	1,080
14·0	695	665	32·0	1,160	1,090
14·5	710	678	32·5	1,170	
15·0	725	690	33·0	1,180	
15·5	740	700	33·5	1,190	
16·0	755	710	34·0	1,200	
16·5	768	722	34·5	1,210	
17·0	780	735	35·0	1,220	
17·5	793	747	35·5	1,230	
18·0	805	760	36·0	1,240	
18·5	818	770	36·5	1,248	
19·0	830	780	37·0	1,255	
19·5	845	793	37·5	1,265	
20·0	860	805	38·0	1,275	

From "Metabolism and Growth from Birth to Puberty," Benedict and Talbot, Carnegie Institute of Washington, 1921.

Table VI.—*Amount of Oxygen Absorbed (in cc. per minute) under Basal Conditions, and at* 0° *C. and* 760 *mm., in Relation to Height and Weight.*

WEIGHT IN KILOGRAMS	HEIGHT IN CENTIMETERS											WEIGHT IN POUNDS
	140	145	150	155	160	165	170	175	180	185	190	
30	142	145	149	152	156	159	163	166	170	173	177	66
1	144	147	151	154	158	161	165	168	172	175	179	68
2	145	149	153	156	160	163	167	170	174	177	181	70
3	147	151	155	158	162	165	169	173	177	180	184	73
4	149	153	157	160	164	167	171	175	179	182	186	75
5	151	155	159	162	166	170	174	177	181	184	188	77
6	153	157	161	164	168	172	176	179	183	187	191	79
7	155	159	163	166	170	174	178	182	185	189	193	81
8	156	161	164	168	172	176	180	184	188	191	195	84
9	158	162	166	170	174	178	182	186	190	194	198	86
40	159	164	168	172	176	180	184	188	192	196	200	88
1	161	165	169	174	179	182	186	190	194	198	202	90
2	162	167	171	176	181	184	188	192	196	200	204	92
3	164	169	173	178	182	185	189	194	198	202	206	95
4	165	170	175	180	184	187	191	196	200	204	208	97
5	167	172	177	181	186	189	193	198	201	205	210	99
6	169	174	179	183	188	191	195	200	203	207	212	101
7	171	176	180	184	189	192	197	202	205	209	214	103
8	172	177	182	186	191	194	199	204	207	211	216	106
9	174	179	183	188	192	196	201	206	209	213	218	108
50	176	181	185	189	193	197	202	207	211	215	220	110
1	178	183	186	191	195	199	204	209	212	217	221	112
2	179	184	188	192	196	200	205	211	214	219	223	114
3	181	186	189	194	198	202	207	212	216	220	225	117
4	182	187	191	195	199	203	208	214	217	222	227	119
5	184	188	193	197	201	205	210	216	219	224	228	121
6	185	189	194	199	203	207	212	218	221	226	230	123
7	186	191	196	200	205	209	213	219	222	228	232	125
8	188	192	197	202	206	210	215	221	224	229	233	128
9	189	194	199	203	208	212	216	222	226	231	235	130
60	190	195	200	204	209	213	217	223	228	233	237	132
1	191	196	201	206	211	215	219	225	230	235	239	134
2	192	198	202	207	212	216	220	226	231	236	240	136
3	193	199	203	209	214	218	222	228	233	238	242	139
4	195	200	205	210	215	219	223	229	234	239	243	141
5	196	201	206	212	217	221	225	231	236	241	245	143
6	197	202	207	213	218	222	227	232	237	242	247	145
7	199	204	209	215	220	224	228	234	239	244	249	147
8	200	205	210	216	221	225	230	235	240	245	250	150
9	201	207	212	218	222	227	231	237	242	247	252	152
70	202	208	213	218	223	228	233	238	243	248	253	154
1	203	209	214	219	224	229	235	240	245	250	255	156
2	204	210	216	220	225	231	236	241	246	251	256	158
3	206	212	217	222	227	232	238	243	248	253	258	161
4	207	213	219	223	228	234	239	244	249	254	259	163
5	208	214	220	224	229	235	241	246	251	256	261	165
6	209	215	221	225	230	236	242	247	252	257	263	167
7	210	216	222	227	232	238	244	249	254	259	264	169
8	212	218	224	228	233	239	245	250	255	260	266	172
9	213	219	225	230	235	240	246	251	257	262	267	174
80	214	220	226	231	236	241	247	253	258	263	268	176
1	215	222	227	232	237	242	248	254	259	264	270	178
2	217	223	228	234	239	244	250	256	261	266	271	180
3	218	225	230	235	240	245	251	257	262	267	273	183
4	220	226	231	237	242	247	253	259	264	269	274	185
5	221	227	233	238	243	248	254	260	265	270	276	187
6	222	228	234	239	244	249	255	261	266	271	277	189
7	223	229	235	240	246	251	256	262	268	273	279	191
8	224	230	236	242	247	252	258	264	269	274	280	194
9	225	231	237	243	248	254	259	265	271	276	282	196
	55	57	59	61	63	65	67	69	71	73	75	

HEIGHT IN INCHES

Table VI.—*continued.*

HEIGHT IN CENTIMETERS

WEIGHT IN KILOGRAMS	150	155	160	165	170	175	180	185	190	195	200	WEIGHT IN POUNDS
90	238	244	249	255	260	266	271	276	282	287	292	198
1	239	245	250	256	261	267	272	277	283	288	293	200
2	240	246	251	257	262	268	273	278	284	289	294	202
3	241	247	252	258	264	269	275	280	285	291	296	205
4	242	248	253	259	265	270	276	281	287	292	297	207
5	243	249	254	260	266	271	277	282	288	293	298	209
6	244	250	255	261	267	272	278	283	289	294	299	211
7	245	251	256	263	269	274	279	284	290	295	300	213
8	246	252	258	264	270	275	281	286	292	297	302	216
9	247	253	259	266	271	277	282	287	293	298	303	218
100	248	254	260	267	272	278	284	289	294	299	304	220
1	249	255	261	268	273	279	285	290	295	300	305	222
2	250	256	262	269	274	280	286	292	297	302	307	224
3	251	257	263	270	275	281	288	293	298	303	308	227
4	252	258	264	271	276	282	289	294	299	304	309	229
5	253	260	266	272	278	284	290	296	301	306	311	231
6	254	261	267	273	279	285	291	297	302	307	312	233
7	255	262	268	274	280	286	293	298	303	308	313	235
8	256	263	269	275	281	287	294	300	305	310	315	238
9	257	264	270	276	282	288	295	301	306	311	316	240
110	258	265	271	277	283	289	296	302	307	312	317	242
1	259	266	272	278	284	290	297	303	308	313	318	244
2	260	267	273	279	285	291	298	304	309	315	320	246
3	261	268	274	280	286	293	299	305	310	316	321	249
4	262	269	275	281	287	294	300	306	312	317	322	251
5	263	270	276	283	289	295	302	308	313	319	324	253
6	264	271	277	284	290	296	303	309	314	320	325	255
7	265	272	278	285	291	298	304	310	315	321	326	257
8	266	273	279	286	292	299	305	311	317	323	328	260
9	267	274	280	287	293	300	306	312	318	324	329	262
120	268	275	281	288	294	301	307	313	319	325	330	264
1	269	276	282	289	295	302	308	314	320	326	331	266
2	270	277	283	290	296	303	309	315	321	327	332	268
3	271	278	284	291	297	304	310	316	322	328	333	271
4	272	279	285	292	298	305	311	317	323	329	335	273
5	272	279	285	292	299	306	312	319	325	331	336	275
6	273	280	286	293	300	307	313	320	326	332	337	277
7	274	281	287	294	301	308	314	321	327	333	339	279
8	275	282	288	295	302	309	315	322	328	334	340	282
9	276	283	289	296	303	310	316	323	329	335	341	284
130	277	284	290	297	304	311	317	324	330	336	342	286
1	278	285	291	298	305	312	318	325	331	337	343	288
2	279	286	292	299	306	313	319	326	332	338	344	290
3	280	287	293	300	307	314	320	327	333	339	345	293
4	281	288	294	301	308	315	321	328	334	340	346	295
5	281	288	294	302	309	316	323	329	335	341	347	297
6	282	289	295	303	310	317	324	330	336	342	348	299
7	283	290	296	304	311	318	325	331	337	343	349	301
8	284	291	297	305	312	319	326	332	338	344	350	304
9	285	292	298	306	313	320	327	333	339	345	351	306
140	286	293	299	307	314	321	328	334	340	346	352	308
1	287	294	300	308	315	322	329	335	341	347	353	310
2	288	294	301	309	315	323	329	336	342	348	354	312
3	289	295	302	310	316	324	330	337	343	349	355	315
4	289	296	303	311	317	325	331	338	344	350	356	317
5	290	297	304	312	318	326	332	339	345	351	357	319
6	291	298	305	313	319	327	333	339	346	352	358	321
7	291	299	306	314	320	328	334	340	346	353	359	323
8	292	300	307	315	321	329	335	341	347	354	360	326
9	293	301	307	315	322	329	336	342	348	355	361	328
	59	61	63	65	67	69	71	73	75	77	79	

HEIGHT IN INCHES

From Sanborn, "Basal Metabolism," 1922, Sanborn Co , Boston.

Males.—

20—50, as shown in table.

16—18, add 1 per cent. to value in table.

18—20, add 5 per cent. to value in table.

50—60, subtract 4 per cent. from value in table.

60—70, subtract 7 per cent. from value in table.

Females.—

Subtract 7 per cent. from value for male of same age.

In the present case we have—

Volume of expired air = 85 litres in ten minutes, which, reduced to dry volume at 0° and 760 mm., is

$$\frac{85 \times \cdot 93}{10} = 7 \cdot 905 \text{ litres per minute.}$$

Oxygen consumed is 3·42 per cent. of this, *i.e.*, 270 c.c.

From the table the normal oxygen consumption of the patient should be 191 c.c.

$$\therefore \text{ Increase above normal} = \frac{270 - 191}{191} \times 100 = 41 \text{ per cent.}$$

The difference between the results by the two methods is due to the fact that different tables, all involving certain approximations, have been used. Thus the first calculation utilises the tables giving surface area according to height and weight, and calorific value according to the experimentally determined R.Q., while the second considers oxygen consumption in relation to height and weight. As will be seen later, these differences are generally negligible so far as the clinical interpretation of the result is concerned.

It is advisable to carry out more than one determination by the open method rather than to rely on the result of a single determination.

The second or closed method uses some form of the Benedict portable respiration apparatus (Fig. 16), the principle of which has already been described.

The oxygen container consists of a cylindrical reservoir

like a gasometer, with a water or oil seal. The reservoir is connected to a recording apparatus which indicates changes of volume of the contained gas. A tube passes from the reservoir to a valve box from which a return tube passes to a vessel containing soda-lime. From the latter another tube passes to the oxygen reservoir. A mouthpiece is

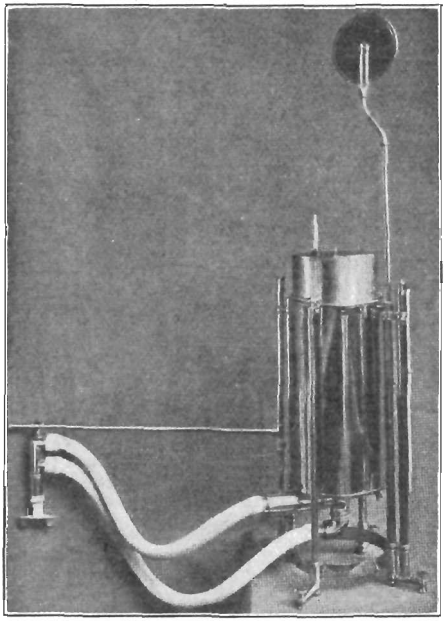


FIG. 16.—The Benedict (Roth modification, with valves) ready for use.

attached to the valve box. The valves allow of the direct passage of oxygen from the reservoir to the patient, while expired gases pass to the soda-lime container which removes CO_2. What then remains of the expired gases, namely, oxygen, passes into the oxygen container.

When the apparatus has been properly assembled and tested for leakage the reservoir is filled with oxygen. The

patient then fits the mouthpiece and his nostrils are closed by a clip. When the breathing has become regular and natural the test is commenced by noting the reading on the dial at a given time, and the test is concluded after a definite interval (*e.g.*, five or ten minutes) by again noting the dial reading. The temperature in the oxygen cylinder is also noted, and the barometric pressure. Three tests are usually carried out, either in immediate succession or with short intervals between tests, according to circumstances. The difference between the dial readings at the beginning and end of each test indicates the volume of oxygen absorbed during the period of the test. The volume in each case is corrected to standard conditions of temperature and pressure by means of a table supplied with the instrument. (In some instruments water absorption takes place to a considerable extent so that the gas in the reservoir is not saturated with respect to moisture. Hence the table for reducing gas saturated with moisture to standard dry conditions must not be used unless it is known that the gas concerned is in fact saturated with moisture.)

Any great variation between the results suggests an error in technique, and the test should be repeated. If the results are fairly close together their mean is used for the calculation of the B.M.R., which is carried out as already indicated. If the result is to be expressed in calories the R.Q. is taken as 0·82 and the calorific value of oxygen as 4·825 calories per litre.

Clinical Value of B.M.R. Determinations.

Owing to variations in normal individuals and errors involved in the methods employed, no significance can be attached to results which are within 15 per cent. of the normal standards. Definitely abnormal results, however, are frequently obtained in certain conditions, and the test is sometimes of considerable value in the investigation of these conditions.

All the factors controlling metabolism are not fully understood, but it is known that certain of the endocrine glands, especially the thyroid, affect it considerably, and it is in connection with disease of the thyroid gland that the determination of the B.M.R. has been principally used as a clinical test.

The B.M.R. offers its contribution to the investigation of thyroid disease by indicating the level of thyroid activity, since the degree of thyroid activity is closely reflected by the B.M.R., increased activity on the part of the thyroid resulting in an increase in the B.M.R. and *vice versâ.*

Hence the test helps to distinguish cases of simple goitre from cases of true hyperthyroidism. In the former there is little or no increase in the B.M.R.; there may, indeed, be a decrease. In the latter an increase can be demonstrated in most cases, and often this increase is very great (up to about 75 per cent. above normal).

The B.M.R. is also sometimes of value in affording evidence of increased thyroid activity when other signs of the condition are inconspicuous or indefinite.

Some help is offered in the differentiation between exophthalmic goitre and toxic adenoma. In the former remissions and exacerbations are frequent, and these changes can perhaps be best followed by determining the changes in the B.M.R. In toxic adenoma there is a tendency for the condition to follow a steady course over a long period, which is reflected by a steadily increasing or continually high B.M.R.

The B.M.R. is obviously of value in supplying indications for treatment, whether surgical or medical, in showing the results of treatment and in indicating the course and prognosis of individual cases.

In the same way hypothyroidism causes a decrease in the B.M.R., values down to 40 per cent. below normal being sometimes obtained. The test is therefore useful in this type of case in diagnosis and in the determination of the response to treatment by thyroid administration.

Pituitary disturbances also affect the B.M.R., but not to the same extent as thyroid disturbances. Hyperpituitarism tends to cause an increase and hypopituitarism a decrease in the B.M.R. To distinguish whether thyroid or pituitary is responsible for an alteration in the B.M.R. clinical evidence must be mainly relied on, but injection of pituitrin sometimes helps. Thus with a decreased B.M.R., due to hypopituitarism, an injection of pituitrin causes an increase in the B.M.R., but such a rise does not occur if the reduction was due solely to deficient thyroid activity.

Other conditions in which B.M.R. may be increased are the leukæmias, severe cardiac and renal conditions, and fevers, while a decrease may be found in the terminal stages of various diseases and in prolonged malnutrition.

While on the subject of basal metabolism it may be pointed out that tables indicating the normal basal metabolic rate are useful as a basis for the construction of dietaries in certain special conditions, *e.g.*, diabetes, since the values indicate the minimum energy requirements.

Reed's Formula.—This is a formula for the calculation of the B.M.R. from determination of the pulse rate and pulse pressure (*i.e.*, the difference between systolic and diastolic blood pressure) taken under basal conditions.

It is as follows :—

$$\text{B.M.R.} = 0{\cdot}683\ (\text{P.R.} + 0{\cdot}9\ \text{P.P.}) - 71{\cdot}5$$

For example, where pulse rate is 98 and pulse pressure 65, we have

$$\begin{aligned}\text{B.M.R.} &= 0{\cdot}683\ (98 + 0{\cdot}9 \times 65) - 71{\cdot}5 \\ &= +\ 35 \text{ per cent.}\end{aligned}$$

In about 70 per cent. of cases close agreement is found between the B.M.R. calculated from this formula and the B.M.R. obtained from the rate of oxygen consumption.

Respiratory Quotient.—Apart from its use in the determination of the B.M.R., the determination of the R.Q. has certain

other clinical applications. It has been shown that the R.Q. for carbohydrates is unity while that for fats and proteins is decidedly lower. When energy is mainly derived from carbohydrates, the R.Q. of a patient will therefore approach unity, whereas in conditions like diabetes where oxidation of carbohydrate is impaired, the R.Q. will tend to be low. Use of these facts may enable us to distinguish between hyperthyroidism and diabetes as the cause of a hyperglycæmia, for if we determine the R.Q. after administration of glucose, the result in hyperthyroidism is in the neighbourhood of unity, while in diabetes it remains at a low level. The R.Q. may be determined experimentally, as already indicated, by using the Douglas bag and the Haldane apparatus.

CHAPTER XI

ANOXÆMIA

ANOXÆMIA, the condition in which the tissues are suffering from deficiency in their oxygen supply, occurs in a number of different conditions. The obvious remedy, namely to supply oxygen to the patient whose tissues are labouring under such difficulties, is not by any means of equal value in all cases. Hence it is important to have some understanding of the subject, in order to apply treatment intelligently, and to the best advantage.

Barcroft has divided anoxæmia into three types, as follows:

1. **Anoxic Type.**—In this type the blood is not carrying the amount of oxygen it is capable of carrying, or in other words the oxygen saturation is below the normal value. This may occur either because the partial pressure of oxygen in the atmosphere is below normal or because certain pathological conditions in the lungs or air passages prevent proper oxygenation of the blood. Conditions of diminished oxygen pressure in the atmosphere are met with at high altitudes and hence are of importance in mountaineering and in flying, but hardly concern us in the ordinary, everyday work. Pathological conditions giving rise to anoxic anoxæmia include pneumonia, acute bronchitis, pulmonary œdema and various other acute and chronic inflammatory diseases of the lungs which, by causing damage to the alveolar epithelium of the lungs, shallow breathing or obstruction to the air passages, prevent the proper oxygenation of the blood. It also occurs in congenital cardiac malformations in which blood is able to pass from the right to the left side of the heart without passing through the lungs.

2. **Anæmic Type.**—In this type the blood is carrying as much oxygen as it is capable of carrying, but its capacity is low, either because the amount of hæmoglobin is reduced, as in anæmia, or because a part of the hæmoglobin has been rendered incapable of carrying oxygen as, for example, in poisoning by carbon monoxide, in which some hæmoglobin has been converted into carboxy-hæmoglobin, or in poisoning by drugs such as acetanilide, phenacetin and potassium chlorate, in which methæmoglobin or sulphæmoglobin may be formed.

3. **Stagnant Type.**—Here the blood is normally saturated with oxygen, but tissue shortage of oxygen results from interference with the circulation, so that the amount of oxygen reaching the tissues in a given time is less than normal. This type occurs typically in uncompensated cardiac disease and may also occur under conditions causing constriction of the arterioles, as in prolonged exposure to cold, and locally in Raynaud's disease, etc.

More than one type may be present in the same case. This is frequently seen in cardiac cases in which, in addition to stagnant anoxæmia, an accompanying pulmonary œdema may produce anoxæmia of the anoxic type. Similarly the anoxic anoxæmia of pneumonia may be complicated by stagnant anoxæmia due to cardiac failure.

Anoxæmia may be studied quantitatively by analysis of arterial and venous blood. Under normal conditions the oxygen capacity of the blood is from 18 to 23 c.c. per 100 c.c. of blood. Arterial blood contains from 94 to 98 per cent. of the total amount it is capable of holding when fully saturated, *i.e.*, the normal arterial saturation is from 94 to 98 per cent. of the full carrying capacity. Venous blood contains between 65 and 75 per cent. of the carrying capacity, or in other words is only 65 to 75 per cent. saturated. Thus the normal difference between the oxygen of arterial and venous blood amounts to 20 to 30 per cent. of the full oxygen capacity.

In the anoxic type of anoxæmia, the oxygen saturation of arterial blood is below normal, *i.e.*, below 94 per cent. of the carrying capacity, though the carrying capacity may be unimpaired.

In anæmic and stagnant anoxæmia, the arterial oxygen saturation is normal, *i.e.*, it has the normal ratio to the carrying capacity, but in the former the actual carrying capacity is low. In both venous saturation is low, since there is a normal tissue demand for oxygen in spite of the diminished supply.

Hence it will be seen that full information concerning any given case could be obtained by determining :—

(i.) The oxygen-carrying capacity of the blood.

(ii.) The arterial saturation.

(iii.) The venous saturation.

In practice it is often not necessary or practicable to make such determinations. For information concerning anoxæmia and for indications for treatment we depend mainly on the two symptoms cyanosis and dyspnœa. In appropriate cases these symptoms may be considerably relieved, with considerable benefit to the patient, by oxygen administration.

It is necessary to consider these symptoms in relation to anoxæmia, for they are not always indications that oxygen treatment is called for.

Cyanosis is perhaps the most valuable clinical sign of anoxæmia and is due to the presence of reduced hæmoglobin, or of certain other derivatives of hæmoglobin, in the capillaries. Hence it depends largely on the degree of unsaturation of the arterial blood, occurring, with normal hæmoglobin concentrations, when oxygen unsaturation reaches 15 to 20 per cent. But it depends, too, on the actual amount of reduced hæmoglobin present. Hence its normal relationship to anoxæmia is altered if there are marked changes in the hæmoglobin content of the blood. In anæmia, for instance, the oxygen supply to the tissues may be definitely inadequate, but cyanosis fails to appear because

there is not sufficient reduced hæmoglobin present, whereas in polycythæmia, although the oxygen supply may be adequate, there may be enough reduced hæmoglobin present to cause cyanosis.

Dyspnœa, too, is frequently an expression of oxygen want, but not in all cases. The dyspnœa of diabetes and of renal disease are due, as we have seen, to acidosis and not to want of oxygen. The dyspnœa of hyperthyroidism is due, not to deficient supply of oxygen to the tissues, but to excessive consumption of oxygen on their part.

Hence, before seeking to relieve either dyspnœa or cyanosis by administering oxygen, we must first be reasonably certain that anoxæmia is the underlying cause. Even then success will depend on our ability to increase the amount of oxygen carried by the blood to the tissues.

It is in the anoxic type of anoxæmia, due to pulmonary disease, and especially in pneumonia, where oxygen administration is of greatest benefit. In these conditions the arterial oxygen saturation can be raised, in some cases very considerably, by supplying oxygen to the patient, provided that the oxygen so supplied has access to the pulmonary alveoli. This access to the alveoli may, of course, be prevented if there is massive pulmonary œdema, excessive secretion or excessive inflammatory exudate, etc. In the absence of these conditions, however, the benefit derived in such conditions as pneumonia is frequently very considerable. Cyanosis and dyspnœa are relieved or abolished, sleep is promoted and the tendency to delirium is lessened. As a result of these changes, and of the improvement in oxygen supply to the myocardium itself, heart failure may be avoided and the patient thus considerably helped through the most critical period of his illness.

It is not suggested that oxygen should be administered in all cases of pneumonia, but where anoxæmia develops to such a degree that cyanosis or marked dyspnœa make their appearance, oxygen is certainly called for.

In other conditions in which the same type of anoxæmia develops, oxygen therapy may also tide a patient over a critical period. It is of little or no value, however, in the treatment of the anoxæmia of congenital cardiac disease.

In uncomplicated stagnant anoxæmia due to circulatory failure, oxygen treatment may be of little benefit. Unless there are pulmonary complications the blood is already fully oxygenated. The most that can be done is to increase the oxygen in physical solution in the blood, and to do this the partial pressure of oxygen in the alveolar air must be raised as much as possible. Hence only the most efficient means of administration are likely to be of value. Where there are pulmonary complications, however, with urgent dyspnœa and cyanosis resulting from an accompanying anoxic anoxæmia, the heart is further embarrassed by these added difficulties and a vicious circle is established. Here oxygen treatment, by relieving the anoxic anoxæmia may break the circle and thus help to restore the patient.

In anæmic anoxæmia, too, the amount of oxygen in the blood can only be increased with oxygen treatment by increasing the amount of oxygen in physical solution. Hence while such treatment might be of help in an emergency, real improvement depends on regeneration of hæmoglobin.

The amount of air breathed can be increased by applying a stimulus to the respiratory centre. It is known that the centre is extremely sensitive to increases of CO_2 in the blood—CO_2 is, in fact, the best respiratory stimulant we know of. Hence administration of oxygen enriched with CO_2 forms a means of dealing with certain cases of anoxæmia. While it is not a satisfactory method for most clinical conditions in which anoxæmia is present, it has been found very useful in the treatment of carbon-monoxide poisoning.

Methods of Oxygen Administration.—The commonest fault in oxygen administration is to give too little of the gas. It is quickly absorbed and quickly used up, and no storage can take place in the body fluids or tissues. Hence if any

benefit is to be obtained it must be given as continuously as possible, and not for a few minutes at a time. Moreover, it is useless to supply oxygen under such conditions that no appreciable increase in the percentage of oxygen in the alveolar air is obtained, and this frequently occurs with rates of oxygen flow commonly used, in conjunction with the simpler types of apparatus.

These simpler methods are of the "open" type and include the tube and funnel method and the nasal catheter method. In the former, oxygen is led through a tube to a funnel, which is held close to the patient's face. Little effect is produced unless the funnel is pressed closely to the nose and under the chin of the patient. In the latter method a rubber catheter is passed into one nostril until its tip lies in the naso-pharynx. Passing the gas through a wash-bottle containing warm water is of advantage to the patient, and moreover has the advantage of making the flow visible. By these methods the rate of oxygen flow should be not less than 2 litres per minute, which is indicated by a continuous and vigorous stream of gas passing through the wash-bottle. It is advisable to have a flow meter to indicate the rate of flow of the gas. Provided a sufficient rate of flow is used considerable increase in the alveolar oxygen percentage can be obtained by these methods. The nasal catheter method has been found of considerable use with children.

A great disadvantage of open methods is their wastefulness. Approximately only half the oxygen administered can be utilised, for the oxygen flowing during expiration is carried away with the expired air, and lost. On this account many "closed" methods of administration have been devised. By them, not only is this waste prevented, but most of them allow of considerably greater increases in the oxygen content of the alveolar air of the patient than the open methods.

Probably the best known is that of Haldane. In this method oxygen is delivered into a small bag attached to a

mask which fits on the patient's face. During inspiration oxygen is sucked from the bag, and from an additional opening in the mask ordinary atmospheric air may be admitted in such amounts that the total oxygen taken from

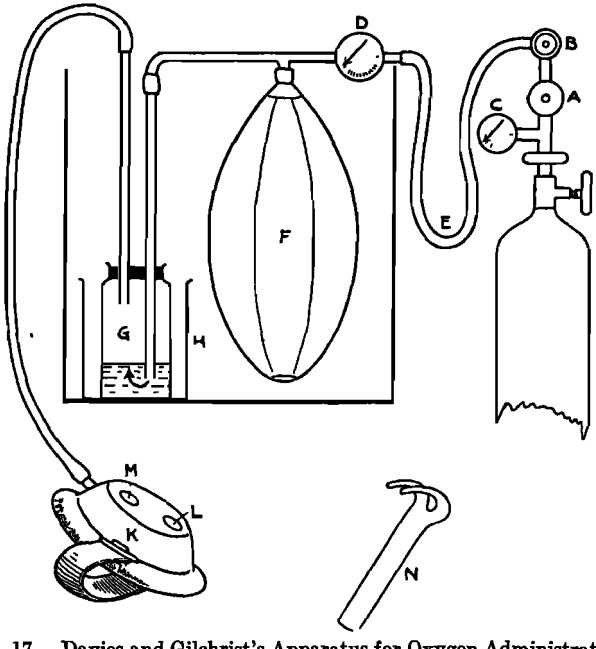


FIG. 17.—Davies and Gilchrist's Apparatus for Oxygen Administration. A, Reducing valve; B, Flow regulator; C, Pressure gauge; D, Flow meter (indicating rate of oxygen flow in litres per minute); E, Flexible tube; F, Bag of about 6 litres capacity; G, Wash-bottle which also acts as valve; H, Outer vessel which can be filled with hot water; K, Face mask with pneumatic face-pad; L, Expiratory valve; M, Variable extra air orifice; N, Forked nasal tube.

the air and from the bag may be sufficient for the needs of the patient. During expiration the slight increase in pressure due to the air passing out through the opening in the mask is sufficient in ordinary circumstances to hold the oxygen back in the bag. The rate of oxygen flow can be

regulated as desired by suitable valves. This apparatus gives very good results in all but very severe degrees of oxygen want and is largely used.

Davies and Gilchrist [1] have devised a modification of the Haldane apparatus, which is extremely efficient under all conditions of oxygen want. The apparatus (Fig. 17) can be arranged so that the patient breathes pure oxygen or any desired mixture of oxygen and air. If, when the patient is breathing pure oxygen, the rate of flow is carefully adjusted to his needs, then this rate of flow (as indicated by the flow-meter of the apparatus) gives approximately the patient's respiratory minute volume. When this is known the amount of oxygen in the gas breathed by the patient, when he is taking a mixture of oxygen and air, can be calculated from the observed rate of flow of oxygen through the apparatus. For example, if the respiratory minute volume is 10 litres and oxygen is delivered at the rate of one litre per minute, the patient is breathing 9 litres of air containing approximately 20 per cent. of oxygen, together with 1 litre of pure oxygen, so that the actual percentage of oxygen in the mixture is approximately 28. The advantage of being able thus to determine the percentage of oxygen in the air breathed is that we can ascertain the percentage necessary to abolish the symptoms of oxygen lack and so obtain some quantitative indication of the severity of the condition.

In addition to a face mask Davies and Gilchrist have introduced a forked nasal tube which may be used as an alternative to the mask, without loss of efficiency when the flow of oxygen is not more than one third of the respiratory minute volume. The tube is of glass and is fixed on the patient's head so that each limb of the fork passes into one of the nostrils of the patient.

For a full description of the apparatus and its method of use, the author's paper should be consulted.

Quite recently, Davies has introduced a simpler form

[1] *Lancet*, Vol. I., p. 916. 1925.

of this apparatus (Fig. 18) for ordinary clinical purposes, and this is of considerable value for all cases except those requiring very high oxygen percentage in the inspired air. This apparatus is easily portable and is inexpensive.

Hilton [2] has introduced a mouth mask which allows the patient to breathe oxygen by the mouth while leaving the nose free to breathe air. This, he says, appears to be more

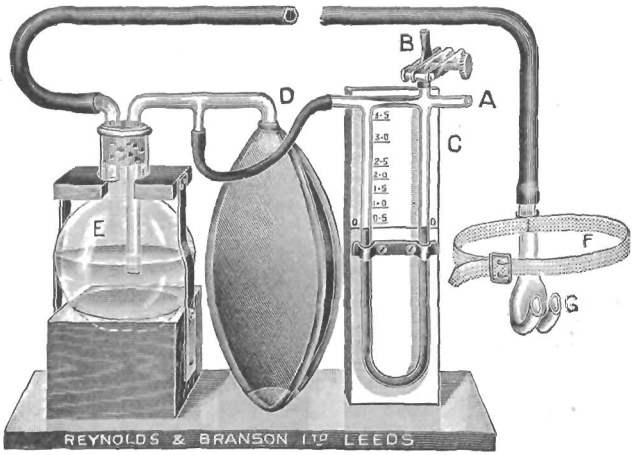


FIG. 18.—Davies' Apparatus for Oxygen Administration. A, Connection for oxygen cylinder; B, Tube and clip to allow access to fluid in flow-meter, for purposes of adjustment; C, Flow-meter; D, Rubber bag; E, Wash-bottle, which also acts as a non-return valve; F, Forehead band; G, Forked nasal tube.

comfortable and more willingly borne by some patients than a face mask.

It will be realised that the Douglas bag filled with oxygen, with face mask and suitable valves, may also be a very useful "closed" method for administering oxygen. The Benedict metabolism apparatus may also be used for the same purpose.

Other methods include the provision of a special oxygen chamber for the treatment of anoxæmia. This has the great

[2] *British Medical Journal*, vol. 1, p. 441. 1928.

advantage that the necessity for a mask or special apparatus is abolished, but the cost limits the use of such chambers to a few of the larger hospitals.

The first object to be aimed at in the treatment of anoxæmia is the abolition of cyanosis. Indeed one should go a little further and rather more oxygen should be given than just suffices to abolish cyanosis completely. Relief of dyspnœa is, too, a very desirable object and is always obtained to some extent. In certain cases, however, the relief may not be great, since respiratory embarrassment may be due to causes which continue to act after oxygen want has been abolished. A third result of successful oxygen administration is a fall in pulse rate.

Provided methods of administration are chosen which can be relied on to be fully efficient to meet any possible demands of a particular case, and that the rate of administration is carefully controlled by reference to its effect on the symptoms just mentioned, much of the disappointment which has formerly attended the use of oxygen in treatment will be avoided.

CHAPTER XII

GOUT

So long ago as 1848 it was shown by Sir A. B. Garrod that the blood of patients suffering from gout had an increased uric acid content; but it has only been since the recent developments of accurate methods of blood analysis that the determination of blood uric acid has developed into a common procedure in the investigation of this disease.

Uric acid is one of a group of substances known as purines, and is derived from nucleo-proteins. The uric acid of the body has therefore two sources—one, endogenous, from nuclear material set free on the breakdown of cells within the body, and the other, exogenous, from articles of diet containing nucleo proteins, both of animal and vegetable origin.

Under normal circumstances uric acid from either exogenous or endogenous sources, is excreted by the kidney, chiefly as mono-urates. The excretion is subject to fairly wide variations in different individuals and may vary from day to day in the same individual. On the other hand, the amount present in the blood is normally fairly constant. Variations in the purine-content of the diet have little effect on the blood uric acid of normal individuals. Their effect on the blood uric acid of patients suffering from gout is more marked. Thus a purine-free diet will cause a definite reduction of the blood uric acid of these patients, though not usually to the normal level.

The cause of the increased blood uric acid in gout and its relation to the symptoms of this condition are not definitely known. One theory attributes gout to a defect of elimination of uric acid on the part of the kidney. But this does

not appear to explain the condition fully, for other conditions are known in which the blood uric acid reaches abnormally high values, yet such conditions are not accompanied by other signs of gout. Uric acid retention occurs in nephritis, and the blood picture in gout is so similar to that of early interstitial nephritis that the suggestion has been made that gout may be a very early manifestation of nephritis, which may or may not further develop. Another view is that gout is due to a primary lesion in the joints, but the fact that the blood uric acid is increased suggests a more general disturbance. Still another view attributes the condition to a primary tissue defect, by which the uric acid diffused in the tissues is not returned to the body fluids for excretion in the normal way. It seems probable, from recent work, that uric acid may occur in the blood in more than one form. Hence the possibility that gout may be due to some abnormality in the distribution of uric acid between different forms has been suggested. Lastly, it may be mentioned that the possibility has been pointed out that what we include under the term gout may include quite different conditions; that gouty arthritis may be a condition in which there is a primary joint disease, with deposits of urates in the diseased tissues, uric acid excretion being normal, whereas constitutional gout may be due to defective excretion of uric acid.

According to Folin and Denis, the blood uric acid of normal individuals lies between 0·7 and 3·7 mgm. per 100 c.c., the average being about 2 mgm. In gout values between 4 and 10 mgm. may be found. But it is important to bear in mind that a high blood uric acid value is not necessarily indicative of the presence of gout. There appear to be exceptions even to the rule that gout is always associated with raised blood uric acid, but these exceptions are rare. On the other hand, raised blood uric acid values may be found in leukæmia, in pneumonia, in malignancy, in lead and mercury poisoning, in the toxæmias of pregnancy, and

in acute and chronic nephritis (excluding parenchymatous nephritis). Of these conditions the only one of considerable importance, from the point of view of differential diagnosis, is chronic nephritis, and it may be mentioned here that higher blood uric acid values have been found in chronic nephritis than have ever been obtained in uncomplicated gout. Hence before any raised blood uric acid figure can be taken as evidence of gout, the possibility of chronic nephritis as a cause of the increase must be excluded. Hence it may be necessary to examine renal function very carefully in many cases showing raised blood uric acid values, since chronic nephritis is not uncommon at the age at which the question of the diagnosis of gout frequently arises. Moreover there is the possibility of the co-existence of gout and nephritis which may render the diagnosis, so far as blood analysis is concerned, very difficult or impossible. Provided chronic nephritis can be excluded, or correctly assessed, examination of the blood uric acid may, however, be of considerable value. In classical gout the clinical picture hardly needs any laboratory confirmation, but in less typical cases and in the absence of tophi the blood findings may be of importance from a diagnostic point of view. It may be mentioned here that in gouty patients the blood uric acid is highest during acute attacks. Following the attack a reduction is found which persists until the next attack, but even the lower figures are generally above the normal for healthy individuals.

No increase in blood uric acid occurs in rheumatism, which fact may be an important point in the diagnosis of certain arthritic conditions. It is claimed that cases of non-gouty arthritis sometimes show high blood uric acid values, but in some of these at least impaired renal function has been demonstrated. Certain cases of sciatica, fibrositis, etc., have been found to give high values for blood uric acid, and many of these show good response to treatment by colchicine, etc., thus suggesting a gouty origin of the condition.

A large proportion of patients suffering from various dermatoses have been found to have increased blood uric acid, suggesting some basis for the term "gouty eczema," in that certain skin lesions may be in certain persons a manifestation of the so-called "gouty diathesis." Luff [1] says that amongst those who have inherited a gouty tendency the skin affections may constitute the only manifestation of gout.

In addition to its aid in diagnosis, the determination of blood uric acid may be of value in estimating the effect of treatment and the course of the disease.

Of the drugs used in the treatment of gout, viz., colchicine, salicylates and atophan, colchicine appears to exert no influence on the elimination of uric acid. The salicylates and atophan, however, induce definitely increased elimination, with a fall in the blood uric acid. In normal individuals this lowering of the blood uric acid lasts only for a day or two, but in gouty subjects it may persist for a longer period and is much more marked. These drugs have little or no effect in reducing the high blood uric acid of advanced chronic nephritis.

Practical Points.—For the determination of uric acid in blood, whole blood is required, potassium oxalate being the usual anti-coagulant. Sodium fluoride may be used as an alternative when preservation is desired. Care should be taken to avoid excess of the anti-coagulant. About 5 c.c. of blood should be taken from the patient for this determination.

[1] "Gout." London, 1908.

CHAPTER XIII

CHANGES IN CHOLESTEROL, PHOSPHORUS, CALCIUM OF THE BLOOD—TETANY, RICKETS

1. **Changes in the Cholesterol of the Blood.**—The normal blood cholesterol content of the blood is from 130 to 190 mgm. per 100 c.c. of plasma.

Some of the conditions in which changes occur in the cholesterol content of the blood have already been mentioned. These include the following :—

(*a*) *Parenchymatous Nephritis.*—Here the blood cholesterol tends to be increased, but the cause of this change is not definitely known.

(*b*) *Urinary Obstruction due to Prostatic Enlargement.*—Patients suffering from this condition, whose capacity to resist the spread of sepsis to the upper urinary tract is low, are said to have also a low blood cholesterol. In other words, low blood cholesterol is related to low defensive powers against infection. This connection is claimed to be of importance in considering the operative risk in cases with enlarged prostate. Here, too, the nature of any connection between cholesterol and defensive mechanisms is unknown.

(*c*) *Cholelithiasis.*—An increase of blood cholesterol is found to be present in about 60 per cent. of patients with gallstones. The raised blood cholesterol is probably indicative of a present or recent attack of the condition responsible for stone formation, and is therefore probably absent in the quiescent stages of the condition. In the great majority of cases, at

any rate, this increase in blood cholesterol is probably due to some obstruction to its excretion by the gall-bladder, with consequent reabsorption into the blood stream rather than to a primary metabolic disturbance. (See also Chapter XIV.)

In addition to these, changes in blood cholesterol are found in a number of other conditions. There is an increase, for instance, in obstructive jaundice, but not in hæmolytic jaundice. The most marked increase in blood cholesterol is to be found in certain cases of diabetes, and figures up to 1·5 per cent. have been recorded.

Amongst other conditions in which an increase has been found are pregnancy (beginning at about the fourth month and increasing as full term is approached), arteriosclerosis, and sometimes in the early stages of malignancy.

Reduction of blood cholesterol is most typically seen in severe anæmias, especially in pernicious anæmia. It is also found in febrile conditions and wasting diseases.

The clinical value of blood cholesterol estimations is chiefly with reference to the conditions discussed elsewhere and briefly recalled above, viz., parenchymatous nephritis, prostatic enlargement and gallstones. With regard to the latter it must be remembered that normal results offer no information bearing on the presence of stones, but where high results are obtained, particularly in the absence of jaundice, they offer valuable confirmatory evidence when other findings point in the same direction. In all cases, however, it is important to bear in mind the other conditions which may influence the blood cholesterol findings.

2. **Changes in the Calcium of the Blood; Tetany.**—The normal calcium content of blood lies between 9 and 11 mgm. per 100 c.c. of plasma or serum. Apart from advanced nephritis, the chief conditions in which a reduction of the blood calcium is found are those associated with the spasmophilic manifestations which we call tetany. The blood calcium is found to be reduced, for example, in practically

all cases of idiopathic tetany of children. In adults, too, certain cases showing symptoms due to spasm of various kinds, show also reduced blood calcium, and it is probable that the symptoms are directly related to the low blood calcium.

The connection between tetanic symptoms and low blood calcium is further brought out by the fact that administration of calcium usually produces relief of the symptoms, and that in idiopathic tetany improvement of the condition is associated with demonstrable increase of the blood calcium.

The nature of the connection between the symptoms observed and the calcium in the blood has been indicated by the work of Loeb and Ewald, who showed that the divalent kations calcium and magnesium have an opposite effect on nervous excitability to the monovalent kations sodium and potassium. The former decrease the excitability of nerves, while the latter increase it. Hence normal excitability will depend on the maintenance of the normal relationship between the exciting ions and the depressant ions. Therefore any relative decrease in the calcium of the fluid bathing a nerve will result in an increase of the nerve's excitability.

Tetany also occurs in persons or animals from whom the parathyroids have been removed, and this tetany is also associated with a fall in the blood calcium, generally of considerable degree. Further, treatment of patients with tetany by parathyroid extract raises the blood calcium and also relieves the symptoms. Hence it is concluded that the parathyroids normally exert control over calcium metabolism, but the exact nature of this control has not been worked out.

So far the connection between the calcium of the blood and tetany seems fairly simple. But certain other considerations complicate the situation.

It has been claimed that in parathyroidectomised dogs there is an increase in the guanidin content of both blood

and urine (guanidin being a product of protein metabolism normally present in the blood in traces only and said to be destroyed by the liver). Increase in the guanidin of the urine is also said to be present in human patients suffering from tetany. Moreover, the injection of guanidin into animals produces the symptoms of tetany and also reduces the blood calcium. Hence the suggestion arises that the symptoms of tetany are due to the action on the nervous system of the toxic substance guanidin, which is also able to reduce the calcium content of the blood.

Another view is brought forward by the observations that symptoms of tetany occur in conditions in which an alkalosis is present. Yet in these conditions there is usually no alteration in the blood calcium content. On the other hand, in those cases of tetany in which low blood calcium is found, there is usually no definite evidence of alkalosis.

A probable connection between the tetany seen in alkalosis, in which the calcium of the blood is normal in amount, and the tetany seen in those conditions in which there is a reduced amount of calcium in the blood can be traced when we take into account the fact that the calcium in the blood does not all exist in the same form. Part of it is diffusible and part is not diffusible. If the appearance of tetany is determined by a diminution of the diffusible or ionised calcium, then it is not necessary that the total calcium of the blood should be diminished. If will be sufficient if a change occurs in which some of the diffusible calcium is transformed to the non-diffusible state, the total still remaining the same. There is certain evidence in support of the idea that in alkalosis the concentration of diffusible or ionised calcium is reduced. Along these lines it is possible to see a connection between the two forms of tetany, and an attractive theory covering the two is that the condition is due to increased excitability of the nervous system due to a diminution of the ionised calcium of the circulating fluids, such diminution being due either to withdrawal of

calcium from the blood or to transference of some of it from the ionised to the non-ionised form.

While attractive, this view can hardly be said to be definitely proved. Moreover, the *rôle* of guanidin is still not explained. It appears to be connected with diminution of blood calcium, but whether this substance is by its toxic action directly responsible for the symptoms of tetany, the fall in blood calcium being an accompanying phenomenon, or whether the symptoms are due to the power of guanidin to remove ionised calcium from the blood is not known.

More recent work has failed to confirm the findings already described with regard to guanidin, and the connection between the toxic effect of guanidin and true tetany is not by any means clear.

From the clinical point of view the determination of the blood calcium is frequently of value in investigating cases showing spasmophilic manifestations. Since also such determinations help to distinguish those cases which are due to an alkalosis from those due to other conditions, they help to indicate what is the appropriate treatment.

It should be mentioned that low blood calcium has also been recorded in certain skin conditions—in eczema, acne vulgaris, folliculitis and gummatosis.

Slight increases in blood calcium have been found in a certain number of patients with gall stones Increases have also been reported in arthritis deformans and in otosclerosis.

3. Changes in the Inorganic Phosphorus of the Blood; Rickets.—The amount of inorganic phosphorus normally present in the blood depends to some extent on age. The serum of infants contains 5·5 to 6 mgm. per 100 c.c., that of children contains about 5 mgm., and of adults about 3·7 mgm.

The only condition of note in which an increase of inorganic phosphorus occurs is nephritis, and in advanced cases of

the azotæmic type of this disease, phosphorus retention may reach a very high value, figures up to 30 mgm. per 100 c.c. of serum having been reported.

Decrease in the inorganic phosphorus of the blood is found in rickets. It is a common mistake to suppose that rickets is generally associated with reduced blood calcium. In uncomplicated rickets, however, this is seldom true, most cases showing values for blood calcium which are quite within the normal limits. Where rickets is accompanied by tetany, however, reduction of blood calcium is usually found, with a tendency for the phosphorus to rise to a more normal level.

Ossification depends not merely on a sufficient supply of calcium and phosphorus, but also requires a rough balance between the two. If the amount of calcium in the diet is greatly in excess of the phosphorus, deficient absorption of phosphorus takes place. In the same way, too great a preponderance of phosphorus has an adverse effect on calcium absorption. In rats fed on a diet containing a minimal amount of the anti-rachitic vitamin, it has been shown that rickets may be produced if the diet contains either abundant phosphorus and low calcium, or abundant calcium and low phosphorus. In the former case the blood contains low calcium and normal phosphorus, resembling the blood findings of tetany in children, and in the latter case the blood contains low phosphorus and normal calcium, resembling the blood findings of rickets in children.

The work of Howland and Marriott shows that ossification does not depend on one factor alone. They state that the occurrence of rickets depends on the product of the blood calcium and blood inorganic phosphorus values (in milligrams per 100 c.c. of serum). In the normal child this lies between 50 and 60. If it falls below 30 rickets is invariably present. If it exceeds 40, the diseased bones are healing, or rickets has not been present.

It is interesting to note that when healing of the bones

occurs in rickets, a rise in the blood inorganic phosphorus is also found to occur.

Rickets is known to be a deficiency disease, and does not normally occur when there is an abundant supply of the anti-rachitic vitamin in the diet. Hence it appears likely that in the presence of abundant vitamin the body is capable of obtaining sufficient calcium and phosphorus to carry out normal ossification, from diets varying widely in their content of these elements. Where the supply of the vitamin is not abundant, relative deficiencies in the diet with respect to calcium or phosphorus may have an important bearing on ossification, while the absence of the vitamin is sufficient in itself to determine the occurrence of rickets. Hence it is believed that the absence of the vitamin results either in a failure to retain calcium and phosphorus or in a failure to absorb them.

But there is another explanation. Rickets has been shown to be frequently associated with acidosis. Pritchard believes this to be the essential cause of the bone changes of rickets, since, he says, all claims on alkaline bases for the purpose of neutralising this acidosis must be met before those of developing bone are attended to. The acidosis is of the starvation type, due to a chronic condition of malnutrition. The connection between malnutrition and vitamin deficiency is found in the view (which has some experimental support) that the action of the vitamin is essentially on the digestive tract, a deficiency leading to atrophy of the intestinal mucosa, so that a general deficiency in absorption results, and not a deficiency limited only to calcium or phosphorus.

Osteomalacia is very probably due to the same conditions as those responsible for the production of rickets, the difference in the manifestations of the two diseases being due to the fact that in rickets the factors responsible operate during the period of bone formation, while in osteomalacia they operate after bone formation is completed.

It is said that low blood phosphorus may be found in cases which show no evidence of rickets. Hence low blood phosphorus is not an infallible sign of the presence of rickets. Nevertheless, it is often of considerable value in the early diagnosis of this condition. From this point of view it is also frequently of value to determine the product of the blood calcium and phosphorus, following the indications suggested by the work of Howland and Marriott. Blood phosphorus determinations are also of use in following the course of the disease in any particular case, and in determining the effect of treatment.

It has been noted that following major fractures in adults, arise in the inorganic phosphorus of the blood to 4 or 5 mgm. per 100 c.c. of serum generally occurs, the rise taking up to two or four weeks, and disappearing again following repair. As a rule, cases with non-union do not show this change in blood phosphorus following fracture.

Practical Points.—For the determination of blood cholesterol, plasma is used. About 4 c.c. of blood should be obtained and treated with potassium oxalate.

For calcium determinations, either serum or plasma may be used. About 5 c.c. of blood should be obtained and should be treated with sodium citrate if the determination is to be made on plasma. Neither potassium oxalate nor sodium fluoride should be used as anti-coagulant in this case.

For inorganic phosphorus the requirements are the same as for calcium, except that there is no objection to the use of potassium oxalate or sodium fluoride as anti-coagulant.

CHAPTER XIV

OSSIFICATION; CALCIFICATION; CALCULUS FORMATION

THE formation within the body of solid material containing a large proportion of inorganic substances occurs in many different conditions. In some cases, as in the formation of bone, the process is physiological and is to be encouraged. In others the process is pathological and is to be prevented as far as possible.

The ultimate factors which determine the deposition of this solid material are essentially chemical, though the conditions under which these chemical factors operate may be altered or controlled by such agencies as diet, infection, mechanical obstruction, etc.

It is of importance therefore to study the formation of these solid bodies so as to understand as far as possible what processes are occurring in any given case. We may then be in a position to consider whether it is possible to take any steps to influence these processes to the patient's benefit, and if so, to determine what those steps should be.

A brief examination soon convinces us that ossification and calcification differ considerably from calculus formation. In bone and in calcified tissues calcium salts are always present in considerable amount. In calculi, though calcium salts are frequently present and often preponderate over other substances, such salts may be absent altogether, or present in relatively insignificant amounts. Calculi in fact may contain little or no inorganic material of any sort. Ossification and calcification are processes of deposition of calcium salts in body tissues; calculus formation is the

deposition of various materials in solid form within the cavities of hollow organs or in the ducts or passages leading to or from those organs. The processes are entirely different and require separate consideration.

Ossification and Calcification.—The composition of the inorganic salts in calcified tissues of the body seems to be practically the same, if not identical, whether the salts are laid down normally, as in ossification, or abnormally, as in certain pathological conditions. They contain 10 to 15 per cent. of calcium carbonate and 85 to 90 per cent. of tri-calcium phosphate.

Any degenerated or dead tissue that is not infected, and that is so large or so situated that it cannot be absorbed, will probably become infiltrated with calcium salts. There is, however, one exception to the rule that some form of tissue degeneration is required before calcification occurs, and that is in what is known as metastatic calcification. This takes place in conditions where there is much destruction of bone (caries, osteosarcoma, osteomalacia). In such conditions deposits of calcium salts are sometimes found distributed diffusely in various organs, particularly lungs, stomach and kidneys. This must depend on oversaturation of the tissue fluids by calcium salts which have been liberated from their normal sites by the diseases mentioned. Under these conditions of oversaturation, very little chemical change will be required to effect deposition, the most potent being a change towards an alkaline reaction, since calcium salts are precipitated by alkalis. In the organs most affected we have excretion of acids into their cavities, leaving the tissue fluids correspondingly alkaline, and so the calcium salts are rendered less soluble, and tend to be deposited. There is also true metastic calcification in the large arteries, pulmonary veins and beneath the endocardium of the left side of the heart, *i.e.*, where the blood contains least CO_2.

With regard to calcification in general, we have to take into account the following facts :—

1. The calcium salts must come from the blood, where they are held in solution or suspension by the proteins either as inorganic salts (carbonate or phosphate) or as calcium-protein compounds, or both. Under normal conditions the blood is near its saturation point with respect to calcium. Hence comparatively slight changes may so alter the stability of such solutions or suspensions that precipitation results. The changes which may bring about this result are :

(*a*) Increased alkalinity or lowered CO_2 content.

(*b*) Changes in the proteins.

(*c*) Changes in the quantity or composition of the calcium salts.

Evidence has been produced suggesting that the calcium in the blood is present as a complex $2CaHPO_4.2CO_2.Ca(HCO_3)_2$, whose existence is obviously dependent on a sufficient quantity of CO_2.

2. Except in metastatic calcification, retrogressive changes are necessary.

We have to consider therefore what is the connection between retrogressive changes in tissues and precipitation of calcium salts from the blood and tissue fluids within them.

This connection might be due to altered circulation and physiological activity brought about by such changes, or to the production within damaged tissues of substances having a special affinity for calcium salts.

The latter alternative has generally been assumed to occur. Thus it has been considered that calcification is due in the first place to the presence of fatty acids in the tissues concerned, that these have combined with the calcium of the circulating fluids, forming calcium soaps, and that subsequently the calcium soaps are changed to phosphate and carbonate. Though this may be true with respect to tissues rich in fat, *e.g.*, in calcifying lipomas or in fat necrosis it is very probably not generally true, for in the first place, in many cases calcifying tissues, even in the early stages of the

process, have been found to contain very small amounts of either soaps or fatty acids. In the second place it has been found that when calcium soaps are implanted in the tissues they do not become transformed into calcium phosphate or carbonate, but are largely absorbed.

We have, however, in the altered physiological activity of damaged or dead tissues, certain factors which do appear to explain the process which occurs, especially when we also take account of the nature of the material which becomes calcified. We have, for instance, an enfeebled circulation, and lowered tissue activity. Little oxidation is occurring and there will therefore be decreased production of CO_2. There is stasis, a condition always favourable to the deposition of solids.

In materials which become calcified there is a certain similarity in physical properties, though there may be wide differences in chemical composition. Such materials tend to become homogeneous and often hyaline, *e.g.*, cartilage in ossification and degenerated and therefore structureless (or becoming structureless) material in pathological calcification. Materials of such physical properties have been shown to exhibit a special affinity for calcium salts. When they are saturated with a solution of such salts of a similar nature to the body fluids, any decrease in CO_2 content will lead to precipitation of these salts in them.

Moreover, such materials are in similar physiological condition, which is favourable to the precipitation described. Thus cartilage and the trabeculæ of bone are relatively inactive tissues, and degenerating tissues are dying or dead. Hence in both, CO_2 tension is low on account of low cellular activity.

Hence the explanation of both calcification and ossification appears to be as follows :—

Blood serum contains calcium and inorganic phosphorus in relatively unstable solution, the solution only being maintained by a sufficient CO_2 tension. The intercellular

fluids of the tissues probably contain calcium and phosphorus in relatively more unstable condition.

In materials in which the CO_2 tension is low, and particularly if the same materials have in addition an affinity for calcium salts, the conditions are therefore specially favourable for precipitation of calcium salts from such fluids, and it is because materials which become ossified or calcified exhibit these conditions that deposition of calcium salts takes place in them.

In support of this view it has been found experimentally that from an artificial serum containing calcium salts in the same proportion as in normal serum, increasing the alkalinity (equivalent to removing CO_2) causes the production of a precipitate of the same composition as the inorganic matter of bone and of calcified tissues.

Howland says: "This view of the factors that control calcification and of the mechanism of calcification, explains the normal process and the failure in rickets and tetany of children and the rickets of animals. It also explains calcification in dead or inactive tissues, such as tuberculous lesions and in the fascial planes of the muscles in myositis ossificans, where the first change seems to be a hyaline transformation of the connective tissue. What is further of much importance it explains the constancy of composition of the bones of all animal species in which the calcium and inorganic phosphorus concentrations of the serum, so far as they have been studied, do not differ greatly from those of man."

It also explains the unfavourable effect on ossification of states of acidosis.

Formation of Calculi.—There is one general and fundamental principle underlying the formation of true calculi, namely that there must be alterations in the composition of a fluid which result in simple physical or chemical precipitation of solid material from it.

These alterations may be:—

(*a*) Increased concentration leading to supersaturation

and hence to crystallisation. This is the cause of the presence of cholesterol crystals in gallstones.

(*b*) Chemical changes leading to the production of less soluble substances, as in the case of phosphate, uric acid and oxalate deposits.

In addition, certain other factors have considerable bearing on the formation of stones, once the condition just mentioned is attained. Such are :—

1. *The Presence of a Nucleus.*—It is a well-known fact that supersaturation may occur to a considerable extent without crystallisation occurring, if no nucleus is present. Use is made practically of the value of a nucleus in the method of inducing crystallisation in a supersaturated solution of a substance, by adding a few crystals of the substance to the solution, or of inducing crystals of sugar to form around a string, as in the formation of rock candy.

Substances which are important as nuclei in the formation of calculi are bacteria, desquamated cells or foreign bodies.

2. *Stasis or Obstruction, whether Partial or Complete.*—There is always more *débris* at the side of a stream where the flow is slow than in the centre. In a fluid from which solid is being deposited the rate of flow may determine whether the solid is deposited within a certain cavity through which the fluid passes or outside it. Moreover, even when solid is actually deposited within a cavity the rate of flow may determine whether the solid continues to grow in size within the cavity or is washed out while still small enough to pass through the opening. Thus stasis aids deposition and aids growth when deposition has once occurred.

3. *The Presence of a Binding Substance.*—This would seem to apply particularly to urinary deposits, for it is frequently found that a person may pass urine containing sediment over a long period and yet no stones form. That is, the deposit remains as small discrete particles which are removed, though the actual amount of solid formed may be

greater than in cases where large stones are retained. The binding substance is protein in nature—it may be mucin resulting from the effect of inflammatory processes in stimulating mucous secretion or it may be the protein of inflammatory exudates.

(In this connection deposition of solid from a fluid *after the fluid is passed from the body* is not necessarily an indication of deposition, or tendency thereto, within the body, *e.g.*, urates are often deposited from urine on cooling, but would easily be kept in solution at body temperature.)

Not only are inflammatory processes instrumental in causing the production of a binding substance, but they may also give rise to any other of the factors concerned in the formation of stones. Undoubtedly inflammation is the most important condition concerned with the production of calculi. It may be responsible for the presence of a nucleus, *e.g.*, bacteria, pieces of fibrin, cells, etc. It may, by causing swelling of cavities or ducts, produce stasis. It may in fact be responsible for the primary requirement, namely, actual precipitation, for the protein-containing fluids of inflammatory exudates contain positive colloids capable of precipitating certain negative colloids present in some secretions, *e.g.*, the calcium bilirubinate of bile. Or the inflammatory process may be accompanied by certain changes in reaction ; *e.g.*, the production of alkaline urine in some forms of cystitis, which causes the precipitation of phosphates.

The causes of stone formation are often periodic. Hence stones exhibiting concentric rings may be found, or different "families" of stones may be present in the same organ. Whether further deposit is limited entirely to existing stones or fresh families are formed will depend on the presence of further nuclei.

It is also to be noted that the presence of stones is in itself a cause of stone formation, since it may give rise to stasis, obstruction, damage or inflammation in the organ concerned.

Having considered the general conditions relating to the formation of stones, let us turn our attention to the different varieties of stones met with.

1. **Gall-stones.**—Many classifications of the types of gall-stones which occur have been made. These are of no theoretical value as indicating their mode of formation. For descriptive purposes the following is a sufficiently good classification :—

(*a*) Pure cholesterol stones.

(*b*) Laminated cholesterol stones.

(*c*) Mixed stones, containing cholesterol, calcium salts and bile pigment in various proportions.

There have been many theories concerning the formation of gallstones. According to Naunyn, they are caused through the deposition within the gall-bladder of cholesterol derived from degenerating desquamated epithelial cells of the gall-bladder and bile tracts. According to another view they are due to hypercholesterolæmia.

A more recent view attributes their formation to the production of stasis in the gall-bladder. This stasis is brought about principally by inflammation, but may also be due, in a small proportion of cases, to mechanical causes. On this view cholecystitis is a most important factor in the production of cholelithiasis.

It is now know that the gall-bladder concentrates the bile it receives from the liver to a considerable degree. Moreover, certain substances are absorbed by the gall-bladder and passed on to the general circulation. As a result of inflammatory swelling of the mucosa of the gall-bladder and cystic duct (or possibly, in some cases, of altered mechanical conditions within the abdomen), a partial obstruction to the outflow of the viscid gall-bladder bile results, while the entry of the more dilute, mobile hepatic bile is not appreciably affected. The concentrating activity of the gall-bladder, operating in the presence of normal supply but diminished output, must succeed in producing a bile of greater concen-

tration than normal. If this continues, supersaturation of the bile with respect to certain substances will result, and deposition of solids from such a solution must occur, *i.e.*, we have the production of stones. The type of stone deposited will depend on such factors as the rate and the degree of supersaturation of the bile, the presence or absence of suitable nuclei, etc.

Another consequence of the process described is that the gall-bladder, which normally absorbs cholesterol, is now in contact with a bile which is richer in cholesterol than usual. Hence the amount of cholesterol absorbed and passed on to the circulation is now greater than normal, and a hypercholesterolæmia results—that is if the functional activity of the gall-bladder has not been impaired by previous disease.

Hence hypercholesterolæmia is associated with the stage of active formation of gall-stones and disappears when this stage is recovered from, though the stones remain. The association between hypercholesterolæmia and an intact gall-bladder in patients with gallstones was shown by the fact that in a number of patients with hypercholesterolæmia and gallstones the hypercholesterolæmia was found to disappear after the removal of the gall-bladder.

2. **Urinary Calculi.**—Infection and stasis are the principal factors concerned in the formation of stones in the urinary tract. Infection plays its part in a number of ways. In the first place it is usually the cause of marked changes in the reaction of the urine. Infection by *B. coli* results in the production of an acid urine; if other organisms are the cause of the infection the urine becomes markedly alkaline. Marked changes of reaction in either direction tend to cause precipitation—uric acid, for instance, is rendered less soluble by increasing the acidity, while alkalinity causes the precipitation of phosphates and oxalates. In the second place, infection is responsible for producing both nuclei and binding substance.

Other factors favouring stone formation are :—

1. Changes in reaction of the urine due to causes other than infection. Such causes have reference to diet, drugs, nervous and other conditions.

2. The production of a highly concentrated urine which may become supersaturated with respect to one or more constituents. This may occur in any condition causing oliguria, provided the kidneys maintain their concentrating power.

3. Certain metabolic disorders resulting in excessive output in the urine of certain substances, whose concentration in the urine may exceed the saturation point.

4. Vitamin A deficiency seems to be associated with tendency to formation of stones in the urinary tract. This is discussed elsewhere.

The types of urinary calculi are as follows :—

Uric Acid Stones.—Stones consisting wholly of uric acid are rare, though uric acid is very frequently present in mixed stones. Uric acid is very insoluble in water, but certain organic bodies (including pigments) and Na_2HPO_4 render it more soluble.

Deposition of uric acid is favoured by high urinary acidity, high concentration of urine, or by excessive elimination of uric acid, such as would result from taking a diet rich in purine bodies.

Uric acid stones are formed chiefly in the pelvis of the kidney, but they may pass into the bladder, where they frequently act as nuclei for further deposition of other substances. They are yellow or brown in colour.

Urate Stones.—Pure urate stones are not common. They are generally coloured, soft and easily powdered. The urates are very often found in mixed stones.

Oxalate Stones.—Stones consisting mainly of calcium oxalate are said to be the commonest type found in the urinary tract. They are very hard and rough and frequently cause bleeding. Usually they are first formed in the renal

pelvis and are due chiefly to excessive oxalate excretion, due to ingestion of much oxalate-containing foods (*e.g.*, rhubarb, grapes, spinach, etc.) and probably also to gastric fermentation.

Phosphate Stones.—These are mostly formed as a result of the decomposition of urine, with the formation of ammonia; hence they usually consist largely of the triple phosphate. Their commonest site is the bladder, where they usually arise as a result of cystitis. Similar deposits are common around foreign bodies in the bladder, including other calculi.

Stones consisting mainly of the dicalcium or tricalcium phosphate arise under conditions of non-ammoniacal alkalinity of the urine, but are not very common.

The formation of phosphatic deposits in the urine is always the result of alkaline reaction and does not depend on the phosphate of the diet.

Calcium Carbonate Stones are rare in man but common in herbivora.

Cystine Stones, due apparently to some abnormality of protein metabolism, are also very rare.

Xanthine Stones are also very rarely met with.

3. **Pancreatic Calculi.**—The cause of these is not definitely known. Infection is probably the most important factor, as they are not formed as a result of experimental stasis alone. They consist chiefly of calcium carbonate, but phosphates also are often present.

4. **Salivary Calculi.**—Concerning these there is also some uncertainty as to the factors responsible for their formation. It has been said that the entrance of foreign bodies into the ducts is the chief factor. Increased akalinity of the saliva may also be a cause, and infection no doubt plays an important part.

The calculi contain calcium phosphate and carbonate, together with some organic matter, and resemble in chemical composition the tartar which forms on the teeth.

5. **Prostatic Calculi.**—These are of somewhat rare occurrence and are usually associated with chronic prostatitis. They are generally multiple and appear to be the result of deposition of inorganic material round the corpora amylacea. They consist mainly of calcium phosphate.

CHAPTER XV

VITAMINS AND DEFICIENCY DISEASES

SATISFACTORY growth and the maintenance of the health and proper nutrition of the body have long been known to depend on a " well-balanced " diet, that is, a diet containing adequate amounts of all three classes of foodstuffs, viz., proteins, carbohydrates and fats, together with certain mineral salts. Certain facts have long been known, however, which have suggested that even all these may fail to achieve the desired object, and that something still more is needed, though it is only within the last few years that the true significance of these facts has been recognised and our knowledge developed concerning the additional substances required.

As early as 1804 it was so well recognised that fruit juices added to the diet of sailors prevented the development of scurvy amongst them, that the issue of a ration of lemon juice was then made compulsory in the British Navy. Later the disease of beri-beri, which was common in the Japanese Navy, was largely abolished when a portion of the polished rice of the sailors' diet was replaced by barley. Subsequent work showed that the disease was due to the absence from the diet of the outer husk of the rice which had been removed in the process of polishing.

It has also been shown that certain animals cannot be satisfactorily reared on a " pure " diet, that is a diet consisting of purified proteins, fats and carbohydrates, together with mineral salts and water. On such a diet growth soon ceases to take place. It has therefore become evident that, in addition to the ordinary food materials, certain substances known as " accessory food factors " or " vitamins " must be

present in a diet in order to prevent certain diseases or to ensure satisfactory growth, and in recent years careful experimental work has added much to our knowledge concerning such substances. Such work first indicated the presence of three vitamins, viz., a fat-soluble factor chiefly concerned with the promotion of growth, called A, a water-soluble factor capable of preventing beri-beri, called B, and a water-soluble factor capable of preventing scurvy, called C.

It was soon recognised that a diet rich in materials known to contain a good supply of vitamin A tended to protect children against the onset of rickets, or if such a diet were given to children already suffering from rickets, the condition improved or was entirely cured. On the other hand rickets was also found to be associated with poor, unhygienic surroundings, particularly with overcrowding and lack of sunlight, while cures resulted by correcting these conditions and by exposure of the patient to the action of sunlight or artificial ultra-violet light. Hence there arose two views as to the cause of rickets, one that the disease is due to a vitamin deficiency and the other that it is due to unfavourable conditions of environment, and particularly to lack of sunshine. The two views were reconciled by the discovery of a fourth vitamin, D, which is fat-soluble and generally associated with A, and which can be produced by the action of sunlight or ultra-violet light on the skin of a patient, or on certain chemical substances. Rickets is now known to be due to lack of vitamin D, which is generally termed the anti-rachitic vitamin.

In experimental work on vitamin deficiency it has often been noted that animals on deficient diets, in addition to other defects, frequently showed impaired or lost reproductivity. This has now been traced to deficiency in the supply of a fifth vitamin, now called E. Like A and D, E is fat-soluble.

What is known as vitamin B, has for some time been suspected of being a complex containing at least two separate factors. This appears now to have been established, for two

different substances have been recognised in the B factor, one having the original action which constituted the chief feature of vitamin B, namely, the prevention of beri-beri, and the other (also water-soluble), appears to be able to prevent pellagra. The latter is at present known as the P.P. (*i.e.*, pellagra preventing) factor, and the former the B.P. (beri-beri preventing) factor.

Up to the present, then, six different vitamins have been recognised, and it is possible that as a result of further research work, the number may be further increased.

With the exception perhaps of vitamin D it does not appear that the vitamins are synthesised in the animal body. We are dependent ultimately on the vegetable kingdom for our supply of these materials. The vitamin content of foods of animal origin, *e.g.*, milk, is dependent on the vegetable diet of the animal from which the food is obtained.

Vitamins are present, even in foodstuffs considered to be rich in these substances, in extremely small amounts, *e.g.*, pigeons, which readily show the effect of deficiency in vitamin B in a characteristic manner, can be maintained in perfect health over long periods by the addition of 0·5 gm. of dried yeast per day, to a vitamin B-free diet. The same result has been obtained with 0·08 mgm. per day of a specially prepared vitamin B concentrate prepared from yeast. On account of the difficulty of isolating such relatively small quantities of material in a pure form, the pure vitamins have not been prepared, and their actual chemical constitution has not been ascertained.

Chemical tests for their recognition and estimation have therefore not been devised, except in the case of vitamin A, for which a colour test has recently been developed.

Both quantitative and qualitative work on the vitamins is carried out by means of feeding experiments on animals.

For example, to ascertain whether a given foodstuff contains a certain vitamin, and if so in what amount, appropriate animals are fed on a diet which, apart from the

material to be tested, is known to contain none of the vitamin in question. To this diet the material under examination is added in known amounts, and observations are then made as to whether the diets so given are sufficient to maintain normal growth, to prevent the occurrence of the diseases characteristic of lack of the vitamin, or to cure the disease in animals in which it has previously been developed. If the desired object is attained it is obvious that the foodstuff examined possesses some of the vitamin in question, and its amount is indicated by the minimum amount of the foodstuff capable of producing the desired results.

The appropriate animal for each vitamin has been found as a result of much experience. The same animal is not equally useful for tests of all the vitamins.

Although vitamin A has been specially associated with growth-promoting properties it is probable that all exert some effect in this direction. In the same way lack of A, besides resulting in retardation of growth, is responsible for a specific disease, as is the case with lack of the other vitamins. No ill-effects have been observed following feeding with excessive quantities of the vitamins.

We can now pass on to a separate consideration of each of the vitamins.

Vitamin A.—Important sources of this vitamin are cod-liver oil and other fish liver oils, butter fat and certain other animal fats (but not lard), milk, eggs and glandular organs, such as liver and kidney, tomatoes, spinach and lettuce. It is absent from vegetable oils, and hence is not present to any great extent in those kinds of margarine in which the fat is of vegetable origin.

If fats containing vitamin A are saponified with boiling alcoholic potassium hydroxide in an atmosphere of nitrogen (to prevent oxidation), the whole of the vitamin may be recovered in the unsaponifiable residue, which amounts on the average to about 1 per cent. of the original material. By this means vitamin A concentrates may be prepared

and may be used to enrich foods otherwise deficient in this vitamin, *e.g.*, vegetable margarine. Such concentrates have been further treated, and by removal of cholesterol and by subsequent fractional distillation, materials with a much greater concentration of vitamin A have been obtained. In these the vitamin is associated with unsaturated alcohols of high molecular weight. Processes which affect the unsaturated character of these alcohols (*e.g.*, oxidation, hydrogenation, bromination, etc.), cause the destruction of the vitamin.

The colour test for vitamin A, which has already been referred to, depends on the production of a blue colour when arsenic trichloride is added to an oil containing the vitamin. The colour develops immediately the two liquids are mixed together and soon fades. Hence, immediately the colour develops it is compared with an artificial standard. Experience so far has shown that the intensity of the colour developed is proportional to the concentration of vitamin A in the material tested, as ascertained from the results of feeding experiments.

Antimony trichloride appears to be preferable to arsenic trichloride, and by the courtesy of Messrs. Planters Foods, Limited, I am able to give details of the test used by this firm, using the former reagent. The test determines the concentration of the substance examined, in chloroform solution (1 c.c.) which, when treated with 1 c.c. of reagent, gives a barely perceptible blue colour. The method is as follows :—

For material which is expected to give a result between 1 in 500 and 1 in 10,000, about 0·03 gm. is weighed accurately into a 50 c.c. beaker, while for material showing a result in a dilution of over 1 in 10,000, about half this quantity is taken. As the material is usually a liquid, these weights can be obtained approximately by taking a large or small drop from a glass rod.

The material is carefully washed from the beaker with

chloroform into a 25 c.c. measuring cylinder, and the volume adjusted to give a solution of 1 in 500 for the larger weight of material, or 1 in 1,000 for the smaller weight. In both cases the volume of the solution will be in the region of 15 c.c.

One c.c. of this chloroform solution is transferred by means of a pipette into a colourless test tube, which is held over a sheet of white paper; 1 c.c. of the reagent is then added from a quick-delivering pipette, a slight shake being given to the solution as the reagent enters it. The reagent is a 20 per cent. solution of antimony trichloride in chloroform, not more than one week old. A transient blue colour appears in the solution after mixing as above, and at this dilution is usually fairly strong. From the original solution, therefore, solutions of increased dilution are made, until a dilution is reached, such that 1 c.c. of the solution when treated with 1 c.c. of the reagent gives a blue colour which is scarcely perceptible. The dilution at this point, expressed as a fraction, is inversely proportional to the vitamin-strength of the material. Hence, the reciprocal of this fraction which is directly proportional to the vitamin strength, is the number used with regard to the substance tested, and is called the "dilution strength" of the material.

The test, as above used, is suitable for cod-liver oil or vitamin concentrates in oil. For other substances, *e.g.*, margarine, it is best to extract the unsaponifiable matter, make a solution of it in chloroform, remove any artificial colouring matter by means of decolourising carbon, and then test the resulting solution. The result can be calculated back to the weight of margarine taken. A similar type of modification would probably be necessary for egg yolk, butter and greenstuffs.

Vitamin A is fairly resistant to heat, particularly in the absence of oxygen. Foods with a good content of A are not appreciably affected, with regard to vitamin activity, by

ordinary cooking or by canning. Little or no loss occurs when milk is boiled for a few minutes, or dried or pasteurised by modern methods. Butter exposed to air at 37° C. gradually loses its vitamin A. The vitamin is destroyed by the process of hardening oils by hydrogenation.

The rat is the most suitable animal for feeding experiments on vitamin A.

Effects of Deficiency of Vitamin A.—The first effect to be studied was the cessation of growth in young animals. This does not immediately follow withdrawal of the vitamin from the diet. Its onset depends on the previous feeding of the animal and is due to the fact that the body is able to store this vitamin. Hence, evidence of deficiency is only seen after any store obtained from previous diets is exhausted. If deprivation of the vitamin continues, the animal ultimately dies.

Adult animals do not show effects of lack of the vitamin to the same extent as young ones—again probably due in part to utilisation of previously stored vitamin. But even adults do show some impairment of health, as shown by increased susceptibility to bacterial infections and lowered reproductive powers.

A pathological condition frequently associated with lack of vitamin A is xerophthalmia, a characteristic eye condition which if untreated may end in complete blindness. The primary lesion appears to be inhibition of the lachrymal glands, and the same effect seems to be associated with the salivary glands. If not too far advanced the condition can usually be cured by administration of vitamin A, without any other treatment.

Another effect to which attention has recently been called is the increased liability to the formation of calculi in the urinary tract, in animals on a diet deficient in vitamin A. It is suggested that this effect may be secondary to changes in the epithelial cells of the urinary mucous membranes, degenerated cells produced by these changes forming

suitable nuclei around which stones may form. Increased liability to infection may also be a factor.

The storage capacity of the body for vitamin A appears to be considerable, and is much greater than for B or C.

Vitamin D.—As already mentioned this vitamin is fat-soluble and closely associated with vitamin A in the unsaponifiable fraction of many fats and oils. In general it is obtained from the same sources, but many facts brought out within the last four or five years have clearly established it as an independent substance. While in general the distribution of D is similar to A, certain interesting differences have been noted. Thus the anti-rachitic action of butter is much less than that of cod-liver oil, but the ability of butter *to cure xerophthalmia is rather greater than that of cod-*liver oil. In other words, cod-liver oil contains much more vitamin D than butter, but rather less vitamin A. Similarly spinach is much more active with respect to A than with respect to D.

While substances containing Vitamin D give a colour with arsenic trichloride, it is not the same as that given by substances containing vitamin A.

Many foods ordinarily incapable of preventing rickets were found to develop anti-rachitic properties after exposure to ultra-violet light. It was also found that animals fed on a rickets-producing diet could be kept free of the disease if they were periodically subjected to the action of ultra-violet light. It appeared therefore that something present, both in certain foodstuffs and in the animal body was capable of being acted on by ultra-violet light so as to produce the anti-rachitic vitamin. The foods capable of being "activated," *i.e.*, made to possess anti-rachitic properties, all contain cholesterol, which forms a large part of the unsaponifiable matter of fats and saponifiable oils. Cholesterol is also a well-known constituent of the blood and tissues of animals. Hence attention was directed to this substance.

Ordinary pure cholesterol has no anti-rachitic properties, but these are developed to a marked degree after treatment of cholesterol with ultra-violet light. Cholesterol so activated can be separated into fractions of widely differing activity. Hence it appears that not all the cholesterol is activated, but only a small portion of it. Hence it was concluded that ordinarily pure cholesterol contains something not cholesterol, but difficult to separate from it, which gives rise to vitamin D on irradiation with ultra-violet light. This substance was called the "pro-vitamin." It was also noticed that the spectrum of the cholesterol before irradiation contained certain marked absorption bands, which disappeared after irradiation. When other sterols were examined it was found that ergosterol shows these same bands with marked intensity, and feeding experiments have proved that irradiated ergosterol will protect rats from rickets in doses of less than one ten-thousandth of a milligram. Ergosterol is therefore considered as the pro-vitamin, but the nature of the change which is brought about by irradiation, thus producing the vitamin, is not yet known, neither has the vitamin been prepared by any other method but irradiation with ultra-violet light.

The present view, therefore, is that vitamin D can be produced from ergosterol, the pro-vitamin by natural ultra-violet light, such as is present in sunlight, or by artificial ultra-violet light, acting on the animal's food or on its body.

Ergosterol is a sterol which was first prepared from ergot, but is widely distributed amongst the lower plants. It is also present in small quantities along with cholesterol (about 1 in 2,000) from practically all sources, and is only separated from it with difficulty.

Vitamin D is much more stable than vitamin A to heat or oxidation. Hence, by suitable treatment, *e.g.*, by heating at 100° in the presence of oxygen for twelve hours or more, cod-liver oil may be made to lose its vitamin A, while still

retaining anti-rachitic properties. Prolonged exposure to ultra-violet rays seems to cause loss of vitamin D.

Young rats or puppies are most suitable for experimental work on this vitamin.

Effect of Deficiency of Vitamin D.—The characteristic sequel to lack of vitamin D is the onset of rickets. Clinically, rickets is not a disease limited entirely to deficient bone formation, but it is this aspect of the disease that has received most attention. The relation of bone formation to calcium and phosphorus supply has been dealt with in a previous chapter and the probable influence of vitamin D in promoting absorption of these elements has been suggested. The relation between calcium and phosphorus supply on the one hand, and vitamin D on the other, to the production of rickets seems to be as follows :—

1. With a good and well-balanced supply of calcium and phosphorus, the absence of vitamin D will result in the production of rickets.

2. With a moderately deficient or imperfectly balanced calcium and phosphorus supply, minor deficiencies in vitamin D may determine the onset of rickets.

3. With abundant vitamin D supply, rickets probably occurs only in such gross deficiency or unbalance of calcium and phosphorus supply as is seldom met with.

It is probable that the body is capable of storing vitamin D to a certain extent.

Vitamin B.—Probably the best known source of this vitamin is yeast, and yeast extracts or dried yeast contain it in abundance. Other important sources are plant seeds and egg yolk. It is also present in many fruits, nuts and vegetables. Whole cereal grains are also a good source, but as the vitamin is present in the embryo and outer covering the vitamin is largely lost in the milling process. which removes these, leaving a starch core of low vitamin content.

Many highly-concentrated extracts containing vitamin B

have been prepared, and attempts made by experiments on these, to obtain some insight into the chemical composition of the vitamin, but so far few definite or conclusive results bearing on the subject have been obtained.

Vitamin B is less easily destroyed by oxygen than A or C. It is also resistant to heat, temperatures of over 120° C. being required to cause its rapid destruction; hence little loss occurs in ordinary cooking. It is also very resistant to drying. It is soluble in water and in alcohol, but insoluble in ether.

Birds are used for experimental work on vitamin B, particularly pigeons or chickens. Rats are also used for certain purposes (growth tests).

Effects of Deficiency of Vitamin B.—Until very recently, the effects of lack of this vitamin were recognised as the development of beri-beri in man, or of its equivalent, avian polyneuritis, in birds. In addition there was a failure to maintain normal growth, exhibited particularly in young rats. In this respect withdrawal of the vitamin from the diet produces an effect almost immediately. Cessation of growth occurs, followed soon by progressive loss of weight, leading to the death of the animal. Adult animals also suffer from lack of the vitamin. Loss in weight occurs, which may only be very gradual at first, but eventually becomes rapid and may reach a fatal termination. Symptoms of beri-beri appear in the later stages.

In birds, though loss in weight also occurs, the symptoms of polyneuritis predominate and appear at a much earlier stage than in mammals. Absence of vitamin B results in the rapid development of paralysis, complete helplessness and death. Administration of vitamin B to birds suffering severely from polyneuritis generally results in rapid cure.

It has already been mentioned that from what is known as vitamin B a factor has been separated whose absence appears to determine the onset of symptoms of pellagra.

It also appears from recent work that the characteristic growth-producing effects of vitamin B are associated with the anti-beri-beri substance, rather than with the anti-pellagra substance.

The power of the body to store vitamin B must be extremely small, since characteristic effects due to its absence begin to appear almost immediately it is withdrawn from the diet.

Vitamin C.—This vitamin is notably present in fresh fruits and vegetables, and of these oranges and lemons are the best sources; limes as a source of it are distinctly inferior to lemons. In contrast to vitamin B, this vitamin is usually not present in seeds in a resting state, but appears when the seeds begin to germinate. Green leaves, swede turnips and tomatoes are also good sources, while meat and milk are generally poor.

By removal of citric and other acids, protein, sugar, etc., from lemon juice, very concentrated preparations of vitamin C can be obtained. From work on such preparations it is suggested that the active substance approaches in molecular magnitude to the dimensions of a hexose molecule, and is distinct from the nitrogenous and reducing substances which are found in the concentrated preparations.

Vitamin C is readily destroyed by oxidation, and also withstands drying very badly. It is also easily destroyed by heat, especially in the presence of oxygen or of alkali. Acid, on the other hand, tends to preserve it.

In general, most foods which in the fresh state are good sources of vitamin C, lose most of the vitamin during cooking, especially in the presence of alkalis. Hence the practice of boiling vegetables in the presence of sodium carbonate or bicarbonate is not to be recommended from this point of view. Processes of preservation of foods by evaporation or canning should be carried out in the absence of air, and preferably in the presence of acid, if it is desired to conserve vitamin C.

The guinea-pig is the animal generally used for experimental work on vitamin C.

Effects of Deficiency of Vitamin C.—The typical result of withholding vitamin C is the development of scurvy. Guinea-pigs on a diet devoid of this vitamin show normal growth for a period of 2 to 3 weeks, following which symptoms of scurvy appear, followed by loss of weight and finally death in 4 to 5 weeks from the commencement of the period of deficient dieting.

In man, scurvy and infantile scurvy are the typical results of vitamin C deficiency, but in addition to a frank manifestation of the disease, certain less typical manifestations of ill-health and lowered resistance may appear in persons whose vitamin C supply is barely adequate. These conditions disappear as a result of increasing the supply of the vitamin.

The ability of the body to store vitamin C is much below its ability to store vitamin A.

Vitamin E.—The best source so far discovered is the oil extracted from the wheat embryo. It is also present in other cereal embryos, in certain green leaves (lettuce, alfalfa, kale) egg yolk, beef liver, and some vegetable oils. It is only present in very small amount in milk, cod-liver oil and yeast.

Like the other fat-soluble vitamins, E is associated with the unsaponifiable matter of fats and oils. Little is known concerning its chemical properties.

Vitamin E is remarkably stable to heat, light and air and also appears to be resistant to oxidation and reduction.

The rat is the animal which has been used in experimental work on this vitamin.

Effects of Deficiency of Vitamin E.—Lack of E causes the development of complete sterility. Female rats either do not become pregnant, or if they do, development of the fœtus soon ceases, death of the fœtus then occurs, with subsequent resorption. No marked changes have been noted in the

ovary, and the process of ovulation appears to be normal; the effect seems wholly concerned with fœtal development. If the vitamin is present, but deficient in amount, females may give birth to dead or emaciated young. In the male, lack of E is followed by degenerative changes in the testicles. There is destruction of the germ cells and ultimately of the seminiferous epithelium. The effects so caused can be cured in males provided vitamin E is supplied within a period of 90 to 150 days from birth. If treatment occurs after this period sterility persists. In females the cure of the condition apparently results by treatment at any time during the reproductive period.

It is also suggested that vitamin E is required in liberal amounts for the purpose of lactation. Otherwise, it is said, the mothers' milk fails to nourish the young which often die shortly after birth, or fail to grow at a normal rate. Hence it is thought that vitamin E may be a complex, consisting of an anti-sterility factor and a lactation-promoting factor.

Quite recently experiments have been reported which indicate that vitamin E has a specific action with respect to the assimilation of iron. Since beef liver contains iron, and its fats contain vitamin E, a possible explanation is suggested of the value of the liver treatment of pernicious anæmia introduced by Minot and Murphy.

Rats have a considerable capacity for storage of vitamin E, at any rate so far as the anti-sterility factor is concerned, but it is said that the female has at best only a very limited capacity for storing the factor required for successful lactation.

Some Practical Considerations.—The practical value of our knowledge concerning the vitamins will be already apparent from what has been said concerning each one. The general conclusion is that a sufficient supply of each must be present in the diet, in order to ensure good health, normal growth and efficient reproduction.

Little time has been lost in putting into practice the knowledge gained from the study of vitamins, with respect to the cure of deficiency diseases. The value of cod-liver oil, of artificial and of natural sunlight has been generally recognised and these agents everywhere employed. It has also been recognised that ordinary glass cuts off the valuable ultra-violet rays from sunlight, so that most of the beneficial effect of sunlight is lost if it comes to us through such glass. Already a special type of glass which is free from this defect has been devised and is now on the market, and is being largely used in schools and other institutions. Materials specially rich in certain vitamins, *e.g.* irradiated ergosterol, have been prepared and made available for curative purposes. Deficiencies in certain articles of diet have been recognised. Most margarine, for instance, is deficient in the fat-soluble vitamins. This deficiency is being corrected and margarine enriched by admixture with specially prepared vitamin concentrates is now available and is at least equal in vitamin content to fresh butter.

Amongst other important consequences of the study of vitamins is the realisation of the necessity for a completely satisfactory diet for pregnant and lactating women. Not only do such women require vitamins to maintain their own health and functions in a satisfactory state, but they must be able to pass on a liberal supply in their milk to the children, for whom breast milk is the only source of supply of vitamins during the important period of growth comprising the first nine months or so of post-natal life. The statement that breast feeding of infants is superior to the best system of artificial feeding is not true, unless the mother is taking a diet sufficient to enable her to secrete a milk of good quality containing sufficient vitamins to meet all the requirements of her child.

It is recognised that in addition to cases showing all the typical signs of a deficiency disease there are many other cases of ill-health and defective nutrition which are due to

restricted vitamin supply, and which can be corrected or prevented by suitable diet. In this connection it may be pointed out that much attention has recently been drawn to the relation between defective diets and imperfect development of the teeth.

Attempts have been made to exploit the interest which the public has shown in vitamins. Numerous proprietary articles, for which extravagant claims as to vitamin content have been made, have been put on the market. With respect to these it should be pointed out in the first place that a study of what we know concerning the distribution of vitamins proves that, with a little intelligence, diets can be devised which are perfectly satisfactory as regards vitamin content, from ordinary, readily obtainable foodstuffs. There is no need (except in cases where margarine must be used instead of butter) to have recourse to special and possibly expensive proprietary articles, in order to maintain good health. Where disease due to vitamin deficiency is threatened or has supervened, recourse to specially prepared vitamin concentrates may be advisable, for here the greatest effect in the shortest time is to be aimed at. In the second place, where an article specially rich in vitamins is definitely required, only one whose claims in this respect can be fully substantiated should be accepted.

It is the duty of the medical man to acquire sound knowledge of the subject in order to correct the half-knowledge or the ignorance he will frequently find in his patients, and to be able to advise his patients on dietary questions as well as to treat on sound lines the cases of deficiency diseases with which he may come into contact.

Vitamins in Verse

The following poem first appeared in the *St. Bartholomew's Hospital Journal* for January, 1928. Subsequently one verse was quoted in the *British Medical Journal*, and later the whole poem was given. As a reason for offering the whole poem, following the quotation of one verse, the editor of the *British Medical Journal* says, "So far from incurring blame for introducing light verse, however apt, into a serious discussion, we have had a number of requests to reprint the poem in full. Some readers wish for it as *memoria technica*, because they find difficulty in recalling off-hand the properties of the several vitamins." Like the editor of the *British Medical Journal*, I have been impressed with this argument, and therefore reprint the poem here :—

The A B C of Vitamins.

A.

Oh fine and fat was Ralph the rat,
  And his eye was a clear cold grey.
How mournful that he ate less fat
  As day succeeded day,
Till he found each cornea daily hornier,
  Lacking its Vitamin A.
    "I missed my Vitamin A, my dears,"
      That rat was heard to say.
    "And you'll find your eyes will keratinize
      If you miss your Vitamin A."

B.

Now polished rice is extremely nice
  At a high suburban tea,
But Arbuthnot Lane remarks with pain
  That it lacks all Vitamin B,
And beri-beri is very very
  Hard on the nerves, says he.
    "Oh take your Vitamin B, my dears!"
      I heard that surgeon say;
    "If I hadn't been fed on standard bread,
      I shouldn't be here to-day."

C.

The scurvy flew through the schooner's crew
As they sailed on an Arctic sea.
They were far from land and their food was canned,
So they got no Vitamin C.
For "Devil's the use of orange juice,"
The skipper 'ad said, said he.
They were victualled with pickled pork, my dears,
Those mariners bold and free.
Yet life's but brief on the best corned beef
If you don't get Vitamin C.

D.

The epiphyses of Jemima's knees
Were a truly appalling sight;
For the rickets strikes whom it jolly well likes
If the Vitamin D's not right,
Though its plots we foil with our cod-liver oil
Or our ultra-violet light.
So swallow your cod-liver oil my dears,
And bonny big babes you'll be.
Though it makes you sick it's a cure for the rickets
And teeming with Vitamin D.

E.

Now Vitamins D and A, B and C
Will ensure that you're happy and strong;
But that's no use; you must reproduce
Or the race won't last for long.
So Vitamin E is the stuff for me,
And its praises end my song.
We'll double the birth-rate yet, my dears,
If we all eat Vitamin E.
We can blast the hopes of Marie Stopes
By taking it with our tea.

C. H. A.

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