Summary.

From the account now given of the working of this appliance it will be seen that:

1. The clock, by its control of an electric circuit, can actuate, hourly or oftener, any required number of electro-magnets for a given number of seconds.

2. Each electro-magnet can, during that time, open a valve which will deliver more or less fluid to the siphon below it, in accordance with the size of exit aperture selected for the particular wound to be treated.

3. The required quantities of fluid, when accumulated, can be delivered by the siphon through a tube of sufficient calibre to flush the distributing tubes in the wound.

This clockwork controlled douche, which has only recently been completed, has been tested on a severe case of compound fracture of the tibia, infected with *Bacillus pyocyaneus*, in Professor John Fraser's ward in the Royal Infirmary, Edinburgh. It irrigated the wound quite satisfactorily. In about a fortnight the wound had improved so much that the clockwork control, being no longer required, was discontinued.

There are many septic surfaces and cavities met with in civil practice, from different causes, for which the Carrel-Dakin treatment will be required. It is hoped, therefore, that this appliance will serve a useful purpose for these, apart from the possibilities of war wounds, which, unfortunately, cannot yet be excluded from the horizon.

In working out the details of this appliance new problems had to be faced and many experiments were necessary. I am much indebted to several co-workers whose services have been invaluable:

To Mr. Hurford, of Messrs. Smith, Hurford, and Drysdale, for adapting the clock for its new purpose and working out the details of the supply valve for me, also for devising and making several experimental stopcocks; to Mr. T. Alexander, the head of the dispensary in the Royal Infirmary, Edinburgh, for testing the action of eusol on metal and keeping me right in chemical questions; and, very specially, to Mr. A. H. Baird, for the electrical outfit and all glass work, and, along with him, his ingenious and skilful mechanic, Mr. George Prentice.

The complete outfit will be supplied by Mr. A. H. Baird, 39, Lothian Street, Edinburgh.

THE PATHOLOGICAL LABORATORY IN GENERAL PRACTICE.*

BY

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THE conception of the pathological laboratory which I wish to put forward is that of a centre for the diagnosis and investigation of disease. By diagnosis I do not mean the mere application of a name to a particular morbid condition or syndrome, but a comprehension of the disordered processes underlying any particular set of symptoms. That correct diagnosis is the first step towards efficient treatment—where such exists—will, I suppose, be universally admitted, and it is as an instrument for the achievement of correct diagnosis that I would regard the pathological laboratory of a general hospital. In spite of the accumulation of physiological and pathological knowledge which has marked the last few decades, it must, I fear, be admitted that the points at which actual contact is established between the science and the art are still few. None the less such contacts do exist, and are increasing. The function of the pathologist in the medical community, as I see it, is to familiarize himself with those points of contact and to place the knowledge won by the workers in medicine the science at the disposal of the workers in medicine the art.

Of the ways in which recent advances in biochemistry have added to our knowledge of disease one of the most important is the devising of a simple and easy method for the estimation of the sugar in a small sample of blood. Several methods have been worked out within the last few years; the one most generally used in this country is that devised by Professor H. Maclean of St. Thomas's Hospital, London.

*An address delivered before the Wolverhampton Division of the British Medical Association.

Which method is used is of no particular importance. The point of importance is that the introduction of this procedure has brought about a better understanding of that group of conditions having the common symptom of glycosuria than was ever before possible.

Time was when the presence of a reducing substance in the urine was always regarded as an ominous symptom. Soon it became recognized that lactose might appear in the urine of pregnant and nursing women without being of any serious prognostic significance; later the occurrence of pentosuria was recognized. When faced with a reducing body in the urine of a patient it is necessary to make sure that that body really is glucose. A fragment of brewer's yeast will, of course, give the answer. The presence of glucose being established, the question demanding an answer is, Is this, or is it not, a "diabetic" condition? The answer is readily afforded by the examination of the blood glucose.

To make clear how this answer is given, I must go briefly into the variations of the blood glucose level after the ingestion of carbohydrate by a normal subject. In investigating the rise and fall of the blood sugar after the ingestion of carbohydrate it is obviously desirable that some standard method should be employed. All the curves given below are plotted as suggested by Professor Maclean on the results of blood sugar estimations made after the ingestion of 50 grams of glucose following a fast of at least three hours.

The Normal Sugar Curve (Fig. 1).

You will note that from a fasting level of about 100 mg. per cent. the blood sugar rises rapidly to 180 mg. per cent. This height is attained in about one hour, after which there is a rapid fall to the original level or just below it, so that in a normal person within one and a half hours the blood sugar is back to where it started from. The two points to which I particularly wish to draw your attention are this rapid fall and the maximum height of the curve. The rapid fall is due to some mechanism for the storage of glucose in the body, the actual nature of which is not understood; it is apparently the disturbance of this storage mechanism which is the essential lesion in diabetes. The height of the curve is of importance because it represents the level to which the sugar may rise in the blood without passing through the kidney into the urine—that is to say, there is a threshold for glucose in the blood. This threshold occurs at a level of about 180 mg. When below that level in the blood, glucose will not normally appear in the urine; when above, it will.

FIG. 1.—Normal blood sugar curve.

FIG. 2.—Diabetic blood sugar curve.

Ordinates=Blood sugar in milligrams. Abscissae=Time in half-hours from ingestion of 50 grams of glucose by the mouth. T=Normal renal threshold for glucose.

The Diabetic Curve.

The level of the diabetic curve may vary, but its shape is perfectly characteristic (Fig. 2). There is a complete absence of that rapid fall due to the coming into play of the storage mechanism which is characteristic of the normal subject. This, as I have remarked before, is apparently the actual physiological basis of the diabetic condition; the level of the blood sugar rises well above the threshold, and this, of course, accounts for the glycosuria. It may be, and usually is, above the threshold to start with. That is immaterial.

A further very important point in the diabetic condition

is that the threshold may be raised; this is so frequently the case as to be almost the rule in elderly persons. Thus no sugar may be excreted in the urine until a hyperglycaemia of 300 mg. per cent. has been established, as opposed to only 180 mg. per cent. in the normal subject. You will at once perceive from this that the absence of sugar from the urine is no proof of the absence of a hyperglycaemia; and it is the hyperglycaemia which matters.

The importance of the estimation of the blood sugar as an aid in insulin dosage will be apparent to you without further comment on my part. In diabetes it is the level of the blood sugar that matters; the appearance of sugar in the urine is in the nature of an accident; its amount is really neither here nor there, and its disappearance is no indication that the hyperglycaemia is under control.

Before I leave this question I will draw attention to two other forms of glycosuria.

It happens in some cases showing glycosuria that the blood sugar curve shows that the level of the blood glucose rises and falls in a perfectly normal manner. If samples of urine are taken half-hourly throughout the estimation, however, one finds that sugar is passed in the urine when the blood sugar is at its highest level. Careful observation will reveal a definite level below that of the usual threshold at which sugar passes from blood to urine—that is to say, there is a lowering of the threshold for glucose. This condition is compatible with perfect health and requires no treatment. Its recognition, however, is of obvious importance, and this is only made possible by plotting the blood sugar curve.

The "Lag" Curve.

A further somewhat rare type of blood sugar curve is the "lag" curve (Fig. 3).

FIG. 3.—"Lag" type of blood sugar curve.

pathological conditions. Roughly, however, they may all be grouped under three heads: (1) acute nephritis; (2) chronic nephritis, secondary to acute; (3) primary chronic nephritis.

Clinically Group 1 is characterized by oedema and albuminuria. Group 2 in its early stages is characterized by the same symptoms; later, however, if the patient survives, the oedema may disappear and the albuminuria become less. Group 3 in its early stages is characterized by no marked symptoms and is one of the most insidious of all diseases.

Of cases belonging to Group 1, I have, as a result of my own observations, been able to satisfy myself that two types exist. The symptoms of these two types in the early stages are practically identical, but their actual pathological bases are entirely different and the prognoses poles asunder. I have been able to demonstrate that in the one type, which, following the German authorities, I may speak of as a nephrosis, there is no evidence of inflammation of the kidney; in the second type the whole renal substance, but particularly the glomeruli, shows evidence of intense inflammation. Clinically in the early stages the two types are indistinguishable—both show oedema and albuminuria; the former may persist for months, the latter for life. But the outlook in the two types is quite different. In the first recovery is the rule; the second

tends to go progressively downhill. The oedema may disappear, but even so chronic interstitial fibrosis progresses in the kidneys, and death ultimately occurs from renal failure.

By examination of sections of the kidney removed during life it would be an easy matter to give a prognosis. I have done this, but do not recommend it as a routine. Fortunately examinations of other sorts are almost as efficacious. These examinations depend upon the ability of the kidneys to excrete urea. In both the types of nephritis of which I have spoken there is during the first week or so a failure on the part of the kidney to excrete urea, but the later course of the two types shows a marked difference in this respect. In the nephrotic type, even when the oedema and albuminuria still persist, the kidneys are soon able to excrete urea as well as those of a normal subject. In the inflammatory type, on the other hand, the power to excrete urea undergoes a progressive impairment, and this substance tends to become banked up in the blood.

By estimations of the blood urea and the power of the kidneys to excrete a dose of urea given by the mouth, as recommended by Maclean and De Wesselow, one can usually gauge in which direction any given case is likely to proceed and gain important information both as to prognosis and treatment.

Consideration of the findings in two typical cases may make the matter clearer. Clinically these cases were of the same hydraemic type, both showing albuminuria and oedema.

Case 1.—The facts are contained in the following table:

Urine urea before ingestion of 15 grams of urea			
1 hour after	...	...	1.7 per cent.
2 hours after	...	...	2.7 "
3 hours after	...	...	2.9 "
...	...	...	3.0 "

Blood urea 30 mg. per 100 c.cm.

Case 2.—In this case the results were as follows:

Urine urea before taking urea			
1 hour after	...	...	1.1 per cent.
2 hours after	...	...	1.1 "
3 hours after	...	...	1.2 "
...	...	...	0.9 "

Blood urea 68 mg.

In the first case there is no failure of urea excretion; in the second there is such a failure. In Case 1 the prognosis is good; in Case 2 some degree of recovery may take place, but the ultimate prognosis is poor.

Case 3.—A third case indicates the usefulness of this procedure in another direction. It is that of a boy who originally suffered from an attack of acute nephritis. The oedema disappeared but the albuminuria persisted, and the boy suffered from bouts of headache and vomiting. It was plain that these might be renal in origin, and he was kept on a strict low protein diet and treated more or less as an invalid. Investigation of the case revealed the following state of affairs:

Urine urea before urea by mouth			
1 hour after	...	...	1.7 per cent.
2 hours after	...	...	2.1 "
3 hours after	...	...	2.5 "
...	...	...	2.3 "

Blood urea 35 mg. per 100 c.cm.

Obviously in this case there is no urea retention and therefore no necessity for a low protein diet. The patient was put on a full diet, his parents were told no longer to regard him as an invalid, an error of refraction was corrected by suitable glasses, and as a result the bouts of sickness ceased, and he is now in excellent health in spite of a slight persistent albuminuria.

Nephritis of the last type—the primary chronic interstitial—is essentially a disease of the fourth and fifth decades, but may appear and run its insidious and unchecked course at all ages. Albuminuria and oedema are never marked and are frequently altogether absent. Often the only complaint of the patient is of headache and dizziness. The outcome is always death in uraemia. This is above all the type of nephritis associated with urea retention. The following case is typical.

Case 4.—A man, aged 42, complained of headache and malaise for some months past. His skin was muddy; he was anaemic and showed pouching under the eyes, but no oedema. Examination of the power of disposing of urea yielded the following results:

Urine urea before taking urea			
1 hour later	...	...	1.1 per cent.
2 hours later	...	...	1.1 "
3 hours later	...	...	0.9 "
...	...	...	0.85 "

Blood urea 90 mg.

Two months later the condition is as follows:

Urine urea before taking urea	...	...	0.9 per cent.
1 hour later	...	...	0.9 "
2 hours later	...	...	0.8 "
3 hours later	...	...	0.75 "

Blood urea 120 mg.

After another two months:

Urine urea before taking urea	...	...	0.65 per cent.
1 hour after	...	...	0.65 "
2 hours after	...	...	0.5 "
3 hours after	...	...	0.4 "

Blood urea 210 mg.

Death took place in a few weeks, with a blood urea of 450 mg. per cent.

As to treatment, the only point I should like to make is that in cases in which urea is being well excreted there is obviously nothing to be gained by withholding its principal mother substance—the protein of the diet. In fact, in the nephrotic type of case of which I have already spoken definite harm results. Urea is an admirable diuretic, and when it can be excreted its presence in the blood is invaluable in getting rid of oedema. In this type of nephritis not only should the patient be encouraged to take a full protein diet, but urea may with benefit be administered in large quantities by the mouth.

There is one other type of case in which examination of the renal function is of the greatest value, and that is in prostatic enlargement when an operation is contemplated. In these cases, when there has been prolonged obstruction to the urinary outflow, the kidney function as a rule becomes to some extent impaired. The degree of impairment varies and is subject to very great improvement with treatment. In many cases where the prostatic enlargement has persisted for some time examination of the urea concentrating power of the kidney shows definite failure. If prostatectomy is performed while the patient is in this state the results are bad—a fatal issue is common. If, on the other hand, a preliminary cystotomy is performed and the urine is allowed to drain, subsequent tests usually show a progressive improvement of renal function and indicate with comparative certainty when the operation may be completed with safety.

I would not have you think that it is only on the biochemical plane that the pathological laboratory may be of assistance in the diagnosis of renal disease. In all forms of infection of the urinary tract—coccal, coliform, or tuberculous—the ultimate diagnosis must be made by the microscope or culture medium. Here, however, let me point out that although information of the very greatest importance as to the nature of infections of the urinary tract can be gained by an intelligent use of the pathological laboratory, the attainment of those given results depends entirely upon close co-operation between the clinician and the pathologist. There is no more useless specimen than the bottle of urine unaccompanied by details of the case and the mode of collection. For the interpretation of results it is necessary to know something of the history of the case and also of the particular specimen. Often, in order to arrive at a definite result, it is necessary to call in the surgeon to collect specimens from each ureter separately. All this may seem to entail a lot of trouble, but, unfortunately, correct diagnosis is like that. It does entail trouble, in this and in most other instances. On the whole, however, it is worth it. I will cite two instances.

Case 5.—A medical man had suffered for two weeks from an irregular pyrexia, with diffuse abdominal pain. The diagnosis, however, lay between infective endocarditis, typhoid fever, and a grumbling gall bladder. The urine was said to show nothing beyond a trace of albumin. Culture of the blood, the Widal reaction, and various other procedures were without result. Examination of the urine gave an immediate diagnosis of *B. coli* infection of the right kidney.

Case 6.—A boy had suffered for many weeks with painful and frequent micturition. The urine showed pus and blood but no organisms. X rays showed a shadow that might have been a stone in the left ureter. Catheterization of the ureters showed that the pus was coming from the right kidney only. Examination of suitably stained films of this catheter urine showed numerous tubercle bacilli. At operation the right kidney was found to be almost destroyed by a tuberculous infection.

Assistance can be given in many other directions. There is, for example, the examination of the test meal in the differential diagnosis between simple and malignant gastric ulcer. The x rays will frequently detect the presence of the ulcer, but they are powerless to diagnose malignancy

or its absence. The presence of lactic acid and the absence of free hydrochloric acid are almost proof positive of malignancy. The examination of the faeces as to the relative amounts of split and unsplit fat will often throw light upon the nature of obscure diarrhoeas. In such conditions a relative increase of the unsplit fat due to the absence of the pancreatic lipolytic ferment is practically diagnostic of a pancreatic lesion. In the differential diagnosis of jaundice the van den Bergh reaction for the detection of urobilin in the serum is often of the greatest assistance. This reaction appears to depend upon the fact that the urobilin which ultimately finds its way into the bile is not produced in the liver, but in the widespread endothelial-reticular system, its source being the haemoglobin of broken-down red cells. When first produced the urobilin is apparently linked to a protein molecule, but becomes separated from it on passage through the liver cells into the bile. When still linked to the protein the urobilin will give no colour reaction with the van den Bergh reagent; the linkage, however, can readily be dissolved by treatment with alcohol, whereupon the reaction occurs. The occurrence of a colour reaction on simply bringing the van den Bergh reagent in contact with the serum constitutes the direct reaction and indicates an obstructive icterus. If, on the other hand, no reaction occurs until the serum has been treated with alcohol, the reaction is spoken of as indirect and indicates that the jaundice is due to pigment that has never passed through the liver. Such reactions occur in those cases of haemolytic jaundice where, presumably owing to rapid blood destruction, so much urobilin is produced that the liver cannot handily dispose of it. It is in the identification of this particular type of icterus that the test has its particular use.

Very valuable information may be provided by the examination of the blood picture in the various anaemias. I can best indicate how important such an examination may be by citing a case.

Case 7.—A man presented himself with the statement that he was suffering from leukaemia. His spleen was large, reaching to the umbilicus; he was slightly jaundiced and showed ulcers on both legs just above the ankles. He stated that he had been ill for seven years. Examination of the blood showed the following picture:

Red cells	...	...	...	2,500,000 per c.mm.
White cells	...	...	...	18,300 " "
Haemoglobin	...	...	...	45 per cent. "
Differential count:				
Polymorphs	...	...	...	75 per cent.
Lymphocytes	...	...	...	20 "
Monocytes	...	...	...	4 "
Eosinophils	...	...	...	1 "

This is obviously and emphatically not the picture of a leukaemia. Guided by the slight jaundice and the splenomegaly I estimated the fragility of the red cells, and found that lysis commenced at a concentration of 6.5 per cent. of sodium chloride and was complete at 4 per cent.—a very marked increase of fragility. The van den Bergh reaction gave an indirect positive result, indicating the haemolytic nature of the jaundice. The whole picture was that of haemolytic or acholuric jaundice. The importance of the differential diagnosis here lies in the fact that whereas in leukaemia removal of the spleen is invariably fatal, in acholuric jaundice it is equally invariably followed by marked improvement. A spleen weighing some 2 lb. was removed by Mr. E. Deanesly, F.R.C.S., and the patient is now doing excellently.

I could cite many other instances of the value of laboratory methods in providing diagnosis and indications as to treatment. In conclusion, however, I should like to lay stress upon a point which I have already mentioned, and that is the absolute necessity for close co-operation between practitioner and pathologist if really useful results are to be attained. With the possible exception of the examination of sputum for tubercle bacilli, I can think of no laboratory procedure used in diagnosis from which the best results can be obtained without some knowledge of clinical details. All results obtained in a laboratory require interpretation in the light of experience and the nature of the individual case. In many instances a few minutes' consultation between practitioner and pathologist over the case may lead to the opening up of fruitful lines of investigation of which neither would have thought alone. In short, to get the best results from a pathological laboratory it is necessary to regard it, not as a slot machine which, on the insertion of a bottle of something and a fee, produces a diagnosis and a bottle of vaccine in return, but as an institution for the practical application of some of the accumulated knowledge and experience of the nature of disease.