THE VALUE OF LABORATORY TESTS IN DISEASES OF THE LIVER AND PANCREAS.*

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It is clear that in the time at my disposal nothing more than a very general review of this large subject can be attempted. The liver and pancreas are both developed as outgrowths of the alimentary tract, and their ducts are innervated in the same general way as the canal from which they develop. Their close co-operation is further shown in the way they pour their secretions into the alimentary tract at the same point, in their complementary roles in the utilization of fat and in carbohydrate metabolism, as well as by the circulatory conditions which ensure that any internal secretion from the pancreas shall pass straight to the liver. Situated on the path by which all the blood from the digestive organs enters the systemic circulation, it is not surprising to find that the liver helps to prepare all three foodstuffs for utilization by the tissues. The bile it forms is at once an excretion and a secretion. But further, the liver is an important agent in detoxication and in maintaining the constant composition of the blood.

The earlier and simpler attempts to estimate the functional efficiency of the liver failed because its great reserve capacity was not realized. For, like the heart, lungs, and the kidneys, the liver does not normally exert its full activity, and so does not reveal its failure of function to ordinary tests until this has fallen to so low a limit that grave hepatic damage is no longer in doubt, and the time for successful treatment is past. Moreover, not only must the power of the liver to undergo compensatory hyperplasia be remembered, but, its various functions not being equally inhibited by disease, it is necessary to apply tests covering different fields of hepatic activity.

In the first place I shall consider tests related to the action of the liver in preparing the three foodstuffs for the tissues.

I. TESTS FOR HEPATIC METABOLISM.

(1) Protein.

It has been clearly recognized for some years¹ that the protein molecule is broken down into its ultimate amino-acids before absorption, and that these end-products are less toxic than the intermediate proteoses and polypeptides from which they arise. Further, as there is a chemical specificity of tissues, by no means all of such end-products are capable of being utilized for tissue repair at the time of their entering the blood stream. Those which cannot be used at once by the tissues are turned into urea and other excretory products. Indeed, the method of maintaining the nutrition of the body is as far as possible the same on an ample protein diet as in starvation. In both, amino-acids are used to make deficiencies good, though in starvation they are obtained by pooling the autolytic products obtained, as it were, by levying a tax on all the cells of the body. From this pool individual organs are allowed to draw, according to their functional importance to the body. But even in the well fed body the excess of protein food above what is required for tissue repair is not stored but excreted. Naturally, therefore, much more nitrogen is excreted by the well fed than by the starving body, any storage being provided from non-nitrogenous sources.

It would appear that each amino-acid has its own method of breakdown, and very probably its own ferment for achieving that purpose. This has been brought out clearly by Garrod in his study of the inborn errors of metabolism. He says:

"If any one step in the process fail, the intermediate product in being at the point of arrest will escape further change, just as when the film of the biograph is brought to a standstill the moving figures are left, foot in air."

Now it happens that most of such inborn errors as alkaptonuria, pentosuria, and cystinuria are inconvenient rather than serious. They are also rare, and although their study has established points of great theoretical importance as to protein

breakdown, they do not throw light on the estimation of hepatic efficiency. The ferments involved are evidently very resistant normally, since these substances do not appear in extensive degenerations of the liver, although porphyrinuria, which is sometimes an inborn error, may also occur in hepatic disease. The detection of leucin and tyrosin in the urine was thought at one time to be evidence of failure of the liver to turn them into urea, but they are now regarded merely as signs of hepatic disintegration. Though most prominent in acute yellow atrophy, they may be found in other diseases. Thus I saw them in a case of cirrhosis, where a severe haematemesis had been followed by coma for forty-eight hours, yet ultimately recovery took place. But it must be admitted that nothing has been found clinically to correspond to the experimental results obtained by Eck's fistula, even, for instance, after the Talma-Morrison operation, and certainly nothing that would form the basis for a test of hepatic inefficiency in respect of protein metabolism.

The nitrogen partition test aims at doing this by determining any loss of the dis-aminating and urea-forming functions of the liver. *A priori* one would expect to find that in failure of hepatic efficiency the urea excretion would fall, while the excretion of the precursors of urea such as ammonia and amino-acids would rise. But in practice we are met with the following difficulties: (1) Quite a small proportion of the total liver substance is adequate to make the normal amount of urea. (2) As so much of the urea comes direct from the food, the total amount excreted varies with the diet. On a liberal protein diet the urea forms about 86 per cent. of the total nitrogen, while in the healthy fasting individual it forms a much smaller proportion. This variation seriously affects nitrogen partition, without implying any disease. (3) An absolute increase in ammonia formation may be, and usually is, simply a protective step against acidosis, and is not evidence of a failure of urea formation. (4) Variations in the kidney threshold may materially affect nitrogenous excretion. This last difficulty can be surmounted by examination of the blood rather than of the urine, but the other three seem to me largely to vitiate the nitrogen partition test.

Again, in normal pregnancy de Wesselow and Wyatt have shown that a low urea excretion is the rule, because nitrogen is being diverted to the use of the foetus, so much so that a rise of blood urea above 40 mg. per cent., which would be within normal limits otherwise, implies a failure of renal function in pregnancy. This adds to the difficulty in applying nitrogen partition tests to the hepatic toxæmias of this condition.

(2) Carbohydrates.

All sugars are absorbed as monosaccharides. Although they can be rapidly stored in the liver and muscles, the absorption from the alimentary tract of any such sugar, with the important exception of levulose, leads to a rise of blood sugar from the fasting level of 0.1 per cent. to something like 0.16 per cent., falling again in about one and a half hours. This would imply that levulose, although its limit of tolerance tends to be rather lower than that of dextrose, can within that limit be stored as rapidly as it can enter the blood stream. Years ago H. Strauss regarded a diminished tolerance for levulose as evidence of impaired hepatic function, but this did not afford a satisfactory basis for a test. It is not sensitive enough, and the kidney threshold for the excretion of sugars is not a constant. Maclean and de Wesselow,¹ having determined that levulose when given by the mouth in doses of from 30 to 50 grams does not raise the blood sugar in healthy subjects with an intact liver, went on to show that when the liver is defective it is not able to store levulose fast enough to prevent it from entering the blood stream, and thus increasing the blood sugar proportionately to the hepatic defect. This is the basis of the modern levulose test, which seems to me one of the best we have for hepatic efficiency. According to Spence, it shows that so-called catarrhal jaundice cannot be due to mere ascending catarrh of the main bile ducts, but must involve some hepatitis, since administration of levulose raises blood sugar in this disease even before the onset of jaundice. It has enabled several observers to show a similar change in sarsaparilla poisoning, while Mackenzie Wallis has found that in every case where a course of such an arsenical preparation has been given, some degree of hepatic inefficiency exists for at least three months. Clearly a second course should not be given within this interval; while, if levulose cause a rise of blood sugar of 0.05 per cent. above the fasting level, careful treatment is required, however slight the other clinical manifestations may be. In pure obstructive jaundice this rise of blood

* A paper read to open a discussion at the Medical Society of London, March 12th, 1923.

sugar does not occur, or is very slight. As further evidence that catarrhal jaundice may involve a toxic hepatitis I should like to refer to a group of cases I saw last year where, in addition to a large and tender liver, with jaundice, there was cyanosis, air hunger, and almost complete suppression of urine, followed by intense albuminuria, sometimes with haematuria and casts. Yet the patients made a good recovery and soon became free from albumin. Sometimes they showed an increased diastase output, which might be held to prove pancreatic involvement as well.

It is perhaps convenient to discuss the diastase test here, even though this anticipates the subject of pancreatic tests. It was originally designed by Wohlgemuth as a test for renal efficiency. He took the amount of urine which could digest 2 c.cm. of a 0.1 per cent. solution of starch paste in half an hour as the measure of its diastatic activity, which normally may range between 10 and 33.3 units. He claimed that if renal efficiency were impaired the output of diastase would fall. Working with Mackenzie Wallis in cases of war nephritis I was of opinion that this method of using the test was a guide to the amount of renal damage, for cases showing 5 units or less proved more obstinate than those with a more normal output. But subsequent work has shown that the diastase in the urine does not necessarily run parallel with the diastase in the blood, which is perhaps what we might expect from what we know of the behaviour of the kidney threshold towards substances useful to the body. The test has proved of more value in the recognition of pancreatic disease because here the alteration of the amount in the blood is so gross that the renal threshold is, as it were, flooded. In acute pancreatitis one might find 300 to 500 units—in one case of mine 1,000 were present—while in less acute cases 50 to 100 units may be found. In very chronic conditions there may be no excess, but even a deficiency. In ordinary clinical diabetes a low value is the rule. It was at first assumed that this diastase was merely pancreatic amylase reabsorbed into the blood stream, and was evidence of some obstruction to the pancreatic ducts, though in that case it would not be easy to explain its presence in normal urine. But Cammidge,² with Forsyth and Howard, has adduced cogent reasons for believing this diastase is hepatic in origin. The diastase value rises as more and more of an animal's pancreas is excised, right up to total extirpation. As it is clearly impossible for a non-existent gland to produce an enzyme, diastase cannot come from the pancreas. On the other hand, hydrazine phosphate, which has a toxic effect on the liver but not on the pancreas, reduces and may completely abolish the diastase output. These authors conclude that diastase is the agent which converts glycogen into sugar, and that its action is controlled by the internal secretion of the pancreas. If such control fails there is for a time a greatly increased production of diastase by the liver, though this may not by itself produce glycosuria. So far, however, though gross increase in diastase output certainly suggests pancreatic insufficiency, a defect of diastase in the blood has not helped much as evidence of hepatic insufficiency. Harrison and Lawrence³ found in twenty cases of hepatic disease that the blood diastase was low in three severe cases. In two this rose again as the clinical condition improved. Certainly defective output in the urine could not provide such evidence because of the behaviour of the threshold of the kidney.

One thing appears clear about the glycogenic function of the liver: in the presence of an ample supply of glycogen the metabolism of the liver proceeds more smoothly. It was first stated that it was the antitoxic power of the liver which chiefly was affected by the glycogen store. But it seems more far-reaching than this, though it is certainly true that a liver is less liable to post-anaesthetic poisoning if it is well supplied with carbohydrate, while starvation, which would deplete the glycogen store, increases the liability to this catastrophe. And Colonel Harrison, at Maclean's suggestion, has found giving sugar, usually dextrose, of material benefit in preventing toxic jaundice after salvarsan. In a group of patients receiving sugar before injection there were only two or three cases, while in another group not receiving sugar there were nearly fifty cases of toxic jaundice.

(3) Fats.

Leathes has shown that the fat normally present in the liver is in the more active unsaturated form, but that the fatty deposit which occurs there in poisoning by phosphorus or tetrachlorethane or after anaesthetics is in the more inert, saturated form. He makes out a good case for regarding as

a function of the liver the conversion of saturated fat into the more active unsaturated form for utilization by the tissues. When the liver is thrown out of gear by various toxins the tissues, starving for prepared fats, send unprepared fats to the liver, but in vain, for it is unable to deal with them. The liver may be compared to a miller—the saturated fats are the wheat he grinds and the unsaturated fats are the flour that results.

Foulerton pointed out that chloroform, ether, and tetrachlorethane are solvents of fat, while phosphorus, dinitrobenzol, and trinitrotoluene are readily soluble in fats, so that the destructive effects of these poisons on the liver may be due to their being conveyed with the fats to the liver in the attempt to carry out this process. In some cases, such as phosphorus or post-anaesthetic poisoning, this carriage of fats may lead to a gross increase in the size of the liver, but we require a much more sensitive test than this. Whipple devised the lipase test to this end. Normally blood contains a very constant amount of fat-splitting ferment, but in diseases of the liver this lipase is increased, as measured by the power of the blood to split ethyl butyrate. It has been supposed, therefore, that normally the liver inhibits the formation of lipase, so that its increase in the blood is a measure of hepatic damage. Whipple has applied this to chloroform poisoning, and Mackenzie Wallis⁴ to salvarsan poisoning. The damage has, however, to be rather gross before the lipase increase is enough to be relied upon.

The latter observer has further reported that in toxic jaundice due to salvarsan poisoning the cholesterol in the blood is diminished, while in this condition and in phosphorus poisoning the liver is found loaded with cholesterol esters *post mortem*. This suggests that the liver normally plays the same part both in cholesterol and fat metabolism. It may be, however, that the cholesterol is merely on its way to be excreted in the bile, but the diseased liver cannot accomplish this. Its presence in the kidney under similar conditions may be an attempt at an alternative channel of excretion. In the toxæmia of pregnancy, including a case of icterus gravis, this cholesterol disturbance was not found.

II. TESTS OF ANTITOXIC FUNCTION.

Apart from the reactions against bacterial poisons the antitoxic processes of the body are few and simple—such as oxidation, reduction, hydration, dehydration, and methylation. The protective substances are few, and the process of rendering a poison harmless by conjugating it with a protective substance is most often carried out by the liver. Thus the toxic indol is conjugated with sulphuric acid into a harmless ethereal sulphate, indican. Although we regard marked indicanuria as evidence of intestinal toxæmia, we must remember that we are testing for that part of the indol which has been rendered innocuous. A more accurate method is to estimate the ratio between ethereal and total sulphates; the larger fraction the former constitutes of the latter the nearer are we to the limit of the antitoxic power of the liver. But if the liver cells are diseased such conjugation cannot occur, so that toxic substances like indol, skatol, and phenol can pass direct into the blood, even though the urinary output of ethereal sulphate is low. There does not appear to be any simple test for recognizing this.

Glycuronic acid is another important protective substance, and the formation of harmless glycuronates after administration of camphor, morphine, and the like is a function of the liver. It is claimed that $7\frac{1}{2}$ grains of camphor given by the mouth should be completely conjugated with glycuronic acid and recognized by its reducing action in the urine, but if the liver is diseased no such glycuronic acid is formed. A simpler test is that introduced by Roch.⁵ He gives half a grain of sodium salicylate an hour before food. This should be turned into a glycuronate which would not yield a purple colour with 1 per cent. ferric chloride solution. If the urine excreted for the four hours after a meal does give this colour hepatic insufficiency is present.

The *haemoclasic crisis* may also be regarded as due to a failure of the antitoxic power of the liver. As C. M. Wilson expresses it, under this rather forbidding name is concealed a test disarming in its simplicity. Widal⁶ maintained that when the liver was diseased the normal post-prandial leucocytosis was replaced by a leucopenia, which was accompanied by a fall of blood pressure. This was believed to be due to the hepatic failure permitting the entrance of incompletely digested proteins into the systemic circulation. It recalls the anaphylactic reaction to material unsuitable for assimilation. Before breakfast a white count is taken, then 7 oz. of

milk are drunk, and another count taken twenty minutes later. Wilson concludes that, with the possible exception of the levulose tolerance test, this is the only test which gives an early warning of hepatic insufficiency.

III. TESTS OF BILIARY FUNCTION.

Turning to the external secretion of the liver, the bile, we may first consider tests for alterations in its discharge into the bowel. The gall bladder not only regulates the occurrence of this discharge at the time it is required, but by adding cholesterol and mucin to the bile while absorbing water alters its composition, making it more concentrated and viscid. Therefore with complete obstruction to the cystic duct, the bile entering the intestine is unusually dilute. H. E. Griffiths¹ confirmed the general clinical impression that gall stones produce reflex hyperchlorhydria by finding this in 90 per cent. of the test meals on his cases. If this was not accompanied by regurgitation into the stomach there was usually x-ray evidence of marked pylorospasm. He attributes this regurgitation to the unregulated flow of bile into the duodenum which follows such diseases of the gall bladder as render it incapable of acting as a reservoir. A rise in the alkalinity of the duodenum at inappropriate times would relax the pyloric sphincter. This would occur when the cystic duct is occluded, or where the muscle of the gall bladder has been replaced by fibrous tissue as the result of prolonged disease, but would not follow complete obstruction of the bile duct, which would diminish the alkalinity of the duodenal contents. If it agrees with the other findings we may consider hyperchlorhydria to be the rule with disease of the gall bladder and bile ducts, while if there is regurgitation as well there is probably chronic disease of the gall bladder itself. Additional interest has been aroused in this part of the subject by the claim that if 1 to 4 drachms of magnesium sulphate in concentrated solution be introduced into the stomach a sharp flow of bile into the duodenum is excreted by reflex contraction of the gall bladder. By the use of an Einhorn tube this can be removed from the duodenum for examination. This claim has been disputed, and it is clear that if there is complete obstruction of the bile ducts the method is not applicable. But that it is occasionally of service is shown by a case in which I diagnosed inflammation of the gall bladder as the cause of dyspepsia. By this method purulent fluid was obtained, and at operation empyema of the gall bladder was found. Lyon² has extended this method by collecting three samples of bile by the duodenal tube. The first sample should be of transparent, yellow-golden colour from the common duct, the second darker and more viscid from the gall bladder, and the third much thinner and lighter in colour from the hepatic and intrahepatic ducts. By examination of these he claims that infection and inflammation of the various parts of the biliary system may be located.

If bile fails to enter the bowel the ill effects are principally due to the absence of bile salts, which may be regarded as the main secretion, the other ingredients being largely excretory. As they help in the emulsification and absorption of fats which have been previously split into fatty acid and glycerin by the pancreatic juice, the steatorrhoea which follows biliary obstruction is due to the increase of soaps and fatty acids in the stools, while in failure of the pancreatic secretion it will be the unsplit or neutral fat that will be in excess. Interference with absorption of proteins will lead to increased intestinal putrefaction with a consequent increase in the indican of the urine. The absence of bile pigment from the stools causes the familiar clay colour, but as the excess of fat may mask the presence of a small amount of bile we must not conclude from this colour alone that no bile is entering the intestine. Extraction of such faeces with acid alcohol or amyl alcohol may still show the presence of urobilin by the band in the blue of the spectrum or by green fluorescence on the addition of zinc chloride and ammonia. This would indicate incomplete obstruction, such as is usual with gall stones, while the entire absence of urobilin is suggestive of the more complete obstruction produced by new growth of the head of the pancreas. The presence of obvious bile pigment in the stools in a case of jaundice is, of course, against its being of obstructive origin.

I am obliged to Sir Humphry Rolleston for calling my attention to the phenol-tetrachlor-phthalein test. When phenolphthalein is given subcutaneously it is only excreted by the liver, but when this organ is damaged by phosphorus or chloroform, or when cholangitis is present, the output of the dye into the bile is diminished, as determined by faecal

analysis or by Einhorn's tube, and it appears in the urine. This test is naturally inapplicable when the common duct is completely obstructed.

Van den Bergh's Test.—Of late, however, interest has chiefly centred round the distinction between obstructive and toxic jaundice, based on van den Bergh's test. It has long been recognized that bile pigments originate from haemoglobin, but recently it has been urged by Brule³ that the liver merely separates bilirubin from the blood as the kidneys do urea, and Whipple regards the star-shaped Kupffer cells of endothelial origin along the capillary walls as responsible for this work. Van den Bergh⁴ has described two varieties of bilirubin, which can be distinguished in the serum by Ehrlich's diazo-reaction. In obstructive jaundice the test comes off directly, while in haemolytic jaundice the bilirubin, being linked with some constituent of the serum, does not give the reaction until the combination is broken up—for example, by alcohol. McNee has suggested that it is normally the work of the Kupffer cells to do this, and that when they are damaged the bilirubin escapes this modification and gives the indirect reaction only. Dr. Christopher Andrewes has been trying this test at St. Bartholomew's Hospital, and I am much indebted to him for placing his as yet unpublished results, based on 108 cases, at my disposal. He says:

"Practically all the cases are compatible with the theory that the direct reaction is due to obstruction (either of larger or finer ducts) and that the indirect reaction is due either to disordered function of liver cells or to increased haemolysis. So that the cases might be classified into (1) gross obstruction, including cholelithiasis, new growths, etc.; (2) haemolytic jaundice, such as pernicious anaemia and acholuric jaundice; (3) conditions such as catarrhal jaundice and heart failure, in which the factors of liver cell damage and obstruction to the finer ducts can probably occur together or separately. Other observers have found that cases of this third group may give an indirect reaction at first, and go through a biphasic to a direct reaction. It is this mixture in many diseases which seems to me to limit seriously the clinical value of this test. My cases of catarrhal jaundice show 8 direct reactions. Others have found more numerous cases giving indirect reactions. Schiff and Eliasberg⁵ in an 'epidemic' in children found all indirect reactions at one stage and all direct reactions at another."

The general conclusions to which Dr. Andrewes comes are these:

1. As a test of liver function it is very gross, being, however, a little more sensitive than clinical evidence of jaundice. Thus several cases of cirrhosis gave normal results.
2. As an aid to diagnosis of the cause of jaundice, it is of very little value. A well marked indirect reaction indicates catarrhal jaundice rather than stone. A direct reaction may mean either.
3. In anaemia an indirect reaction above normal indicates a haemolytic cause, probably pernicious rather than secondary. The test is probably rather more reliable than examination for urobilinuria.
4. The estimation of bilirubin in blood-stained fluids (pleural, peritoneal, cerebro-spinal) can decide whether the bleeding is old or produced at the time of puncture.
5. With direct reactions above 3.5 units, bile will be present in the urine; with direct reactions below this figure, and with indirect reactions, bile will be absent there.

One must conclude, I fear, from this careful study, that in its present form the test is of very limited value. It will be noted that the levulose test has given more positive evidence than van den Bergh's that catarrhal jaundice is often a hepatitis.

The Fate of the Bile Pigment.—It will be gathered from what I have already said that I lean to the view that urobilin or its chromogen is formed in the intestine by reduction of bile pigment through bacterial agency. The evidence in favour of this seems very strong, for when all bile escapes through a biliary fistula, or when complete obstruction prevents bile from entering the intestine, no urobilin is found. Again, it is absent from the faeces at birth, not appearing till bacteria have had time to establish themselves in the bowel, while if bilirubin is inoculated with intestinal bacteria urobilin is formed. Normally this urobilin colours the faeces, where it is often called "stercobilin," while a small amount is reabsorbed and appears in the urine. If there is polychromia from increased haemolysis there will be increased formation of urobilin, while if there is partial or complete obstruction to the bowel there will be increased reabsorption of urobilin. In either case urobilinuria will occur, but it has most significance as evidence of haemolysis. Against this view has been urged the presence of urobilin in the duodenal contents—that is, above the point at which bacterial activity begins. But I do not think this is sufficient to counter-

balance the mass of evidence in favour of the intestinal origin of urobilin. I am aware that urobilinuria is often regarded as evidence of "floating gall stones" or of cholangitis. I can only say I have far more often seen this diagnosis made than confirmed, when based on this test.

Bile salts in jaundice are by no means always to be found. Matthew Hay's test with flowers of sulphur is the simplest way of detecting them. I have found them present at the beginning of obstructive jaundice, and in one case even before bile pigment appeared in the urine. But later on they are generally absent, probably in part because the biliary cycle is interfered with. When bile is drained through a fistula the amount of bile salts in it soon sinks to one-tenth of the normal (Copeman). This suggests that the reabsorbed bile salts are used over again ten times. Naturally, then, in obstructive jaundice such bile salts as escape into the urine at the beginning are permanently lost, and the amount available sinks below the kidney threshold. In toxic jaundice bile salts are not likely to appear in the urine at any stage, both because they can get into the bowel and because their formation throws greater labour on a diseased liver than the excretion of bile pigment. The presence of bile salts, therefore, in the early stages of jaundice suggests an obstructive rather than a toxic cause.

IV. TESTS FOR PANCREATIC INADEQUACY.

I can deal quite briefly with this part of my subject, because our views have now crystallized into something like definite form.

(1) Signs of Defective External Secretion.

(a) *Failure of Tryptic Digestion.*—Unaltered muscle nuclei may be found in the faeces after a meat meal, but this is not always easy to do, nor does it help much to stain the muscle fibres and give them with lycopodium grains as a guide. Sahli's method of administering iodine in gelatin capsules hardened by formalin, and testing for iodine in the urine and saliva, cannot be recommended. It is also claimed that trypsin can be demonstrated in normal stools by placing a small quantity of faeces on a gelatin plate, when a small area of digestion will result. Apart from detection of muscle nuclei I have not found these methods much help. A negative result is of no value.

(b) *Failure of Starch Digestion.*—Starch granules may be detected in the stools after unboiled starch has been given. Boiled starch can be digested by saliva. Chronic pancreatitis may cause oxaluria from intestinal fermentation of carbohydrates (Cambridge and Mayo-Robson).

(c) *Failure of Fat Digestion.*—As already explained, the steatorrhoea of pancreatic defect takes the form of an excess of neutral, unsplit fat. This is the most valuable of the tests for deficient external secretion.

(2) Signs of Defective Internal Secretion.

(a) *Diminished Sugar Tolerance.*—This may be expressed in glycosuria, and almost certainly in hyperglycaemia, two hours after a dose of 50 to 100 grams of dextrose. The normal tolerance for dextrose is 150 to 200 grams. It must be remembered, however, that this may be a comparatively late symptom, and that it can be also produced by chronic alcoholism, hyperthyroidism, hyperpituitarism, and probably by hyperadrenalism.

(b) *Diastase Test.*—This has already been discussed. In my opinion it is one of the best tests for recent pancreatic damage.

(c) *Adrenaline Eye Test.*—Loewi showed that if adrenaline is instilled into the eye the pupil does not normally dilate. But if the pancreas is inadequate the pupil dilates in twenty to sixty minutes after one drop of the 1 in 1,000 solution is instilled, and another drop five minutes later. This is based on the antagonism between the adrenals and pancreas, of which there is other evidence. But if there is hyperthyroidism the test may also be positive, as this upsets the balance by reinforcing the adrenals. The dilatation is often an eccentric one. The test may fail if repeated within a week. Taken in conjunction with other signs, it is a simple test of some value and is easily applied. Recently, however, I saw a positive reaction in a case of acute appendicitis.

(3) Signs of Pancreatic Disintegration.

(a) If pancreatic lipase escapes into the circulation it can be found in the urine by the ethyl butyrate method (Opie).

(b) A pentose may sometimes be found in the urine from the breakdown of pancreatic nucleoproteins. This is also the

basis of Cambridge's test, which, however, does not seem to be very much relied upon at the present time.

To sum these tests up: If the adrenaline eye test and the diastase test are negative it is seldom worth while to undertake more elaborate investigations. If they are positive, and there is excess of unsaponified fat in the stools, it is very suggestive of pancreatic disease. If there are also muscle nuclei in the stools, it greatly strengthens the diagnosis. If all these signs are present in addition to glycosuria, the diagnosis is almost certain.

But here, and still more with the liver tests, clinical evidence must not be neglected. When Falstaff asked his page, "Sirrah, you giant, what says the doctor to my water?" the boy replied, "He said, Sir, the water itself was a good healthy water; but for the party who owned it, he might have more diseases than he knew for." I think I know that doctor; entrenched in the laboratory, he is quite prepared, without seeing the patient, to diagnose the existence of many more diseases than the medical attendant ever "knew for" or even suspected. The reaction against this was shown in a recent discussion on renal tests, when several surgeons expressed their willingness to abide by clinical signs alone. I am neither so bold nor so sceptical, but I would urge that these laboratory tests are still themselves on trial; and that the ultimate diagnosis must rest on the clinical as well as the biochemical findings.

REFERENCES.

- ¹ *Quart. Journ. Med.*, January, 1921. ² *Proc. Roy. Soc. Med.*, Urological Section, 1922, xv, pp. 37-39. ³ *BRITISH MEDICAL JOURNAL*, 1923, i, 317. ⁴ Medical Research Council's Report on Salvarsan, No. 2. ⁵ *Rev. Méd.*, Suisse, 1922, xlii, p. 291. ⁶ *Presse Méd.*, Paris, 1920, xxviii, p. 830; 1921, xxix, p. 121. ⁷ *Lancet*, 1923, i, 270. ⁸ *Amer. Journ. Med. Sci.*, Philadelphia, 1922, cxliii, pp. 60, 223. ⁹ *Recherches récentes sur les icteres*, 1919. ¹⁰ *Presse Méd.*, Paris, 1921, xxix, pp. 441-443. ¹¹ *Klin. Woch.*, 1922, xxxviii, p. 181.

THE USE OF RADIUM IN THE TREATMENT OF DISEASE.

BY

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IN CHARGE OF RADIUM TREATMENT AT THE EDINBURGH ROYAL INFIRMARY.

IN a previous paper published in this JOURNAL (January 20th, p. 100) I discussed the dosage of radium; I now desire to deal briefly with the principal conditions in which radium has been found useful in the Edinburgh Royal Infirmary. They include malignant disease, exophthalmic goitre, spleno-medullary leukaemia, Hodgkin's disease, keloids, and naevi.

The records show that radium has been chiefly used for malignant disease, and on the whole with encouraging, and in some cases with excellent, results. As cases of undoubted malignant disease, confirmed by operation and pathological examination, which remain perfectly well for more than seven years after the primary treatment are relatively rare, I quote the following case of recurrent sarcoma:

A woman, aged 49, recommended by Dr. MacLagan of Ayrton, had developed sarcoma four years before. Several operations for the removal of the growth were unsuccessful. She was admitted to the Royal Infirmary by Mr. Miles on July 15th, 1915. A large nodular mass projected in the left suborbital region; it interfered with vision and was adherent to the maxilla. Pathological examination showed that it was a large spindle-celled sarcoma.

As Mr. Miles considered the tumour inoperable, radium treatment was recommended. By internal and external applications a dose of 5,180 milligram hours was given. In November, 1915, a further external dose of 5,180 milligram hours was given. During the applications the growth diminished markedly. In February, 1916, the tumour had greatly shrunk and was movable; it had been fixed before. The patient was better, stronger, and could see normally. The condition had so much improved that Mr. Miles removed what was left of the growth; this was followed by a prophylactic dose of 4,120 milligram hours. In November, 1916, the growth had disappeared and Mr. Miles could detect no sign of recurrence. Seven years have now elapsed since the radium treatment was begun, and Dr. MacLagan writes on January 19th, 1923: "The patient keeps well without any trace of recurrence."

Of malignant affections, rodent ulcers, epitheliomata, lympho-sarcomata, spindle-celled sarcomata, malignant disease of the cervix, sarcomata of the nasal passages, and of the non-malignant affections, exophthalmic goitre, early keloids, and certain naevi are, in my experience, very amenable to radium treatment. They might be termed first-class subjects, because they admit under favourable conditions of actual cure. Under second-class subjects—meaning thereby conditions which may be ameliorated but in which a cure can rarely be expected—might be placed carcinomata, lymphadenomata, and spleno-medullary leukaemia.