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PART I.

ORIGINAL COMMUNICATIONS.

ART. X.—*Diabetes*.^a By JOCELYN SMYLY, M.A., M.D.
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I do not propose to enter into the history of the study of diabetes ; suffice it to say that it was recognised by Aretaeus as long ago as 150 A.D.

A. PHYSIOLOGY OF DIABETES.

I. Physiology of Metabolism of Carbohydrates.

Before entering upon its discussion, a few words on the metabolism of the carbohydrates may not be out of place.

A carbohydrate, as the name suggests, is a compound of carbon united with the elements of water. The simplest of them is formaldehyde CH_2O .

Those of interest in the present connection are those whose molecule contains six C atoms or a multiple of that number. These are of three classes :—

1. Monosaccharides : formula $\text{C}_6\text{H}_{12}\text{O}_6$, such as dextrose and lævulose.

^a A Thesis read for the Degree of Doctor of Medicine in the University of Dublin, June, 1912.

2. Disaccharides : formula $C_{12}H_{22}O_{11}$, such as cane sugar, lactose and maltose.
3. Polysaccharides : formula $C_6H_{10}O_5$, such as starch, glycogen, cellulose.

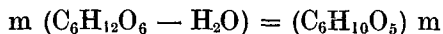
These compounds undergo a series of changes during digestion. Under the action of ferments in the saliva, the pancreatic juice, and the succus entericus the more complex compounds are broken up into monosaccharides, chiefly dextrose.

Thus, *e.g.*, cane sugar is hydrolysed into dextrose and lævulose



These sugars are absorbed into the system through the intestinal mucous membrane, but exactly what happens to them at this stage is still a matter of debate. Two rival theories are held. Claude Bernard held, as a result of his experiments, that dextrose passed as such into the portal veins and was conveyed to the liver, and in this opinion the majority of physiologists concur. Pavy, on the other hand, believed that the concentration of glucose in the portal blood was no greater than in the rest of the system, and that the sugar was decomposed in the intestine and converted into fat and protein, and passed into the system as such, through both lymphatic and portal vessels. Any excess of sugar above this he believes passes to the liver and is transformed into glycogen.

All are agreed that the liver acts as a "warehouse" for carbohydrate, and that in whatever form it arrives there the liver cells convert it into the starch-like substance glycogen



The liver, however, is not the only store-house in the body for glycogen, the muscles also contain it, the total amount of the two deposits being about equal. It is from this glycogen that the energy of the body is derived, it is the fuel which supplies the heat and the power to work ; hence its indispensable nature to the organism.

The blood contains carbohydrate in the form of dextrose

in a concentration of about 0.2 per cent. If it rises above this it is excreted by the kidneys and appears in the urine. It is practically certain that the glycogen in the muscles is derived from this supply of glucose. The manner in which the muscles make use of the glycogen, how it undergoes combustion and supplies them with energy, has been elucidated by experiments of Cohnheim's published in 1903-4, and confirmed by Rahel-Hirsch. He observed that if muscle juice is left to act upon glucose nothing happens, so also with pancreatic extract, but the mixed juices cause its decomposition into alcohol and carbon dioxide. Thus



The importance of this bearing on diabetes will appear presently.

II. *Experimental Diabetes.*

Much of our present knowledge of diabetes is based on experiment on living animals. Let us now consider some of this work.

Glycosuria can be produced in animals in three ways ; we may call the three forms *puncture diabetes*, *phloridzin diabetes*, and *pancreatic diabetes*.

1. *Puncture Diabetes*.—Claude Bernard produced diabetes in dogs and rabbits by his classical piqure experiment, driving a needle through the back of the skull into the floor of the fourth ventricle. The diabetes in this case is the result of irritation of the diabetic centre (L. Hill, p. 341). If the rabbit is previously starved, and the liver consequently free from glycogen, no glycosuria results.

The stimulation of various afferent nerves has been found to produce a like result, and the nerve-path by which the impulses go to the liver has been traced.

2. *Phloridzin Diabetes*.—The administration of phloridzin, or its derivative phloretin, causes a glycosuria, but no hyperglycæmia. Its action is either to cause the kidney to act as a secreting gland for glucose, or else to

so damage its epithelium as to allow glucose to leak through it.

3. *Pancreatic Diabetes*.—Finally, the most interesting form of all, diabetes can be produced by total extirpation of the pancreas.

This epoch-making discovery was made by von Mehring and Minkowski in 1889.

If the pancreas is completely removed from dogs glucose appears in the urine, and an excess of it in the blood—i.e., hyperglycæmia. The animal wastes and dies with symptoms of diabetes like those in the human subject. Similar results were obtained with many other vertebrates, including eels. That this result is not due to loss of the pancreatic secretion poured into the duodenum is shown by the fact that diabetes does not follow the formation of a pancreatic fistula; and secondly, that if a portion of the head of the gland with its blood supply intact is kept and grafted into the anterior abdominal wall diabetes does not ensue. Consequently we are driven to the conclusion that the pancreas supplies an internal secretion which is necessary to the metabolism of carbohydrates, enabling the tissues to utilise them.

As I have already mentioned, the more recent discovery of Otto Cohnheim that mixed pancreatic and muscle juice causes conversion of dextrose to alcohol and CO_2 , indicates the rôle of this internal secretion.

This pancreatic substance is not an enzyme, because it withstands boiling and is soluble in alcohol, but not in ether. It is in fact a substance like adrenalin and iodothylin, the active substances secreted by the suprarenals and thyroid gland respectively.

Cohnheim compares its action to an activating substance in the duodenum discovered by Pavlov. Pavlov found that pancreatic secretion did not digest proteins till it was rendered active by a duodenal secretion. Trypsinogen from the pancreas in combination with enterokinase from the duodenum forms the digestive substance for proteins which we call trypsin. Similarly the internal secretion of the

pancreas in combination with the activating agent in the muscles forms the glycolytic substance for sugars in the muscle.

To explain how this comes about he makes use of Ehrlich's side-chain theory. The pancreas, he believes, supplies amboceptors and the muscle juice complement. This theory not only accounts for the facts, but is supported by the observation that an excess of pancreatic secretion inhibits the glycolytic action, which is a feature in the action of amboceptors observed by Neisser and Wechsberg in bacteriolysis.

Rahel-Hirsch made the additional discovery that liver extract mixed with pancreatic extract caused a similar rapid decomposition of glucose.

III. Source of Sugar.

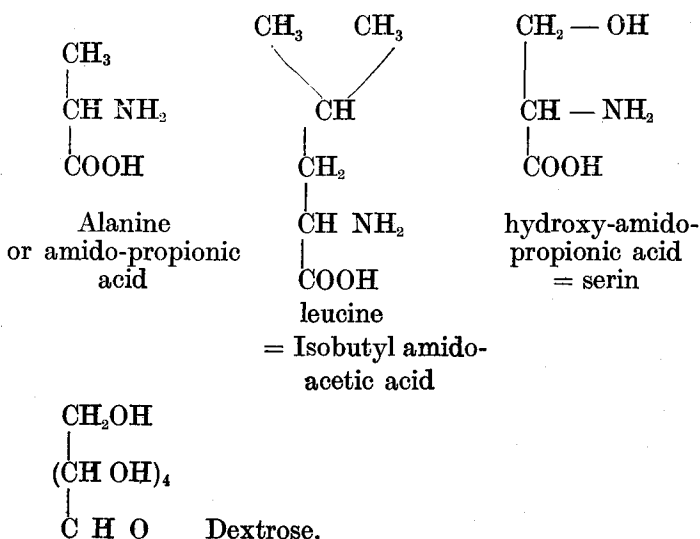
Let us now inquire what is the source from which the sugar is derived which appears first as an excess in the blood and then as an excretion in the urine.

At first it is undoubtedly derived from the stored up glycogen in the animal's system, for if the dog is killed a few days after removal of the pancreas hardly any glycogen can be obtained from the liver; and this occurs even if the dog is fed with either protein or carbohydrate. An interesting exception to this is lævulose, which does induce glycogen formation, a point which I venture to suggest might be of value clinically in feeding diabetics. The possible sources once the glycogen is used up are fat and protein, and we can get an indirect clue as to which of these it is in the following way :—

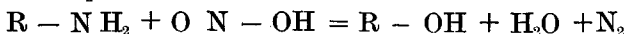
If the total excretion of sugar by a depancreatized dog is estimated, and also the total nitrogen excretion, it is found that after a few days they come to bear a constant ratio to one another, $D : N = \text{about } 3$, as an average ratio of a large number of observations. Practically the same ratio is obtained whether the dog be starved or fed on purely protein diet, whereas if carbohydrates are included

in the diet the sugar excretion is increased, while the N remains the same or less and $\frac{D}{N}$ becomes 7 or more. From which we must derive the conclusion that after the stored up glycogen is gone, the source of the glucose is protein.

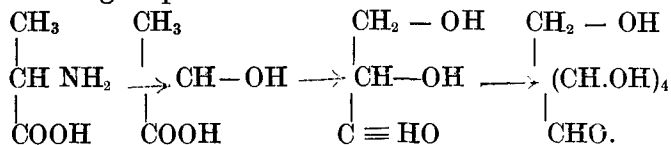
A great deal of chemical investigation has been made to determine the possibility of deriving sugars from protein material. Pavy and others have obtained glucosamine from mucin, egg-albumen, serum globulin and other substances by boiling them with acids, which is taken to prove that these proteins contain a carbohydrate group in their molecule which is split off by hydrolysis. This, however, accounts for only about 2 per cent. or less of the protein, and is insufficient to account for the large excretion of sugar. This leads one to ask, can sugar be formed in the body from decomposition products of proteins? The answer to this question is that probably it can. Among the most important of these decomposition products are amido-acids, some of which have structural formulæ closely related to the sugars. Compare, for instance—



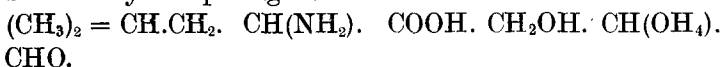
The NH_2 group is readily replaceable by OH by treating with HNO_2



Thus alanine can be made to afford glucose by the following steps—



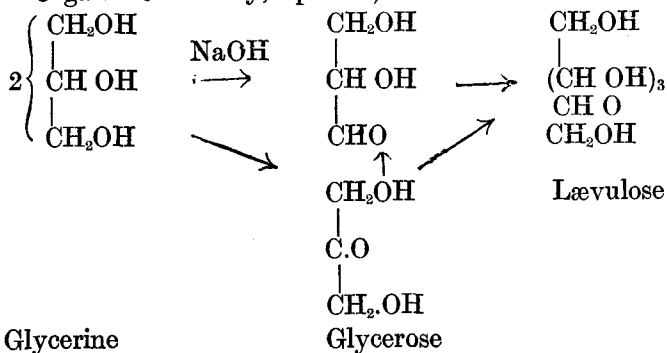
Leucine is related in constitution to dextrose, as will be seen by comparing their formulæ—



Evidence of the conversion of leucine to glucose in metabolism has been obtained by Mohr in the case of a man with severe diabetes. On a constant diet his daily sugar excretion was 49–63 grammes. On adding 20 grammes leucine to the diet it rose to 72–75 grammes, sinking again to 55–59 grammes after leucine feeding was stopped (L. Hill, p. 382). All this goes to show that the body can derive carbohydrates from protein; both its own body protein and also from protein diet.

Let us now consider whether fat may not also be a source of sugar.

Glycerine has been found by Emil Fischer to afford glycerose on mild oxidation, two molecules of which will undergo condensation to form lævulose (Richter's "Organic Chemistry," p. 553).



Some experiments have been made which tend to show that such a process may actually occur in the living body.

The fatty acid portion of the neutral fat probably cannot be converted into sugar, and this may possibly be a reason why fatty acids, such as β -hydroxy-butyric occur in diabetic urine.

Thus our general conclusion is that carbohydrates can certainly be derived from proteins, and possibly from the glycerine radical of fats.

B. DIABETES IN THE HUMAN SUBJECT.

We may now pass to consider diabetes as it is observed in the human subject.

I have mentioned three forms of experimental diabetes—puncture, phloridzin and pancreatic; and clinically three forms of diabetes have been described more or less corresponding to these.

Certain cerebral and spinal lesions cause glycosuria, though some of these have been found not to have involved the diabetic centre.

Again, what is known as renal diabetes has been described by good authorities in cases of kidney disease in which there was no hyperglycæmia. Fletcher, who writes on the subject in Osler and Mc'Crae's "System of Medicine," says there is considerable doubt as to its occurrence (Vol. I., p. 758). If it occurs it is the analogue of phloridzin diabetes.

Lastly, that diabetes mellitus corresponds to pancreatic diabetes may now be considered to be beyond a doubt. In Osler's words—"The present status may be thus summarized—(a) Extirpation of the gland in dogs (and occasionally in man—W. T. Bull) is followed by glycosuria: If a small portion remains sugar does not appear. (b) In a considerable percentage of cases of diabetes lesions of the pancreas are found; 50 per cent. show a chronic interstitial inflammation (Hansemann, Williamson. (c) In view of the experimental work it is reasonable to infer that diabetes is secondary to the pancreatic lesion.

I. Pathology of Diabetes Mellitus.

1. *Hyperglycæmia*.—The essential feature of diabetes is an excess of sugar in the blood plasma. Glucose is normally present in amount of 0.05 to 0.2 per cent., any excess over this latter amount causes excretion by the kidneys. In diabetes mellitus it may reach as high as 0.6 per cent. (Pavy, Seegen, quoted by Osler and M'Crae, p. 765) and even 0.7 per cent. (Naunyn).

Adami makes some important generalisations on conditions such as this depending on internal secretions. "The elaboration and discharge of internal secretions has its limits. It is, therefore, possible to have an intake or production of the substance acted on by those internal secretions, over and above the capacity of the internal secretions to convert or neutralise them. . . . An alimentary glycosuria is thus to be expected in case of excessive intake of carbohydrates."

Morbid states such as this "are not the outcome of one, but of the interaction of at least two, factors; they represent a want of balance between amount of internal secretion and amount of substance on which it acts. . . . The same symptoms may be brought about (a) by diminution of the internal secretion in the presence of normal production of the substratum or substance upon which it acts; and (b) by no diminution in the amount of internal secretion elaborated and discharged, but by excess of the substratum upon which it acts."

In the case of glycolysis "the same syndrome . . . may be set up (a) by excessive development or intake of the substratum; (b) by lesion of the organ or organs in which that substratum undergoes disintegration, preventing that disintegration; and (c) by lesion in the organ affording the hormone, without which the disintegration cannot be effected." (Vol. I., p. 386).

That is to say, diabetes may be caused by an excessive intake or production of carbohydrate, and this we know to be the case; glycosuria follows an excessive consump-

tion of sugar, or it may be caused by disease at the seat of combustion in the muscles, or by failure of the pancreas to supply the substance without which that combustion will not occur. And diabetes may vary in severity in proportion to the amount of deficiency of this substance.

2. *Pathological Anatomy*.—The discovery of experimental pancreatic diabetes turned the attention of pathologists to that gland in the case of diabetics.

It has been found more frequently diseased than any other organ. Occasionally gross lesions, such as a calculus or cancer or chronic interstitial pancreatitis, are found. More frequently the lesion is microscopic. Opie's studies, published in 1900 and confirmed in 1901 by Ssobolew demonstrate a hyaline degeneration of islands of Langerhans in three cases with no naked eye appearance of abnormality. Opie also describes two forms of chronic interstitial pancreatitis, interlobular and interacinar. Out of eleven cases of the interlobular variety one was diabetic, and out of three cases of interacinar two were diabetic (Osler and M'Crae, p. 755). These findings have, however, been stoutly opposed in certain quarters. According to Adami the islands of Langerhans have been shown by Dale, Swale Vincent and Mrs. Thompson not to be independent structures, but to be convertible into active acini and *vice versa*; he admits, however, that this does not disprove the contention that they are the source of the pancreatic glycolytic substance, while Opie's results would indicate that they undoubtedly are.

3. *Abnormalities of Metabolism*.—Abnormalities in metabolism closely resemble those observed in experimental pancreatic diabetes of animals.

(1) In the *first* place there is *hyperglycæmia*. The amount of glucose in the blood is increased from the normal maximum of 0.2 per cent. to 0.6 per cent. or even 0.7 per cent. (Osler and M'Crae, p. 765). This increase may be due to an over-production of glucose from a given quantity of food, or of deficient consumption; and the evidence available seems to point strongly to the

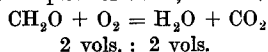
latter. First, if there is an over-production of glucose it must be at the expense of body glycogen which would become exhausted, whereas there is almost invariably some glycogen in the liver of diabetics. Secondly, we can get evidence from what is known as the respiratory quotient.^a In persons suffering from diabetes respiratory quotient is about 0.7 when dextrose is given in the food (Magnus Levy, quoted by L. Hill, p. 368), showing that the subject is consuming fats or proteins, not carbohydrate. Thirdly, we can get evidence by giving a patient a certain quantity of dextrose on an otherwise constant diet. It is generally found that most of the dextrose can be recovered from the urine. Van Noorden records a case in which it was all recovered.

We thus have several pieces of direct evidence that diabetes mellitus is a deficient power to utilise carbohydrates.

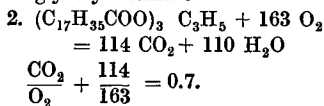
(2) Secondly, although the liver is never entirely deprived of glycogen, its power of storing it is greatly depressed. The reason for this has not yet been conclusively proved. One explanation is that "the glycogen stored in the liver and elsewhere is called upon, and in this way becomes uselessly used up in the attempt of the

^a The energy for the body is derived from the oxidation of its food material, the resultant products being excreted mainly in the forms CO_2 , H_2O and urea. If the intake and output of O_2 and CO_2 are measured we can find certain definite relations between their relative quantities.

When carbohydrates are burnt the CO_2 evolved is equal in volume to the O absorbed. Thus the simplest of them, formaldehyde—



They contain sufficient O for combustion of the H. Fats contain less O, thus glyceryl stearate—



The ratio of the volume of CO_2 to the volume of O, written $\frac{\text{CO}_2}{\text{O}_2}$ is called the *respiratory quotient*, and for carbohydrates it is $\frac{2}{2}$ or 1; for fats 0.7; and similarly for proteins $\frac{\text{CO}_2}{\text{O}_2} = 0.8$.

tissues to try to oxidise sufficient dextrose by working on an excess of it " (L. Hill, p. 357). M'Cleod mentions this reason only to condemn it, and advances another of his own (also mentioned in Osler and M'Crae's "System," p. 765) that glycogen is formed in the liver by a ferment which is a combination of an inactive substance in the liver activated by a pancreatic substance, deficient in diabetes. I venture to offer an explanation which seems reasonable, though I have not seen it in print, that the glycogen is drained from the liver as fast as it is formed owing to the fact that the tissues of the body are crying out for carbohydrate. It is proved that the liver discharges glycogen into the circulation as a result of a reflex nerve impulse, and the path of the impulse has actually been traced. And the fact that glycogen is found in the diabetic liver would indicate that its glycogen-forming power was not lost.

(3) Thirdly, there is an increased output of nitrogen; partly physiological owing to larger consumption of protein food by the patient, and partly pathological from combustion of the body proteins to supply the energy necessary to life.

It is worth observing that this waste of nitrogenous matter is greater in proportion to the glycosuria.

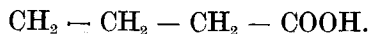
(4) Fourthly, there is a disturbance of fat metabolism. The power of the tissues to oxidise fat is depressed as a series of substances appear in the urine, acetone, acetoacetic acid, and β -hydroxy-butyric acid which during recent years have been proved to be derived from fats (Osler and M'Crae, 766; L. Hill, p. 373).

The chemistry of this change is easily understood by comparing their structural formulæ.

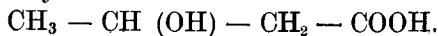
The general formula for a fatty acid is—



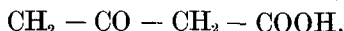
Butyric acid is—



β -hydroxy-butyric is—



Aceto-acetic acid (or di-acetic (bad name)) is



Acetone is—



A large ingestion of butter is followed by increased excretion of these bodies showing their origin from butyric acid, as at all events one source.

At present it is uncertain if fat alone is their source.

II. *Diagnosis.*

There is no disease more readily diagnosticated than diabetes, and it will be necessary to devote only brief attention to some of its chief symptoms, although a full discussion of all the symptoms of the disease and its complications might easily fill a book. Allow me then to merely enumerate the most striking ones and to devote particular attention to only one or two.

1. *Classification.*—No satisfactory classification of diabetes has been made. Some cases are severe and acute, others are mild and chronic. A pathological classification is made, on the lines I have taken above, into nervous, pancreatic, diabetic and possibly renal.

2. *Symptoms.*—The most important symptoms are as follows :—

(1) Polyuria—varies from 3–4 litres up to 15–20 litres. Urine pale in colour, from dilution of colour matter.

(2) Dryness.—Under this head fall a number of symptoms :—

1°. Thirst.

2°. Skin dry and harsh ; sweating rare.

3°. Mouth dry ; tongue dry, glazed and red ; saliva scanty.

4°. Constipation.

(3) Glycosuria.—This leads to high specific gravity : 1025–1045.

- (4) Wasting and hunger, from inability of tissues to utilise carbohydrate, and consequent drain on proteins and fats.

The temperature is subnormal, the pulse frequent and high. There are nervous symptoms of moroseness, and often sexual impotence.

In the final stages the urine is albuminous and contains abundance of hyalin and granular casts.

Testing for sugar is an important step in the diagnosis. It can be done by the reduction of Fehling's or Nylander's solutions, or by fermentation by means of yeast. The last is the most certain qualitative test ; the first the best method for ordinary quantitative estimations.

3. *Complications.*—Time will not permit of one's dealing with a variety of complications which occur in the disease. Suffice it to mention two of the most important :—

(1) Diabetic Gangrene.—Tissues of diabetics have their resistance lowered, and form a suitable nidus for bacteria, and hence operations on them should not be performed until they are rendered aglycosuric by treatment.

(2) Coma.—This is of three types.

By far the most common is that first described by Kussmaul in 1874, called the air hunger type.

Second is the alcoholic type—headache, feelings of intoxication and deep coma.

Third—diabetic collapse—the patient, after exertion, is seized with syncope and deepening coma (Osler).

Coma used to be thought to be due to acetone, but it has been found by experiment on animals that a much larger dose of acetone can be tolerated than is found in the blood in diabetes. The blame was then laid upon acetoacetic acid, but it was also proved not to be the culprit. It is now known to be caused by β -hydroxy-butyric acid ; and the condition is called acidosis.

While not denying this view Marcel Labbé has recently put forward the theory that acidosis may not be the sole cause of coma ; but that some cases, in particular those

which do not respond to treatment by administering alkalis, are due to intoxication by polypeptides (*Universal Medical Record*, June, 1912).

It is important to recognise the threatened onset of coma, and for this the most convenient test is ferric chloride solution. This gives a burgundy red colour with aceto-acetic acid in the urine, and the latter being derived from β -hydroxy-butyric acid suggests its presence.

There is no colour reaction for β -hydroxy-butyric acid.

(3) Treatment.—Finally, a few words as to treatment. Broadly speaking, present day treatment is of three kinds :—

1. Dietetic.
2. Drugs.
3. Pancreatic extracts.

The general aim of dietetic treatment is to free the urine from sugar, and this can be effected to a greater or less extent by a rigid protein diet.

The vindication for the treatment is that by diminishing the hyperglycæmia the power to assimilate carbohydrates is improved and patients can return to a restricted carbohydrate diet. Futcher advises ten days on a rigid diet every three months.

2. Of drugs the best are the opium alkaloids, codein is now most used.

3. Opinion on pancreatic extracts is somewhat divided. Futcher considers them disappointing. In Dublin, I think, the general opinion is that they give the patient his best chance.

So many diseases once purely medical have now been given surgical treatment that he would be a rash man who would deny the possibility that diabetes may one day be added to the number. I venture to think myself that that day may not be so very far off.

The account of a somewhat analogous case appeared in the "Annals of Surgery" of March, 1911.

A patient, a woman, aged twenty-four, was seized with tetany after thyroidectomy by W. H. Brown, of Victoria,

Australia. On a diagnosis that the tetany was the result of removal of the para-thyroids, she was treated with para-thyroid emulsion by injection, which gave slight temporary improvement. Implantation of para-thyroids from a living dog gave great improvement for twelve days, when the symptoms returned. Implantation of ox's para-thyroids gave a similar result. Monkey's para-thyroids were then tried, and she had very little stiffness for sixteen days. Finally, human para-thyroids were obtained half an hour after death from a man who died of Bright's disease, and were implanted within an hour in the anterior abdominal wall, following which there was a steady improvement in the patient's condition. The success of such an operation, taken with the mass of evidence of the cause of diabetes being a deficiency of internal secretion of the pancreas, would justify one in the opinion that the implantation of living human pancreas is at least a procedure worth considering.

REFERENCES.

- Recent Advances in Physiology and Bio-Chemistry. Leonard Hill.
Principles of Pathology. Adami.
System of Medicine. Osler and M'Crae.
Richter's Organic Chemistry. Smith.
Principles and Practice of Medicine. Osler.
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LITERARY NOTE.

So much attention is being directed to the social welfare and betterment of the poorer classes from a hygienic and eugenic point of view that a practical text-book for the use of health visitors, school nurses, members of guilds of help and other charitable associations, and indeed all those who are interested in the rules of hygiene which must be observed to keep the home and family healthy, will be cordially welcomed. Such a volume is announced for immediate publication by Messrs. P. S. King & Son. The author, Dr. C. W. Hutt, is Senior School Doctor to the Brighton Education Committee and late assistant Medical Officer of Health to the County Borough of Warrington.