BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 16 1937

CLASSIFICATION OF THE GLYCOSURIAS *

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If the mortality statistics of diabetes mellitus be consulted it will be found that the expectation of life for all classes of the disease has been increased by some three and a half years since the introduction of insulin. On analysis it will be seen, however, that this gain is confined entirely to the younger patients, and after the age of 55 the mortality has continued to increase at approximately the same rate as prior to 1922. This surely is a fact of the greatest significance, and while the value of insulin cannot be overestimated, anyone with a considerable experience of the disease can recall a number of cases in which it has failed to produce the results expected of it. This failure is commonly, and often rightly, attributed to the patient's inability to keep strictly to the regime prescribed for him; but in a proportion the blame is unjust and the failure lies elsewhere.

The glycosuria of a man of 80, which has been present for twenty years, and the acute diabetes of a child of 8 may both give the same fasting blood-sugar figures, and both are labelled as diabetes; but clinical experience teaches us that the outlook and the treatment necessary differ entirely in the two cases. In other words, we have not made a sufficient attempt to differentiate the types of glycosuria, and may use our remedy blindly in cases where the primary fault is not a deficiency of the pancreas.

Unfortunately this confusion is increased, as many textbooks of medicine state definitely that diabetes mellitus is due to a deficiency of islet tissue, though physiology has demonstrated that glycosuria may be due to a large variety of causes. Again, statistics show that while the mortality in patients under 14 is due to coma in 100 per cent. of the cases, in patients over 75 no deaths are due to this cause, and in fact the liability to coma decreases continuously as the age advances. So while the young patient dies directly from the disturbance of his metabolism, in the older one the complications are the dominant factor, a fact which alone suggests a wide difference of aetiology.

Carbohydrate Metabolism

The classification of the cases is therefore a matter of supreme importance in deciding both on the prognosis and on the line of treatment to be followed, and it can only be attempted if we bear in mind the physiology of carbohydrate metabolism and differentiate our cases on this basis. Before trying to make such a classification I would recall certain facts in the complicated subject of carbohydrate metabolism.

Three groups of organs appear to be involved. In the first we have the nervous system, the pituitary, the

* Presidential address delivered on October 14, 1936, to the Manchester Pathological Society.

thyroid, and the adrenals, which seem to be concerned with katabolism and the mobilization of carbohydrate from the carbohydrate stores. The production of glycosuria by nervous stimuli has been known for many years, but the fact that it only occurs when the pituitary is intact suggests that its action is an indirect one. Recently an extract of the anterior lobe of the pituitary has been prepared which will produce hyperglycaemia, ketosis, and lipaemia in a normal dog. One school considers that many cases of diabetes mellitus are primarily due to a pituitary overactivity. Again, the thyroid will produce an increased breakdown of liver glycogen, and the blood-sugar curve in hyperthyroidism may closely resemble that of a case of mild diabetes mellitus. Although I am unaware of any case of permanent glycosuria due to an overaction of the adrenals, the action of adrenaline in producing hyperglycaemia is well known, and as it does not occur if the liver has been removed it is almost certainly due to a breakdown of liver glycogen.

In the second group we have the islet tissue, and though fourteen years have elapsed since the discovery of insulin its action is still incompletely understood. It does appear, however, to be concerned with the storage of glucose as glycogen, and it seems that glucose must undergo this process before it can be used by the tissues. Insulin is therefore anabolic, and in some respects antagonistic to the first group.

Thirdly, we have the liver and the muscles, which are the great storehouses of carbohydrate. The latter also are the principal users of sugar, but their share in the production of glycosuria I will leave for the moment, until I am discussing the subject from its clinical aspect.

Possible Causes of Hyperglycaemia

There would appear, then, to be four possible causes of hyperglycaemia:

1. An increased katabolism leading to an increased mobilization of carbohydrate and fat from the storehouses, in which the nervous system, the pituitary, the thyroid, and possibly the adrenals are involved.
2. A diminished capacity to store owing to lack of insulin.
3. A defect in the storehouses themselves—the liver and muscles.
4. An inability of the tissues to use.

Unfortunately the cases are not always clear-cut—two or more organs may be involved or the disturbance of one organ may throw such a strain on another that it, too, gives way. Nevertheless I will attempt on this basis to make a clinical classification of the glycosurias. Before doing so I would draw attention to two factors which

may modify temporarily the course of the disease, whatever its basic cause may be.

First, rapidity of mobilization may be increased by a stimulus which is often an infection, but which may be purely psychic and may suddenly convert a comparatively mild case into a very grave one. When this happens enormous doses of insulin may prove to be insufficient to reduce the hyperglycaemia until the stimulus has subsided. An alternative explanation of the huge doses required is that the infection interferes directly with the action of insulin; but this has not been proved, and if it really were the case we should expect to find glycosuria in non-diabetic persons whenever they were subjected to a profound toxæmia. Secondly, the functional capacity of the utilizing tissues has to be considered. The muscles differ from any machinery known to us in that they can burn themselves to provide their own fuel. Muscles must have carbohydrate in order to function, and if it is not supplied they will destroy themselves in order to produce it. It would seem unreasonable to expect them, while so engaged, to use fuel to their maximum capacity. This, I believe, is the explanation of the benefit seen in the modern high carbohydrate diet, as it renders this wasteful chemical process unnecessary, and it also explains in many diabetics the improved tolerance, which may continue long after their insulin dose has been apparently stabilized.

These factors—the rapidity of mobilization and the health of the tissues—must be borne in mind in every case that is under treatment, and a careful search should be made for septic foci in teeth and tonsils, and in particular for tuberculosis of the lungs. If insulin is to be regarded as a diagnostic as well as a therapeutic weapon it must be remembered that it will lower the blood sugar, temporarily at any rate, in every one, whether there is any pancreatic deficiency or not; and if the pancreas be normal there will be overstorage, and we will be dealing with a toxicological rather than with a pharmacological effect. This is a point which I cannot emphasize too strongly.

Twenty years ago the state of the urine was regarded as the criterion of successful treatment. Later the recognition of renal glycosuria showed that this might be fallacious, and the blood-sugar level took its place. Taken by itself a fall in the blood-sugar level may be equally fallacious, and it can only be considered beneficial if it be accompanied by an improvement in the patient's general health.

Increased Mobilization

In the first group, due primarily to overproduction, are the comparatively rare cases following acromegaly, in which there is a pituitary overactivity, and in them, as would be expected, the response to insulin is poor. Probably many of the cases associated with hyperthyroidism also belong to this group. It is a not very uncommon combination, and in my experience these cases do badly both with diet and with insulin, and the only successful treatment I have seen has been the prompt removal of the thyroid, although insulin may have to be continued after the operation, as there is often a combination of defects. Thus in a woman aged 55, with a basal metabolic rate of +52 per cent., the urine was loaded with sugar and acetone, and the fasting blood sugar was 0.395 gram per 100 c.cm. despite 50 units of insulin a day. Thyroidectomy was performed, and the urine is now sugar-free and the fasting blood sugar is 0.162 gram per 100 c.cm. on 20 units daily, and the patient is in good health.

In a certain number of cases the primary lesion appears to be in the brain itself. There may be a history of over-

anxiety for some time prior to the illness, or a family history of nervous instability, and while 70 per cent. of adult diabetics give a history of obesity these patients may have been thin always. I invariably suspect overmobilization if such a history is obtained. I will quote two cases in illustration of this.

Case I

A girl, aged 18, had a history of meningitis (cause unknown) in infancy. Two brothers had died of meningitis and another brother later committed suicide. Sugar was discovered in her urine prior to an operation for chronic appendicitis. She was dieted and underwent the operation successfully. For the next two years she remained in good health, but it became more and more difficult to keep the blood sugar at the normal level and the urine free from sugar. When insulin was introduced into this country it was therefore decided to try it. For a time she became sugar-free, but her health did not improve; she became obese, and in spite of the fact that she had several alarming reactions after exercise it became impossible to keep her free from sugar, and a further increase of the dose of insulin made her ill. For a time she was in the London Hospital, under the care of Dr. Otto Leyton, to whom I am indebted for further information. It was found that when given a dose of 50 units of insulin just before a meal containing only 5 grams of carbohydrate the blood sugar fell very slowly from 0.25 to 0.167 gram per 100 c.cm. in eight and a half hours. Without insulin the fasting blood sugar varied from 0.26 to 0.16 gram per 100 c.cm. Dr. Leyton agreed that she was resistant to insulin, and its use was discontinued. Although insulin produced no clinical improvement it did produce two effects—hypoglycaemic attacks and obesity.

The hypoglycaemic attacks, which always occurred after exercise, showed that the muscles were capable of utilizing sugar, but insulin had interfered with the supply, and the obesity was apparently the result of overstorage. After insulin had been discontinued her health improved, and she continued to live a normal life on a moderate dietetic restriction and without insulin, until she dislocated a cartilage in the knee. She said this made life unbearable. In view of the previous successful appendicectomy the risk of another operation was not considered to be an undue one, and it was accordingly performed. Acetone appeared in the urine in large amounts two days later, and in spite of the administration of 600 units of insulin, which had no effect whatever on the blood sugar, a fatal coma developed a week later. Unfortunately the brain and pituitary could not be examined, but Dr. Susman, who examined sections of the pancreas, and who at that time knew nothing of the history of the case, found that the islet cells were few in number, were largely made up of alpha cells, and a few showed degeneration. He reported that "the features as a whole suggest that the pancreas and islet function have been interfered with through paralysis of the nerve supplying the pancreas, the histological findings closely resembling those described by Opie as due to paralysis."

Here, although there was a deficiency of islet tissue, the case was definitely resistant to insulin, and there was no defect of utilization. I can only explain it as one in which the primary lesion was due to disturbance of mobilization arising from meningitis in childhood, mobilization being so stimulated by operation that a profound ketosis developed, terminating in coma. Another point in this case, which I think should be emphasized, is that for a time insulin brought the blood sugar to normal, but as a result made her fat and ill.

Case II

Another case, a male aged 53, developed diabetes after a prolonged period of overwork. He complained of palpitation, nervousness, and tremulousness, but the basal metabolic rate was not increased and an x-ray of the pituitary fossa was normal. He responded poorly to insulin. The fasting blood sugar varied from 0.26 to 0.365 gram per 100 c.cm., even

when he was given 50 units a day, and he complained that he felt ill with it. It was eventually reduced to 24 units daily, with which the blood sugar remained at 0.24 to 0.29 gram per 100 c.cm., and he felt better.

I saw him later in deep coma; the blood sugar gradually rose from 0.38 to 0.95 gram per 100 c.cm.; coma persisted in spite of 260 units of insulin, and he died in twenty-four hours. A necropsy was done, which showed that the thyroid contained an adenoma undergoing toxic changes. The brain showed scattered areas of recent softening and the islet tissue of the pancreas varying degrees of hyaline degeneration up to complete destruction.

In this case there were probably multiple causes giving rise to the disease, and I would regard it as one in which both the nervous system and the thyroid combined to produce over-mobilization, throwing an ever-increasing strain on the islet tissue. I had considered the advisability of thyroidectomy, and now regret that the normal basal metabolic rate dissuaded me from calling in a surgeon. Occasionally a gross organic lesion of the brain may be responsible for glycosuria. I have twice seen cases of encephalitis lethargica in which the glycosuria was at first the predominant feature, and on one occasion a diabetes of long standing appeared to be associated with a temporo-sphenoidal tumour.

The nervous element is therefore a very real one, and it explains the rapid deterioration in diabetics who have been subjected to nervous strain. Probably the beneficial effects from opium and codeine seen in the former treatment of diabetes were due to their inhibition of a nervous mobilization.

Diminished Storage Capacity

A diminished capacity to store owing to lack of insulin is undoubtedly the commonest cause of diabetes, and is found especially in the diabetes of children and young adults. Here the age of the patient alters the clinical appearances. In the young patient growth dominates the picture, the ductless glands, especially the pituitary, are in full activity, mobilization is rapid, acetone as well as sugar appears in the urine early in the case, and there is no history of obesity. Usually the response to insulin is good, but owing to the rapidity of mobilization stabilization may be difficult and the patient will pass from hyperglycaemia to hypoglycaemia in a few hours. In older patients, where growth has ceased and especially where sexual maturity has been passed, the disease is not so rapid. Acetone appears later, and there is often a history of a rapid increase of obesity for one or two years prior to the onset of the disease, followed by an equally rapid fall.

It would seem that there has been time for a compensatory mechanism to function, and the increased carbohydrate has been stored as fat. This history I regard as almost pathognomonic of a pancreatic type of diabetes, and the case almost invariably responds to insulin. The appearance of these pancreatic patients also is often characteristic, and the brick-coloured cheeks on a yellow-tinged background are in themselves a clear call for the immediate use of insulin. It is the pancreatic type of diabetes, too, in which acetonuria is so common, and the great danger is from a direct disturbance of metabolism ending in coma. On the other hand, complications such as cataract, true carbuncle, and gangrene are comparatively rare. Even if the disease occurs later in life and there are repeated attacks of coma the patient usually escapes them.

Liver Disturbance

Many varieties of liver disturbance appear to be responsible for a glycosuria. Haemochromatosis is one of the more obvious and by no means rare causes. It occurs

only in men, and a bronzed tinge of the skin combined with an enlarged liver is always suspicious. Here liver, pancreas, and muscles are all involved, so that it is difficult to assess the responsibility of one particular organ, but the poor response to insulin is evidence that factors other than the pancreas are concerned. In one case an enlarged hard liver had been noted seven years before the onset of glycosuria, which suggested that a hepatic disturbance was the primary condition.

Glycosuria, too, is commonly associated with a cholecystitis. Usually it is mild in type and responds to diet alone, and often it clears up completely after the gall-bladder has been removed. Although the appearance of sugar is usually attributed to an associated pancreatitis insulin is rarely either necessary or advisable, and it has been pointed out that, while in pancreatitis the head of the organ is chiefly involved, the bulk of the islet tissue is in the tail.

The glycosuria of extreme obesity, often found in beer drinkers, is probably entirely hepatic. It responds well to diet, and I believe is wholly due to an excessive deposit of fat in the liver.

The glycosuria of gout is also probably associated with the liver disturbance. It is usually of mild type, and in my experience does not respond to insulin. Thus a man who is now 60 has been under my observation for the past ten years; he is liable to occasional attacks of gout and has had sugar intermittently for twenty years. The family history is remarkable: six out of eight brothers and sisters have glycosuria, but all have reached the age of 60 or over. He did not respond well to insulin, and with 40 units a day did not become sugar-free and there was no clinical improvement. For a time he took 8 units daily, but the blood sugar was high (a fasting level of 0.312 gram per 100 c.cm.). For the last six months, however, he has taken no insulin at all, and the fasting blood sugar has dropped to 0.231 gram per 100 c.cm., and he says he feels better without it.

Acute liver disease associated with diabetes is very rare, but recently I saw a case in which it appeared to be undoubted. A man aged 40, who had passed as a first-class life for insurance two years before, developed a severe lobar pneumonia. Two days later jaundice appeared and sugar was found in the urine. When I saw him in consultation he was intensely jaundiced, the liver was palpable, and the blood sugar 0.336 gram per 100 c.cm. As we thought the case was hepatic rather than pancreatic he was given glucose and only a moderate dose of insulin, 10 units twice a day. The pneumonia cleared up by lysis and the temperature was normal six days later, the jaundice also disappeared, the urine became sugar-free, and the insulin was then stopped. The last blood sugar was 0.129 gram per 100 c.cm. one and a quarter hours after a mixed meal, and he was then taking an ordinary diet and apparently in perfect health.

Diabetes and Pernicious Anaemia

The association of diabetes mellitus with pernicious anaemia is a well-recognized although not very common condition. Here we seem to be on surer ground, for in pernicious anaemia we have a disease which is definitely cured by liver therapy, and when this has been achieved the diabetes mellitus may clear up completely. It is important to bear the association in mind or serious consequences may ensue.

Thus in March, 1935, I was asked to see a woman of 40 who had been taking 15 units of insulin twice a day for the past six months. She was very ill, and although sugar-free she was convinced that the insulin

made her feel worse. There was a considerable anaemia, and as it was associated with numerous retinal haemorrhages (a very rare condition in uncomplicated diabetes under middle age) I had a blood count done. This showed a typical pernicious anaemia. Insulin was stopped and liver treatment substituted, and she is now able to take a diet containing 8 oz. of bread without any insulin at all, and she has since remained in good health.

A still more remarkable case was admitted to the Infirmary in June, 1936. A woman of 56 was on the verge of coma; the urine was loaded with sugar and acetone and the blood sugar was 0.336 gram per 100 c.cm. A blood count showed 1,830,000 red cells, 44 per cent. of haemoglobin, and a colour index of 1.22. There was also auricular fibrillation. Owing to the proximity of coma it was felt to be unjustifiable to withhold insulin altogether, and she was given two doses of 15 units on the day of admission and liver injections were started immediately. No more insulin was given, and the red cell count dropped to 980,000 during the next three days, but after that a rapid improvement set in and two months later the count was 4,018,000, with 78 per cent. of haemoglobin, and on an ordinary diet without insulin the fasting blood sugar was 0.19 gram per 100 c.cm.

Effects of Arteriosclerosis

Perhaps the most difficult group is that in which arteriosclerosis is the predominant feature. Here the glycosuria is often mild—apart from an infection there is no acetonuria—the diabetic symptoms are not severe, and there may be no loss of weight. Often, indeed, sugar is discovered accidentally when the patient comes under treatment for some condition such as gangrene, carbuncle, cataract, or a coronary thrombosis. It may be that the glycosuria clears up spontaneously for a time, and every surgeon is familiar with cases of carbuncle and gangrene in which the sugar disappears after the infection has been dealt with. In some of these patients a considerable improvement follows the administration of insulin, and in them the usual explanation that we are dealing with an arteriosclerosis of the pancreas is probably correct. In others, however, only a partial improvement or no improvement occurs, and a defect in some factor other than the pancreas may be responsible. What this factor is I am unable to say; possibly it is an insulin kinase as postulated by Himsworth; but I believe that here the primary condition is not an inability to store glucose and make it usable, but an inability of the tissues to use the sugar.

I have already mentioned the question of efficient utilization and I will now return to it in more detail, as its importance is often overlooked. Diabetics are liable to attacks of hypoglycaemia when taking insulin. Now hypoglycaemia may be due to one of three causes:

- (i) A deficient mobilization of carbohydrate such as occurs in von Gierke's disease;
- (ii) Overstorage; or
- (iii) Over-utilization.

In young diabetics these hypoglycaemic attacks are most likely to occur after exercise—that is, although the capacity to store is deficient, utilization is unimpaired. In the arteriosclerotic group exercise is an uncommon cause of hypoglycaemia. Hypoglycaemia does occur, but it is of a different type; it may come on at any time, possibly during the night, and does not seem to follow any particular exertion. Often excess of insulin is shown not by any definite attack but by a feeling of vague ill-health, periodic headaches, or an increasing obesity. Priscilla White has shown that even young diabetics may

develop arteriosclerosis if given too much fat, and clinically we find that a young patient who in the early stages of treatment was very liable to hypoglycaemic attacks after exertion gradually becomes free from them. Here the most probable explanation is that a developing arteriosclerosis adds an impaired utilization to the clinical picture.

At the same time the renal threshold tends to rise, and the patient will often tell you that he only feels well when the blood sugar is considerably above the figure of 0.1 gram per 100 c.cm. This heightening of the renal threshold is commonly found in arteriosclerotic diabetics, and I regard it as not due to any deficiency of the kidneys but rather to a conservative process. It is necessary for these people that the blood sugar should be considerably above the normal level in order that they may overcome a deficient utilization. Indeed I have seen an arteriosclerotic diabetic who was in insulin coma, although the blood sugar was exactly 0.1 gram per 100 c.cm. Later I again examined the blood when he was feeling well, and although sugar-free the fasting level was then 0.225 gram per 100 c.cm.

The optimum level for a particular person, therefore, may be very much above the so-called normal level, and the distinction between the two is of great practical importance. Arteriosclerosis is a gradual process which may take many years to develop, and, like diabetes, it may be strongly hereditary. When examining cases inquiry should be made not only about a history of glycosuria in other members of the family, but whether there has been any liability to the arteriosclerotic forms of heart disease, cerebral haemorrhage, or gangrene. There is often a history of obesity in these cases, usually of long standing, but when the symptoms of diabetes develop the loss of weight may be trivial. There is no history of a rapid increase followed by a rapid decrease of weight, such as I have described in the pancreatic cases, and despite the obesity acetonuria does not arise except in the presence of an infection. In some of the cases there appears to be an associated pancreatic defect, and insulin may be required either permanently or temporarily, but in others it either has no effect or it makes them definitely ill.

We can only find out what its action will be by a cautious trial, relying not on the blood sugar, the optimum level of which we cannot know for each particular patient, but on the clinical findings. I will quote two instances to illustrate the type of case to which I am referring. The first is so mild that it cannot be called a true diabetes.

A female, aged 25, complained of boils, and a little sugar was found in the urine. This disappeared after infection had ceased, and a blood-sugar curve taken then was normal. There were no symptoms of diabetes, the general health was good, and there was no obesity. Her father had had diabetes and gangrene of both legs, and a sister, aged 45, weighed 18 st. and had had glycosuria for many years.

My interpretation of this case is that she is a potential arteriosclerotic with a defective utilization. The boils led to a stimulus of mobilization and sugar appeared temporarily, but a normal blood-sugar curve showed that storage was normal. In the course of time she will become an arteriosclerotic diabetic like the rest of her family. A second case was more advanced.

A woman, aged 46, complained first about her eyesight, and incipient cataract was found in both eyes. There were no symptoms of diabetes. She felt well, and had no loss of weight; the blood pressure was 180/86 mm. Hg, and the urine contained sugar but no acetone and no albumin. The blood sugar was 0.203 gram per 100 c.cm. Her father had had diabetes with cataract, and died of arteriosclerosis and heart failure. She was given a diet of 2,400 calories and 20 units

of insulin twice daily. The blood sugar fell to 0.162 and then to 0.081 gram per 100 c.cm.; later it returned to 0.25 gram per 100 c.cm., and remained about this figure for six weeks. With insulin discontinued but the diet kept the same the blood sugar seven days later was 0.286 and fourteen days later 0.304 gram per 100 c.cm. Two months later the fasting blood sugar was 0.19 gram per 100 c.cm.

This patient later went to India, and the last I heard of her was a rather indignant letter from her doctor asking why insulin had been discontinued, and by the next mail an urgent message from her husband asking for instructions, as a determined attempt to get her sugar-free was making her very ill.

In this case, as in many others, insulin did produce a temporary reduction of blood sugar, but this was followed later by a rise to a higher level than before she came under treatment. Evidently the effect of insulin had been to increase storage for a time until the warehouses had reached the limit of their capacity, when the blood sugar returned to its old level.

Other Considerations

I could quote many such instances in which arteriosclerosis, retinitis, or cataract has often been the principal feature, and bearing in mind the success of liver therapy in the cases associated with pernicious anaemia I have used it on them too, and believe I have seen a clinical improvement, although I have not been able to demonstrate any marked fall in the blood-sugar level. Before leaving this matter I would refer to the subject of arteriosclerotic heart disease, and particularly to coronary thrombosis. Here a moderate glycosuria is common, and lowering of the blood sugar either by carbohydrate starvation or by insulin undoubtedly aggravates the disease. Any reduction of the blood-sugar level to the region of 0.1 gram per 100 c.cm. gives rise to symptoms of vague ill-health, and the optimum figure may be two or three times the normal. It is in these cases particularly that insulin must be used with great caution, and if we blindly try to achieve a laboratory ideal there is a grave risk of sudden death. Race, too, has an important bearing, and the arteriosclerotic type is often seen in Jews.

Diabetes mellitus often appears in the Jewish race, but the cases are nearly always past middle life, and the acute pancreatic type with acetonuria is very uncommon. Usually the disease itself is mild, and they first come under observation for cataract, retinitis, or hyperpiesis rather than for glycosuria. The response to insulin is variable, and so a cautious prognosis should be given. Even when diabetes does occur in the young Jew its clinical picture and response to insulin differ from those of the young Gentile, in whom a dramatic onset and a dramatic response to treatment is the rule, so that we can only conclude that the aetiology is entirely different.

The following case will illustrate my meaning.

A girl of 12 first consulted her doctor complaining of blueness and coldness of the legs, and glycosuria was discovered in the course of routine examination. Apart from a little thirst there were none of the usual symptoms of diabetes; there was no loss of weight and her general health was good. The family history was suggestive. The mother had had a mild diabetes for many years and an aunt and cousin suffered from Raynaud's disease. The fasting blood sugar was 0.285 gram per 100 c.cm., and with 5 units of insulin twice a day it fell to 0.128 but gradually rose again, and later was 0.346 gram per 100 c.cm. on 15 units twice a day. There has never been any acetone, nor has the child had any of the hypoglycaemic attacks which so commonly affect non-Jewish children. When I saw her a few days ago she had stopped the insulin of her own accord. The fasting blood sugar was

0.212 gram per 100 c.cm., and she said she felt better without it.

Here the presence of Raynaud's disease in both the patient and her aunt and the poor response to insulin strongly suggest a peripheral rather than a pancreatic cause.

Conclusion

The classification I have suggested is unorthodox and will have to be modified considerably as time goes on, for it is certain that other factors, the sex organs in particular, enter into the production of glycosuria. At present, however, our knowledge of them is so meagre that they cannot yet be considered.

Some of my conclusions, however, I do not think will have to be modified.

First.—That glycosuria is a symptom and not an entity, and each particular case must be studied to find the primary disturbance.

Secondly.—The optimum blood-sugar level may not coincide with the so-called normal blood-sugar level.

Thirdly.—The criterion of successful treatment is not the achievement of a laboratory ideal, the rationale of which we do not fully understand, but whether the patient does or does not show a clinical improvement.

DIRECT BRONCHOSCOPIC INVESTIGATION IN HAEMOPTYSIS WITHOUT PHYSICAL OR RADIOLOGICAL MANIFESTATIONS

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Etymologically haemoptysis denotes "spitting of blood," but the term has become by general usage commonly restricted to the expectoration of blood originating from that portion of the respiratory tract situated below the vocal cords. In certain cases of haemoptysis there is not infrequently a lack of signs on complete clinical examination and direct or contrast radiological study, so that it is impossible by these means to ascertain the cause or source of the bleeding. It is to such cases that the following notes refer.

The significance of haemoptysis as a sign of serious pulmonary disease has been long recognized, and it is impossible and unnecessary in this short article to enumerate in detail the many causes of this accident. It is a matter of experience, however, that in a large proportion of cases haemoptysis is caused by pulmonary tuberculosis, and it is not surprising, therefore, to note in the older literature the great significance accorded to blood-spitting in the diagnosis of this disease. Commonly the majority of patients who spat blood were regarded as cases of pulmonary tuberculosis, and many correctly so diagnosed succumbed to the disease: the remainder either died as the result of an unrecognized causative lesion or lived an invidious existence under the stigma of "consumption."