For Joslin's 45 living cases the latest information is:

From February-April, 1926	...	...	...	4 cases
" June-July, 1926	...	...	...	9 "
" September-October, 1926	...	...	...	7 "
" November, 1926	...	...	...	9 "
" December, 1926	...	...	...	4 "
" January, 1927	...	...	...	6 "
" February, 1927	...	...	...	9 "
" March, 1927	...	...	...	3 "

45* (51)

It will be seen that Joslin's results—I am very glad to recognize it—are a little better than mine. On the other hand, his information from his patients is in part not so recent as mine; I hope that later information will not raise the number of his fatal cases.

That so many of our coma patients are still living is very creditable to them; the great majority are under observation in the out-patient department, and we know that they follow the advice given concerning diet very carefully. If we have deserved some credit for the result it is because we have used our influence in educating them, and the patients have understood that it was best for them to follow our advice.

A short time ago Dr. de Jong of Leyden sent me the figures of the mortality from diabetes in Holland during recent years; he had recently told me that there had been a great increase in the mortality from this disease. The figures, however, show, when divided into age groups, that the curve for the mortality for all ages below 50 takes a quite horizontal course; for the age period 50 to 64 also the curve shows no very evident rise, but for the years after 64 the number of deaths from diabetes has increased during the years 1911 to 1926 about 200 to 300 per cent. It is quite evident that the enormous difference shown for the years 1911 to 1926 must be due to the attention now given to diabetes and the development of a more accurate diagnosis as to the cause of death in patients dying at a late age. This is the opinion that I have defended for many years to explain all those statistical differences which appear to indicate that the disease is increasing in frequency.

CLASSIFICATION OF GLYCOSURIA FROM THE POINT OF VIEW OF INSULIN TREATMENT.*

BY

P. J. CAMMIDGE, M.D.

Most observers, including Banting (Nobel Lecture, 1925), are now agreed that, as I predicted on theoretical grounds in 1922, insulin is not a cure for diabetes. It is true that many diabetic patients exhibit a considerable recovery of carbohydrate tolerance after treatment with insulin, but similar recovery occurred as a result of the "fasting" treatment, and the cause is probably the same—namely, the physiological rest provided for an exhausted function; in the one case by vicariously performing its work, and in the other by reducing the demands upon it to a minimum. There is, however, the important difference that in the fasting treatment "the horse is starving while the grass is growing," whereas with insulin the patient can be fed; but as the rest obtained by regulated fasting is not confined to the structures directly concerned in carbohydrate metabolism and has a beneficial influence in other directions, maybe helping to eliminate the cause of the disease, the full diet possible from the commencement of treatment with insulin is not always a real advantage to the patient.

In suitable cases, and used intelligently in conjunction with careful dieting and other forms of treatment, there can be no doubt that insulin is invaluable in diabetes mellitus. This is clearly evident in my own statistics, for in a series (Table I) of 250 unselected cases of which I have complete records during three years immediately preceding the discovery of insulin there were 66 deaths (26 per cent.), while in the same number of cases treated in three years after the introduction of insulin there were

TABLE I.

	Pre-insulin Period.			Insulin Period.		
	Cases.	Deaths	Percent- age.	Cases.	Deaths	Percent- age.
Defective utilization (achriatic)	115	56	49	97	20	21
Defective storage (anapothectic)	117	10	9	138	6	4
Lowered threshold (epithyric)	18	0	0	15	0	0
Total	250	66	26	250	26	10

only 26 deaths (10 per cent.). The improvement was accounted for mainly by a complete disappearance of pneumonia, influenza, and post-operative fatalities as causes of death, and by a reduction in the number of deaths attributed to coma from 19 to 6 during the insulin period.

For purposes of comparison and treatment cases of glycosuria may be divided into three main groups, irrespective of any theory as to the cause of diabetes, by relatively simple tests. (1) Those where there is defective utilization and defective storage of sugar, or, briefly, the "achriatic" variety (α =absence of, $\chi\pi\epsilon\alpha$ =use), characterized by a high blood sugar and a low lactic acid content of the blood in a fasting condition. (2) Those where there is difficulty in storage but no obvious defect of utilization, the "anapothectic" variety (α =absence of, $\alpha\pi\omicron\theta\eta\kappa$ =storehouse), in which the fasting blood sugar and lactic acid are normal, although hyperglycaemia develops on feeding. (3) Those where the utilization and storage of sugar are normally carried out and the sugar content of the blood is not high, even after a test meal of glucose, but glycosuria occurs on feeding, from unusual permeability of the kidneys for sugar, which may be termed the "epithyric" variety ($\epsilon\pi\iota$ =upon, $\theta\upsilon\pi\alpha$ =a door). It is instructive to see how the introduction of insulin has affected the death rate of each group. As might be expected, achriatic glycosuria was a much more fatal condition than the anapothectic variety in pre-insulin days, the death rate in my cases working out at 49 per cent. in the one group and 9 per cent. in the other. After insulin became available the percentage of deaths in the achriatic group fell to 21, and in the anapothectic group to 4, so that, although insulin effected a noteworthy saving of life in both, the relative mortality remained practically unchanged.

It is true that all my patients since 1923 have not been treated with insulin, for I have always maintained that the inconveniences necessarily attending its use are not compensated by the advantage gained, except where a suitable diet is not otherwise obtainable, and I think my results support this view. The twofold power possessed by insulin of promoting the storage and the utilization of sugar should render it particularly useful in cases of achriatic glycosuria, where both functions are at fault, and I found it necessary to prescribe it in 64 out of 97 (66 per cent.) of the cases of that type coming under my care in the period under

TABLE II.—Insulin Period.

	Diet.			Insulin.		
	Cases.	Deaths	Percent- age.	Cases.	Deaths	Percent- age.
Defective utilization (achriatic)	33	6	18	64	14	22
Defective storage (anapothectic)	131	6	5	7	0	0
Lowered threshold (epithyric)	15	0	0	0	0	0
Total	179	12	7	71	14	20

review (Table II). Of these 14 (22 per cent.) have died, 2 of coma, which developed shortly after the injections were discontinued contrary to my advice, 2 apparently from the effects of insulin, but in the remaining 10 death

* One of the papers read in opening a discussion on insulin therapy in diabetes mellitus at the Annual Meeting of the British Medical Association, Edinburgh, 1927.

occurred from causes not directly connected with defective carbohydrate metabolism, such as cancer, tuberculosis, and nephritis. There were 6 deaths in the 33 cases of achriatic glycosuria not treated with insulin (18 per cent.), 3 were due to coma occurring in patients who refused the injections, and the other 3 resulted from cancer, nephritis, and old age respectively, causes which could not have been prevented by insulin.

In my experience patients suffering from glycosuria arising from defective storage rarely need insulin, and I have found it necessary in only 8 out of 138 cases (6 per cent.). Seven of these improved rapidly and their condition has remained satisfactory, but one who refused the treatment died of coma. This patient accounts for one of the 6 deaths in the anapothectic group not treated with insulin, where there was a total death rate of 5 per cent.; all the other patients died from causes not susceptible to the influence of insulin. (Table III.)

TABLE III.—*Causes of Death, Insulin Period.*

	Achriatic.		Anapothectic.		Total.
	Diet.	Insulin.	Diet.	Insulin.	
Accident	0	1	0	0	1
Age	1	0	2	0	3
Carbuncle	0	1	0	0	1
Graves's disease	0	1	0	0	1
Insulinism	0	2	0	0	2
Malignant disease... ..	1	2	2	0	5
Nephritis	1	1	0	0	2
Pancreatitis... ..	0	3	0	0	3
Refused treatment	3	2	1	0	6
Tuberculosis	0	1	1	0	2
	6	14	6	0	26

Epithyric glycosuria is not a fatal condition, and, since there is no defect of carbohydrate metabolism, treatment with insulin is not called for; in fact it is contraindicated, as a disturbance in the balance between the internal secretions of the ductless glands which may cause serious or even fatal hypoglycaemia results.

The effects of insulin upon the activities of the ductless glands have not received the attention they deserve. The acute symptoms arising from a large overdose are well known, but the results of chronic hyperinsulinism from therapeutic doses are, as yet, almost unrecognized, although they are of considerable practical importance. The most common is polyuria, due probably to the neutralizing effect of insulin upon the internal secretion of the pituitary; this may develop occasionally into a condition closely resembling diabetes insipidus. Conversely a partial chemical neutralization of the injected insulin by the pituitary secretion, with a compensatory hyperactivity of the suprarenals, thyroid, and parathyroids, appears to explain to some extent the varying effect of the same dose on carbohydrate metabolism in different cases and in the same case at different times, which is often so puzzling. Occasionally patients are met with in whom insulin has comparatively little effect on the hyperglycaemia unless very large doses are given, and if these are continued hypoglycaemia suddenly develops, probably owing to exhaustion of the pituitary and overstimulation of the suprarenals, with consequent asthenia. Two of my patients died from rapid heart failure, probably brought about in this way, and in three others where death was attributed to "pancreatitis" the symptoms were of a similar character, but associated with acute abdominal pain. It is important to realize that, although injected insulin may be chemically as efficient as the internal secretion of the pancreas, it is not physiologically equivalent, and the larger the dose the greater is the difference between the artificial and the natural condition which results, with consequently increasing risk of disturbances like those I have mentioned developing. In the acute diabetes of children and young adults there is

some justification for comparatively large doses of insulin being given, at least for some time, if constant supervision is possible, but in chronic cases, and especially when the patient is over 25 or 30, they are not necessary, and, in my opinion, entail needless risks. I usually aim at restricting the dose to an amount sufficient to protect the patient from ketosis and enable him to metabolize 60 or 70 grams of carbohydrate a day, irrespective of whether sugar is passed in the urine or not. This plan appears to work satisfactorily, and I have cases where as much as 50 or 60 grams of sugar have been excreted daily for several years without any apparent ill effect. In some instances I give a preparation of insulin by the mouth, for, although this does not improve sugar utilization, I have experimental and clinical evidence that it may materially assist the storage of carbohydrate, so that, alone in anapothectic glycosuria or in conjunction with small injections of insulin in the milder forms of achriatic glycosuria, it is a useful method of treatment if its limitations are borne in mind. Dried preparations of pancreas containing the active digestive ferments, given by the mouth, are also useful in some cases, particularly when analysis of the faeces shows that there is defective digestion owing to sclerotic changes in the gland, or when growth and development are delayed or have ceased in children.

The most spectacular results of insulin therapy are seen in connexion with the treatment of diabetic coma. The effect is often almost magical, especially in young people, but some elderly comatose diabetics respond very little to insulin injections, and then only temporarily. The blood analyses made in my cases have shown that, as a rule, the failure of the treatment is actually more apparent than real, for the hyperglycaemia and ketosis are controlled in the usual way if appropriate doses are given, but, owing to the presence in the circulation of accumulated toxic products of defective nitrogenous metabolism upon which insulin has no effect, the coma either persists apparently unchanged or is relieved only for a time, death ultimately occurring from uraemic or amino-acid poisoning. It is therefore never wise to give too sanguine a prognosis as to the outcome of the insulin treatment unless it is certain that the coma is only a direct consequence of defective fat and carbohydrate metabolism, and is not dependent upon, or complicated by, the effects of serious renal and hepatic damage preventing the detoxication and elimination of nitrogenous waste products.

DISCUSSION.

Dr. R. D. LAWRENCE (London) agreed that the use of insulin in patients with uncomplicated diabetes could restore them to normal health and strength. In fact, it was impossible to recognize these patients as diabetics unless they were watched critically at meals or seen having injection treatment. Insulin might fail, however, to restore health in those who did not use it properly, and in cases where other organic disease was undermining the health. In infections much larger doses than usual were necessary. Dr. Lawrence had seen only one case which failed to respond to insulin, and even then it kept the patient free from coma. He had lost several coma cases in spite of energetic insulin treatment, and in all these the cause of death seemed to be an intensely depressed circulation. When the patient was pulseless, or nearly so, insulin could not be expected to act. The speaker had found it impossible to keep severe cases sugar-free continuously with only two doses of insulin a day, but rarely thought it necessary or wise to give more, since the patients did equally well on two doses and led a more comfortable existence. The only contraindication to insulin in severe diabetes was angina or cardio-vascular degeneration. Here insulin should be given with great care, and no chance of hypoglycaemia should ever be risked, as the latter was apt to precipitate an attack of angina. Dr. Lawrence had tried most of the mouth preparations advertised as being useful in diabetes, and had found them quite useless. He did not agree that senile diabetes was different from the juvenile type, and thought that Professor Maclean had produced no evidence that the difference was one of kind and not merely of degree. Moreover, the evidence on which Professor Maclean had based his condemnation of alkalis

in the treatment of coma did not seem sound. The speaker thought that small doses of sodium bicarbonate must tend to restore the diminished alkali reserve to its physiological normal, and at any rate could do no harm. He pointed out the advantage of "double strength" insulin in the case of patients who required large doses of insulin, because most practitioners were unaware of its existence. His experience with synthalin led him to believe it was of no practical value in its present form. It might be gathered from Professor Maclean's paper that there was no need to weigh the food in diabetes, whereas Dr. Lawrence considered this essential until the patient could gauge the correct quantity of food without actual weighing.

Dr. O. F. F. LEYTON (London) said that insulin did not always succeed in uncomplicated diabetes mellitus, and gave details of a few cases which had failed to react. He suggested that it was possible that the glukhormone of von Noorden was absent in these cases, and that this might account for the apparent improvement referred to by Dr. Cammidge following the administration of pancreas by the mouth. He did not agree that synthalin proved too toxic in all cases. Occasionally when a man's occupation made hypoglycaemic attacks probable if he took insulin, then synthalin might prove useful; he had seen more than one case in which this had happened. He had circularized his patients who had been on insulin, and 325 had replied; of these, insulin had been increased in 27 per cent., remained unchanged in 35 per cent., diminished in 26 per cent., and was no longer needed in 2 per cent. The diet had not remained constant; it had been increased in 33 per cent., remained the same in 62 per cent., and been diminished in 5 per cent. Some 6 per cent. of his patients had died; this was probably too low a figure, since it was difficult to trace those who did not reply. Incidental infections accounted for many patients who had to increase the insulin. True recovery occurred most frequently among patients who were treated shortly after the onset of the disease. He did not wish to be dogmatic, but would like to record the view that if patients with early acute diabetes were well fed and given enough insulin to keep the sugar in their blood below 0.15 per cent. all the time, there was a chance of true recovery.

Professor D. M. LYON (Edinburgh), as the result of examining his records, had found that of some 760 patients treated by him only about 300 had required insulin. Dieting alone had sufficed for the treatment of the remainder. There could be no doubt that careful regulation of the food intake still remained the most important factor in the treatment of diabetes. The indications for the employment of insulin were the presence of clinical acidosis or of acetoneuria threatening coma; severe emaciation; a too low limit of tolerance; and failure to respond to simple dietary restriction. When the patient was first seen the decision must be taken whether he could be safely treated by dieting only, which must be carefully and conscientiously carried out by the patient. Weighing and measuring the food substances were essential at first, but later any intelligent patient could estimate the correct values at sight. The urine must be kept sugar-free at all times, and the patient's weight be maintained at a satisfactory level. Although a continuous absence of sugar was no guarantee that the blood sugar values were normal, practical experience had proved that this method of control was adequate. Experience had shown that patients taking insulin did best when the weight was not allowed to exceed the average for age and height.

Diabetes, when properly treated, was not a continuously progressive condition. Definite improvement commonly occurred, and most cases after careful treatment were able to reduce the amount of insulin or add considerably to their dietary. Many showed variability in pancreatic activity, the reason for which was not always obvious. Insulin therapy probably promoted complete arrest of the disease in many instances. It was not the case that once a patient had taken insulin it was dangerous to discontinue it. Some 33 patients in Professor Murray Lyon's series, after courses of insulin lasting two to eighteen months, had been able to give up its use for a time. In 10 of these

the improvement had only been temporary, sugar returning for some cause such as toxæmia or careless dieting. The degree of recovery in some of the subjects had been so striking as to suggest that certain cases of diabetes were curable; the most striking examples had occurred in young adolescents where the condition had been of short duration. A few of the other subjects were admittedly borderline cases where the maximum insulin employed had been only 10 or 15 units, but seven patients had at one time required over 40 units daily. In one remarkable case a young woman for a long period received as much as 170 units a day, then improvement followed fairly rapidly, and eventually she was able to do without the drug altogether; she had not had any for fifteen months. This type of result suggested that the pancreas could not have been badly damaged, but that something was neutralizing both the patient's and the injected insulin. In cases where the disease advanced this was not uniformly continuous, but moved in definite stages, punctuated by intercurrent attacks of coma or infection, or by a period of dietary indiscretion. In Professor Murray Lyon's series only some ten cases belonged to this type, and it was very important to realize that the disease was not necessarily continuously progressive. Factors in the return of glycosuria included suspension of treatment or the use of a new batch of insulin weaker than usual; for some time past, however, the standardization seemed to have been entirely satisfactory and uniform. Other causes were improper feeding; "nervous" or emotional states; conditions characterized by toxæmia, such as tonsillitis, respiratory catarrhs, influenza, and various forms of sepsis; and lack of exercise. Some of these causes of glycosuria were easily recognized, and if discovered in time did little damage. The most harmful appeared to be the toxic conditions. The occurrence of an attack of coma often appeared to be followed by a reduction of tolerance. In the speaker's series of cases 47 patients had died, 7 apparently from cancer, and 5 from apoplexy; 3 were otherwise accounted for, and in 5 cases the cause of death had not been ascertained. This left 27 deaths due to diabetes, and in 10 of these the dieting was known to have been unsatisfactory. Death was preceded in the majority of the cases by coma, which was brought on by pneumonia in 5 instances, by various infections in 11, and by alimentary upset in 5. Most of these deaths did not occur in hospital. The patients who died were not necessarily the most severely diabetic, and their deaths could not have been predicted before the onset of the fatal illness.

Professor L. BLUM (Strasbourg) said that there were two indications for the use of insulin: (1) the absolute or vital, as in coma, severe acidosis, infectious disease, or surgical intervention with anaesthesia; and (2) the relative—the temporary use for a short time only in milder cases in order to give them new strength, or to cure complications such as furunculosis, eczema, pruritus, or neuritis. It was generally necessary to continue the insulin until the end of life in severe cases, or when coma had occurred. He had had three cases, however, where the coma was produced by intercurrent disease such as influenza and angina, in which it was possible to stop the insulin after a few weeks. The great danger for diabetic patients under chronic insulin treatment was infection, and particularly tuberculosis; it was essential to examine the lungs from time to time not only by the usual physical methods but by x rays. In the treatment of coma three things were necessary: (1) Sufficient doses of insulin (40 to 50 units for an injection) given intravenously every half-hour under careful and permanent supervision. In order to avoid hypoglycaemia it was necessary to watch the patient carefully during the injections; if unconscious patients showed signs of reaction (opening the eyes), or conscious patients experienced any special sensations, then the insulin had already produced an effect. Glycosuria was a sure sign that more insulin was necessary; if the urine was sugar-free there was danger of hypoglycaemia if more insulin was given. As a general rule when the patient was under clinical observation glucose was not given. (2) Lavage of the stomach. This organ often contained a great quantity of retained food; after lavage the blood pressure might rise.

(3) Medium doses of sodium bicarbonate (20 to 30 grams), to restore the sodium content of the organs and fluids, which was greatly diminished in coma. Professor Blum thought that the cardiac failure in the form of coma which he had called the cardio-vascular form of coma was partly due to the low alkali content of the organs. The use of insulin was particularly difficult in some cases of diabetes where a low hyperglycaemia (0.15 to 0.24 per cent.) co-existed with a severe acidosis, and where diabetes was complicated by nephritis with hypertension; in these latter cases the urine was sugar-free but the blood sugar was high. He had treated over 2,000 patients with insulin, but had never seen a case resistant to insulin. By increasing the dose he had always been able to reduce the hyperglycaemia, though very large doses were sometimes needed.

Dr. G. GRAHAM (London) thought that the mortality tables referred to by Professors Maclean and Petróen were rather astonishing. The tables for England and Wales showed that there had been a steady increase since 1900, and even before that year. In 1917 a big decrease occurred which was almost entirely in the deaths of persons over the age of 50. This period was coincident with the severe rationing of the war and continued until 1919. From then until 1923 the increase reappeared, but since the introduction of insulin there had been a slight decrease in the males and an increase in the females. This result was rather perplexing until the figures were examined in decades. These showed that a decrease took place in both males and females until the age of 50; after this age there was a slight decrease in the males but an increase in the females. The speaker's analysis also showed how few people died of diabetes in the early decades compared with the large number who died after 50. The decrease in the figures for the young people was quite satisfactory when the varying conditions of treatment were considered and it was remembered that insulin was still a new form of treatment. He disagreed with Professor Maclean in the distinction drawn between true diabetes and the glycosuria as seen in elderly people. The speaker believed that there was no essential difference between the condition of the elderly person with a high blood sugar and glycosuria and the young adult. The elderly person had a low sugar tolerance and the condition grew worse very slowly, but after five, ten, or fifteen years, if the patient had not died of something else meanwhile, the condition might be indistinguishable from that of a young adult. The primary action of insulin was to enable the sugar to be stored in the muscles, and this was the defect which was first seen in the patient with mild diabetes. The belief that the condition was not a true diabetes was partly responsible for poor and inefficient treatment. This was most regrettable, since the elderly person was very liable to suffer from the effects of boils, carbuncles, and gangrene of the leg. The eye complications (retinitis and cataract) were also more liable to progress if the diabetes was untreated, whereas with insulin the condition seemed to be arrested. This type of patient responded very well to treatment either by diet alone or with the assistance of insulin. A carbohydrate tolerance of 50 to 70 grams might be regained and the patient be able to give up insulin, since the condition had a tendency to improve instead of slowly getting worse. Dr. Graham believed that if patients older than 50 were treated more carefully the mortality figures would show a definite fall instead of an increase. He disagreed with Professor Maclean about the harm which alkalis could do to a comatose patient, and added that Professor Blum had shown that the tissues of the comatose patient contain very little sodium. The experiments of Dr. Goldblatt, to which Professor Maclean had referred, were made on a healthy man with a normal alkali reserve, and the large dose of alkali would produce an alkalosis. This alkalosis was the probable cause of the persistence of the ketosis after the alkali had been given. The comatose patient had a low alkali reserve, and the dose of alkali was usually insufficient to do more than make the alkali reserve normal. For these reasons the speaker did not think that reasonable doses of alkali could do any harm, but nowadays they were rarely necessary, since insulin acted so well. Professor Petróen had said that the adminis-

tration of dextrose to the comatose patient did harm. If there were facilities for estimating the blood sugar it was unnecessary to give any dextrose, but if the blood sugar could not be estimated it was a wise precaution to start the active treatment with a dose of two ounces of dextrose together with 70 units of insulin.

Dr. C. G. LAMBIE (Edinburgh) said that there were many causes of glycosuria; while insulin was a specific remedy for pancreatic diabetes, its value in other conditions had not been firmly established. Some controversy had ranged around the question as to the essential difference, if any, between pancreatic diabetes in young persons and the common glycosuria of elderly individuals. Certain differences between the two types could be noted as regards their response to insulin. Thus many of the cases of glycosuria in elderly persons were remarkably resistant to insulin, a given dose producing a relatively small decrease in the output of sugar. Moreover, sudden withdrawal of even large doses of insulin might be followed by little if any acidosis, whereas in pure pancreatic diabetes the development of severe acidosis under these conditions was the rule. Administration of glucose to such patients caused the respiratory quotient to rise to levels which indicated that carbohydrate was being utilized. Further, improvement in tolerance in patients under treatment took place slowly over a long period. It seemed possible that the underlying cause of the peculiar features presented by these cases was an interference with the diffusion of glucose from the blood plasma into the tissue cells, without necessarily much interference with the utilization of glucose once it got into the cells. This was suggested by the fact that the renal threshold was often remarkably high, owing to the impermeability of the kidneys for glucose, and by the appearance of symptoms of hypoglycaemia with blood sugar concentrations sometimes much above the normal level. In such cases it was impossible to keep the blood sugar at a normal level, a relatively high concentration of sugar in the blood being necessary to bring about sufficient diffusion into the cells. The permeability of the kidneys to glucose gave a rough measure of the permeability of cells in other tissues, and in treatment it was sufficient to abolish the glycosuria or to find the dose of insulin which would be just less than sufficient to produce symptoms. Some recent experimental work by Loewi, Hausler, and Dietrich seemed to have an important bearing upon the point at issue. These workers found that hyperglycaemia, however produced—whether by glucose administration, pancreatectomy, or administration of adrenaline—caused the appearance in the blood of a dialysable substance to which they had given the rather unfortunate name of "glycaemin." This substance, when injected into rabbits, caused hyperglycaemia, and its addition to a suspension of red blood corpuscles *in vitro* inhibited the diffusion of glucose into them from the surrounding medium. If it were to be supposed that in certain individuals there was an excessive production or defective elimination of such a substance, it would seem possible to interpret many of the facts and to reconcile the conflicting views which had been expressed.

Dr. F. B. SMITH (Harrogate) agreed with Dr. Lawrence that there was a definite group of patients in whom it was impossible to restore food tolerance even with insulin; in such cases several other possibilities must be considered—namely, sepsis, disease of the thyroid or pituitary gland, malignant disease, and mental instability. He wished to draw particular attention to this last factor, as the association of mental instability with diabetes was more frequent and of greater importance than was recognized. In one of his patients, in whom anxiety neurosis was latent, acute diabetes occurred, apparently as the result of financial worry; it was satisfactorily controlled with insulin and dieting. Three years later, while constantly balanced without glycosuria, the patient became acutely and fatally maniacal. In another case markedly "temperamental" it had so far been impossible even with insulin to obtain any improvement either in tolerance for food or in the general condition. Apparently such patients possessed some substance capable of neutralizing insulin.