THE CLINICAL USE OF INSULIN.*

BY

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THIS paper is based on my personal experience of the treatment of 130 cases of diabetes, in 52 of which I have used insulin; of these 52 cases rather more than one-half had previously received treatment by dieting at my hands.

Selection of a Suitable Patient.

The first problem that suggests itself in the clinical use of insulin is the selection of a suitable patient, and here I must stress the importance of a thorough clinical examination. The presence of sugar in the urine is so impressive a fact that not uncommonly after its discovery all the symptoms of which a patient complains are immediately attributed to diabetes. During the past six months I have seen in consultation 5 glycosuric patients in whom death appeared imminent from inevitable causes in no way connected with the loss of sugar tolerance. Three of these have since died. Treatment of this type of case with insulin is obviously undesirable.

In some instances the use of insulin may be said to be imperative—for example, in cases of coma and of extreme wasting; or when the patient has fallen into the hands of the surgeon and must be prepared for an anaesthetic and an operation; or, again, when he has been attacked by an infection like pneumonia or tuberculosis; and finally, it is essential to the treatment of young children. In such cases as these it is bad practice to withhold insulin if it can possibly be obtained.

The time at my disposal will not permit me to discuss the methods appropriate to these emergencies, for I have been asked to devote my attention chiefly to the type of case most frequently met with—that is, to the diabetic of moderate severity.

There is fairly general agreement that patients with mild diabetes, whose condition can be controlled by reasonable restriction of their diet, do not require further treatment, but there is still considerable difference of opinion as to the degree of restriction to which it is proper to ask a patient to submit before help is sought in insulin. Let me say at once that the aim of the clinical treatment of diabetes is neither the solution of a metabolic problem nor the demonstration of the fact that a diabetic can live a long time in a state of semi-starvation, but rather the comfort and efficiency of the patient. In my experience very few people in this country can live comfortably if they are unable to take a little bread daily, and, consequently, as a broad general rule I recommend insulin treatment to every patient who cannot take the appropriate basal diet that I shall describe presently and remain sugar-free with a normal blood sugar while taking it. Patients, I know, may live and work on diets very much more restricted than mine, but they do not live happily and they do not work comfortably.

Cases Unsuitable for Insulin.

There are certain patients other than those with very mild diabetes for whom insulin is unsuitable. Chief of these are the fools. The administration of insulin requires intelligence, not only of the physician but also of the patient. If the latter cannot learn to appreciate the importance of careful dietary or if he lacks the will to restrict himself moderately, elaborate treatment is almost invariably a waste of time and money, though transitory benefit may result from spasmodic control. Similarly, in the vast majority of cases the patient must be capable of giving himself a hypodermic injection and of testing his urine qualitatively for sugar, unless he is wealthy enough to pay for these services for the rest of his life.

Again, there are numerous patients in whom glycosuria is found in the course of routine examination, and who have none of the other symptoms of diabetes—no thirst, no polyuria, no wasting. These are not cases for treatment until thorough investigation has shown it to be necessary. Investigation must never be delayed, for most of them are mild diabetics readily controllable by dieting at this stage. A small proportion of them have renal glycosuria—that is, a condition in which the kidney excretes sugar although the percentage in the blood is normal or subnormal.

A certain amount of harm has been done by the constant emphasis in the literature on the possible danger of the administration of insulin to cases of renal glycosuria; several general practitioners have told me that they would have used insulin for their patients but for this fear, and I may therefore be pardoned for dwelling on the fact that cases of renal glycosuria do not have symptoms of diabetes. In passing I should like to record my opinion that the condition is excessively rare; to my knowledge I have seen only one case—particulars of which will be published shortly—and in the latest report that I have read Joslin mentions only one in his very much wider experience. I suspect that many cases of slight glycosuria that as the result of one blood sugar curve have been labelled renal in type are in reality mild diabetics at an early stage of the disease. A few weeks ago I saw a man very near coma, who was assured in 1920 that his glycosuria might be ignored as his blood sugar curve after 50 grams of glucose by the mouth was almost normal. Tolerance tests by means of blood sugar estimations are no more free from fallacies than other laboratory procedures, and in view of the fact that they have only been performed in any number during the past five years it is obvious that it is as yet quite impossible to attribute to them any final value in prognosis.

For the reason that under-nutrition and restricted activity are valuable adjuncts to the treatment of some cases of high blood pressure, myocardial degeneration, and nephritis, I feel that it is wiser not to use insulin in cases of diabetes complicated in this way if it can possibly be avoided. I am also a little sceptical of its value in the senile.

The treatment of a suitable case of diabetes of moderate severity I will consider in three sections:

(1) The general treatment.
(2) The diet.
(3) Method of control of insulin administration—(*a*) during the preliminary period of standardization, (*b*) in the later stages.

THE GENERAL TREATMENT.

The most important part of the general treatment is the education of the patient. Let me urge you as far as possible to have no secrets from your diabetic patients. In nursing homes it is my practice to discuss fully every detail with the nurse in the presence of the patients. On admission they are taught to test their own urine, and in two or three days assume full responsibility for the simpler qualitative test for sugar and sometimes for diacetic acid; a rack of test tubes, a spirit lamp, bottles of Fehling's solution, and of liquor ferri perchloridi are kept by the bedside for the purpose, and are taken home on discharge. I give elementary discourses on diet and on the known pathology of diabetes practically every time I meet them. A few of the patients keep their own charts entirely.

I hope I need not emphasize the importance of the general symptomatic treatment, but I would like to dwell on the outstanding necessity of the eradication of focal sepsis wherever it may be. The teeth in diabetics are commonly septic, and occasionally it is necessary to deal with infected tonsils and accessory sinuses of the nose as well. Apart from gross excess of diet nothing hastens the deterioration of a diabetic so much as toxic absorption, and another important point is that insulin is not nearly so effective in its action in the presence of untreated sepsis. Drugs are rarely necessary, except for relief of constipation; in young and nervous patients I sometimes use a little bromide.

THE DIET.

Prior to the introduction of insulin a suitable diet was the basis of treatment, and it is still so. Insulin enables us to increase and to alter the diet in many ways, but it does not

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remove the necessity for careful regulation of it if the best results are to be obtained.

Before I describe the basal diets that I have adopted I wish to point out that there is as yet no method by which the best type of diet for any particular patient can be determined other than the somewhat crude one of trial and observation of the result. Basal diets I have found to be convenient and suitable to a large proportion of the patients sent to me, but in the more serious cases, where there is very little margin between sufficiency and excess, alteration in the balance and in the total content has to be made. The more severe the case the more individual must the treatment be.

The essentials of a diet for a diabetic are as follows:

1. It must be tolerable—that is, it must permit of a certain variety and correspond as far as possible with the desires and habits of the patient. I do not mean that the physician must weakly assent to a diet which he knows in his heart is indiscreet; our duty is to strike a balance between what is theoretically desirable and what is actually attainable. I have already stated my opinion that bread is essential to make a diet tolerable.

2. It must possess a sufficient calorie value. There is experimental evidence that 30 to 35 calories per kilogram of body weight is enough for a man doing light work, and, what is more important, clinical experience bears out this conclusion. Inasmuch as there is general agreement on this point I need not discuss it further.

3. It must contain sufficient protein to maintain nitrogenous equilibrium. Here again there is no controversy, for it is admitted that 1 to 1.5 grams of protein per kilogram represents an adequate supply. A larger supply of protein than this is undesirable, for there is evidence that excess predisposes to acidosis, and protein on combustion yields a good deal of carbohydrate.

4. The total amount of glucose in the diet must be reduced to that which the body can utilize by means of the secretion of the islets of Langerhans either alone or with the assistance of insulin. The total glucose of a diet is not represented by the amount of carbohydrate. Roughly it may be said that—

100 grams of carbohydrate yield 100 grams of glucose
100 grams of protein " 58 " "
100 grams of fat " 10 " "

So if G = total glucose—

$$G = C + 0.58\,P. + 0.1\,F.$$

5. The total fatty acid must not exceed that amount which can be absorbed into the metabolism without the production of acidosis. The sources of fatty acid are fat and protein. Carbohydrate yields none.

100 grams of fat yield 90 grams of fatty acid
100 grams of protein yield 46 " "

Thus:

$$F.A. = 0.9\,F. + 0.46\,P.$$

It seems clear that in the body the efficient oxidation of fatty acids depends to a large extent on the proper oxidation of glucose. In the diabetic, as the result of the failure of the combustion of glucose, the oxidation of the fatty acids may break down with the production of acetone bodies, and it thus becomes a matter of importance to determine how much fatty acid may be given to a patient with a limited glucose tolerance without giving rise to acidosis. On purely chemical grounds Shaffer came to the conclusion that the proportion of fatty acid to glucose should not exceed 1.5 : 1. As the result of observation of patients on maintenance diets containing this ratio, Woodyatt found "that acetone does not appear in the urine of an uncomplicated case of diabetes, or remain permanently if present, provided that the diet is completely absorbed and katabolized." From this ratio Woodyatt calculated the convenient clinical formula for the balance of an optimal diet—

$$F. = 2\,C. + \frac{P.}{2}$$

The protein is always the lowest possible to maintain nitrogenous equilibrium.

After an extensive (and I may add laborious) review of the diets of the patients that I treated in the pre-insulin days I find that I can support Woodyatt's contention, but I also find that I can make this addition to it—namely, that in a certain proportion of patients (about 25 per cent.) it is possible to use a diet with a fatty acid-glucose ratio of approximately 2 : 1 without causing acetonuria or any other symptoms of acidosis. The point is an important one, for it means that in certain cases it is possible to give a higher calorie value than the Woodyatt formula would allow. The patients that I have considered for this purpose were all sugar-free and had normal blood sugars. On the basis of a fatty acid-glucose ratio of 2 : 1 it is possible to calculate the formula—

$$F. = 3\,C. + P.$$

This I call the Thomson formula.

I can sum up my present opinion in this matter by saying that I regard the Woodyatt formula as a safe one and mine as a possible one for about a quarter of the cases that I see. Since I have been using insulin I have become more impressed with the possibilities of my own formula, but it is too early to speak with any definiteness; I certainly seem to be able to use it more frequently now without giving rise to acidosis.

Basal Diets.

The basal diets that I use are as follows:

	Protein.	Fat.	Carbohydrate.	Calories.
DIET A.				
Breakfast: Porridge (cooked) 2 oz. ... Bacon 2 oz. ... ... Egg 1 ... ... Milk 1 oz. ... ... Bread ½ oz.	16	43	15	570
Lunch: Lean meat 3 oz. ... ... Vegetables (5 per cent.) 6 oz. Butter 1 oz. ... ... Bread ½ oz.	21	32	14	436
Dinner as for lunch	21	32	14	436
Total	53	107	43	1,402
DIET B.				
Breakfast: Porridge (cooked) 2 oz. ... Bacon 2 oz. ... ... Egg 1 ... ... Milk 1 oz. ... ... Bread ½ oz. ... ... Thick cream or butter ½ oz.	16	54	15	636
Lunch: Lean meat 3 oz. ... ... Vegetables (5 per cent.) 6 oz. Potato 1 oz. ... ... Butter 1 oz. ... ... Bread ½ oz. ... ... Cheese ½ oz.	25	37	20	531
Tea: Bread ½ oz. ... ... Butter ½ oz. ... ... Cream ½ oz. ... ... Egg 1	7	17	7½	223
Dinner as for lunch	25	37	20	531
Total	73	145	62½	1,921
DIET C.				
Breakfast: Porridge (cooked) 2 oz. ... Bacon 4 oz. ... ... Eggs 2 ... ... Milk 1 oz. ... ... Bread 1 oz. ... ... Thick cream or butter ½ oz.	29	96	22½	1,113
Lunch: Lean meat 4 oz. ... ... Vegetables 5 per cent.) 6 oz. Potato 1 oz. ... ... Butter 1 oz. ... ... Stewed fruit 2 oz. ... ... Bread ½ oz. ... ... Cheese ½ oz.	31	40	24	600
Tea: Bread ½ oz. ... ... Butter ½ oz. ... ... Cream ½ oz. ... ... Egg 1	7	17	7½	223
Dinner as for lunch	31	40	24	600
Total	98	193	78	2,536

As shown in the table, the fatty acid-glucose ratio of these three diets is approximately 1.5.

Diet A.
Total fatty acid ... ... 120 grams.
Total glucose ... ... 80 ,,
Ratio 1.5.

Diet B.
Total fatty acid ... ... 160 grams.
Total glucose ... ... 120 ,,
Ratio 1.4.

Diet C.
Total fatty acid ... ... 220 grams.
Total glucose ... ... 150 ,,
Ratio 1.5.

If all the bread be removed from the diets these values become—

Diet A.
Total fatty acid ... ... 120 grams.
Total glucose ... ... 58 ,,
Ratio 2.0.

Diet B.
Total fatty acid ... ... 160 grams.
Total glucose ... ... 90 ,,
Ratio 1.8.

Diet C.
Total fatty acid ... ... 220 grams.
Total glucose ... ... 120 ,,
Ratio 1.8.

Diet A yields roughly 30 calories per kilo for a patient of 44 kilogram weight (7 st.).
Diet B yields roughly 30 calories per kilo for a patient of 64 kilogram weight (10 st.).
Diet C yields roughly 30 calories per kilo for a patient of 89 kilogram weight (14 st.).

In each case the protein is in the proportion of just over 1 gram per kilo of body weight.

By the addition of 2, 3, or 4 oz. of fat to Diets A, B, and C respectively an increased calorie value is obtained without exceeding the fatty acid-glucose ratio of 2 : 1.

For the sake of clearness I will not consider now the problem of variety of the diet.

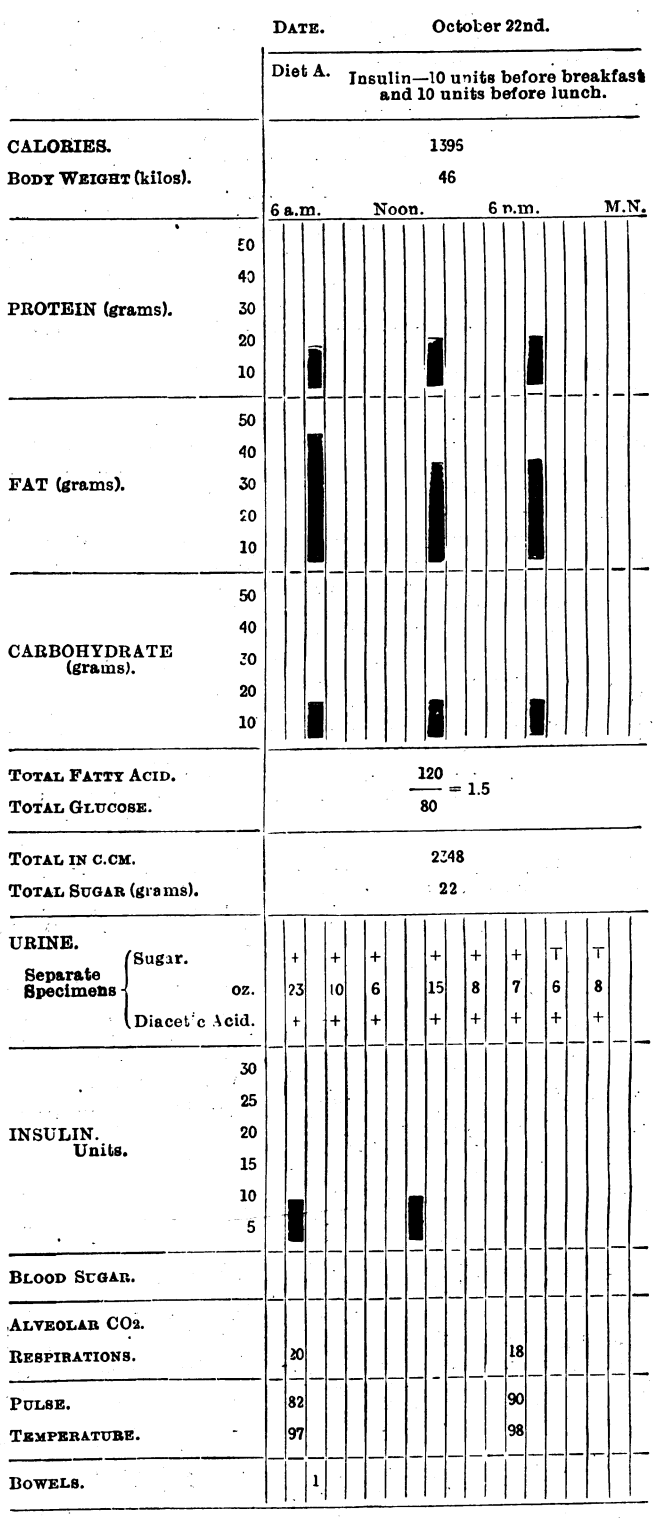
METHOD OF CONTROL OF INSULIN ADMINISTRATION.

Preliminary Period.

I will assume that you have kept the patient on the basal diet most suitable to his weight and needs for a week or two, and that you are satisfied that dieting alone will not control the condition.

The first step is the admission of the patient to a nursing home or hospital where he may be under close and skilled observation. Hitherto I have regarded this as essential, but lately, since I have employed the chart system of control, I have treated in their own homes one or two patients who for various reasons were unable to go into hospital, with the assistance of their doctors and of a nurse familiar with my methods and the details of control necessary. With larger experience it may be possible in the future to avoid nursing homes and hospitals, but, frankly, at present I am reluctant to begin treatment in a private house.

Soon after I began to use insulin it became clear to me that the outstanding necessity for proper control was a method of recording dosage and diet and of correlating these factors with the effects to be observed in the urine and blood in respect of sugar and acidosis. Elaborate notes are cumbersome, and more and more difficult to disentangle as they accumulate. To meet this difficulty I have designed charts which have been printed for me by Messrs. Birbeck and Sons, Ltd., and which may be obtained from Messrs. Philip Harris and Co., Edmund Street, Birmingham. The general principle of the charts is that each day is allotted a space of three inches, which is ruled vertically in twenty-four lines, each representing one hour. As each specimen of urine is passed the quantity is entered at the appropriate time, and the presence or absence of sugar and diacetic acid is noted. A dose of insulin is charted in the same way, and the amount of the dose is shown by the cross-ruling in units. The constitution of the separate meals and the times at which they are taken are indicated similarly. A space is left at the top of the chart in which notes of the patient's history and progress are written. A glance at the charts will sufficiently explain the whole matter; they are easy to keep, and I am satisfied that I am able to control treatment very much more satisfactorily since I have used them.



Now the aim of insulin treatment is the maintenance of a normal blood sugar. I am aware that certain physicians consider that the level of glycaemia may be disregarded if the general condition of the patient remains good, but I feel that there is as yet insufficient experience to warrant that opinion in the face of the considerable body of evidence to the contrary. How, then, are we to know that the blood sugar is normal? Is it necessary to make frequent estimations? This is practically an important matter, for the estimation of the sugar in the blood is a laborious and expensive proceeding. My experience leads me to say quite definitely that in the cases of moderate severity it is quite unnecessary, and that examination of the separate specimens of urine is all that is required. I should not

make so definite a statement were it not for the fact that several general practitioners who attended my post-graduate lecture on this subject some months ago have been good enough to tell me that they have since used the chart method that I have described to you without difficulty and with success. Broadly speaking, I only estimate the blood sugar in the moderate cases towards the end of the period of preliminary treatment, in order to be sure that the patients are not completely free from sugar in the urine while a certain degree of hyperglycaemia persists. This condition is, however, unusual; it occurs most commonly in patients who are getting on in years and who have had diabetes for a long time.

The Initial Dose of Insulin.

For two or three days after admission to hospital careful estimations of the total loss of sugar in the urine are made while the patient is on the basal diet that he has been taking previously. A convenient method of calculating the first dose of insulin is to divide the average total number of grams of sugar excreted daily by three; the result gives the number of units of insulin that may be employed in the early stages as a daily dose, but at first the total dose should not exceed 20 units, and not more than 10 units should be given at one injection. The most convenient times for injections are before breakfast and before lunch if more than a single dose is necessary. During this period estimations of the twenty-four hour excretion of sugar are continued, while the diet remains the same. The diminution in the amount of sugar excreted in the day can now easily be compared with the amount of insulin administered, and an estimate can be made of the total dose required to render the urine sugar-free. Slight increases of the insulin are then made until this result is reached. Subsequently the diet can be increased if necessary, the dose of insulin being suitably modified. If during this time you chart your results in the way that I have suggested, and take care to obtain specimens of urine every two hours (an easy matter in practice if water or bovril or coffee is given freely), you will now be in a position to observe two other points of importance—first, the time at which insulin becomes effective in your patient after injection; and secondly, the duration of its activity. In some patients the time of effective action is delayed, and the period of activity also varies to a considerable degree, but a glance at the chart will usually indicate the most suitable time for injection if any modification is necessary.

I find that, using this method, the patients are commonly almost entirely sugar-free after eight or ten days, and the question that naturally arises is why it should be necessary to keep them in hospital any longer. There are two reasons.

The first reason is that it is not rare to find that, after the patient has become sugar-free on a relatively small dose of insulin, while the diet is unaltered glycosuria recurs, and it is necessary to increase the dose of insulin to control it. The cause of this is not clear, but I account for it by assuming that the action of insulin is twofold: that it stores sugar, and that it aids in the combustion of sugar. In a patient with active glycosuria the storage areas are relatively empty, and consequently the storage action of insulin operates to great advantage; when the storage areas are filled insulin acts mainly as an aid to combustion. I find that this slight glycosuria occurs so frequently in the second week that I have christened it "the period of discouragement," and sometimes warn a patient that it is to be expected.

The second reason for the retention of the case in hospital for the full period of three weeks is that after the period of discouragement to which I have referred there often ensues a period of recovery, during which it is necessary to reduce the dose of insulin; this recovery appears to be strictly comparable with the restoration of carbohydrate tolerance which occurred after treatment by under-nutrition. It would obviously be dangerous to send a patient out of hospital while there is a possibility of any considerable degree of recovery in this way. It is clear that instead of decreasing the dose of insulin in this phase the diet may, in suitable cases, be increased.

During the first week of treatment the patients are confined to the hospital or nursing home, but they are allowed to be up. Later on they take gradually increasing amounts of exercise.

Complications.

The chief complication in treatment is the so-called hypoglycaemic crisis, the symptoms of which are now well known, and I do not think that I need describe them in full; in cases that I have seen the commonest early complaint has been occipital headache, a sense of weakness and hunger, and in two cases muscular twitching. In none of my patients have the symptoms been severe, and I have steered clear of all of them in my last forty cases. Relief from the symptoms can immediately be obtained by the administration of sugar by the mouth, or by glucose intravenously if the condition is sericus and the patient is unconscious. Before proceeding to intravenous methods a hypodermic injection of a few minims of adrenaline should be tried. I am satisfied that these toxic symptoms after insulin are less likely to occur when the general condition of the patient has improved and when he has gained weight. In my opinion, the hypoglycaemic crisis is not the result of an absolute hypoglycaemia, but rather a sudden upset of the blood sugar level which has existed previously; at all events I have known the symptoms to occur in patients in whom the blood sugar has been well above normal, and in the course of some experimental work with Dr. A. F. Wright we saw several animals die with the symptoms of hypoglycaemia, in which the level of the sugar in the blood was no lower than it was in control animals who appeared perfectly comfortable.

Oedema occasionally occurs after insulin, but usually only in severe cases; it is sometimes very distressing. Reasonable limitation of the fluid intake and small doses of caffeine control it satisfactorily.

I have seen albuminuria develop in the course of treatment, but the case was complicated by a high blood pressure. No casts were found in the urine after repeated examinations. Haematuria I have seen three times, always after large doses; two of the cases were my own, the other I saw recently in Professor von Pirquet's clinic in Vienna. In my cases the condition lasted only a few hours and there were no signs of kidney damage. Diuresis frequently persists even after the urine has become sugar-free, but it seems to have very little clinical importance.

Local reactions are sometimes very painful, and I have had to interrupt treatment on account of the distress of the patient, but an immunity to them seems to be gradually acquired.

After-Care.

I encourage all my patients to keep notebooks, in which they enter their weight and the results of the urine tests that they make. I advise them to test for sugar every night and morning if possible, and I find that most of them can do so without inconvenience. In the cases of moderate severity it is sufficient to see them weekly for two months after leaving hospital; subsequently I see them once a month.

Summary.

I have outlined a method of handling a case of moderately severe diabetes, which is simple and which I believe can be used in general practice; I shall count this paper a failure if I have not induced you to treat your patients with insulin, for there is no question that the results are excellent, provided there is suitable control; and, finally, I should like to say this: to every general practitioner an emergency in the treatment of diabetes is bound to come in which he may not be able to obtain help of any kind. I have said that to withhold insulin at such a time is bad practice, and I feel sure that medical practitioners will approach a situation of that sort with more confidence if they have previously obtained experience in the treatment of a moderate case.