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PROTAMINE INSULIN AND ZINC PROTAMINE INSULIN IN THE TREATMENT OF DIABETES MELLITUS*

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It is now nearly sixteen years since insulin was discovered, and in this period the treatment of diabetes mellitus has been changed profoundly. The first stage of this period was occupied in learning how to adopt the use of insulin to that dietetic treatment which had been devised to eke out the diabetic's existence before the introduction of insulin. The second stage saw a less theoretical outlook develop when, as a result of the empirical trial of high carbohydrate diets, physicians were emboldened to adjust insulin to the patient's requirements when taking a more natural diet. The last two years have seen us enter a third stage—the stage in which insulin itself is being artificially modified to meet more effectively the requirements of the diabetic patient.

As yet the protamine insulin preparations have not been widely used in this country, and this is largely due to the commendable caution of the various manufacturers of insulin who refrained from putting on the market, without adequate investigation, modifications of such a vital agent. But very shortly now these new preparations will be available for general use and, judging by past history in therapeutics, it is possible that their general acceptance will be inaugurated by a period of considerable disagreement as to their value. Such a period may be inevitable, but it is to be hoped that it will not delay a just appreciation of the new remedies nor vest them with pretensions which have later to be discarded. The risk of either of these unfortunate possibilities can be minimized if at this time we take the trouble to review the present state of diabetic therapeutics with the object of placing ourselves in a position to decide exactly what improvement in treatment we may expect from the new preparations.

To do this we must begin by considering clearly two questions. What is the object of our treatment of the individual diabetic patient? How far towards this aim does the treatment available to-day carry us? Then, from what is already known of the new preparations, we may try to see how much nearer they can bring us to the attainment of this same object.

The Object of Treatment

At the risk of being trite I shall define the aim of treatment in our individual diabetic patient as the production of a normal sense of physical health and mental well-being. The significance of this definition will become more apparent when it is insisted that no chemical definition, of normality, such as freedom from glycosuria or a blood-sugar value within normal levels, can justifiably be taken in substitution. In medicine the ultimate achieve-

ment must be measured by clinical not by chemical standards. The diabetic without complications has nowadays the right to feel well; and if he does not do so then treatment is at fault. But patients, with their differing temperaments, have different measures of well-being, and it is necessary that we as clinicians should have some standard by which the vague generalizations of several individuals can be assessed in relatively precise terms. I suggest that a diabetic may be considered to have achieved satisfactory physical and mental health when he has satisfied the following three standards. He must have sufficient energy for his needs; he must maintain his weight about the accepted normal figure for his height and age; and he must not be subject to hypoglycaemic symptoms. Each of these standards is worthy of further consideration.

For a diabetic to feel that he has at his disposal sufficient energy to take again his place in the world with healthy men and women the physician must have dealt successfully with two problems. He must have controlled the physical disability arising from the disease, and he must have sustained the patient to overcome the psychological shock consequent upon the realization that he has diabetes. The latter feat presents varying degrees of difficulty, but the persistence in the lay mind of prognostic standards derived from medical experience before insulin was available still engenders a real psychological factor in each case. There is no weapon so potent against this as the knowledge on the part of the physician that diabetes mellitus, in all save the severest cases, can now be so effectively controlled that the conscientious patient need suffer no disability from his disease; and I would urge the importance of imparting to the patient this conviction and the knowledge of the experience upon which it is based.

In a disease which is characterized by deficient assimilation of certain foodstuffs a knowledge of the variations in the patient's weight provides us with a valuable index of the general effect of our treatment (Himsworth, 1936). When the wasteful excretion of food as glycosuria has been either abolished or restricted, a falling of the weight below the normal standard clearly indicates that the diet is unsatisfactory. But an increase in the weight to an abnormal figure is also unsatisfactory, for such gains presage a breakdown in carbohydrate tolerance. A weight at the normal figure for the patient's age and height should be established and preserved.

It is unfortunate, but it is necessary, that the absence of symptoms from overdosage with insulin must be included as one of the standards of the successful treatment of diabetes. It is undeniable that nowadays many diabetics, especially children, lead lives restricted by the

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fear that symptoms of hypoglycaemia may supervene if they depart from a routine of semi-invalidism. This state of affairs results directly from the imposition on clinical medicine of chemical standards of normality to the disregard of clinical evidence. If chemical signs such as freedom from glycosuria or the restriction of variations in the blood-sugar level within certain limits are elevated to the status of objects of treatment, then on the finding of glycosuria, or an unusual hyperglycaemia, treatment must logically be devoted to its removal, even if this involves the periodic induction of hypoglycaemic attacks. It should be realized once and for all that, with the treatment at present available, there are many diabetics whose blood sugar cannot be maintained within normal limits, whose urine can never be kept consistently free of sugar, without giving insulin in such doses that frequent hypoglycaemic attacks will certainly result and prevent the patient attaining a stable and normal degree of health. To satisfy chemical criteria at the price of such disability from over-treatment is the antithesis of rational therapeutics.

First Stage of Treatment

Hitherto we have been dealing with that final phase of treatment which is concerned with the adjusting of the diabetic to normal health, but we must now consider the preliminary phase in which the patient is being removed from the dangers of the uncontrolled disease itself. In this stage we are dealing with the gross objective evidence of disordered metabolism, and the finer subjective appreciations of health are submerged in the general illness of the patient. It is here that chemistry finds its proper place as a guide to treatment.

To-day there are in use three main tests: estimation of the blood sugar, testing of the urine for sugar, and testing of the urine for ketone bodies. Of the information these provide a knowledge of the presence or absence of ketonuria is immeasurably the most important (Himsworth, 1934a, 1936). Ketonuria indicates that the morbid processes of diabetic metabolism hold sway within the body, and until they are under control, as indicated by the cessation of ketonuria, the diabetic is in danger of being overcome by his disease in its crudest form and dying in diabetic coma. We have two simple tests available for detection of ketone bodies in the urine. The ferric chloride test, which detects these substances only when they are present in quantities which indicate the imminence of coma, and the nitroprusside test, which detects them in minute amounts such as occur in the early stages of balancing and in the severe relapses of the previously balanced patient. Patients in whom the ferric chloride test is positive are medical emergencies and should be treated as such (Himsworth, 1932); patients in whom the ferric chloride reaction is negative but the nitroprusside reaction is positive are in no immediate danger, but are as yet still the subject of grossly disordered metabolism. A more detailed discussion of the significance of these tests and the treatment of the states they reveal is out of place here and has already been given in detail elsewhere (Himsworth, 1932, 1936).

It is regrettable that a knowledge of the blood-sugar level should still enjoy the greatest vogue as the guide to treatment. Based on imposing theoretical considerations it yet survives the practical criticism that it bears little relation to the condition of the patient (Himsworth, 1934a). In my opinion its use is comparable to that of the electrocardiogram. Both are useful in research and in diagnosis; both are superfluous as guides to treatment.

Testing the urine for sugar has lost prestige as a result of the authoritative support accorded to the blood-sugar

test. This is unfortunate, as the urine can be made to yield relatively more information than the blood. The finding of glycosuria indicates loss of food in the urine, the testing of specimens passed at different times in the day shows when this waste occurs and points the way to the necessary modification in treatment. If Benedict's test is used the resulting colour measures the concentration of sugar in the urine, and if a sequence of urine specimens are examined the rise and fall of the sugar level in the body is revealed (Fig. 1). Such knowledge permits a much closer control of treatment than do isolated blood-sugar estimations (Himsworth, 1936).

FIG. 1.—Blood-sugar and urine-sugar curves showing the effects of ordinary insulin, insulin retard, and zinc protamine taken from the same patient while on the same diet (Case III). The urine-sugar test is performed by adding eight drops of urine to one teaspoonful of Benedict's solution and boiling briskly for fifteen seconds. After standing for two or three minutes the colour of the test is noted. Red, yellow, and green precipitates and a greenish opalescence (trace) indicate respectively decreasing concentrations of urinary sugar.

We can conclude that the metabolism of a diabetic patient may be considered under control when the urine is always free of acetone bodies and when the waste of glycosuria has been reduced to the minimum compatible with freedom from hypoglycaemic attacks. This control and the attainment of the ultimate objects of treatment can be achieved by the appropriate use of diet and insulin.

Diet

For a considerable time after the discovery of insulin diets greatly restricted in carbohydrate continued to be employed, but the successful trial of higher carbohydrate diets has now resulted in the acceptance of a regime which approximates to that of healthy individuals. The discovery of insulin automatically rendered obsolete the various formulae which were taught for calculating the amount and composition of the diabetic's food intake,

and the realization of this, combined with the acceptance of the modern diets, has permitted a great simplification of treatment.

The calorie value need no longer be calculated, for the amount of food taken by the patient is governed by the weight chart. While it is still a practical advantage to begin balancing a diabetic on a diet in which the amount of food is restricted, the final quantity taken by the balanced patient need only be restricted if he is over weight.

The composition of the diet now advised varies somewhat, but I think it is permissible to say that in this country medical opinion is rapidly accepting a proportion of the order of carbohydrate 2, protein 1, fat 1, so that a 2,000 calorie diet of this type contains about 200 grammes of carbohydrate. Those who are familiar with diets containing 50 or 60 grammes of carbohydrate may raise objections to such a large allowance, but their main practical objection can be anticipated and disproved. Such large allowances of carbohydrate do not necessitate proportionate increases in insulin dosage. Often the dose need not be increased; infrequently a few more units are required (Himsworth, 1934b). The advantages of the new diets are obvious to all who have tried them. It is undeniable that they are more convenient and that they are more palatable. Comparison of the number of admissions to University College Hospital for rebalancing since these diets were used with those of the period in which a low carbohydrate diet was given suggests that they render the patient less liable to relapse. It is probably to the new diets that the disappearance of xanthoma diabetorum and of diabetic dwarfism can be attributed, while evidence already available encourages the hope that this increased carbohydrate militates against the development of the most fatal complication of diabetes, arteriosclerosis (Rabinowitch *et al.*, 1934; Joslin, 1935; White, 1932). And lastly, but most important they increase the patient's subjective sensations of health and energy. These diets have come to stay, and will supplant completely their older rivals in the treatment of diabetes.

Insulin

Nearly all patients who become diabetic before middle age require insulin within two years of developing the disease; of those in whom the condition appears in later life about one-half come to need it. The indications for the administration of insulin can be stated precisely. It must be given immediately to any patient whose urine contains sufficient acetone to give a positive ferric chloride test; it must be given to a diabetic who, after four days' treatment with a modern diet, passes urine which in the majority of specimens contains enough acetone to give a positive nitroprusside test; it must be given to a patient who, while showing no ketonuria, passes sugar in all specimens after a fortnight's dietetic treatment.

Insulin treatment having begun the dose is systematically increased until the chemical tests indicate that the patient's metabolism is under control and the final objects of treatment are in sight (Himsworth, 1936). We must now consider how far modern dietetics and ordinary insulin will carry us along the path of treatment.

Mild diabetes can be treated successfully with diet alone. More severe cases require, in addition, insulin, in one, two, three, or even four doses a day. The severest cases cannot be completely controlled throughout the whole twenty-four hours. In these latter cases by large and repeated doses during the day the disease can be more or less restrained, but at night, in the absence of further injections of insulin, the abnormal metabolism again re-

asserts itself. For half the twenty-four hours such cases are virtually untreated diabetics, and by reason of this are prevented from attaining the normal health which less severe cases can achieve (Fig. 1).

This summary of the possibilities of present-day treatment reveals that it is to the transience and the rapidity of ordinary insulin action that in the severer cases of diabetes the obvious shortcomings of our therapeutics can be attributed. The transient effect necessitates multiple doses for cases of any severity, and makes control of the disease difficult if not impossible during the night. The rapidity of action results in the full effect of the insulin injected being manifested within a short time of injection, and thus, by rendering a hypoglycaemic attack inevitable if insulin in excess of the immediate requirements is given, it precludes either the administration of the multiple daily injections as one dose or the control of the diabetes during the night by a large injection of insulin in the evening. It was to meet the needs created by the shortcomings of ordinary insulin that an attempt was made to find a preparation which would have an action at once longer and slower. The production by Hagedorn, after many years of research, of a preparation in which insulin was linked to a natural protamine from fish sperm was the first attempt which was fully successful (Hagedorn *et al.*, 1936). Modifications of the original discovery have since appeared, and the most notable of these is D. A. Scott's preparation containing zinc, protamine, and insulin (Scott and Fisher, 1936a, 1936b). To avoid confusion we shall refer to Hagedorn's* preparation, protamine insulin, by its trade name of "insulin retard," and to Scott's modification as zinc protamine insulin. The work upon which the following conclusions are based has been carried out in conjunction with Dr. M. R. Thomas at University College Hospital.

Advantages of Protamine Insulins

The slow action of the protamine insulins is seen only after subcutaneous injection. After intravenous injection their action differs little from that of ordinary insulin given by the same route.

In different patients either of the new insulin preparations shows slight variation both as regards duration and speed of action, but of the two the zinc protamine insulin acts more slowly. For the purposes of comparison we may take conditions under which ordinary insulin exerts its maximum effect in two to three hours after injection and is spent at the end of six hours. Insulin retard under such conditions would produce its maximum effect in six to ten hours and have worn off by twelve to eighteen hours. Zinc protamine insulin would show its greatest effect in eight to fifteen hours and be still exerting some action at twenty-four to thirty hours (Fig. 1).

This comparison indicates the respective advantages and disadvantages of the new preparations, and suggests the considerations which must be taken into account when formulating a technique for their administration. The prolongation of action obviously allows reduction in the number of doses, and ensures that the injection of either preparation in the late afternoon controls the disease throughout the night. In the less severe cases, which require one or two daily injections of small amounts of ordinary insulin, the administration of either new preparation in one dose before breakfast will give equally good control. In more severe cases the longer action of zinc protamine insulin permits effective control with a single

* I am indebted to Dr. Hagedorn of Copenhagen and Messrs. Boots Pure Drug Co. for their generous supplies of "insulin retard" and zinc protamine insulin suspensions respectively.

morning dose when insulin retard, with its relatively shorter action, fails to do so (Case III).

The slowness of action by avoiding sudden reduction in the sugar content of the blood minimizes the possibility of hypoglycaemic attacks. This has a great practical advantage in relation to exercise. Exercise, as is well known,

FIG. 2.—Urine-sugar curves from a girl aged 16 years; the first while taking ordinary insulin, the second taking ordinary insulin and insulin retard. The diet was the same in both instances. (Case II.)

FIG. 3.—Blood-sugar curves from a man aged 65 years; the first while taking ordinary insulin, the second taking zinc protamine insulin. The diet was the same on both occasions. (Case I.)

potentiates insulin action, and any diabetic taking ordinary insulin is liable to precipitate a hypoglycaemic attack by unusual exertion. These slower-acting preparations are less affected by exercise, and hypoglycaemia from this influence is infrequent.

Disadvantages

The very characteristics which constitute the advantages of the protamine insulins also have their drawbacks. The first disadvantage they give rise to is the severity and nature of the hypoglycaemic attacks when they do occur. As a result of the prolonged action hypoglycaemic attacks when untreated last for a considerable time, and administration of sugar may need to be repeated many times to counteract the series of relapses occasioned by the persisting insulin effect. The mild attacks, produced by ordinary insulin and consisting of subjective sensations followed by rapid spontaneous recovery, do not occur, for with protamine insulins the attack, once it begins, progresses to severity. A further unpleasant feature is the suddenness with which severe attacks burst on the patient. The fall of blood sugar produced by the new insulins appears to be so gentle that the warning symptoms of hypoglycaemia are not evoked and the blood sugar slides on unchecked to lower levels, where a severe attack is inevitable. The danger of such attacks is naturally more with zinc protamine insulin than with insulin retard, as

the duration of action of the former for more than twenty-four hours favours a summation effect. It is because of these severe hypoglycaemic attacks that one cannot fully utilize this summation effect and give indefinitely large single doses of the protamine insulins in an attempt to enable severe cases to manage with one injection a day. It may be here noted that, as in the case of ordinary insulin, the susceptibility to hypoglycaemic attacks is most marked in the young and least evident in the old.

The second disadvantage is attributable to the slowness with which the protamine insulins come into action. This renders them less efficient than ordinary insulin in restraining the rise of sugar in the body and the consequent glycosuria, following the rapid influx of sugar after meals. It has long been known that the susceptibility of the body to the action of ordinary insulin varies at different times of the day, being least at breakfast, more marked in the evening, and most marked in the middle of the day. Exactly the same variation in susceptibility is revealed by the new insulin. It is for this reason that, in cases of any severity, single morning doses of the protamine insulins are so inefficient in restraining the rise of blood sugar and restricting the glycosuria after breakfast; and it is for the same reason that attempts to remedy this particular inefficiency by increasing the size of the single dose, to amounts which will abolish the post-breakfast glycosuria, may result in hypoglycaemia either during the night or in the middle of the morning, when the body is becoming most susceptible to insulin. Realization of this point has led to the devising of a technique designed to avoid hypoglycaemia whilst restricting post-absorptive glycosuria within reasonable limits.

Technique of Administration

Hagedorn (*et al.*, 1936; Krarup, 1935), using the moderately slow-acting insulin retard, does not attempt to treat any save mild cases with one dose of insulin a day. In the severer cases he gives insulin retard in the afternoon to control the disease in the evening and during the night; and next morning before breakfast he gives a dose of ordinary insulin. This latter by the rapidity of its action controls the glycosuria consequent upon breakfast, and by reason of its transience does not continue acting strongly in the middle of the day when hypoglycaemia is prone to be induced (Fig. 2). The persistence of the insulin retard effect into the next morning ensures that the morning dose of ordinary insulin required is considerably less than if the patient were taking two doses of ordinary insulin a day. If this method proves unsuccessful the diet is modified so that breakfast contains 20 per cent. of the total carbohydrate, lunch 30 per cent., tea 10 per cent., and dinner 40 per cent.

A different technique for zinc protamine insulin has been largely worked out by the Canadian physicians (Rabinowitch *et al.*, 1936; Campbell *et al.*, 1936), and by Lawrence and Archer (1937) in this country. In this the longer duration of action is exploited. One dose of zinc protamine insulin is given before breakfast, and at the same time a dose of ordinary insulin is administered. Mixing of these two types of insulin results in a product whose action is little different from that of zinc protamine insulin, but with care the two solutions can be drawn without mixing into the same syringe and given as one injection (Campbell *et al.*, 1936). The ordinary insulin controls the post-breakfast rise in sugar, and its action has weakened by the time the zinc protamine insulin is coming into full action. For the next six or seven hours zinc protamine insulin is exerting its greatest effect, and thus restraining the rise of sugar following the subsequent

meals. Later, the action still persisting, the disease is controlled during the night. I may add that we have not always found this happy sequence of effects. The development of zinc protamine insulin action may be so long delayed that the full effect of the morning dose does not appear until the evening, with the result that the later meals of the day are inadequately controlled. In such cases the full action of the insulin develops during the night and persists well into the next day, so that the rise in the sugar content of the body following breakfast is suppressed (Fig. 1, zinc protamine insulin curves). A perfect result can be obtained in such cases by giving a small dose of insulin retard, instead of ordinary insulin, along with the zinc protamine insulin.

Principles of Treatment

It is now possible for us to see the indication for the employment of these new insulins, and to formulate, tentatively, principles which should govern their administration.

The protamine insulins are indicated in those cases in which nocturnal glycosuria reveals that ordinary insulin has failed to control the disease during the night; in patients in whom exercise is especially liable to produce hypoglycaemia; and when reduction of the number of daily injections is desired. The principle governing their administration is that the protamine insulins should have as their first object the control of the disease during the night, and only as their second object the restraint of the morbidly exaggerated rises in the sugar content of the body which occur after meals. It is only in mild cases that the new preparations may legitimately be expected to control the disease during the whole twenty-four hours (Fig. 3). In cases of any severity their action should be reinforced by the administration of ordinary insulin at those times when a sudden influx of sugar from the intestine is found to overwhelm their mild action. An analogy may be drawn between the use of the new insulin and a modern technique in anaesthesia. The protamine insulins are comparable to the basal anaesthetics whose effect is both mild and prolonged; ordinary insulin is comparable to the volatile anaesthetic which is superimposed at times when stronger control is required.

Translating these generalizations into practical terms we may say that the dose of protamine insulin should be increased, in accordance with its particular technique, until the urine formed during sleep is free from sugar. If when this has been achieved glycosuria persists, after breakfast an auxiliary dose of ordinary insulin should be given and increased until the urine formed in the second half of the morning is free from sugar. In the present state of our knowledge the danger of hypoglycaemia renders it hazardous to attempt to free from sugar the urine passed in the three hours following breakfast. We should aim at keeping a trace of sugar always in this specimen, and if freedom from glycosuria occurs here the dose of both the new insulin and the ordinary insulin should be reduced until sugar again reappears.

Case Reports

The following cases illustrate various aspects of the use of the protamine insulins.

CASE I

A man of 65 years was admitted with a history of diabetes for four years. He was given a diet of 1,750 calories (carbohydrate 178 grammes, protein 80 grammes, fat 80 grammes), and was found to require insulin. Ultimately he was receiving 40 units a day (15, 10, 15), and yet his disease was not

adequately controlled. After three weeks on this diet and this dose of ordinary insulin blood-sugar estimations were made throughout the twenty-four hours (Fig. 3). Doses of 40 units of zinc protamine insulin were then given one hour before breakfast and the same diet continued. After a fortnight of such treatment the second series of blood-sugar estimations were made (Fig. 3). It will be seen that 40 units of zinc protamine insulin adequately controlled the disease. An attempt was then made to substitute 40 units of insulin retard, but this proved inadequate to prevent the rise of sugar in the body during the night.

This patient is an example of those cases which, while too severe to be controlled by one injection of insulin retard, are sufficiently mild to be controlled by one injection of zinc protamine insulin.

CASE II

A girl aged 16 years, who had been treated for diabetes for seven years, on admission to hospital was grossly unbalanced but showed only traces of ketones. She was given a diet of 1,500 calories (carbohydrate 146 grammes, protein 80 grammes, fat 66 grammes) and the insulin was raised until she was taking 75 units a day (30, 20, 25). The disease was not controlled after ten days of such treatment, when the urine-sugar curve in Fig. 2 was obtained. She was then given 20 units of ordinary insulin before breakfast and 40 units of insulin retard at tea-time, and continued with the same diet. The urine-sugar curve after a fortnight of this regime is shown in Fig. 2. She was discharged on this diet and this dosage, but because of hypoglycaemic attacks in the middle of the morning the dose of insulin retard was subsequently reduced to 35 units. She has continued with the same doses of insulin, but the diet has since been raised to 2,000 calories (carbohydrate 208 grammes, protein 80 grammes, fat 94 grammes). For the past year she has been in the best of health, working and playing hard, and has only occasionally passed traces of sugar.

CASE III

A man of 26 years who was found to have diabetes mellitus eleven years ago was treated then with insulin and a low carbohydrate diet. His insulin requirements gradually rose and he came to take 50 units a day (25, 0, 25). Two years ago he was given a diet of 1,750 calories (carbohydrate 178 grammes, protein 80 grammes, fat 80 grammes), and this necessitated no increase in insulin dosage. An acute infection in the autumn of 1936 unbalanced him, and in January, 1937, he was admitted for rebalancing.

In hospital he was given the same diet and the insulin was raised to 60 units a day (25, 15, 20). On this dose of insulin some of the urine specimens became sugar-free for the first time. After ten days of this dosage the blood-sugar and urine-sugar curves marked "ordinary insulin" (Fig. 1) were obtained. He was then changed to 60 units of insulin retard one hour before breakfast. The same diet continued to be given. After ten days on this diet the blood-sugar and urine-sugar curves, marked "retard" (Fig. 1), were taken. The insulin retard was then replaced by 60 units of zinc protamine insulin, given one hour before breakfast, but two days later the occurrence of a severe hypoglycaemic attack, in the middle of the morning, necessitated a decrease of dosage to 50 units. After one week on zinc protamine insulin the curves thus labelled (Fig. 1) were obtained.

This case illustrates several points. With ordinary insulin the sugar content of the body rose in the late evening and during the night; with insulin retard this rise was delayed to the early hours of the morning; with zinc protamine insulin the nocturnal rise was abolished, and the only evidence of escape of the disease from control was in the late afternoon and early evening when, that day's dose of insulin not yet being in full action, the action of the previous day's insulin was waning. It is noteworthy that while taking ordinary insulin acetone appeared in the urine during the night. While taking the protamine insulins it was absent. The speed with which the different insulins come into action is also demonstrated by this case, ordinary insulin acting quickly,

insulin retard moderately so, and zinc protamine insulin being relatively delayed.

Shortly after the last test shown in Fig. 1 the man had a hypoglycaemic attack just before breakfast. The dose of zinc protamine insulin was dropped to 40 units. As it was feared that this reduction would permit much sugar to escape during the morning, 10 units of ordinary insulin were given along with the zinc protamine insulin. The patient was discharged on these doses and now appears to be satisfactorily controlled.

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NON-SURGICAL RENAL EMERGENCIES

A POST-GRADUATE LECTURE

BY

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It would be an unprofitable exercise to attempt in one lecture an exhaustive survey of what I have called the non-surgical emergencies of the kidney. Suffice it, then, to recall that though there are rare conditions such as paroxysmal haemoglobinuria and less rare ones like the renal crisis of tabes dorsalis, which are independent of any abnormal condition of the kidneys themselves, the great mass of the subject is concerned with some serious anomaly of the function of these organs.

Starting with the kidney itself in a state of disorder, or with some developmental abnormality, or perhaps a constitutional weakness in the general vascular system which renders it incapable of standing up to the progress of "wear-and-tear," we may arrive at substantially the same end-result. That end-result may take on a multiplicity of forms which we group under the term "uraemia." It may be that uraemia is the most natural termination of life that we know, but at the same time in the face of every emergency, medical or surgical, that arises in practice we should ask ourselves the question: "Ought this to have come about or were we in a position to prevent it?" Acute illnesses such as a pneumonia or a fulminating appendicitis we will always meet without having had any forewarning of their approach, but there are other conditions of emergency which are recognizable in their pre-emergency stage—a stage that ought never to be far from our minds.

The boundary between the pre-emergency and the emergency involving the function of the kidneys is so ill marked that it is easy to lose sight of it altogether, but its clinical recognition, by which I mean the bedside recognition, is

so important that I stress it. For it is generally easier to modify the life of an individual so as to bring it within the compass even of a grossly impaired kidney function than to persuade a completely arrested kidney to take up its role again.

Illustrative Case No. 1

Take the case of a woman who has passed the allotted span of years. She has suffered in the last few years from a good deal of headache and pain about the back of the neck; her eyesight is not very good, she is breathless, and she has signs of aortic leakage without the large heart of the "aortic" patient in the prime of life: her aortic valve is the seat of that slow sclerosing endocarditis which we know to be associated with some degree of granular kidney. We are called to see her and find her breathless, but there is no obstruction to the breathing; the respirations are long and deep; there is a hyperpnoea rather than a dyspnoea. She has been unable to sleep for a few nights, the skin is hot and dry, there are many moist rales all over the chest, and she has passed no more than a few ounces of urine during the last twenty-four hours.

She is within sight of acute uraemia. How is she to be treated? Complete withdrawal of all food, abundant water to drink, a warm room and many blankets on the bed, and a large compress of antiphlogistine over the loins are the immediate indications and may achieve a very striking transformation; but the relief of such a condition is at best only temporary: her kidneys are permanently impaired and secondary changes elsewhere are already established.

Illustrative Case No. 2

Here is a very different picture, where a situation which appeared desperate was fortunately got over, with, in all likelihood, little or no damage to the kidneys.

A woman of 43 is troubled with oedema of the legs during the last weeks of her first pregnancy, but no changes are found in the urine. An hour after her successful delivery she has an eclamptic fit and the urine is found to contain much protein. In the next three days the amount of albumin steadily diminishes to little more than a trace, when it begins to rise again and she becomes very breathless. She is admitted to hospital on the tenth day post partum. She is very ill: the pulse 108, the respirations 44 per minute, and the temperature 98.4°; she coughs much and brings up a purulent spit. She is flushed, with a slight cyanosis, there is much oedema of the legs and back; there is a nasty burn on the dorsum of the left foot, a relic of the fit. The urine becomes almost solid on boiling, the blood pressure is 174/88. The breath sounds are loud and harsh with many rales, mostly dry. A large needle is inserted into a vein in front of the elbow and a few ounces of dark viscid blood are withdrawn, but clotting in the needle is so rapid that the vein is exposed by dissection and a cannula inserted. The cannula too is quickly blocked, and in all not more than eight ounces of blood have been drawn and a like quantity of saline infused.

Next morning the patient is in a parlous state. A few more ounces of blood, not so dark and thick as on the previous evening, are aspirated by syringe, more perhaps as a salve to the conscience than anything else. The woman, rather stout and plethoric, is literally struggling for breath, but seems to get a measure of relief from oxygen administered by intranasal catheter. She is coughing incessantly and bringing up much frothy sputum, and there is a dusky cyanosis in spite of the oxygen. Her distress is explained by an examination of the chest; there