will it be with Health as the wise man warned us it is with Happiness: shall we call no man healthy until he is dead?

Ultimately the answer to this question must depend upon the two things, interaction between which constitutes disease: one is the causative agents of disease, and the other is man himself. Changes in either, or in both, of these would delay control, it may be indefinitely, and change is of the very essence of living things: change, but also persistence. Elsewhere I have dealt with an aspect of this matter in speaking about New Diseases and Old. In relation to the large field of microbic diseases, to name only one, there are elemental forces at work which still confound the epidemiologist.

And what of man himself? Will man invent new diseases as time goes on? Is he less inscrutable, less wilful, less errant, because modern psychology has made his nature more clear to us? Or will he always be as Henry Vaughan depicted him?

"... Man hath still either toyed, or Care,
He hath no root, nor to one place is tied,
But ever restless and Irregular
About this earth doth run and ride,
He knows he hath a home, but scarce knows where,
He says it is so far
That he hath quite forgot how to go there.
He knocks at all doors, strays and roams,
Nay hath not so much wit as some stones have
Which in the darkest nights point to their homes,
By some hid sense their Maker gave;
Man is the shuttle, to whose winding quest
And passage through these looms
God ordered motion, but ordained no rest."

Upon the result of such speculations as these depends the answer to the intriguing question with which I began, and with which I now close.

ZINC-PROTAMINE-INSULIN IN DIABETES

TREATMENT BY ONE DAILY INJECTION

BY

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Protamine-insulin compounds have been used in this country for three years, and sufficient time has passed to appraise their value in the treatment of diabetes. The earlier insulin was a clear soluble preparation, but the addition of protamine produces a cloudy precipitated compound which is more slowly absorbed from the site of injection and hence slower and more prolonged in its action. At first a simple insulin-protamine compound (Leo insulin, retard) was used in this country, but later it was found that the addition of traces of zinc made the compound still less soluble and more prolonged in action. Zinc-protamine-insulin is the only protamine compound manufactured here, and it is more generally useful than the original preparation; therefore its use alone will be described.

Insulin treatment has never been as simple as giving a bottle of medicine, and in the past it usually involved two or even three injections a day—no easy matter for many patients. The new type of treatment is sufficiently different from the old to introduce at first new complexities for the practitioner accustomed to the latter. But I hope to show that treatment with zinc-protamine-insulin is easier and simpler for the doctor and his patients, and that it ought to extend the benefit of insulin to thousands of patients who, although they needed it, did

not get it. Indeed, the qualities of zinc-protamine-insulin make it the *practitioner's insulin* for choice.

Insulin Requirements of Different Diabetics

Before we pass to the details of the new treatment it is important to consider the varying degrees of insulin deficiency in diabetics, because the difference between a mild and a severe case is so great as to require an almost entirely different use of insulin. We have reason to believe (Lawrence and Archer, 1936) that in normal people there is (1) a small continuous secretion of insulin, a *basal* secretion, which controls endogenous sugar production and controls the fasting blood sugar, and (2) an increased secretion after meals to deal with the absorbed carbohydrate. In diabetics both these aspects of insulin secretion are defective, but the clinical pictures vary widely with the degree of insufficiency. Mild cases, still producing some insulin, are controlled either by diet alone or by small added doses of insulin which are necessary mainly to deal with carbohydrate food, the patient's own basal supply of insulin being sufficient to keep the blood sugar normal, or nearly so, except after meals. In more severe cases injected insulin is required not only to deal direct with carbohydrate food but to control the continuous outpouring of sugar (and acetone bodies) in the fasting condition. The problem of maintaining diabetic control and good health in mild cases is therefore very different from that of severe cases. The properties of the various insulin preparations are summarized in Table I.

TABLE I.—Adults

Type of Insulin	In Doses	Duration of Action	Commonest Time of Hypoglyc.	Remarks on Type of Action
Soluble	to 10 units	5-6 hours	2-4 hours	Quick and strong. Balances much carbohydrate
	to 20 "	6-8 "	3-5 "	
	to 40 " +	10-12 with big doses	6-8 "	
Retard	to 20 units	8-10 hours	4-6 hours	Slower. Balances less carbohydrate
	to 40 "	12-16 "	6-9 "	
	to 60 "	Occasionally 24 hours	7-12 "	
Zinc-protamine-insulin	to 10 units	6-8 hours	5 hours	Very slow. Balances carbohydrate poorly
	to 20 "	to 12 "	8-12 "	
	to 30 "	to 18-24 hours	8-20 "	
	40 units or more	24 hours or longer	16-24 "	

Soluble insulin is quick and strong in controlling the sugar from the carbohydrate meal following, but it is so short-lived in action that one or even two doses never provide a continuous supply. It acts in strong waves, which may even produce hypoglycaemia twice a day without preventing a relapse of sugar and ketosis in severe cases when its action is exhausted in six to nine hours. Zinc-protamine-insulin, on the contrary, provides a constant small amount of circulating insulin sufficient for a basal supply but too weak to control sugar after carbohydrate meals. It is also more *irregular* in its action from day to day than two doses of soluble insulin, possibly because of more irregular absorption. When these contrasting qualities are realized, the value and limitations of the old and the new insulin in treatment are easily appreciated.

When a new case of diabetes is discovered it is often difficult to decide whether insulin is necessary at once. In this decision the tests for acetone (ketone) bodies are even more important than the degree of glycosuria and hyperglycaemia. If ketonuria is present in more than traces

insulin should be given; if not, diet alone may be tried for some three weeks, and then insulin added if diet fails to control the sugar. With zinc-protamine-insulin, as with all types of insulin, it is impossible to predict what dose will ultimately be necessary. This has to be found by giving a trial initial dose, observing its effect on urine and (when possible) blood tests, and adjusting the dose up and down according to results. The treatment of mild and severe cases with zinc-protamine-insulin is the same at first, and I shall describe the method of treating a new case (with no dangerous ketosis) in which insulin is deemed necessary (see Table II).

TABLE II.—*Mild Case*

Day	Zinc-P.- Insulin Units	7 a.m.	8 a.m.	11 a.m.	1 p.m.	4 p.m.	7 p.m.	10 p.m.
1st	30	+++	+++/250	+++	+++	++/200	++	+++
2nd	30	++	+ /190	++	++	0	0	+
3rd	30	+	0/156	+	trace	0	0	0
4th	30	0	0/110	trace	0	0	0	0
5th	20	0	0/080	+	trace	trace	trace	+
6th	24	trace	0/150	+	trace	0	0	trace
7th	24	0	0/120	+	0/130	0/103	0/090	trace/150
Diet : Carbohydr., grammes : 40					40	20	30	10

Remarks.—Urine sugar by Benedict's qualitative test on specimens passed before meals : +++ = 4% ; trace = 0.5% sugar approximately. Illustrative blood-sugar readings (mg. per 100 c.cm.) taken just before meals are inserted beside the urine test. Insulin given at 8.30 a.m. Breakfast at 9 a.m.

FINDING THE BASAL DOSE

The first step is to discover what I have called the *basal* dose, that which will continue its action for twenty-four hours and keep the blood sugar *normal before breakfast* and yet cause no hypoglycaemia during the night. I usually give adults about 30 units before breakfast as the first dose, unless I have reason to think the case is unusually mild, when 20 might be given. Children mostly receive about 20 units and infants 6 to 10 units. I think it a waste of time to give adults such small initial doses as 5 to 10 units (recommended by some writers), to be increased slowly later. The first dose does not show its full effect for two to four days, as the action is slow and partly cumulative.

Although fasting blood-sugar estimations are the most accurate index of the best basal dose, they are not strictly necessary, and can be replaced by tests on two samples of urine—one passed on waking to void any sugar which may have entered the bladder soon after bedtime, and a second, just before breakfast, to indicate the approximate level of the blood sugar at that time. The importance of two tests (or at least voidings) is shown in Table II, third day, 7 a.m. and 8 a.m. If the bladder had not been emptied at 7 a.m. sugar would have been found at 8 a.m., and the temptation would have been to increase the basal dose and almost certainly to have produced hypoglycaemia.

The case recorded in Table II shows, to my mind, that a satisfactory control can be worked out by urine tests, almost entirely and without blood-sugar estimations, although it is of interest to record them in such a paper as this. By the seventh day the patient passes a little sugar only after breakfast (11 a.m.), before the absorption of insulin is fully started, and after supper (10 p.m.), when the insulin action is nearly exhausted. Such a dose of zinc-protamine-insulin comes into action in three hours and acts mainly by day in helping to deal with the day's carbohydrate food, the level of the fasting blood sugar being partly maintained by the patient's own endogenous

insulin. It is rare to get the balance of diet and insulin so quickly established, and in Tables II and III the results have been rather crowded in time to save space. It is usually better to change the insulin only every three days, as the results of any one dose, or change of dose, are not usually obvious after only one day. Another satisfactory result is shown in Graph I with a somewhat higher dosage—32 units.

GRAPH I

Mild cases may prove to be controlled by even smaller doses of 10 to 16 units, and can be kept sugar-free on this with practically no risk of hypoglycaemia. These patients, especially the elderly, are often so benefited that insulin may be reduced and ultimately omitted, as happens also with soluble insulin.

With zinc-protamine-insulin I have been able to treat more patients successfully from the beginning without admission to hospital, and the practitioner can do the same. I arrange a diet (see later) and order one dose of zinc-protamine-insulin, 20 to 30 units, daily before breakfast. If it is not convenient to give this before breakfast it may be given soon after by a visiting nurse or doctor, until the patient has learned to do his injections. The 7-8 a.m. urine (Table II) should be tested twice a week and the basal dose adjusted by this test. I should advise the practitioner not to give more than 30 units except under close control, as hypoglycaemia at night may be caused. An occasional evening sample of urine should be tested to see if the basal dose is also controlling the day's carbohydrate food. When a sufficient basal dose has been established the doctor has the satisfaction of seeing great improvement in weight and energy.

Severe Insulin Cases

In more severe cases it becomes clear by the end of a week (Table III) that increasing doses of zinc-protamine-insulin do not control the sugar, though they undoubtedly decrease the total glycosuria and the ketosis and improve the patient's weight and general condition. When the basal dose has been raised sufficiently to make the 8 a.m. urine sugar-free (and more we should not dare to give without risking hypoglycaemia at night) the glycosuria by day persists heavily in all other samples of urine, as shown in the sixth to eighth day. The carbohydrate of the food is never balanced by the slow liberation of insulin from the site of injection, and ketosis may be present. The commonest urinary findings are shown on the sixth to ninth day, but the picture seen on the ninth day, when the patient is sugar-free after breakfast, may occur. This may be due to an unusually prolonged action from delayed absorption from the day before or an unusually quick absorption on the same day, or both combined. The picture shown on the ninth day is common when the basal dose is higher than is really necessary to make the 8 a.m. specimen sugar-free. On such mornings the fasting blood sugar is near hypoglycaemic levels, and the insulin carries on its effect sufficiently to control the breakfast carbohydrate. The action of the basal dose should be wearing off at night, and my experience has taught me that if the 8 a.m. urine is sugar-free two days out of three the dose of zinc-protamine-insulin is large enough. If this

specimen is always sugar-free and if the fasting blood sugar is usually completely normal, then sooner or later the patient will suffer from hypoglycaemic attacks in the latter part of the night, often just before breakfast.

TABLE III.—*Severe Case*

Day	Zinc-P.-Insulin Units	7 a.m.	8 a.m.	11 a.m.	1 p.m.	4 p.m.	7 p.m.	10 p.m.
2nd	30	+++	+++	++++		+++		+++
3rd	30	+++	++	+++		+++		+++
4th	40	+++	+ /210	+++		+++		+++
5th	40	++	tr./190	+++		+++		+++
6-8th	40	trace	0/140	+++	+++	+++ /230	++	+++
9th	40	+	0/120	0	0	+++	+++	+++
10th	40	+	0	+++	+++ /210	+++	+++	+++
11th	40+12 sol.	+	0	++	tr./140	0	0	++ /180
12th	40+16 sol.	trace	0/110	+	0/090	0	0	+
Diet: Carbohydrate, grammes:		50*	10	40	20	30	10	

Remarks: Blood sugar, taken just before the meals.
*The 50 grammes are given at 9 a.m., with breakfast.

Addition of Soluble Insulin.—The state of affairs as shown by days 6–10 of Table III is unsatisfactory in that much of the carbohydrate ingested during the day is inevitably lost in the urine, and this cannot be rectified by increasing the basal dose without causing hypoglycaemia at night. The glycosuria can be minimized by reducing the carbohydrate of the diet to a low level, but patients dislike this, and it is not desirable from the nutritional point of view. Fortunately it can largely be rectified by adding soluble insulin to the basal dose, as the former quickly controls the carbohydrate taken at breakfast and lunch. Fortunately, too, this does not necessitate two injections, as zinc-protamine-insulin and soluble insulin can be drawn into the *same* syringe, injected into the same subcutaneous site, and yet *retain their individual actions*—prolonged and quick. The *soluble* insulin should be drawn into the syringe *first*, as it does not matter if a trace of acid insulin from the needle enters the buffered protamine bottle, whereas the entry of alkaline material to the acid bottle may make the soluble insulin alkaline and inert by the time the contents are finished. I add enough soluble insulin to make the blood sugar normal before lunch (see Table III, twelfth day). Even then the patient will often pass some sugar after breakfast before the soluble insulin action is fully established, and again after supper when the soluble insulin is exhausted and the protamine is left to deal with the supper carbohydrate. The evening glycosuria can, if desired, be cut out by giving very little carbohydrate for supper. Another example is shown in Graph II.

GRAPH II

A few points of practical importance should be mentioned. If the urine is sugar-free before breakfast (with consequently a nearly normal blood sugar) the mixed dose should be given not half an hour but almost *immediately before breakfast*, otherwise the soluble insulin may cause

hypoglycaemia before or during breakfast. If quick control of a severe new case is desired, soluble insulin should be added to the basal dose from the start, perhaps before supper as well as before breakfast, and should be reduced or discontinued as soon as the urine tests begin to clear.

With this treatment, in severe cases, it is rarely possible to keep the urine *constantly sugar-free without risk of hypoglycaemia*. Practically all my cases have shown sugar, and I have learned to reduce the insulin if all the urine tests are sugar-free for even one day, and certainly for two days, otherwise hypoglycaemia is sure to occur. These patients ought to pass some sugar after breakfast, and usually some after supper—this is inevitable and is not accompanied by ketosis. In my opinion if the patient never passes sugar after supper or before breakfast the basal dose is too high and should be reduced, perhaps by 4 units; if he never passes sugar after breakfast the soluble insulin should be reduced.

Very Severe Cases

A few very severe cases—for instance, cases which formerly required 60 to 100 units of soluble insulin a day—cannot be satisfactorily controlled, or even kept in good health without ketosis, by a mixed dose given in the morning only. Such a case is shown in Table IV, where it is clear that, after the effect of the morning soluble insulin has worn off, the zinc-protamine-insulin is quite unable to control the heavy glycosuria, except just before breakfast. A second dose of soluble insulin must be given before the evening meal (seventh day) or before tea (ninth day), whichever time is best suited to each individual. Usually, although this may be an inconvenient time for an injection, it is better given before tea, as the patient's metabolism is already requiring it then; also there is less risk of hypoglycaemia between about 1 and 2 a.m., because the strong action of the soluble insulin has been balanced by two carbohydrate feeds and is nearly exhausted by midnight.

The very severe diabetic condition requiring the above treatment may be temporary and be due to infections or complicating factors such as worry or pregnancy, and it may be possible later to stop the evening dose and reduce the combined morning dose. But I have had to keep a few cases permanently on such doses as 60 units of zinc-protamine-insulin and 40 soluble in the morning and 40 soluble insulin in the evening. In such severe cases the total dose of combined insulin required is sometimes more than the previous total of soluble insulin, but the control of ketonuria and morning glycosuria is much better.

TABLE IV.—*Very Severe Case*

Day	Insulin Units	7 a.m.	8 a.m.	11 a.m.	1 p.m.	4 p.m.	7 p.m.	10 p.m.
6th	52 Z.P.I. + 20 soluble	+++	0/100	++ /180	0/90	+ /200	+++ /240	+++ /340
7th	52 Z.P.I. + 20 soluble. 6.30 p.m.: 20 soluble	+++	0	++	0	+	+++ /230	trace /110
8th		0	0	+	0	trace	+ /210	0
9th	52 Z.P.I. + 20 soluble. 4 p.m.: 20 soluble	0	0	++	0	trace	trace /160	0/100

Hypoglycaemia

An excessive dose of zinc-protamine-insulin produces hypoglycaemia and symptoms very similar to those from

an overdose of soluble insulin. On the whole the symptoms are milder at the same level of blood-sugar concentration, are slower in onset, and less obvious to the patient (therein lies a danger), but may be equally severe and even more prolonged. Such mild symptoms as headaches—especially before breakfast and those relieved by breakfast—slight nausea, general tiredness, or intense drowsiness are apt to escape notice as hypoglycaemic symptoms, but are quite characteristic of overdose with zinc-protamine-insulin, and may be the only warning of a severe attack. The time of onset after injection may be at almost any hour of the day or night, but it depends fairly closely on the dose, as might be deduced from Table I. A dose of 4 to 10 units in a very mild or insulin-sensitive case may produce hypoglycaemia three to five hours after injection—usually, therefore, before lunch—but hypoglycaemia within six hours of injection is rare. Doses of 10 to 20 units are most likely to cause hypoglycaemia before tea or the evening meal, 20 to 30 units at a similar time and also in the early hours of the night, and bigger doses later at night or just before breakfast. If a certain basal dose correctly worked out causes hypoglycaemia during the day this should be corrected by giving more carbohydrate before hypoglycaemia usually occurs: if hypoglycaemia occurs at night or in the early morning the basal dose is too high and should be reduced. When soluble insulin is given also, another period of possible hypoglycaemia arises some three to five hours after its injection, quite apart from the hypoglycaemic action of the zinc-protamine-insulin.

The treatment is the same as with soluble insulin—the giving of glucose or cane sugar by mouth, two lumps or two teaspoonfuls. Patients may take longer to recover from protamine hypoglycaemia and may require more carbohydrate later to prevent relapse from its continuous action.

Diet Arrangement and Exercise Effects

It is possible to control patients satisfactorily, as defined in previous paragraphs, on diets containing 120 to 200 grammes of carbohydrate, but it is much easier to keep them aglycosuric at the lower level of carbohydrate, as any large meal unsupported by soluble insulin is liable to cause hyperglycaemia. The carbohydrate arrangements must be different from those adopted when treatment is with soluble insulin, when most of it is given at the meals following injections. To balance the continuous action of zinc-protamine-insulin the carbohydrate must be spread over more frequent feeds, as shown in Tables II–IV. Some carbohydrate must be taken between 4 and 5 p.m.—tea-time in England—to ward off hypoglycaemia before supper, and more carbohydrate at bedtime to prevent hypoglycaemia at night. If this is impossible in the patient's life he is better on two doses of soluble insulin, when the possible hypoglycaemic times are fewer and better defined.

Extra exercise, as with soluble insulin, will produce hypoglycaemia either during or after the added activity and over a more widespread period. This possibility must be met by extra carbohydrate (20 to 30 grammes) before or during exercise, and sometimes afterwards at the evening meal to prevent an overdose during the night.

Cases requiring Change from Old to New Insulin

I now treat all new insulin cases with zinc-protamine-insulin alone or with added soluble insulin, and usually the results are just as good with one injection as they were with two injections of soluble insulin. But of the thousands

of cases already treated, perhaps for years with soluble insulin, whom are we to change? I usually make the change in:

I. Mild insulin cases—for example, those having 5 to 15 units twice daily. This is easily and satisfactorily done by giving approximately the total previous dosage in one injection before breakfast.

II. Cases with severe sugar and acetone before breakfast on two doses, and cases having three doses a day; also patients who are somewhat needle-shy or are very anxious to omit the second dose. It is particularly tempting to change children over to one injection. In this group of cases the alteration is sometimes quite difficult, and I prefer to do it under close control in a hospital or home. The soluble insulin should not be omitted at once, but be continued in reduced amounts until the protamine-insulin exerts its full effect in some three days' time. In most cases the number of injections becomes less, but the total units of insulin required may be more. Some very severe cases do not respond well to protamine-insulin, and I have put these patients back, sometimes at their request, on two or three doses of quick strong-acting soluble insulin, which suits them better. Only close *individual* study can show what is best for some difficult cases.

I do not make the change in the case of the hundreds of patients who have lived a healthy and contented life for months or years on two doses a day which they find no great inconvenience. I also refuse to do so with some patients who are careless or lead very irregular lives: the continuous action of the depot insulin, unbalanced by the necessary frequent small meals, makes them more liable to hypoglycaemia than when two smaller doses of soluble insulin are taken before breakfast and the evening meal.

Zinc-protamine-insulin alone is not suitable for emergency treatment of ketosis and coma, and frequent doses of soluble insulin should be given as before (probably four-hourly) where rapid insulin action is required.

Summary

The treatment of diabetes by *one daily injection* of the new zinc-protamine-insulin, either alone or with added soluble insulin, is described in detail. Mild cases easily respond to this one dose, but more severe cases require the addition of the previous soluble insulin. Most cases can be reasonably controlled and the patients kept in good health by this method, and it represents a great advance in simplicity for the practitioner and in comfort for the patient.

REFERENCE

Lawrence, R. D., and Archer, N. (1936). *British Medical Journal*, 1, 747.

The sixteenth International Congress on Medical Hydrology, Climatology, and Geology will take place in France at Strasbourg from October 8 to 11, under the joint presidency of Professors Danjon, Sartory, and Forster, Dean of the Faculty of Medicine. Arrangements have been made to provide, after the Congress, motor tours in the picturesque districts of Alsace, the Rhine, and the Vosges, and to allow members of the I.S.M.H. to attend the annual meeting of the society in Italy. The following subjects will be discussed: permeability and mineral waters, hydromineral treatment of skin disease, indications for winter sports, mineral waters of petroleum districts, and the evolution of French spa equipment in the past twenty years. Papers on these and other branches of medical hydrology, climatology, and geology are welcomed. Members will be offered travel facilities by rail, sea, and air. A programme and full details will be issued in July. For particulars application should be made to Professor Vaucher, Institut d'Hydrologie, 1, Place de l'Hôpital, Strasbourg (Bas-Rhin).