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BRIEF NOTES AND COMMENTS

Combined Use of Regular and Crystalline Protamine (NPH) Insulins in the Treatment of Severe Diabetes

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SUMMARY

The use of twice daily injections of regular and extended action insulin mixtures, originally described in 1937, is revived and Crystalline Protamine Insulin (NPH) is proposed as the most suitable extended action insulin at present available for use in conjunction with Regular Insulin.

It is suggested that, in severe diabetes, the physician should aim at achieving a blood glucose of below 150 mg. per 100 ml. before breakfast, lunch and supper, and at bed time. This standard of control has been sought in ten pregnant diabetics treated in hospital with twice daily injections of regular + NPH insulin mixtures, and blood sugar results are reported. Experience with the same regimen in 162 diabetic clinic outpatients is also described.

Practical aspects of treatment by twice daily Regular + NPH Insulin mixtures are discussed; it is concluded that this regimen provides a good, and probably the most widely applicable, method at present available for the treatment of severe diabetes. It is sometimes possible to omit one or more of the four insulin dose components of the regimen. DIABETES *15*:219-22, March, 1966.

Diabetes mellitus may usefully be described as severe when withdrawal of insulin is rapidly followed by hyperglycemia and ketosis. The first effective treatment for this condition was by frequent injections of Regular Insulin (RI). Although twice daily administration usually achieved satisfactory symptomatic control, this method of routine treatment fell into disuse in many centers with the development of long-acting preparations which halved the number of injections required. Yet it has always been thought that frequent RI injections mimic more closely the pattern of endogenous insulin secretion in response to carbohydrate intake. Considerations relevant to this form of treatment have recently been reviewed by Lukens[1] in his 1964 Joslin Memorial Lecture. It is, however, usually impossible to maintain the blood sugar close to normal throughout the whole twenty-four hours using two injections of RI alone, and it is certain that late diabetic complications may develop on such a regime.[2,3] Moreover, there is much evidence both from studies of diabetic pregnancy[4,5] and of diabetic complications[6-10] to suggest that it is desirable to keep the blood sugar as closely as possible within physiological limits at all times. These considerations led us in 1958 to start treating most of our severe diabetics with twice daily injections of RI and Crystalline Protamine Insulin (NPH) mixtures. This paper explains the rational basis for this method of treatment and reports our clinical experience.*

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*The three main meals are described throughout as "Breakfast," "Lunch," and "Supper"; "Tea" is used to describe a buffer feed between lunch and supper. Twice daily insulin regimens are expressed as fractions, the numerator being the morning and the denominator the evening treatment. Blood sugars have been performed by a modified Somogyi-Nelson technic giving results only very slightly higher than true glucose values.

THE ASSESSMENT OF DIABETIC CONTROL

We regard estimation of the blood sugar prebreakfast, prelunch, presupper and at bedtime as the optimum way of assessing control in a patient on insulin. We favor blood sugar values because, although each estimation refers only to a single point in time, they can, if correctly timed in relation to meals and insulin, give more information than any form of urine test. The times are chosen both to give the maximum information about the blood sugar level throughout the day and to help as much as possible in establishing the best insulin regimen and dosage.

No objective methods of assessing blood sugar control out of hospital are satisfactory; we therefore attach importance to clinical impressions based on regular hospital interviews and home urine tests. In addition, we find weight gain on unchanged diet to be a useful index of improved control.

THE LOGICAL BASIS FOR USING TWICE DAILY MIXED INJECTIONS OF REGULAR AND CRYSTALLINE PROTAMINE (NPH) INSULINS IN SEVERE DIABETES

Satisfactory control of the blood sugar in a severe diabetic, who usually has little or no endogenous insulin action, requires insulin activity to be peaked in relation to carbohydrate intake; for this reason single injection regimens are seldom successful in this type of case. Moreover, as really short-lived peaks of insulin activity can only be obtained with RI, it is not surprising that, without it, good blood sugar control is seldom achieved. It must, nevertheless, be accepted that few patients are prepared to take more than two injections of insulin a day.

As moderate doses of RI act for only about eight hours, twenty-four-hour coverage cannot be expected on a program of twice daily injections without the addition of a long-acting insulin preparation. Crystalline Protamine Insulin (NPH)[11] can be added to RI without significant effect on the activity of either component of the mixture, and we regard this as the most suitable preparation for mixing with RI in order to provide extended action. Clarke et al.[12] have recently described preliminary results with Actrapid and Crystal II insulins[13] used in a manner exactly similar to that described in this paper for RI and NPH. It is, however, probably undesirable to introduce two further insulins unless these are shown to be superior to those at present available. In our experience mixed injections of RI + NPH given before breakfast and before supper have given satisfactory control (defined as a blood sugar usually below 150 mg. per 100 ml. before breakfast, lunch and supper and at bedtime, without hypoglycemia) in most severe diabetics. This regimen may be regarded as basic, and can be modified by the omission of one or more of its components (i.e., morning RI, morning NPH, evening RI, evening NPH). Usually all four components are required, for reasons that will become clear when the practical use of the regimen is discussed.

CLINICAL EXPERIENCE

a. *Severely diabetic patients under supervision in hospital*

Four blood sugar determinations (before breakfast, lunch and supper and at bedtime) are carried out on a single day, once a week, in all pregnant diabetics under supervision in hospital. The serial blood sugars of ten of these patients admitted consecutively to hospital and treated with $\frac{\text{RI + NPH}}{\text{RI + NPH}}$ have been analyzed. A total of 180 blood sugars is made up of forty-five complete sets of four specimens taken during a single day; details of these are shown in table 1. Only eighteen (10 per cent) fall outside the range of 40 to 190 mg. per 100 ml., and only three are above 250 mg. per 100 ml. Individual patients may achieve even closer control; in one, all of sixteen blood sugars (four days) fell between 100 and 166 mg. per 100 ml.

TABLE 1

Blood sugar levels (mg. per 100 ml.) in ten hospitalized severely diabetic pregnant women treated with twice daily injections of RI + NPH mixtures

Time	Total number of estimations	Median value	Mean value	Standard deviation
Prebreakfast	45	106	112	42
Prelunch	45	132	135	57
Presupper	45	142	142	45
Bedtime	45	140	137	44

b. *Severely diabetic outpatients*

A retrospective survey has been made of all severely diabetic patients changed from other regimens to $\frac{\text{RI + NPH}}{\text{RI + NPH}}$ at King's College Hospital since the introduction of the method seven years ago. The total experience in 162 patients amounts to 350 patient-years. The series contains virtually all the "difficult" patients attending the department—which is, moreover, one to which many such diabetics are referred from other clinics. In all cases the reason for changing to the new method of treatment was inadequate blood sugar control. In our experience $\frac{\text{RI + NPH}}{\text{RI + NPH}}$ has produced better blood sugar control than any other regimen. In 134 (83 per cent) of the 162 diabetics reviewed, both patient and physician were satisfied with the diabetic control achieved at the time of review. Moreover, no patient has been changed from this regimen, and there is a considerable patient preference for this method of treatment. Body weight has been compared before and after changing to $\frac{\text{RI + NPH}}{\text{RI + NPH}}$ in 115 patients free from obfuscating conditions such as normal growth, diet changes, pregnancy, thyrotoxicosis and heart failure. Regarding a change of 2 kg. as significant, sixty-one (53 per cent) increased in weight, while only fifteen patients (13 per cent) lost weight. This finding supports the clinical impression of improved control in most cases.

PRACTICAL CONSIDERATIONS IN THE USE OF $\frac{\text{RI + NPH}}{\text{RI + NPH}}$

Two important factors influence the planning of a twice daily injection regimen based on RI; the first is the patient's way of life and the second his sensitivity to insulin. As the morning dose can only reasonably be given before breakfast and the evening dose before supper, the two injections may be separated during the day by as little as eight or as much as fourteen hours. In the case of a patient taking a late breakfast and early supper even a moderate dose of RI before breakfast may keep the blood sugar controlled until the evening injection takes over; in such a patient there may, however, be an

interval of up to sixteen hours between the evening injection and that given next morning, and an NPH supplement will usually be needed with the evening RI dose. Conversely, if breakfast is taken early and supper late, hyperglycemia before supper may only be prevented by adding NPH to the morning dose of RI while a mixed injection in the evening may be avoided. The larger the insulin dose, the longer its duration of action, so that patients who tolerate large doses of RI without hypoglycemia may be well controlled on two injections of RI alone; conversely, very insulin sensitive patients, unable to tolerate even small doses of RI without hypoglycemia, may sometimes be well controlled with two injections of NPH alone. As much less carbohydrate is taken by night than by day, the optimum dose of RI is usually less in the evening than the morning, and its duration of action therefore shorter; moreover, exercise tends to potentiate the action of insulin given in the morning. For these reasons the $\frac{RI}{RI + NPH}$ regimen is more frequently required than $\frac{RI + NPH}{RI}$.

In practice, a twice daily injection regimen is best introduced in the form of morning and evening injections of RI. If normoglycemia before lunch and at bedtime is found to be associated with significant hyperglycemia in the late afternoon and before breakfast, the action of either or both RI doses may be prolonged by the addition of NPH; any attempt to prevent such relapses by increasing the dose of RI is almost certain to produce hypoglycemia. In severe insulin sensitive diabetics on $\frac{RI}{RI}$ the commonest indication of poor control is heavy glycosuria, and often ketonuria, before breakfast. The presence of a high blood sugar at this time may enable a sufficiently large dose of RI to be given to prevent relapse before the evening injection, but in this event it is impossible, without risk of severe nocturnal hypoglycemia, to give enough RI in the evening to prevent a high blood sugar before breakfast the following morning. This pattern of widely fluctuating blood sugars on $\frac{RI}{RI}$ is characteristic of the so-called "brittle" diabetic. The addition of NPH to the RI prolongs the period of blood sugar control and so limits the size of the dose of RI that can safely be given at the next injection; for this reason it is usually necessary to add NPH to both morning and evening injections of RI in the treatment of severe diabetes. In other words, when the blood sugar is normal, it is seldom possible to give a dose of RI large enough to prevent hyperglycemia before the next injection and, when NPH is added to one dose of the $\frac{RI}{RI}$ regimen, it is usually necessary to add it to the other as well.

Once approximate control has been established on $\frac{RI + NPH}{RI + NPH}$ then small changes in any one component can be made independently of the others; this greatly facilitates the patient's adjustment of his own insulin. It is useful to regard the day as divided into four periods, during each of which a different insulin component of the $\frac{RI + NPH}{RI + NPH}$ system controls the blood sugar; these divisions, together with the timing of blood sugar estimations and urine tests from which changes in insulin dose should be made, are shown in table 2.

DISCUSSION

The practical value of any insulin regimen is proportional to the percentage of insulin-requiring diabetics in whom it can attain satisfactory control. The use of only a small number of insulin preparations means that the physician can become really familiar with their properties—an essential prerequisite to correct use. Although other regimens may achieve equally good, but seldom better, control in individual cases, the great advantage of the $\frac{RI + NPH}{RI + NPH}$ system is its wide applicability, as illustrated by the high percentage of successfully stabilized patients in the retrospective outpatient survey.

This type of treatment is not new, for Graham[14] in 1937 advocated the use of morning and evening injections of RI and Protamine Insulin[15] in the treatment of severe labile diabetes. Mixtures of short and long-acting insulins were, however, originally introduced as a means of controlling diabetes by a single daily injection, and this fact has been responsible for the neglect of a method of treatment which involves both mixing insulins and two daily injections; these disadvantages must be weighed against the assets of better blood sugar control and less danger of severe hypoglycemia.

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TABLE 2

Management scheme for treatment of severe diabetes with twice daily injections of RI + NPH mixtures

Insulin dose	Period of maximum action	Timing of blood sugar for dose adjustment	Timing of urine specimen for dose adjustment
Morning RI	Breakfast — Lunch	Prelunch	Prelunch*
Morning NPH	Lunch — Supper	Presupper	Presupper*
Evening RI	Supper — Midnight	Bedtime	Bedtime* or on rising†
Evening NPH	Midnight — Breakfast	Prebreakfast	Prebreakfast*

*The bladder should be emptied one-half to one hour previously.
†Inpatients who go to bed early.

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L-Leucine in Secondary Sulfonylurea Failure

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SUMMARY

Ten diabetic patients, secondary failures to sulfonylureas, seven of whom were receiving maximal doses of tolbutamide and three of chlorpropamide, were concurrently given L-leucine, as tablets, in a daily dosage of 12 gm. for four to eight weeks. Good diabetic control, with most blood glucose values below 130 mg. per 100 ml., was achieved in three; a good response, as indicated by a fall in blood glucose values of 20 per cent or more, occurred in eight; two patients did not respond. Of four patients receiving thiazide, which might have contributed to their secondary failure, three responded. Reversal of osmotic diuresis and symptoms of nocturia occurred in five patients. No untoward effects of any significance were noted. Adjunctive use of L-leucine for better diabetic control in patients who have become refractory to sulfonylureas, or are receiving thiazides, is suggested. DIABETES *15*:222-24, March, 1966.

Although diabetics, as well as normal subjects who have been pretreated with sulfonylureas, have been shown to respond to the hypoglycemic action of L-leucine in acute experiments,[1-4] no mention has been made of any possible therapeutic utility of administration on a chronic basis. In a study devised to investigate this possibility, use was made of a group of patients who were receiving sulfonylureas, but who were no longer responding satisfactorily to the action of these drugs.

METHODS

Rigid criteria were applied for selection of patients to include those who were: (1) forty-five years of age or over, with maturity-onset diabetes; (2) without evidence of infection; (3) without gross increase in caloric intake and weight; (4) in secondary failure to sulfonylurea drugs after a period of fair-to-good control with these agents and diet, but who had developed rapid onset of glycosuria with elevation of fasting and postprandial blood glucose levels within the last three to twelve months; (5) having nocturia which had also begun several months previously; and (6) known to be cooperative and consistent in following directions. Ten patients from the Diabetes Outpatient Clinic of Montefiore Hospital and Medical Center were selected as fitting these criteria. The average age was 59.9 years, with eight of ten patients in the age range of fifty-one to sixty-four years; the average duration of diabetes was 11.7 years, with a range of four to nineteen years. Nine of the patients were females. Three of the patients were uncontrolled on 0.5 gm. per day of chlorpropamide, six on 2.0 gm. per day of tolbutamide, and one on 3.0 gm. per day of tolbutamide. Four of the patients were also receiving hydrochlorothiazide.

All patients had been receiving dietary instruction; diets were restricted in carbohydrate and adjusted in calories at a level to maintain the body weight satisfactory for age and height; individual weights had stabilized and were maintained, with the patients being encouraged to limit variation of diets during the course of the study. Patients were seen at weekly intervals; at each visit they arrived in a fasting state, having taken their medication before leaving home, and bringing with them a twenty-four-hour urine collection. Fasting, two-hour postbreakfast, and two-hour postlunch blood samples were withdrawn, with the patients having a standardized cafeteria breakfast and lunch in keeping with their home diet.

During a three-week control period, the patients followed the above routine, continuing their basic sulfonylurea; during the next four to eight weeks they were given, in addition to their maximal doses of tolbutamide or chlorpropamide, L-leucine tablets in a dosage of sixteen per day, taken in four divided doses

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