

PROTAMINE-ZINC-INSULIN IN DIABETES

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Since the appearance of Hagedorn's paper in January, 1936,¹ regarding the use of protamine-insulin, a wide interest in it has developed. The original claims that it had a prolonged action, gave better control in most cases, a tendency to less frequent insulin reactions with a diminishing number of injections and a reduction in actual dosage have largely been corroborated by other investigators.^{2,3,4,5} More recently, the addition of zinc to protamine-insulin has received considerable attention and it appears likely that a combination of the zinc with protamine will supersede the use of plain protamine-insulin.

The observations reported in this paper were gathered in the management of forty-eight patients, some of whom had been treated with various preparations of protamine-insulin since February, 1936. Since August of 1936, all patients in this group have received protamine-zinc-insulin. Cases of all degrees of severity have been treated and four children are included in the group. The ages of the patients vary from 8 to 76 years.

It has been felt advisable to hospitalize all patients during the first part of their treatment. The hospital stay averaged fourteen days. No patient was confined to bed except for some complication. An attempt was made in each case to maintain physical activity comparable to that of the patient's average day. During the hospital stay, venous blood was taken routinely for determination of the blood sugar at 8 a. m., 12 noon, 4 p. m., and 10 p. m. daily and in some cases at other hours in addition, the Myers-Bailey⁶ method being used. Twenty-four-hour specimens of urine were collected in four periods daily, the periods ending before meals and at bedtime. Each specimen was tested for sugar by Benedict's qualitative method and when sugar was present, the 24-hour excretion was calculated in grams, Benedict's quantitative method being used. Qualitative estimation of ketone bodies was done on all urine containing more than 1 per cent glucose.

PREPARATION

The protamine-zinc-insulin used in this investigation contained 40 units of insulin per cubic centimeter and approximately 0.08 mg. of zinc in combination with protamine in a buffered solution. Since the active material is present in fine particles, careful, gentle mixing is important before the withdrawal of each dose. The use of a cool, dry syringe is advised and it is recommended that subcutaneous injection be done in such a way as to insure a depot of precipitated insulin in the subcutaneous tissues. Originally it was thought necessary to mix the insulin with the protamine buffered solution a few days prior to its

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use but since it has been established that the mixture is stable for at least six months, the material is now supplied ready mixed in 5 cc. vials, each vial bearing the date after which its stability cannot be guaranteed.*

THE DIET

We have been accustomed to use a high carbohydrate, relatively low fat diet for some years and this practice has been maintained. In our attempt to control diabetes of various degrees of severity with one dose of protamine-zinc-insulin, we have in some cases tended to be less rigid regarding the low level of fat which is usually maintained in such diets. The number of grams of fat per day in the routine diet was 60. It is our impression that a smooth control is more readily obtained when the carbohydrate content of the diet is not elevated above 200 grams per day. Some patients have received 250 grams of carbohydrate per day and the carbohydrate intake has been 175 grams per day or more in 32 of the cases. The average daily intake in the entire group has been: carbohydrate, 181 grams; protein, 66 grams; and fat, 76 grams.

The diet for each individual is calculated on the basis of the basal caloric requirement for ideal weight. In obese individuals, we have not usually found it advisable to use a daily caloric intake below such a figure as this is usually considerably less than the basal caloric requirement for actual weight and thus produces a daily caloric deficit sufficient to maintain loss in weight where this is required. In most instances, the total caloric intake ranges between the basal caloric requirement and 40 per cent above it.

The diet has been divided routinely into three meals containing 30 per cent, 35 per cent, and 35 per cent respectively of available glucose. Considerable manipulation of this distribution is advantageous at times. With the use of protamine-zinc-insulin, it has not been found to be of frequent advantage to use one meal containing only 20 per cent of the daily available glucose as it was found by Hagedorn, et al,¹ and Root, Marble, et al,² using plain protamine-insulin. In some cases we have divided the daily intake into four meals, giving a small proportion of the food as a luncheon at bedtime. This has the advantage of creating an even intake of food throughout the 24 hours and thus offsets to some degree the tendency to fasting hypoglycemia. In those cases in which there is an undue rise of blood sugar by noon, it is an advantage to deduct the food for the bedtime lunch from the regular breakfast.

DURATION OF ACTIVITY OF PROTAMINE-ZINC-INSULIN

Estimates of the duration of activity of a single dose of protamine-zinc-insulin in the human have been obtained from three types of observations.

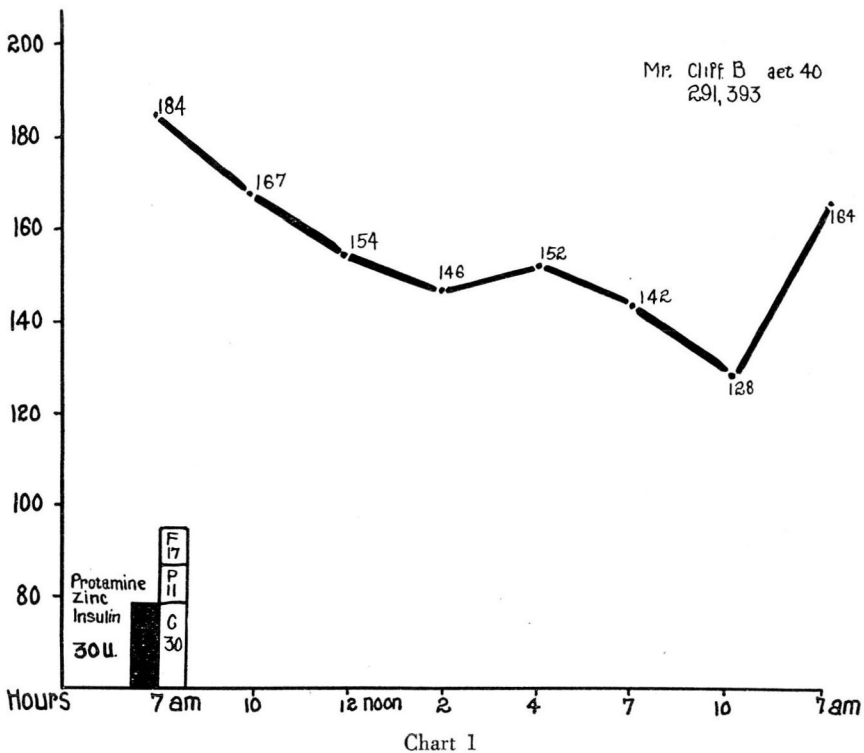
*The protamine-zinc-insulin used has been generously supplied through the courtesy of Dr. F. B. Peck and the Eli Lilly Company.

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1. The effect on the blood sugar level of a single dose given with one meal after which the patient is required to fast until such time as the blood sugar level tends to rise again after the action of the insulin is diminished.

2. The number of hours during which blood sugar levels can be controlled by a single dose when the patient is receiving regular meals. This type of observation applies obviously to those cases in which the diabetes is of such a degree of severity that the blood sugars are almost but not completely controlled by diet alone.

3. The third type of clinical observation which indicates definitely that the insulin compound acts for more than a day is the commonly



observed cumulative effect of daily doses over the first three days of its administration.

Chart 1 shows the effect of a single dose of protamine-zinc-insulin given at 7 a. m., at which time a breakfast of 30 grams of carbohydrate, 11 grams of protein, and 17 grams of fat was given after which the patient had no more food for 24 hours. The distinct fall in blood sugar levels is obvious within three hours, and from then on the fall is gradual and consistent and is still falling at 15 hours. In 24 hours, however, the

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action has distinctly diminished. In several observations of this type, the maximum effect appears in about 18 hours. Larger doses, however, may maintain hypoglycemia for a much longer time, as in Rabinowitch's⁵ case in which a single dose of 50 units of protamine-zinc-insulin maintained hypoglycemia for more than 36 hours.

The second type of observation mentioned is visualized in chart 2. In this patient the diet containing C. 100, P. 50, and F. 60, controlled blood sugar levels through the day except the fasting levels which were 150 to 160 mg. per hundred cubic centimeters. A single dose of protamine-zinc-insulin was given as can be seen by the chart, on the morning of October 28. It will be noted that the fasting blood sugar levels were normal for two subsequent days, after which they rose to their original levels. Another single dose of protamine-zinc-insulin at that time controlled the fasting blood sugar levels for two subsequent days.

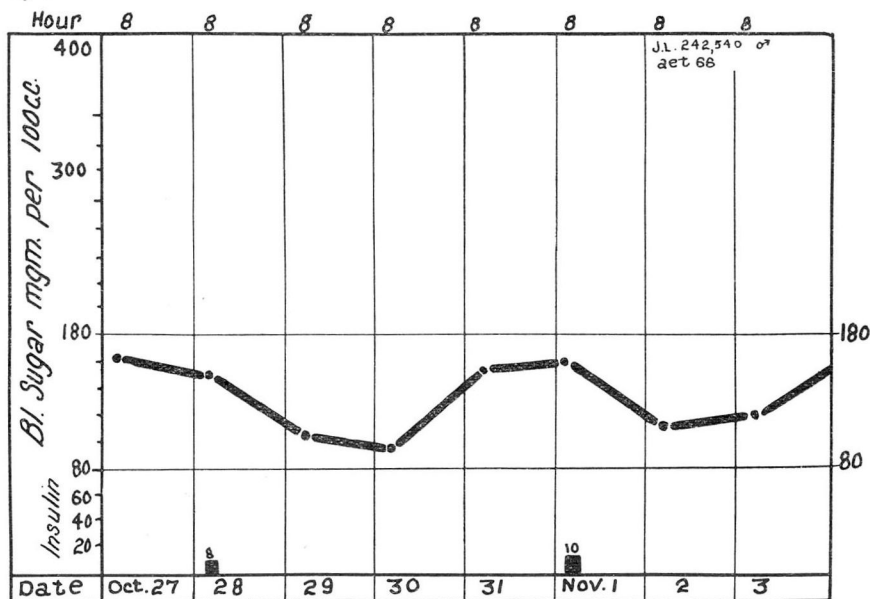


Chart 2

The cumulative effect of daily doses of protamine-zinc-insulin is observed in nearly every instance in which the use of this material is begun. The maximum cumulative effect usually appears to be most marked on the third day and is most obvious in comparing the fasting blood sugar levels. This appears to indicate that the dose given on the first of three days is still active to some degree on the third and also shows clearly why a reduction in dosage, as compared to regular requirements of insulin, usually is necessary. Subsequent reduction in dosage is necessary in many instances. A part of this reduction in dosage is

presumably due to improved control but often makes it difficult to demarcate clearly where the cumulative effect actually is maximal.

Chart 3 shows the blood sugar levels in a case in which fairly satisfactory control was obtained with three doses per day of regular insulin, the doses being given at 8 a. m., 5 p. m., and 10 p. m. The first day depicted on the chart is a fairly typical representation of the previous control obtained and it will be seen that the total required daily dose of regular insulin was 67 units. The patient had a mild afebrile infection of one great toe and had been under control with regular insulin for two weeks prior to the use of protamine-zinc-insulin. On the morning of November 3, 60 units of protamine-zinc-insulin were given in a single dose and this dose was repeated the following day. As will be seen, the fasting blood sugar level on the third day was distinctly lower than

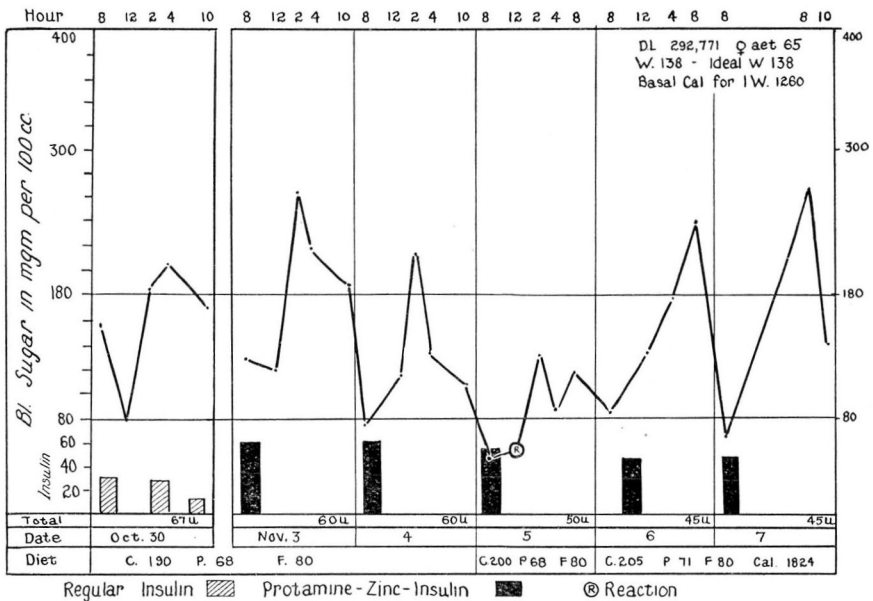


Chart 3

were those the first two days and on this day it was necessary to make an addition to the diet because of excessively low blood sugar levels. When the dose of protamine-zinc-insulin was reduced sufficiently to allow fasting levels to rise to the normal range, normal blood sugar levels during the day were not maintained, indicating the necessity for an additional small dose of regular insulin. This patient was subsequently well controlled with a morning dose of protamine-zinc-insulin of 36 units, together with a dose of 6 units of regular insulin at noon. The total dosage of insulin required to obtain excellent control was, therefore, 42 units, whereas control which was not entirely satisfactory on regular insulin alone had required 67 units per day. The infection

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had shown no apparent variation of consequence during the period of time mentioned.

NUMBER OF INJECTIONS

Since the duration of activity of each dose of protamine-zinc-insulin is distinctly longer than 24 hours, there seems to be little or no advantage in giving more than one dose of protamine-zinc-insulin per day. A single dose per day usually is sufficient to control fasting blood sugar levels and the degree of depression of these levels apparently marks the limit of increase of the protamine-zinc-insulin dose.

TIME OF INJECTION

Although the duration of effect of a single dose is longer than 24 hours, its effect is diminished in most instances after 18 hours. This being true, it seems advisable in most cases to give the single daily

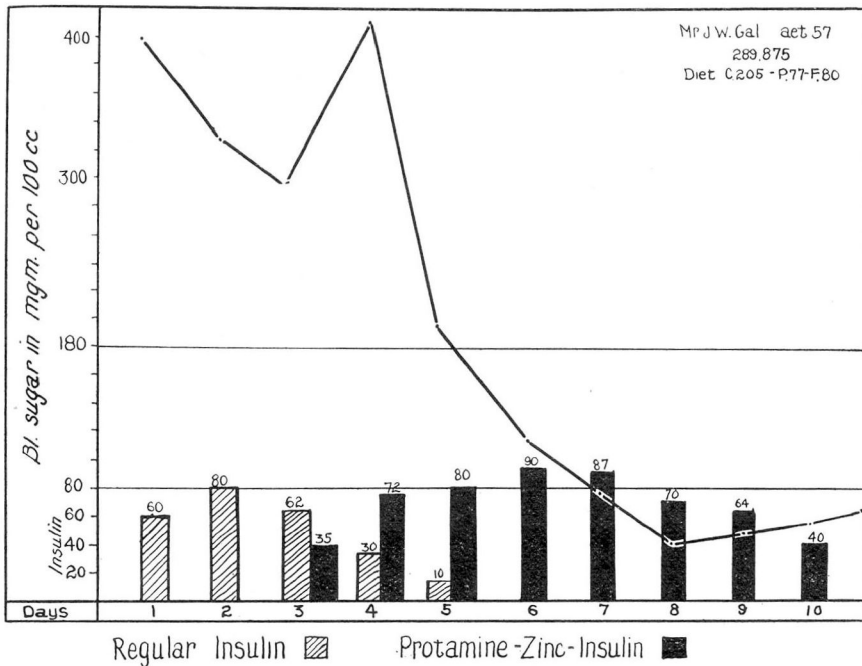


Chart 4

dose at a period longer than 18 hours prior to the low level of the day. For this reason, we have recently used the single daily dose before breakfast in each instance.

ESTIMATION OF THE DOSE

In estimating the dose of protamine-zinc-insulin two chief factors must be borne in mind—firstly, that the effect is cumulative as shown above, and secondly, for this reason the total daily dose requirement must

invariably be less than the regular insulin requirement. Due to improvement in control, the required dosage may subsequently fall considerably. Where poor control is present and rapid improvement can be anticipated, this cumulative effect may be dangerous if it is not considered carefully.

Chart 4 shows the fasting blood sugar levels in a case in which control was poor while the patient was receiving 60 units of regular insulin per day. On raising the daily dose of regular insulin to 80 units, the blood sugar levels fell somewhat but were still far above the normal range. Instead of first obtaining good control with regular insulin as we subsequently have found advisable, it was decided in this case to change to protamine-zinc-insulin, arranging a combination of protamine-zinc and regular insulin in such a way as to make the dose approximate 90 to 95 units per day. After the use of protamine-zinc-insulin for three days, the fasting blood sugar levels had fallen to the normal range. The dose was not reduced sufficiently at this time and the hypo-

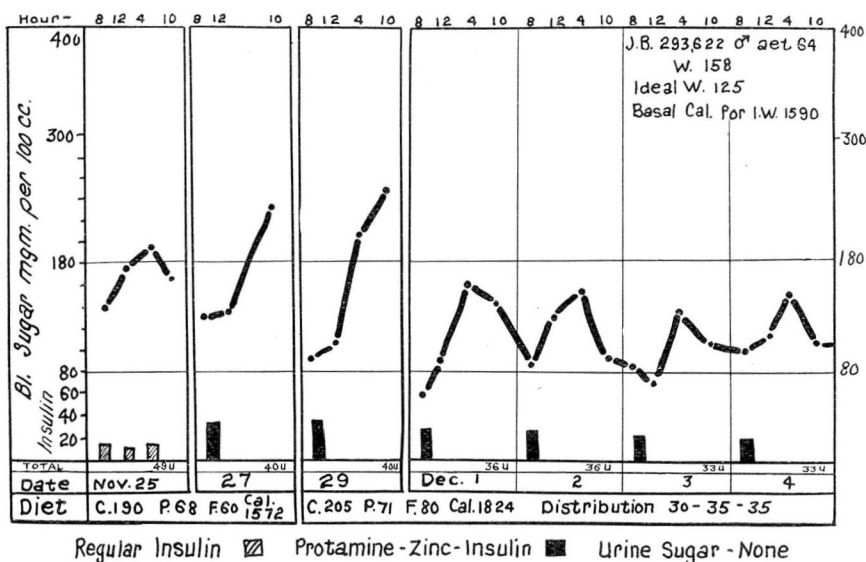


Chart 5

glycemia which followed is apparent. It is interesting to note that no insulin reactions occurred. This case demonstrates the disadvantage of attempting to make the dose of protamine-zinc-insulin equal to the required dose of regular insulin and also the difficulty involved in estimating the proper dosage where good control is not obtained prior to the change from regular insulin to protamine-zinc-insulin.

When fairly stable control is first obtained with regular insulin, an immediate substitution with protamine-zinc can usually be made. However, we feel that the doses of protamine-zinc-insulin should seldom equal

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the doses of regular insulin used and in cases of moderate severity it has been our practice recently to substitute a single dose of protamine-zinc-insulin of about 80 per cent of the regular insulin requirement. In the more severe case, considerable rise in blood sugar levels during the first few days is likely to occur. During this time, glycosuria occurs but we have not seen acidosis of consequence during such a transition period. If the rise in blood sugar levels during the first two days of such a transition period tends to be excessive, it may be prevented by the addition of one or two doses of regular insulin which will not usually need to exceed more than 10 per cent of the previous requirement of regular insulin. Such accessory regular insulin may be necessary for only a few days. Within a week, further reduction in insulin dosage is often necessary and in many of our cases even after leaving the hospital, further reduction may be found advisable within a period of two or three weeks.

Chart 5 shows the blood sugar levels during a typical day of moderately good control with three doses of regular insulin, totaling 49 units. On November 27, 80 per cent of this dose, i.e., 40 units of protamine-

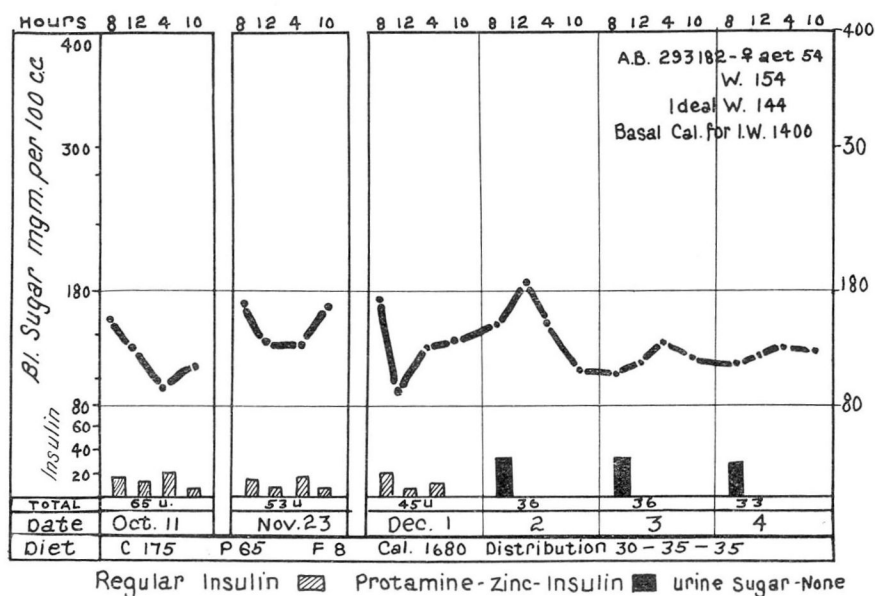


Chart 6

zinc-insulin, was given as a single morning dose. The typical rise in blood sugar levels during the day for the first few days is apparent and the gradual fall in fasting blood sugar levels is also demonstrated. Subsequent reduction in dosage is shown and excellent control has followed the use of 33 units per day of protamine-zinc-insulin as compared to a less satisfactory control previously on 44 units per day of regular insulin.

Chart 6 shows several days of control on regular insulin on diminishing doses, together with a smooth transition period and subsequent excellent control beginning with 80 per cent of the regular insulin requirement with subsequent dosage reduction.

As indicated above, in mild cases where only the fasting blood sugar level remains high, this can readily be controlled by daily single doses of protamine-zinc-insulin and such control can be accomplished by doses as small as 5 units per day.

Even in severe cases, the fasting blood sugar level will be the lowest of the day and with sufficient dosage can be brought within normal range. If it is obvious, however, that the blood sugar levels during the day will not be controlled by such a dose, it will be necessary to add one or two doses of regular insulin. Such a case in which control was difficult is shown in chart 7.

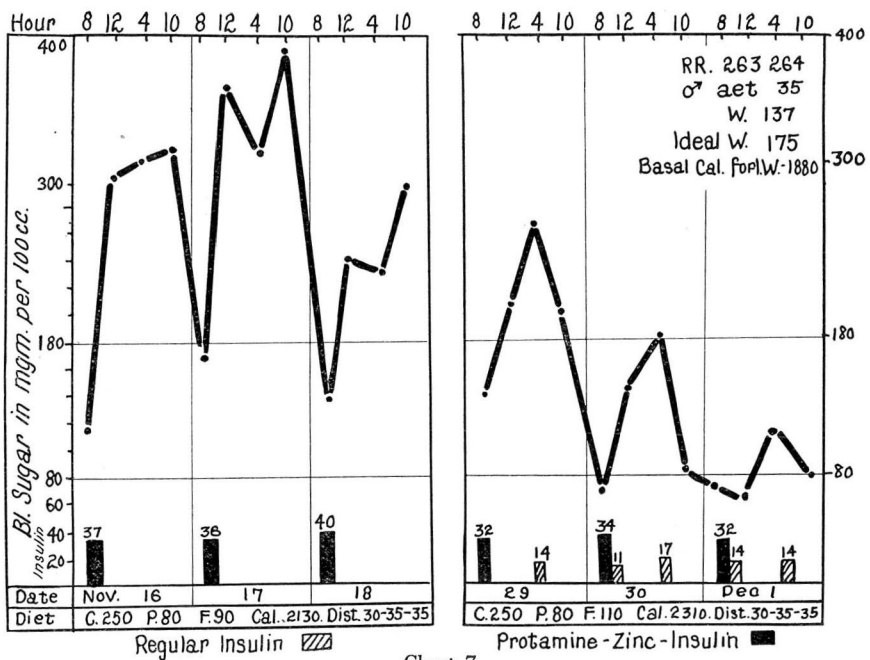


Chart 7

The general rules which we follow at present, therefore, in changing from regular to protamine-zinc-insulin may be summarized as follows:

The patient is placed on a well regulated diet and good control is obtained with regular insulin. An immediate change is then made with a single morning dose of protamine-zinc-insulin which is approximately 80 per cent of the previous requirement of regular insulin.

If the blood sugar levels during the day are excessively high, regular insulin is added to the amount of about 10 per cent of the previous

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requirement of regular insulin. The dose of protamine-zinc-insulin is then manipulated in such a way as to obtain relatively normal fasting levels, changes in dosage not being made oftener than every third day. Subsequently, if morning reactions occur and if the fasting urine is sugar-free or if the fasting blood sugar levels are excessively low for two successive days, a reduction in protamine-zinc-insulin is necessary. If, on the other hand, sugar appears in the morning urine or if the fasting sugar levels remain high for more than two consecutive days, the protamine-zinc-insulin dosage may be increased. Where the fasting blood sugar levels are well regulated, one or two additional doses of regular insulin will be necessary if the blood sugar levels during the day persist at abnormal heights.

REACTIONS

It is a remarkable fact that with the use of protamine and protamine-zinc-insulin, the blood sugar level may reach 40 mg. or below without reactions. Reactions do occur, however, and for the most part tend to be mild and gradual in their onset, thus allowing more time for treatment. Because of the gradual onset of such reactions, it is, however, more difficult for the patient to detect an oncoming reaction. Because of the prolonged effect of protamine-zinc-insulin, the reactions themselves are likely to be prolonged and to recur after treatment. Considerable hypoglycemia may occur without pronounced symptoms. It becomes more necessary than ever, therefore, to elicit any symptoms or signs which may be evidences of hypoglycemia. This is especially true in elderly individuals or in those with arteriosclerosis, especially arteriosclerotic heart disease. Fatigue, tingling, slight disturbance of memory, irritability, slight difficulty in speech, mild nausea, or headache should be suspected as possible symptoms of hypoglycemia. I have seen only one severe reaction with a convulsion, and this occurred in a child whose symptoms of hypoglycemia were present in this instance for nearly 12 hours.

In the treatment of a protamine-zinc-insulin reaction, it is advisable to use small doses of glucose or milk, to be prepared to repeat the treatment if necessary, and to avoid the use of excessively large amounts of sugar at one time.

REDUCTION IN DOSAGE AND IN NUMBER OF INJECTIONS

In 15 cases in this group, previous control had been good and had been maintained at a relatively stationary level for more than six months preceding the use of protamine-zinc-insulin. The average daily requirement of regular insulin had been 37.6 units while that of protamine-zinc-insulin was 22.6 units. Of the entire group, the daily dose dropped from an average of 45.5 units of regular insulin to 25.3 units of protamine-zinc.

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The average number of daily injections necessary in the whole group was 2.8 on regular insulin and 1.6 on protamine-zinc. This difference appears to be increasing with experience since, in the last 16 patients treated, the use of accessory regular insulin has been found necessary in only two cases. The average daily number of injections in this smaller group was 3.1 of regular insulin and 1.2 of protamine-zinc-insulin.

CONTRAINDICATIONS

The usually recognized contraindications are acidosis, infections, and pre- and postoperative care. Attempts are being made to determine the usefulness of protamine-zinc-insulin in these conditions but experience is not sufficient to warrant comments.

COMMENT

Though the advantages of protamine-zinc-insulin outweigh its disadvantages, the latter have not received much emphasis. Better control can be secured with it in many cases but regulation, especially in the severe cases, is more difficult and will require a more intelligent grasp of the problem by the physician than has been necessary before. Hospitalization for control is more important and usually will be more prolonged. The handling of the preparation is more difficult and its injection must be done with greater care. Although reactions are less frequent, if they do occur, they are likely to be more difficult to detect and more prolonged. What effect this will have in the patient with arteriosclerosis remains to be seen. Some of the early disadvantages, such as instability of the solutions and the necessity of mixing them, have already been overcome.

Against these disadvantages we have more stable control, fewer injections, and lower dosage. It is hoped that as a result of the better control there will be a diminution in the incidence of hyperlipemia, liver disease, and degenerative disorders, especially arteriosclerosis. In these respects the responsibility of the profession has increased.

SUMMARY

Protamine-zinc-insulin in common dosage appears to be active for 50 to 65 hours after injection. Its maximum effect is usually reached in 12 to 18 hours. The prolonged effect of single daily doses makes it unnecessary to use more than one dose daily. The cumulative action increases to the third day or longer and reduces the requirement of insulin to less than 75 per cent of the dose of regular insulin in most cases. Total dosage, number of injections, and the frequency of reactions are all reduced by its use. In all cases in which we have used it thus far, control has improved. A normal fasting blood sugar level marks the limit of increase in protamine-zinc-insulin dosage. If, when this limit is

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reached, the blood sugar levels during the day remain high, one or more accessory doses of regular insulin are required for control. In some mild cases, a dose of protamine-zinc-insulin every second or third day may be sufficient to control fasting sugar levels.

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