Insulin and Insulin Mixtures—NPH Insulin

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SUMMARY

There are several distinct types of commercial insulins available, and with combinations of these many curves of timing of insulin action may be obtained, but none can parallel the action of a normal pancreas.

NPH insulin, the newest addition, has a wide range of usefulness and may supplant many of the other types and combinations.

SOME diabetic patients may be managed with weight reduction and diet alone; they may need exogenous insulin for short periods of emergency only. Others (approximately 50 per cent of all diabetic persons) need daily injections of insulin. It is the purpose of this discussion to review the types of insulin at hand with special emphasis on the newer NPH insulin.

No matter what theory of the action of insulin is accepted and no matter whether it is believed that diabetes is always caused by a diminished output of insulin from a sick pancreas or by a greatly increased demand for insulin due to overproduction of anterior pituitary and adrenal cortical secretions with final tiring and decompensation of the pancreas, certain facts are axiomatic. The output of insulin from the pancreas of a normal person not only varies from day to day but must vary by several hundred per cent from hour to hour with ingestion of food and physical exercise. This great variation of demand, reaching the pancreas probably both through the blood stream directly with changes in blood sugar levels and through the vagus nerve, is almost unique in the known endocrine system; it is paralleled only by the output of epinephrine (an insulin antagonist) during stress. In light of the sudden outpouring of insulin required after a high carbohydrate meal, the sudden shut-off of insulin as the blood sugar content falls, and the small continued amounts of insulin required to maintain the blood sugar at normal throughout the fasting hours of sleep, is there any wonder that a person with severe diabetes who takes insulin by injection once a day has a tremendous dosage problem?

Best has said, "We hope some day to make the 'ideal' insulin which will be liberated only on response to need so that hyperglycemia and hypoglycemia will be automatically controlled as in the non-diabetic." Today no such insulin is in sight. Furthermore, no matter what theory of the pathologic physiology of diabetes is accepted, it is now axiomatic that the deprivation of insulin, and not excessive carbohydrate intake, brings about glycogen depletion in the liver and causes the development of diabetic ketosis and subsequent acidosis and coma, as was pointed out by Mirsky[5] and others. High blood sugar levels and sugar in the urine are the result of too little insulin activity and are not the primary disease. A realization of these facts must guide physicians in the choice of the type of insulin and the dosage. Moreover, it must temper the desire to keep the patient always sugar-free.

In discussing the choice of the kind of insulin, and even the action of a given type in various patients, another important fact must be recalled. Diabetic persons who need insulin, although all different, fall into two distinct groups. In one group is the patient with diabetes of the mild, stable type usually observed in older persons. His mechanism of response to insulin demand is nearly normal although it cannot take care of the peak demands and eventually insulin debt and pancreatic decompensation will develop. A relatively small dose of any type of insulin will serve his needs. The strain will be off the pancreas and it will have periods of rest when the exogenous insulin carries the load, and will again be able to handle the postprandial peaks. Such a patient will seldom have an abnormal amount of sugar in the blood or have hypoglycemic reactions, and, as long as he keeps his weight down, will do well. In sharp contrast is the severe, brittle, usually young diabetic person whose endogenous insulin response to demand is extremely variable and completely unpredictable and whose exogenous insulin requirements are high. It is in this group that relatively large amounts of sugar are "spilled" even during periods of starvation (overnight); and, as Peck[9] has said, nocturnal hyperglycemia may well signify the existence of a much more serious and hazardous defect than the simple overflow mechanism of postprandial hyperglycemia and glycosuria. In such patients the insulin dosage is tricky, and even multiple injections and insulin mixtures may be ineffective at times.

DEVELOPMENT AND MODIFICATION OF INSULIN

Regular or amorphous insulin developed by Banting and Best[1] in 1922 was life-saving. In action it was potent and dependable. When given subcutaneously, it began lowering blood sugar levels within a period of minutes. The maximal effect was reached in three to four hours and was gone in six to eight hours. One dose a day was sufficient in many of the milder cases but it was soon learned that its action was not prolonged enough in diabetes of the more severe types, in which three to four injections a day

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were necessary. Many attempts were made to slow its action—giving it in an oil suspension was one such attempt—but it was not until 1936 that Hagedorn's modification of adding to insulin a buffered protamine obtained from the sperm of California rainbow trout proved really effective.[3] With that modification, the action lasted well over 24 hours. Later a small amount of zinc was added to protamine insulin by Scott and Fisher[10] to make it more stable and it was found that a single dose would actually carry over a three-day period, approximately 70 per cent being effective the first day, 20 per cent the next, and 10 per cent the third day. This fact is still important in adjusting the dosage of protamine zinc insulin (Chart 1). This new insulin with its slow prolonged action made it possible in many cases to obtain almost complete control of the disease with a single daily injection, and frequently with an actual saving of the number of units needed per day (Chart 2).

In the really brittle cases, however, the action of protamine insulin was too slow, and if enough was given to keep the blood sugar content normal during the day, night reactions were common. Two injections each morning, one of rapid-acting regular and one of protamine insulin, were necessary. Of course the next step was to combine the regular and protamine zinc insulin in one syringe; but at first this met with variable results,[4, 8] until the reason became apparent. Protamine insulin needs approximately 0.65 mg. of protamine per 100 units of insulin to saturate it but it was marketed as a supersaturated solution with 1.25 mg. of protamine per 100 units. So when regular insulin with its acid reaction was combined with neutral protamine in one syringe, even up to unit for unit, the surplus protamine in the solution combined with it to form a more slow-acting (and less dependable) mixture. As the ratio of regular insulin to protamine insulin in the mixture was increased past a 1:1, an insulin that gave rapid but prolonged action was formed.[2, 12] Adding say 40 units of regular to 20 units of protamine insulin produced the effect of 20 units of fast-acting and 40 units of prolonged-acting insulin for night carry-over, although the curve of action of the mixture actually was monophasic. These "tailor-made" mixtures of 2:1 and 3:1 came to be widely used.

Chart 1.—Action of one dose of protamine insulin (50 units) holding the blood sugar content down over 36 hours of fasting.

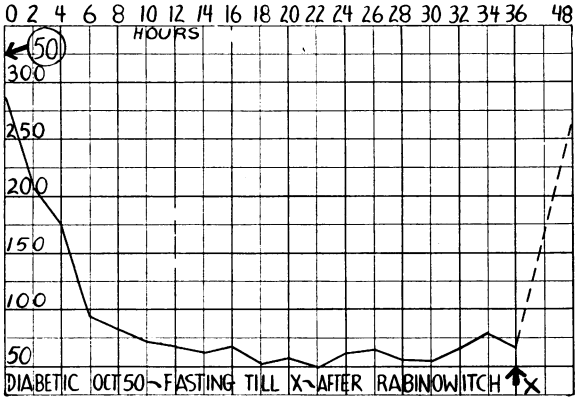
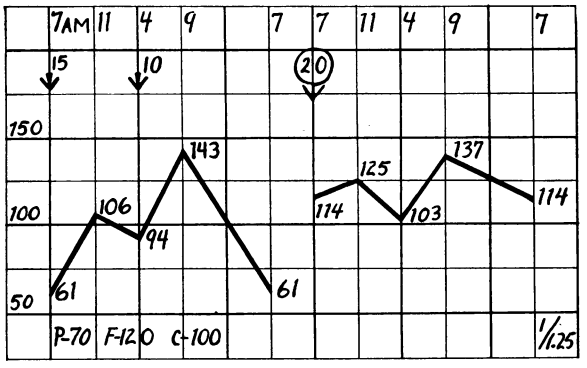


Chart 2.—Action of a single dose of protamine insulin (20 units) on pre-meal blood sugar level as compared with two doses of regular insulin (15 units before breakfast and 10 units before evening meal) with 20 per cent less insulin.



It should be mentioned here that during this transition time crystalline insulin was brought out. Although this is a purer form and therefore causes less allergic reaction, it differs from regular insulin so slightly in action that it may be assumed to be identical in timing.[8] Only economical and technical manufacturing problems keep it from replacing regular insulin on the market. Globin insulin with a maximum action in eight hours and lasting 18 hours[6] controlled some cases of diabetes, but because some patients who used it had afternoon shocks and high blood sugar levels in the morning, it was not universally acceptable and insulin mixtures held the field.

Mixing two insulins in one syringe each morning was a nuisance and for the more ignorant patients and those with poor eyesight was not always accurate. Hence, while the physicians were working out their own particular favorite mixtures, research workers and the manufacturing concerns were working on stable modified insulins, which would give similar results. Many types were tried over a period of years but finally one proved to be the most acceptable. During the period of development it was first called NPC50, then NPH50, and now it has come on the market as NPH insulin. As it is much like protamine zinc insulin in appearance, it is marketed in a square bottle with a distinctive label. This specially modified insulin is a neutral buffered suspension of protamine zinc insulin crystals containing approximately 0.50 mg. of protamine in isophane ratio to 100 units of insulin. It is quite stable. The name comes from: N for neutral, P for protamine, H for Hagedorn and 50 for 0.50 mg. of protamine. In action it is much like the 2:1 mixtures but it is more dependable and more efficient unit for unit. It has a fairly rapid onset of action (two to four hours) and has a good prolonged action of 24 hours or more, insuring an adequate overlap to the next day[7, 8] (Chart 3).

If these points are remembered it is quite easy to change patients to it. If the patient is well controlled on a 2:1 mixture, it is wise to reduce the total units given by 20 per cent the first few days he takes NPH and gradually increase the dosage if he "spills" sugar. As NPH may be a little slower in starting to act, there may be some spillage of sugar after breakfast; but this can usually be controlled by adjusting the diet so that carbohydrate intake at breakfast is reduced and compensated for at other meals. A bedtime feeding is usually wise (Chart 4). Patients with mild cases readily controlled with protamine zinc insulin need not be changed to NPH, but if a switch is desired it may be accomplished without trouble, again cutting the dose 20 per cent at first and watching for insulin shock in the afternoon. In some of the more brittle cases NPH insulin may still be too slow in action. If so, regular insulin may be added to it in one syringe and, as it is not supersaturated with protamine, each unit of regular insulin added will be effective and action such as that of 3:1 or 4:1 mixtures may still be "tailor-made."

Practically all patients taking NPH insulin value its simplicity and state that for some intangible reason they seem to feel better in general. Although there seems to be almost always a saving in the total number of units required daily when switching to NPH, this may be more apparent than real. It must be recognized that in the brittle cases an insulin reaction in the early hours of sleep may not be noted by either the patient or the physician and that such a reaction is frequently reflected in high blood sugar level the following morning. This fasting hyperglycemia then may be erroneously treated by arbitrarily raising the insulin dosage, with the result that the patient is taking far more insulin than is necessary, as was pointed out by Somogyi[11] and others. In such circumstances, if the patient is hospitalized

Chart 3.—Rapid but prolonged action of NPH insulin on the average blood sugar level of six patients (after Peck).

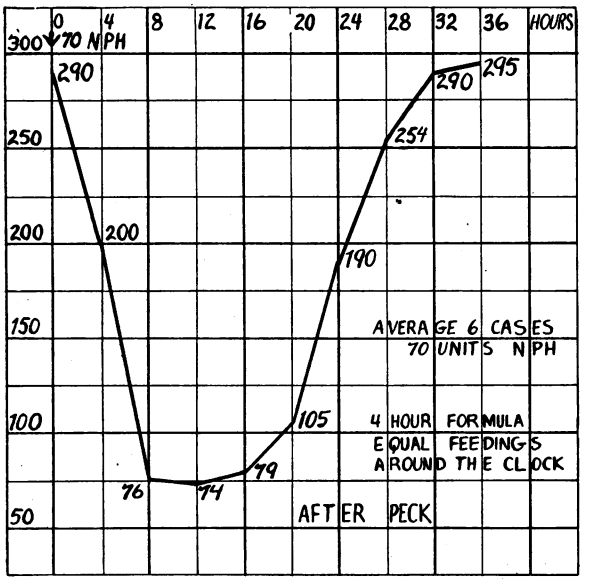
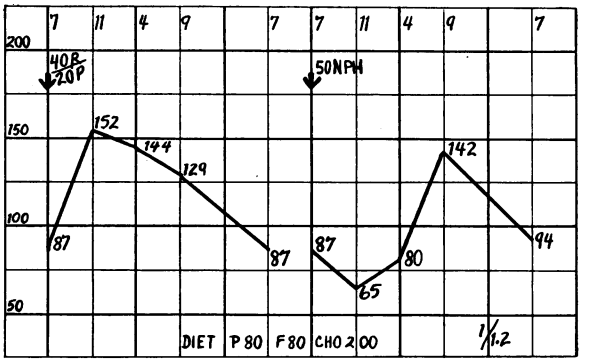


Chart 4.—Action of a single dose of NPH insulin (50 units) on the pre-meal blood sugar level as compared with an insulin mixture in one syringe (40 units regular and 20 units protamine) with 16 2/3 per cent less insulin.



for critical study, it may be noted in switching from one kind of insulin to another that control is obtained with considerably smaller dosage; and from this it may be assumed, falsely, that the kind of insulin to which the patient was switched is more efficient. In any case, NPH insulin is a big step forward and it may be prophesied that it will one day supplant protamine zinc insulin. Regular and/or crystalline insulin will always remain the insulin of choice for use in emergencies.

CONCLUSIONS

The normal pancreas releases variable amounts of insulin from hour to hour to control the ever-changing blood sugar levels. No kind of exogenous insulin in any dosage can possibly parallel this action. Regular or crystalline insulins act rapidly and for short periods. They are the insulins of choice for diabetic emergencies. Protamine zinc insulin bridges over the night but will not prevent postprandial rise in blood sugar levels in severe cases. Daily use of a combination in one syringe of two parts of regular and one of protamine insulin is the most useful insulin mixture.

The newer NPH insulin is a stable, efficient, modified insulin with action like that of the 2:1 mixture. When understood and used with perhaps minor changes in the diet so that carbohydrate intake is properly timed, it will replace all daily mixtures and in time may replace protamine zinc insulin.

Chronic insulin overdosage must be constantly watched for.

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