Present Status of New Insulin Modifications

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Since the discovery of protamine insulin by Hagedorn[1] and its introduction into clinical usage in 1936, there has been a constant stream of modifications of insulin having the common attribute of prolonged action by virtue of differences in solubility in tissue fluids at the approximate *p*H of the body. In general, such modifications have been prepared according to the original principles laid down by Hagedorn, utilizing combinations of insulin with protein precipitants described by him (protamines, histones, globins, kyrins) or by means of chemicals (hexamine, isocyanate, polyvinylpyrroladone) capable of altering solubility. The physical characteristics of such preparations vary from clear to cloudy suspensions, depending upon the occurrence of precipitation at various *p*H ranges. By varying the quantity of the agent used in proportion to the insulin, and the zinc content, or both, either in bulk or extemporaneously by mixing, the preparation of a wide variety of combinations having time activities ranging between the short, profound action of regular insulin and the long, slow effect of protamine zinc insulin is made possible.

All these preparations display the characteristic hypoglycemic action of insulin, but they differ from one another in rate of onset of action and duration of effect. Thus far, duration of action has never been obtained except at the expense of rapidity of onset. The selection of a given preparation for wide-scale use has, consequently, necessitated long-term and laborious clinical comparisons to establish the value of any specific time activity. Clinically, the major problem has been to determine which particular time activity best meets the average daily needs of the greatest number of diabetic patients.

CLINICAL REPORTS

The progress of these studies has been reviewed from time to time[2-6] during the last decade. More than a score of so-called intermediate acting preparations have been tested. They exert their greatest usefulness and display their most critical differences in timing in severe (unstable) cases of diabetes,[7] and their differences tend to be minimized and become unimportant in stable or mild cases. That controversial evidence of clinical differences

in timing between globin insulin with zinc and NPH insulin exists[7-10] is doubtless the result of choice and number of cases subjected to critical analysis. The statistical data compiled by Izzo[7] seems incontestable in this connection and, furthermore, the clinical impressions of longer duration of action of NPH insulin have been borne out by the Toronto assay curves published by Jamieson, Lacey, and Fisher[11] (Figure 1).

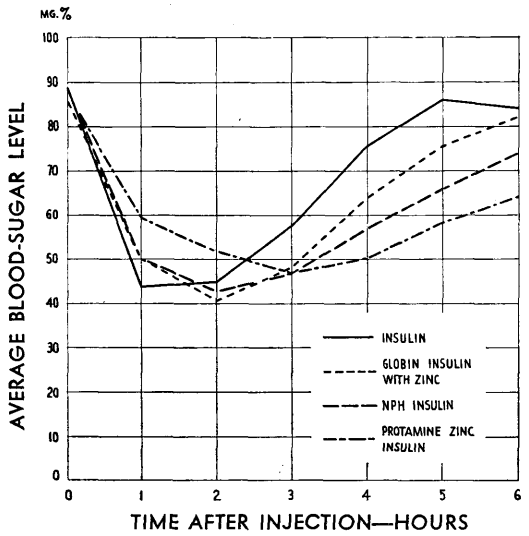

FIGURE 1 Average blood sugar levels in groups of 32 normal rabbits following the subcutaneous injection of the various insulin preparations as indicated. After Jamieson, Lacey and Fisher[11]

The most generally useful of these preparations have been those which have acted in the range exhibited by 2:1 admixtures of insulin and protamine zinc insulin. Many clinical reports[6-9, 12-17] substantiate the essential similarity of action of NPH insulin to 2:1 mixture. Since the clinical usage of NPH insulin has been widely broadened by its introduction on the market in 1950, further review of this more recent experience is presented at this time. The entire bibliography on this subject is far too large to include *in toto,* so for earlier references the reader should refer to the reviews already cited.

A number of recent reports on the comparative effectiveness of NPH insulin have appeared in the literature. Baganz and associates[18] studied 41 patients hospitalized on a metabolic service. All had been standardized on insulin in one form or another before each case was transferred to a single dose of NPH insulin before breakfast. It was found that the postprandial effects of NPH insulin were superior in all cases that had previously received only protamine zinc insulin and were as good in almost all cases previously receiving protamine zinc insulin and unmodified insulin.

Sharkey and King[19] reported an experience gained from 18 months' observation of 28 diabetic patients both in the hospital and in office practice. Sixteen cases were treated satisfactorily with NPH insulin alone, and the remaining 12 required NPH insulin and unmodified insulin in a mixture. Insulin reactions were reduced in severity and over-all control was improved.

Edwards, Vance, and Mulholland[20] made comparisons of 2:1 mixture, NPH insulin and globin insulin with zinc in 21 cases. Their findings bore out the observation that all three modifications can be used satisfactorily in the mild and moderate diabetic, but in the more severe or complicated case the "carry-over" effect of NPH insulin or the 2:1 mixture was found to be highly desirable.

Dolger[21] described a broad experience covering 185 severe diabetic patients observed for extended periods. Seventy-two of his group were satisfactorily controlled with NPH insulin alone. The remainder required mixtures in varying proportions. The author commented that NPH insulin will provide adequate coverage for 40 per cent of the patients with severe diabetes mellitus and is also suitable for patients whose insulin requirements are low or moderate.

Groff, Engelhardt, and Skelton[22] studied 17 hospitalized diabetic patients who had been selected because their cases were moderately severe or severe, and they were free of discernible complicating factors. They found the improvement in control of diabetes in this group to be particularly valuable and noted remarkably uniform activity of the preparation during the 24 hours.

Greenhouse,[23] drawing on four years' experience with various modifications of insulin, pointed out that NPH insulin has other advantages over and above improved timing characteristics. Insulin reactions tend to be less insidious than those resulting from protamine zinc insulin and, therefore, easier to recognize and treat. Furthermore, local allergic reactions tend to be diminished when NPH insulin is used. Palmer and others[24] also reported a lowered incidence of insulin reactions in 28 patients observed over a two-year period.

Swallow and Chute[25] obtained as good or better control with a single injection of NPH insulin as obtained with double injection of unmodified insulin and protamine zinc insulin in 10 out of 18 children. Two of the cases, both under 6 years, were noteworthy in that daytime hyperglycemia was associated with nocturnal hypoglycemia.

Shuman and Francis[26] indicated that NPH insulin was effective in controlling both the fasting and the postprandial glucose levels in the majority of 33 patients studied, despite both medical and surgical complications,

Other published reports[27-31] mention the utility of NPH insulin in a wide spectrum of the diabetic population resulting in satisfactory control with a minimum of inconvenience to the patient.

EXPANDED CLINICAL TRIAL

There are several phases involved in the investigation of any new therapeutic agent which have been successively undertaken in studies of NPH insulin. After determination of its time activity in intensive but small-scale comparisons, the new preparation was applied on a larger scale in hospital wards and in outpatient groups. As a final step, when supplies became available, experimentation was extended and more and more investigators began to test the preparation under conditions of actual wide-scale practice until several thousand cases were under treatment. Reports of this experience were accumulated; 1,281 cases were in sufficient detail to permit analysis. It was anticipated that this study would be heavily weighted with problem cases not previously controlled satisfactorily. As shown in Figure 1, such proved to be the case. Of the 1,281 cases, 522 were classified as severe, brittle, or juvenile, 562 as moderate, and only 197 as mild. Furthermore, in age distribution, one third of the group was under 30 years of age (Figure 2). Practically all patients in these studies were diabetics whose "pedigrees" were well known to the investigators, and it can be assumed that the therapy used prior to NPH insulin controlled the disease as well as possible and had shown the best results in each case.

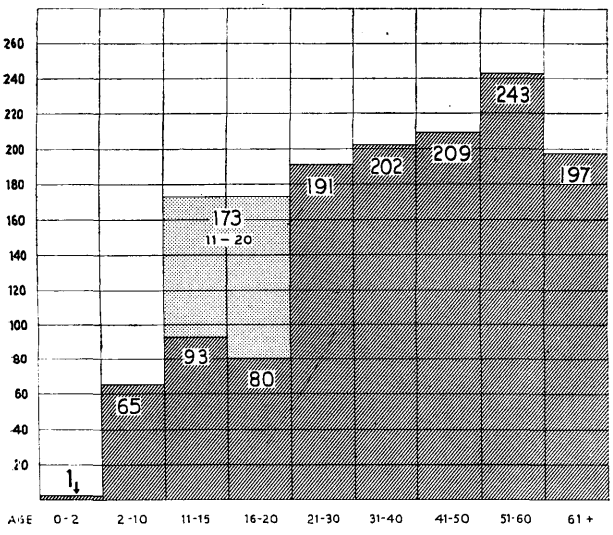

FIGURE 2 Age distribution of 1,281 cases. Total numbers of patients in each age group are indicated

The types of insulin therapy before NPH insulin was utilized are shown in Figure 3. Of all patients, 89.5 per cent were taking protamine zinc insulin in one form or another, with the insulin mixtures accounting for almost one-half of the entire group.

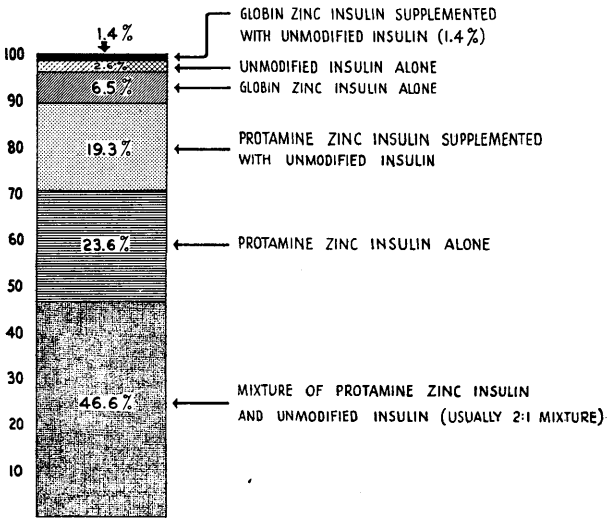

FIGURE 3 Types of insulin therapy utilized prior to NPH insulin study

Of much interest are the data relative to the degree of diabetic control achieved in the comparative study (Figure 4). In all three groups classified mild, moderate, or severe there was a significant shift toward better management when NPH insulin was used. This shift applied not only to the severe group, where it was anticipated that more efficient timing of insulin effect would result in improvement, but also most markedly to the mild group where Izzo has shown that timing characteristics of insulin are least critical.[7] In the mild group, "excellent" control was obtained in 39 per cent of the cases on prior insulin therapy, and this figure rose to 65 per cent following treatment with NPH insulin. Cases previously classified as having "poor" control diminished to 1.7 per cent.

Results in the "severe" group, both before and after NPH insulin, tend to emphasize the limitations of any insulin preparation used, since obviously no one insulin preparation as yet available is capable of controlling satisfactorily all cases of diabetes. Nevertheless, the data do show that improved control resulted when NPH insulin was used. Stephens, Donaldson, and Marble[32] have shown that the employment of supplements of unmodified insulin, either as separate injections or mixed with NPH insulin, provides better results, particularly in the juvenile patients. The possibility of employing such

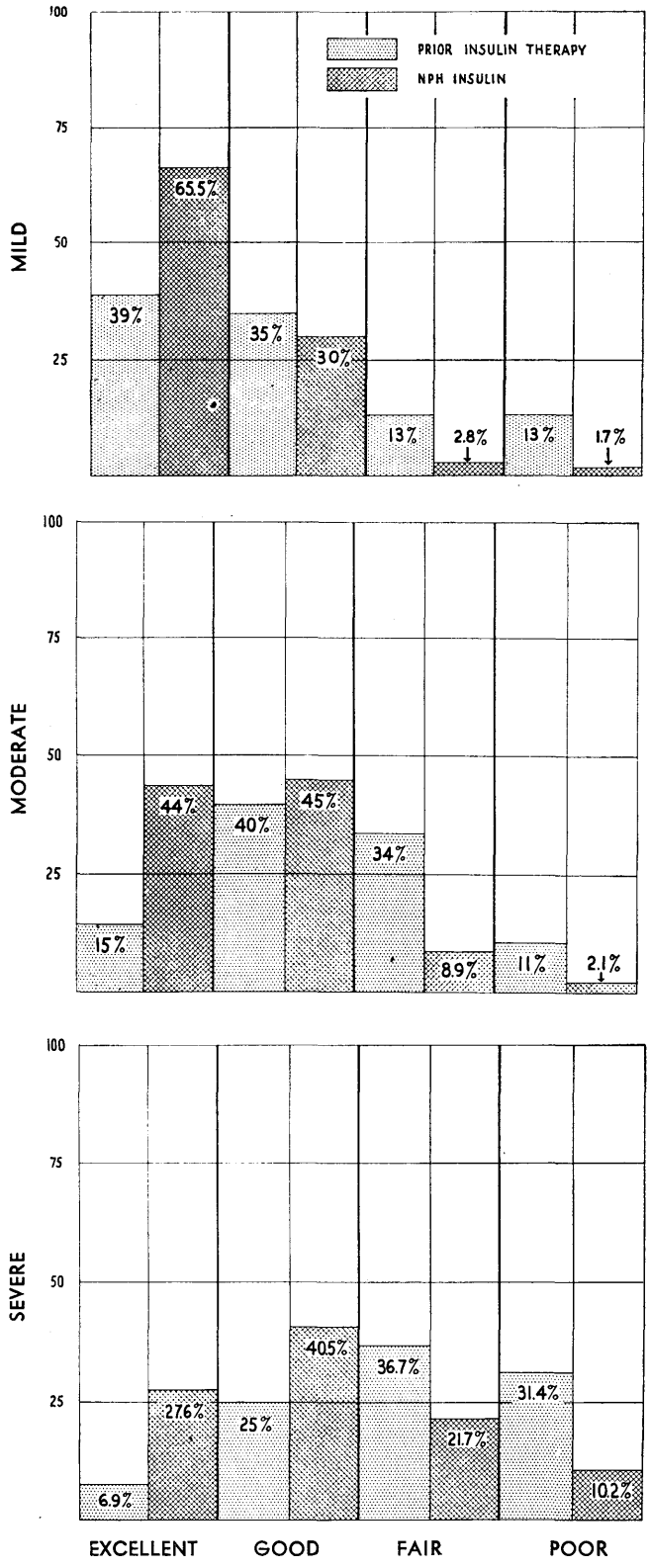

FIGURE 4 Degree of control. Note that the control tends to shift towards improvement in each group

a mixture had been previously suggested by Sprague,[33] and by Shuman and Francis.[26]

The incidence of insulin reactions was also of interest, and investigators were asked to enumerate the number and time of occurrence of reactions in the cases they observed. Over one-half reported a lessening in number of reactions, and an additional 23 per cent indicated that there had been no reactions at all when NPH insulin was used (Figure 5).

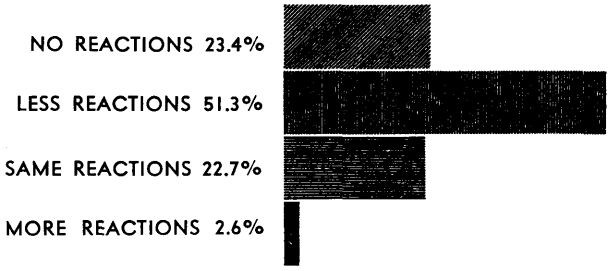

FIGURE 5 Reactions with NPH as compared with other insulins (based on groups reported, not individual cases)

There was a lack of uniformity as to time of day that reactions were observed. This is surprising, since protamine zinc insulin is more prone to cause reactions in the early morning hours and globin insulin with zinc has a tendency to exhibit its peak effect manifested by hypoglycemia in the middle to late afternoon hours. Of those patients who had reactions while using NPH insulin, 34.5 per cent experienced them in the morning, 37.7 per cent reported afternoon reactions, and 27.8 per cent had them in the evening. These figures seem to indicate that hypoglycemic reactions with NPH insulin follow individual variations in the patient's response to insulin, modified by diet and exercise. A similar lack of pattern in time of hypoglycemia was noted by Peck and Kirtley[6] at Indianapolis General Hospital.

CLINICAL EXPERIENCE OUTSIDE THE UNITED STATES

Outside the United States, a number of investigators have also studied NPH insulin.[34-54] The majority of the published reports, mostly from Latin America, are summarized in Table 1. Of the 17 groups tabulated, comprising 240 patients from 10 different countries, approximately 39 per cent were classified as severe, brittle, or juvenile, 46 per cent as moderate, and only 15 per cent as mild. As for previous treatment, 24 per cent were using protamine zinc insulin alone, 47.5 per cent mixtures of unmodified and protamine zinc insulin (mostly 2:1), 5 per cent unmodified alone, 5 per cent

TABLE 1 SUMMARY OF SEVENTEEN GROUPS OF PATIENTS

Investigator	No. Patients	Ages	Severity			Previous Insulin				
			Sev.	Mod.	Mild	PZI	2:1	Unmod.	Globin	Other
Arduino, Brazil	13	20-60	3	10	—	3	10	—	—	—
Bermudez, Mexico	10	40-80	—	10	—	10	—	—	—	—
Cardonnet, Argentina	39	5-75	23	11	5	10	19	2	5	1
Cervino, Uruguay	6	10-60	5	1	—	—	3†	1	—	2
Chanis, Panama	7	?	—	7	—	—	—	7	—	—
Houssay, Argentina	10	5-63	4	6	—	7	3†	—	—	—
Jauregui, Mexico	12	20-75	2	6	4	7	3	—	—	—
Linder, S. Africa	11	?	2	5	4	2	2	—	6	1
Montagna, Argentina	7	5-15	7	—	—	—	7	—	—	—
Osio, Paraguay	34	10-75	4	14	16	3	10	—	—	21
Paniagua, P. Rico	22	5-80	22	—	—	6	12	—	2	—
Richer, Paraguay	7	15-75	1	1	5	—	7	—	—	—
Rocca, Uruguay	12	15-70	5	6	1	3	6	2	1	—
Saldun, Uruguay	15	5-60	15	—	—	—	15†	—	—	—
Schneider, S. Africa	14	?	—	14	—	7	7	—	—	—
Zazaleta, Mexico	10	40-80	—	10	—	—	10	—	—	—
Pulver, Switzerland	11	?	?	11	?	—	—	—	—	11‡
TOTALS	240		93	112	35	58	114	12	14	36

* Two new patients in each group. † Also 1:1, 3:1, and other mixtures. ‡ "Di-Insulin."

TABLE 2 INSULINS: PERCENTAGE OF USE IN FOUR COUNTRIES

Country	Type of Insulin	Year (Per Cent) 1946	1948	1950
Argentina	Unmodified	50	50	50
	Modified	50	50	50
Brazil	Unmodified	60	60	50
	Modified	40	40	50
Mexico	Unmodified	45	45	35
	Modified	55	55	65
United States	Unmodified	35	30	30
	Modified	65	70	70

globin, 5 per cent "Di-Insulin," and 11 per cent a variety of insulin regimens. Six patients (2.5 per cent) were new diabetics.

It is noteworthy, however, that protamine zinc insulin was never as widely adopted in some countries as in the United States, as shown in Table 2. Although a poor appreciation of the clinical attributes of the long-acting insulins has been held partially responsible, another interesting possibility must be considered, namely that the rate of action of protamine zinc insulin might not be well adapted to the dietary habits of the patients in countries where the "continental" breakfast is the rule and the preponderance of daily caloric intake is from 1 to 8 p.m. The 2:1 mixture of unmodified insulin and protamine zinc insulin has actually been used only to a minor extent in Latin America. Table 1 is misleading in this respect, because the authors mentioned do not represent average practice but are leaders in the field of diabetes in their respective countries.

Because of its more ideal rate of onset and duration of action, it was theorized that NPH insulin should facilitate the management of diabetes in countries where the type of diet described above is customary. As a rule, in the studies conducted abroad, distribution of the diet and the mealtimes were made to conform to local habits, only the total caloric intake and the carbohydrate, protein, and fat content being controlled. The impossibility of compelling the diabetic patient to change the habitual mealtimes prevalent in his country is obvious when customs and working hours with their economic implications are considered. The diets outlined in Table 3, satisfactorily adopted by investigators in Brazil, Argentina, Mexico, and suggested by Constam[55] in Switzerland, are worth comparing with the typical diet used in the United States.

In the 240 patients observed for periods of time ranging from 30 to 120 days, NPH insulin afforded a degree of control which paralleled the observations made in the United States. It is of interest to record that results observed with the diet distributions summarized in Table 3 were extremely satisfactory, for they indicate the perfect adaptability of this new modified insulin to types of diet found in Latin America and in some European countries.

DISCUSSION

There has been a gradual evolution of methods of insulin therapy in the management of diabetes over the last quarter century. The original short-acting insulin requiring multiple daily injections ceased to be the sheet anchor of management with the introduction of protamine zinc insulin, which rapidly became the foundation of treatment, embellished with supplementary doses of unmodified insulin. Clinical experience dictated the next

TABLE 3 DIET DISTRIBUTION AND MEALTIME IN FIVE COUNTRIES

	Breakfast	Mid Morning Meal	Lunch	Mid Afternoon Meal	Dinner	Bedtime Meal
	(Figures are percentages of total daily diet)					
Arduino-V. da Silva Brazil	20 7 a.m.	——	30 Noon	10 3-4 p.m.	30 7-8 p.m.	10 10-11 p.m.
Bermudez-Zabaleta Mexico	25 8:30 a.m.	——	50 1:30 p.m.	——	25 8:30 p.m.	——
Cardonnet-Staffieri Argentina	15 8 a.m.	——	35 1 p.m.	15 3-4 p.m.	35 8 p.m.	——
Constam Switzerland	20 7-8 a.m.	6 10 a.m.	27 12-12:30 p.m.	20 4 p.m.	27 6-7:30 p.m.	——
United States	20 7 a.m.	——	40 Noon	——	40 6:30 p.m.	——

step, via a time-consuming series of comparisons of preparations having all sorts of intermediate timing effects, which led to the conclusion that a preparation having the action characteristics of a 2:1 (protamine zinc insulin: insulin) mixture exerted the most desirable effects for most patients. Then followed a deliberate attempt to produce a preparation, stable and uniform, which could duplicate this action in a practical manner. That this preparation was one that could be prepared in crystalline, highly purified form was undoubtedly fortuitous —NPH insulin crystals happened to exert the desired time action. There is but limited opportunity to change this rate of action except by the addition of required amounts of unmodified insulin to the injection in order to provide a more intense daytime effectiveness.

For the majority of patients the timing of NPH insulin represents the most satisfactory action as measured by minimum number of injections, satisfactory overlap (nocturnal effect), and relative freedom from hypoglycemia. Even in the severe unstable cases some improvement can be anticipated. But it is not a panacea, and it does not change the severe unstable case to a stable one. Such exceptional cases remain difficult individual problems even though management of the bulk of cases is simplified and improved.

SUMMARY

The development of modified insulin preparations is briefly summarized and the literature reviewed. Results obtained in a group of 1,281 cases in a general clinical trial of NPH insulin are described. An additional summarization of experience on 240 cases collected from studies outside the United States is presented. These data bear out the conclusion that NPH insulin exhibits the most generally useful time action available to date.

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