Pharmacologic and Clinical Studies on Two New Types of Long-Acting Insulins with Special Reference to Zinc Insulin Preparations (Novo): A Preliminary Report

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Hallas-Moller and his co-workers have reported from Denmark recently the following observations concerning zinc-insulin suspensions.[1-5]

1. In suitable concentration and buffering media zinc ions can bind insulin at the *p*H of the blood to form insoluble zinc-insulin compounds without the presence of modifying agents such as protamine, globin, and so forth, provided that interfering substances such as phosphate and citrate are not present. (2) Such zinc-insulin suspensions show a prolonged insulin effect in biological experiments, the range of activity being dependent mainly upon the physical state of the precipitated insulin—amorphous or crystalline (size and shape of crystals). (3) Clinical experiments on diabetics have confirmed that zinc-insulin suspensions can be prepared with different ranges of activity suitable for clinical use.

We are presenting a preliminary report of adjunct studies on the timing of such preparations in collaboration with the Lilly Research Laboratories where these preparations are under investigation. A long-acting zinc-insulin preparation* somewhat similar to the novo preparation designated as "Ultralente" and bearing the lot No. 2958 has been compared with NPH insulin in respect to: (1) Solubility properties in serum; (2) daily pattern of distribution of insulin activity in patients with unstable diabetes; (3) behavior in patients followed in the clinic under routine conditions. A second new type of preparation, Special Insulin (190-4B-111), a clear acid solution of chemically modified insulin also has been compared.

EXPERIMENTAL DESIGN

1. *Comparison of solubility properties in serum.* The solubility properties of NPH insulin and Insulin 2958 were compared in 60 per cent pooled human sera at *p*H 7.4 and 37 degrees C. according to a method described previously[6]. It was shown[6] that while suspensions of long-acting insulins are not soluble in water they are soluble in serum, the rate and extent varying in a characteristic fashion with the particular type. The high correlation between the solubility curve and relative clinical timing of a given preparation [6, 7] suggest that the timing of such a preparation is a direct function of its solubility properties. In fact, on the basis of cumulative experience, it is possible to predict the approximate relative timing of a given preparation from its solubility curve alone.

2. *Comparison of daily patterns of distribution of insulin activity in patients with unstable diabetes.* The method has been described in detail elsewhere[8]. Briefly, the procedure was as follows: Four patients (two males and two females) with severe unstable diabetes lived quietly on the metabolic floor under routine but controlled conditions throughout the period of investigation. *Only patients with the unstable form of diabetes were chosen because previous studies*[8-11] *have shown that*

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*This preparation will hereafter be referred to simply as Insulin 2958.

significant differences in insulin timing are discernible only in the relatively unstable groups of diabetics. Differences in timing tend to be minimized in the *relatively stable group* and accentuated in the *relatively unstable group.* Each patient was maintained on a constant weighed diet of identical foods and food values considered to be appropriate for the particular individual (Table 1). Each of the three insulins, NPH, 2958 and 190-4B-111, were compared in each of three patients (M.K., H.S. and G.C.). In the fourth patient (H.W.) only Insulins NPH and 2958 were compared.

TABLE 1
Supplementary information about the diets of the patients in this study

Patient	Age	Sex	Meals				
			Time	Protein (in g.)	Fat (in g.)	Carbohydrate (in g.)	Calories
H.S.	68	F	8 AM	18.9	23.1	46.7	
			12 Noon	37.1	33.9	77.0	
			3 PM	7.0	0.2	10.2	
			5 PM	23.2	25.8	77.3	
			9:30 PM	8.2	9.3	18.2	
			Totals	94.4	92.3	229.4	2126
M.K.	34	M	8 AM	28.7	75.0	67.5	
			12 Noon	31.8	34.9	74.6	
			3 PM	7.7	8.5	10.8	
			5 PM	23.2	23.9	73.5	
			9:30 PM	8.0	8.8	21.7	
			Totals	99.4	151.1	248.1	2750
G.C.	54	F	8 AM	15.2	8.0	31.8	
			12 Noon	25.9	23.2	45.7	
			3 PM	0.5	0.2	10.1	
			5 PM	23.7	18.6	45.2	
			9:30 PM	4.6	0.2	14.5	
			Totals	69.9	50.2	147.3	1321
H.W.	76	M	8 AM	21.0	30.0	48.2	
			12 Noon	28.4	24.3	61.2	
			5 PM	30.1	20.0	58.8	
			9:30 PM	8.5	3.4	18.4	
			Totals	88.0	77.7	186.6	1798

The comparisons were based on the blood and urinary sugar responses to single daily doses of the given insulin over periods of four to seven consecutive days. On changing from one insulin to another a period of adjustment (two to three days) was allowed before the comparison was made. Changes in tolerance necessitated slight adjustments in dose from time to time. Blood sugars were determined[9] four times daily at 8:00 a.m., 11:30 a.m., 4:30 p.m. and 9:30 p.m. Twenty-four-hour urines were collected in four periods: 7:30-11:30 a.m., 11:30-4:30 p.m., 4:30-9:30 p.m. and 9:30-7:30 a.m., and analyzed quantitatively for sugar[10].

3. *Comparative behavior in patients followed in the clinic under routine conditions.* The clinical timing of Insulins NPH, 2958 and 190-4B-111 was compared over periods of several weeks in each of 13 patients with unstable and eight patients with stable diabetes followed periodically in the clinic under their routine conditions of life. While this method is not quantitative and is much less sensitive than the two just described it serves to corroborate and confirm their clinical significance.

ANALYSIS OF THE DATA

1. The solubility curves of Insulins NPH and 2958 are shown in Figure 1. For comparative purposes the solubility curve of standard protamine zinc insulin obtained from previous data has also been included. The values plotted are averages of duplicate runs in three different batches of pooled sera performed at three different times. Definite and characteristic differences in the solubility curves of Insulin NPH and 2958 can be

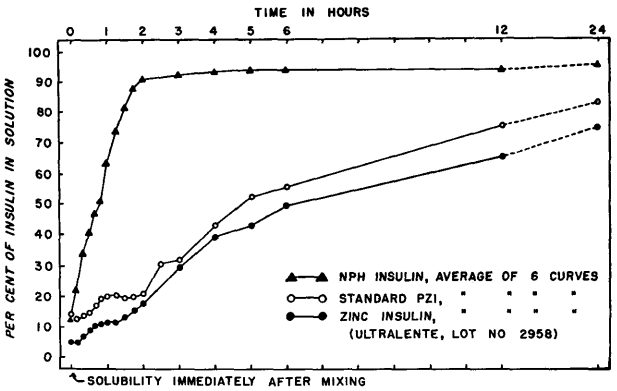

FIGURE 1. Solubility curves of three different types of modified insulin in 60 per cent pooled human sera at 37°C. and pH 7.3.

noted. Insulin 2958 dissolved at a definitely slower rate than NPH insulin. The latter proceeded into solution at a steady rate and by the fifth hour was practically all dissolved. In contrast, Insulin 2958 began to dissolve much more slowly, less than 50 per cent being in solution by the end of the fifth hour and only 75 per cent in solution at the end of 24 hours. It is of interest that the solubility properties of Insulin 2958 and standard PZI are much alike. Note the proximity and similarity in contour of the two curves (Figure 1). However, one important difference in the solubility properties of Insulin 2958 and PZI is that the individual curves (not shown here) of the former are more consistent and uniform than those of the latter.

Comparative solubility properties of Insulin 190-4B-111 could not be studied in the same manner because it is already in solution. Interestingly enough, when the

*p*H of solution was adjusted to that of the body tissues no appreciable precipitate formed. Upon mixing Insulin 190-4B-111 with 60 per cent pooled human sera at *p*H 7.4 and 37 degrees C. only a slight precipitate formed, most of which cleared in a matter of minutes.

2. The blood and urinary sugar data of the four unstable diabetics studied are summarized in Tables 2 and 3. The effect of the insulins on the variability of the blood and urinary sugar responses has been used as the basis of comparison. For a full description of this method of analysis, the principles involved, basic differences from all other methods of comparison and precise definitions of the different components of variability measured refer to previous publications [8, 11]. The total variability among the blood or urinary sugar responses for each patient on each insulin has been divided into two components, intra- and inter-daily variability. It was shown in a larger study[8] that different modified insulins displayed no differential ability to control the extent of intra- and inter-daily variability of the blood or urinary sugar responses. On the other hand, type of insulin did influence the pattern of intra-daily variability but only in the unstable group. Consequently, this analysis includes only a comparison of the effect of the insulins on the pattern of the intra-daily variability, or, in other words, the daily pattern of distribution of insulin activity. In order to describe the pattern of intra-daily variability the deviations from the *daily mean* blood sugar* at the four specified times of the day have been calculated for each patient on each insulin. Figures 2—5 illustrate graphically the daily patterns over periods of

*The deviations have also been calculated for the urinary sugar determinations. Since they reflect the same patterns as the blood sugars, they are not presented.

TABLE II

Summary of blood sugar data

Patient	Insulin Type	Average Daily Dose (Units)	Mean and Range of Blood Sugar in mg. % at 8:00 A.M.	11:30 A.M.	4:30 P.M.	9:30 P.M.	Number of Days of Observation
M.K.	NPH	40	145(105-210)	186(125-302)	258(149-353)	322(256-368)	4
	2958	41.7	253(100-377)	357(182-472)	445(273-524)	460(305-532)	7
	190-4B-111	44.5	366(268-442)	337(235-430)	338(290-392)	404(318-500)	4
H.W.	NPH	50	240(160-350)	276(255-293)	294(277-314)	304(186-378)	3
	2958	52.5	282(67-462)	398(196-504)	366(109-467)	425(244-497)	4
H.S.	2958	76	61(55- 66)	221(199-249)	302(204-321)	297(265-329)	4
	NPH (Commercial)	72	196(95-289)	220(111-317)	136(44-232)	174(83-231)	4
	NPH Ax7147-A	66	56(46- 73)	161(132-198)	165(90-221)	177(103-249)	4
	190-4B-111	62	370(361-407)	219(200-237)	302(232-357)	381(368-437)	4
G.C.	NPH	53	262(189-326)	311(284-331)	290(268-307)	280(209-382)	4
	2958	60	183(130-288)	283(237-340)	315(274-362)	286(261-307)	4
	190-4B-111	46	291(264-305)	275(223-302)	133(99-170)	184(95-260)	4

TABLE III

Summary of urinary sugar data

Patient	Insulin Type	Average Daily Dose (Units)	Mean and Range of Urinary Sugar in G. From 8:00 A.M.-12 Noon	12 Noon-5:00 P.M.	5 P.M.-9:30 P.M.	9:30 P.M.-8:00 A.M.	Daily Total	No. of Days of Observation
M.K.	NPH-Ax7147-A	40	2.17(0.42- 5.74)	7.33(0.56-20.30)	15.41(0.29-33.60)	6.93(0.19-11.45)	25.91(1.39- 71.09)	4
	2958	41.7	11.21(0.99-19.45)	27.10(7.10-52.50)	49.26(34.90-58.40)	48.07(42.70-63.40)	120.91(12.21-169.30)	7
	190-4B-111	44.5	12.72(4.12-24.09)	12.55(1.60-28.01)	24.84(14.45-39.30)	56.48(15.21-88.50)	109.09(43.87-174.20)	4
H.W.	NPH 2958	No data						
H.S.	2958	76	1.80(0.99- 2.95)	19.49(15.35-22.20)	26.17(19.10-37.99)	7.13(4.23-12.10)	54.59(42.24- 65.01)	4
	NPH (Commer.)	72	8.81(1.58-17.40)	6.70(0.30-18.70)	4.24(0.14- 9.35)	3.38(0.74- 9.25)	23.13(3.86- 43.05)	4
	NPH-Ax7147-A	66	1.59(0.66- 2.34)	1.89(0.51- 2.50)	5.45(1.71- 9.59)	1.31(0.44- 2.45)	10.23(5.98- 14.02)	4
	190-4B-111	62	12.90(11.10-14.70)	9.62(3.33-16.40)	30.43(22.30-35.40)	64.30(56.50-68.00)	112.79(93.23-122.43)	5
G.C.	NPH	53	4.69(2.90- 6.05)	13.07(5.69-19.75)	7.36(6.20- 8.56)	5.04(3.17- 7.77)	30.19(18.67- 39.94)	4
	2958	60	1.93(0.27- 6.50)	8.71(7.84-10.45)	8.61(4.86-12.30)	6.87(1.55-16.58)	26.12(24.59- 30.62)	4
	190-4B-111	46	3.56(2.59- 4.47)	1.24(0.63- 1.70)	0.64(0.13- 1.79)	5.99(0.98-11.40)	12.92(5.16- 20.61)	4

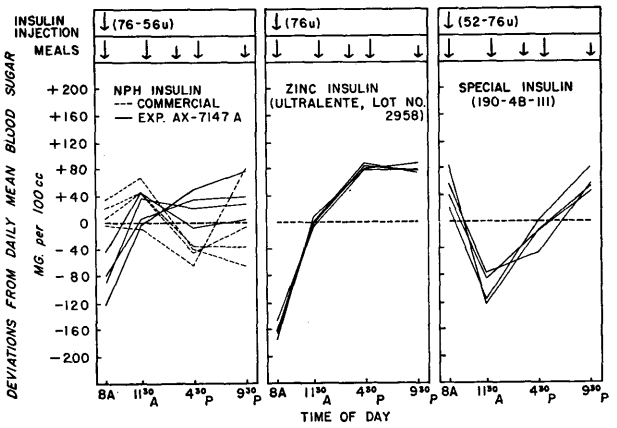

FIGURE 2. Patient H.S.—Patterns of distribution of insulin activity for four consecutive days of single daily doses of three different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

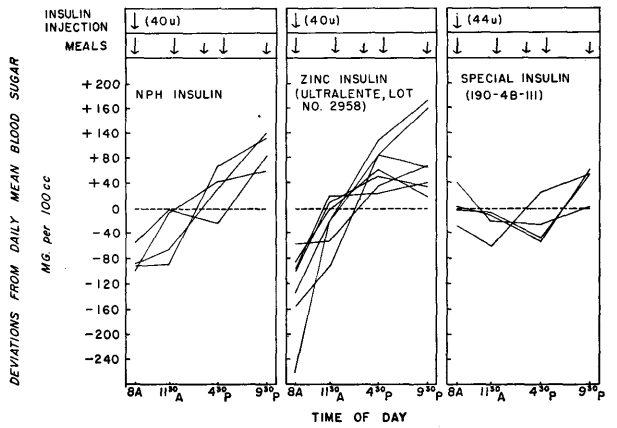

FIGURE 3. Patient M.K—Patterns of distribution of insulin activity for four to seven consecutive days of single daily doses of three different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

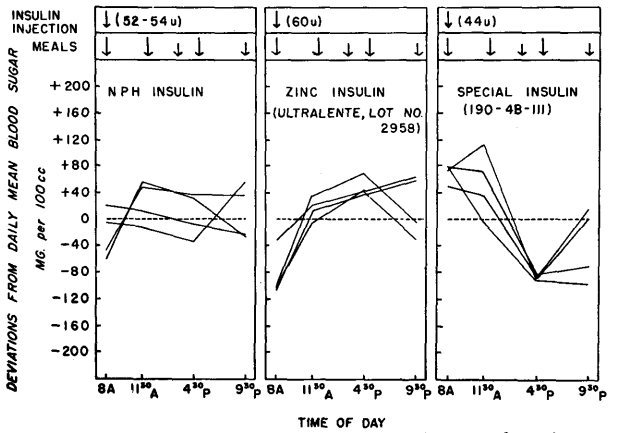

FIGURE 4. Patient G.C.—Patterns of distribution of insulin activity for four consecutive days of single daily doses of three different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

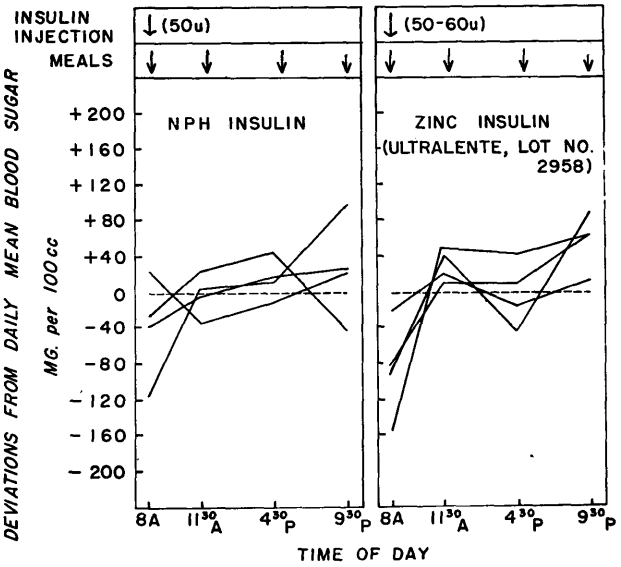

FIGURE 5. Patient H.W.—Patterns of distribution of insulin activity for four consecutive days of single daily doses of two different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

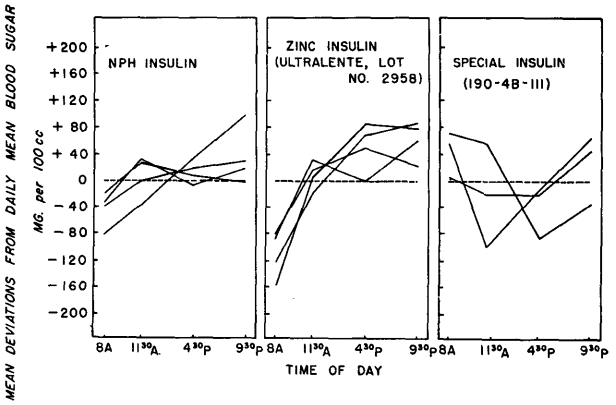

FIGURE 6. Mean daily patterns of distribution of insulin activity of single daily doses of three different types of modified insulin as measured by the mean patterns of intra-daily variation in blood sugar response in each of the four patients with unstable diabetes (H.S., M.K., G.C., and H.W.). Each line represents the average of days in which each patient received the given insulin.

at least four consecutive days for each insulin in Patients H.S., M.K., G.C., and H.W. respectively. The average or mean daily pattern for each insulin in each patient is shown in Figure 6. Each line in Figure 6 represents the average over-all days in which the patient received the given insulin.

A visual inspection of the data indicates that the pattern of intra-daily variability of the blood sugar is affected differently by the insulins studied. The pattern

of Insulin 190-4B-111 displays a consistent tendency toward low points at 11:30 a.m. or 4:30 p.m. and high points at 8:00 a.m. or 9:30 p.m., whereas Insulin 2958 has a consistent tendency toward very low points at 8:00 a.m. and high points at 4:30 p.m. and 9:30 p.m. In contrast, although the pattern of NPH insulin is qualitatively similar to that of Insulin 2958, it is more nearly level. The consistency of the patterns is seen not only in the successive daily patterns in each patient (Figures 2-5), but also in the mean daily patterns from patient to patient (Figure 6). Differences in timing of two different lots of NPH are illustrated in Figure 2 (Patient H.S.). NPH commercial produced a slightly concave type of pattern while NPH Exp. AX-7147-A produced a slightly convex type of pattern.

3. As expected, no large differences in clinical timing of Insulins NPH, 2958 and 190-4B-111 were noted in the seven patients with stable diabetes followed in the clinic. The results in the thirteen patients with unstable diabetes were in accord with the observed patterns of distribution of activity for each insulin. Post-prandial glycosuria was definitely less well-controlled with Insulin 2958 than with NPH. Attempts to correct the post-prandial glycosuria by increasing the dose of Insulin 2958 were apt to produce nocturnal hypoglycemia. On the other hand, Insulin 190-4B-111 had a strong tendency to produce hypoglycemia in the middle of the day. At the same time the action was too weak or absent overnight to control the pre- and post-breakfast sugar levels adequately. These tendencies were more striking in some patients than in others.

COMMENTS

The solubility curves are in good agreement with and serve to complement the respective daily patterns of distribution of insulin activity and clinical behavior of the insulins studied. The results with all three methods of comparison clearly show that Insulins NPH, 2958 and 190-4B-111 display appreciable pharmacologic and clinically significant differences in timing. Insulin 190-4B-111 was found to be considerably faster, while Insulin 2958 was found to be definitely slower than NPH insulin in timing.

The concave type of pattern in distribution of activity of Insulin 190-4B-111, that is, low blood sugar levels in the middle of the day and high levels at night and during the morning, is consistent with its physical characteristics of being already in solution and probably only partially precipitated at the depot site. The "overlapping" effect from dose to dose, which is considered important in a long-acting type of preparation to control post-breakfast hyperglycemia and glycosuria, is lacking. In short, Insulin 190-4B-111 appears to suffer in an exaggerated form from what in our experience has been a consistent defect of clear preparations in general, namely: insufficient prolongation of action to span 24 hours adequately in the majority of patients with unstable diabetes. The pattern of Insulin 2958 is in certain respects opposite to that of Insulin 190-4B-111, that is, high levels during the day and low levels overnight and in the morning. The markedly convex type of pattern produced by Insulin 2958 as contrasted with the more nearly level pattern of NPH insulin is consistent with the much slower rate of solubility in serum of Insulin 2958 than NPH insulin.

The proximity and similarity in contour of the solubility curves of Insulin 2958 and standard PZI are paralleled by the similarity in daily patterns of distribution of activity of Insulin 2958 and those of standard PZI[7]. While the solubility of Insulin 2958 is too slow for the majority of unstable diabetics the significant feature is that a preparation at least as long-acting as standard PZI can be obtained by pure insulin and zinc alone in proper concentration and buffering media. In this respect the present studies fully confirm the reports of Hallas-Moller and associates.

According to the Danish group, three types of zinc-insulin preparations with different ranges of clinical activity can be prepared. These have been designated as "Semilente," "Lente" and "Ultralente." Semilente is a suspension of crystalline insulin in the amorphous state with a reported action range of 12 to 14 hours. Ultralente (somewhat similar to Insulin 2958) is a suspension of crystalline insulin crystals with an action range beyond 30 hours. Lente is a suspension of crystalline insulin, partly in the amorphous and partly in the crystalline state and is said to have the widest range of application with an action range of about 24 hours. Preliminary studies on the solubility curves of suspensions of crystalline insulin in the amorphous state, crystalline state and mixtures of the two indicate that it is possible to obtain a spectrum of solubility speeds in serum with Semilente at one extreme and Ultralente at the other. These studies, together with the respective patterns of daily distribution of insulin activity of different zinc-insulin types, are now in progress and will be reported later.

From a practical standpoint, suitably timed zinc-insulin preparations might have certain advantages over NPH type insulin, such as: (a) possibly more consistent and uniform absorption from the subcutaneous depot; (b) fewer hypersensitivity reactions because of absence

of protein (protamine) modifying agent and purity of insulin; (c) greater flexibility in adjusting optimal timing. Although a single daily dose of NPH insulin tends to produce a nearly level pattern in distribution of insulin activity in the majority of patients in the unstable group, in some cases it produces a convex type of pattern with high sugar levels during the day and low levels during the night and morning, whereas in a few cases it produces a concave type of pattern with low levels during the middle of the day and high levels during the night and morning. The convex pattern may usually be flattened by supplementing NPH insulin with unmodified insulin either in the same syringe or as a separate injection. To flatten the concave pattern it is necessary to split the NPH dose, a larger dose being given before breakfast and a smaller one before supper. The latitude in timing afforded by different types of zinc-insulin suspensions suggests that it may be theoretically possible to treat these smaller but important subgroups with a single daily injection of a suitably timed zinc-insulin preparation.

In spite of the potentialities of the zinc-insulin type of preparations it should be remembered that they suffer from the same limitations of any type of preparation with fixed timing. While type of insulin may influence the daily pattern of distribution of insulin activity as measured by the pattern of intra-daily variability, it cannot control the extent of the variability of blood and urinary sugar responses or, in other words, stability.

SUMMARY

The timing properties of two new long-acting types of experimental insulin preparations: (1) Insulin 2958, a neutral suspension of crystals of insulin and zinc, somewhat similar to the Novo preparation designated "Ultralente," and (2) Special Insulin (190-4B-111), a clear acid solution of chemically modified insulin, were compared with those of NPH insulin. The studies include a comparison of: (1) solubility properties in serum, (2) daily patterns of distribution of insulin activity in patients with unstable diabetes, and (3) behavior in patients in the clinic under routine conditions.

The results with all three methods of comparison are in good agreement and clearly indicate that Insulin 190-4B-111 is considerably faster in timing than NPH insulin whereas Insulin 2958 is definitely slower. Insulin 190-4B-111 was found to have a strong tendency to produce a concave type of pattern of distribution of insulin activity, that is, low levels of blood sugar in the middle of the day and high levels at night and in the morning. On the other hand, Insulin 2958 had a consistent tendency to produce a decidedly convex type of pattern, namely, high levels during the day and low levels at night and in the morning. In agreement with previous studies, NPH Insulin produced a more nearly level daily pattern of distribution of insulin activity.

The present studies confirm in part the reports of Hallas-Moller et al that long-acting preparations with different ranges of activity can be obtained by suspensions of pure insulin and zinc under proper conditions. Studies on suspensions of insulin and zinc with different ranges of activity suitable for clinical use are in progress and will be reported later. The practical implications of suitably-timed zinc insulin suspensions are discussed.

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DISCUSSION

FRANKLIN B. PECK, M.D. (*Indianapolis*): Dr. Izzo should be congratulated on the design of a clinical experiment which will so definitely separate various time actions of insulins.

The number of possible modifications of insulin is almost unlimited. Most of those previously tested have been combinations of insulin with precipitating agents. The latter have included oils, organic compounds such as hexamine, chloroform and various dyes, and combinations devised to slow absorption. Since 1935 the protein precipitants, the protamines, histones and globins have been studied most intensively and have been widely utilized in extending the action of insulin. These compounds cover a wide range of activity and systematic large scale studies have demonstrated that the ones acting in the range of about 2 parts of insulin to 1 part of protamine zinc insulin (mixed) are most practical for general use. It was on this basis that NPH insulin was developed.

One might therefore question what advantage another modification could have. From Dr. Izzo's report it is apparent that neither of the two new modifications fall into the group displaying the best timing characteristics, in that the insulin-zinc suspension acts more like protamine zinc insulin, whereas the chemical modification is too short in action in comparison with NPH insulin. In our own preliminary studies with insulin-zinc suspension one preparation was so slow that it exerted its maximum effect on the fourth morning following a single dose.

Interest in such a preparation as this is two-fold. In the first place, insulin-zinc suspension is composed of crystals formed under special buffering conditions, and has no added protein, owing its long effect to the insulin and component zinc, a normal physiological metal. The range of timing can be shortened, and we are at present working with a preparation having a timing almost like that of NPH insulin. Secondly, there is the possibility that such a preparation may bring at least part of the unstable cases having concave and convex blood sugar curves into the flat curve or stable group. This was suggested by Hallas-Moller on the basis of clinical experience in Denmark. Whether or not this proves to be the case will have to be determined by further studies.

The Use of Potassium in Diabetic Acidosis

There is wide difference of opinion and practice concerning methods of administration of potassium to patients who are recovering from diabetic acidosis. This is understandable. There is no way of estimating with any precision the magnitude of the deficits that are to be corrected nor the rate at which the previously sustained losses can be replaced safely.

Certainly, in some cases, the cells are avid for potassium, so that amounts may be retained that are far in excess of what would be necessary merely to elevate the concentration of potassium in extracellular fluid from a low level to a normal level. This is illustrated by the work of Danowski and associates, who found retention of large amounts of administered potassium in a study of seven patients during recovery from diabetic acidosis. The amounts retained varied from 108 to 450mEq. in periods of 22 to 37 hours; however, since the deficit of potassium may vary widely in different cases, and since the hazards of hyperpotassemia are impressive, we at present administer potassium at a conservative rate of approximately 20 to 25mEq. per hour.

The total amount administered up to the time when sufficient clinical improvement permits stopping intravenous administration of fluid often does not exceed 100 mEq. If necessary, the level of the serum potassium can be determined by flame photometry at any time during treatment, or it can be estimated from the electrocardiogram. As already indicated, the former method is preferable.

Since deficiency of potassium is associated with deficiency of phosphorus, both substances can be supplied in the form of a buffered solution of potassium phosphate. At present we are employing an aqueous solution containing 2.0 gm. of dibasic potassium phosphate and 0.4 gm. of monobasic potassium phosphate in each 5 cc. ampul. This provides 25.89 mEq. of potassium and a mixture of monohydrogen and dihydrogen phosphate (14.4 mM. of phosphate).

The contents of one ampul are added to whatever fluid is being adminstered intravenously at the time, and the rate of flow is adjusted to permit injection of potassium and phosphate at the desired rate. This preparation is preferable to potassium chloride, since the latter may provide an unwanted amount of chloride along with the wanted amount of potassium.

From *Electrolyte Metabolism in Diabetic Acidosis,* by Randall G. Sprague, M.D., and Marschelle H. Power, Ph.D., in The Journal of the American Medical Association, March 21, 1953.