The Lente Insulins

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The results of chemical, biologic, and clinical studies of the interaction between insulin and zinc were published in 1951 and 1952 by K. Hallas-Møller, P. M. Jersild, K. Petersen, and J. Schlichtkrull.[1-4] It was reported that insulin is insoluble at blood *p*H in the presence of zinc ions, since at this *p*H a slowly soluble and slowly resorbable insulin-zinc compound is formed. The degree of retardation of an insulin-zinc suspension is governed first and foremost by the physical state of the suspended insulin. As seen in figure 1, a suspension of the amorphous modification, Semilente, has a somewhat longer action than ordinary insulin, whereas the crystalline modification, Ultralente, may be compared to protamine-zinc insulin.

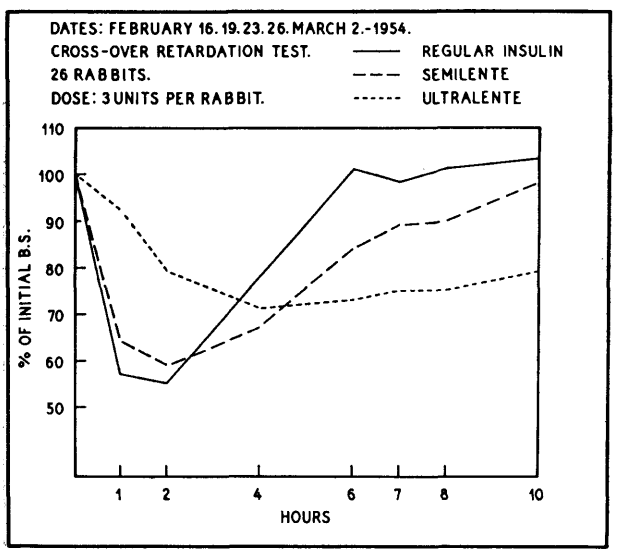

FIG. 1. Means of results obtained in 26 rabbits each given 3 international units of ordinary insulin, Semilente insulin, and Ultralente insulin.

Figure 2 shows, in experiments on 18 rabbits, the relationship between the size of crystals of insulin and the degree of retardation. By a special technic of crystallization it is possible to control the size of crystals, and the figure compares three Ultralente preparations with the crystal size of 5*u*, 20*u*, and 50*u*. The 20*u* and 50*u* preparations give similar blood sugar curves, whereas the action of the 5*u* preparation appears to be of shorter duration. Common practice is to use crystals of about 30*u*.

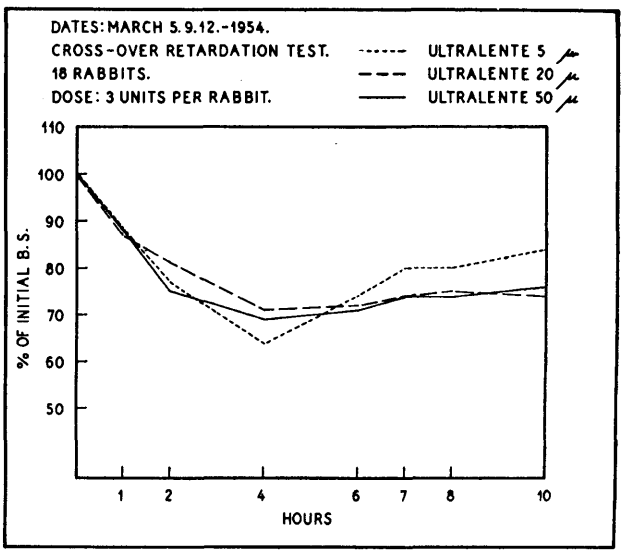

FIG. 2. Means of results obtained in 18 rabbits each given 3 international units of Ultralente insulin of crystal sizes 5μ, 20μ, and 50μ.

In the demonstrated tests, preparations have been used to which had been added 2 mg. of zinc per 1,000 international units. This is the amount of zinc used in protamine-zinc insulin. Considerable variation in the zinc content does not change the action of the Lente insulins. No difference was found in two Ultralente suspensions, the one with 1 mg. and the other with 2 mg. of zinc per 1,000 international units. Figure 3 demonstrates a practical clinical test with two Lente preparations containing 2 mg. and 18 mg. of zinc per 1,000 international units, respectively. This is a considerable quantitative difference in the amount of zinc, but the larger amount retarded the action only a trifle more than the smaller amount. These and many similar experiments established the fact that there was no reason to alter the content of zinc used for so many years in protamine-zinc insulin.

Part of our biologic and clinical investigations with the Lente insulins was directed to show whether the retardation of the insulin effect depended in any way on the species of animal from which the insulin was derived.

Figure 4 compares the results in 24 rabbits given Semilente and Ultralente preparations which were derived

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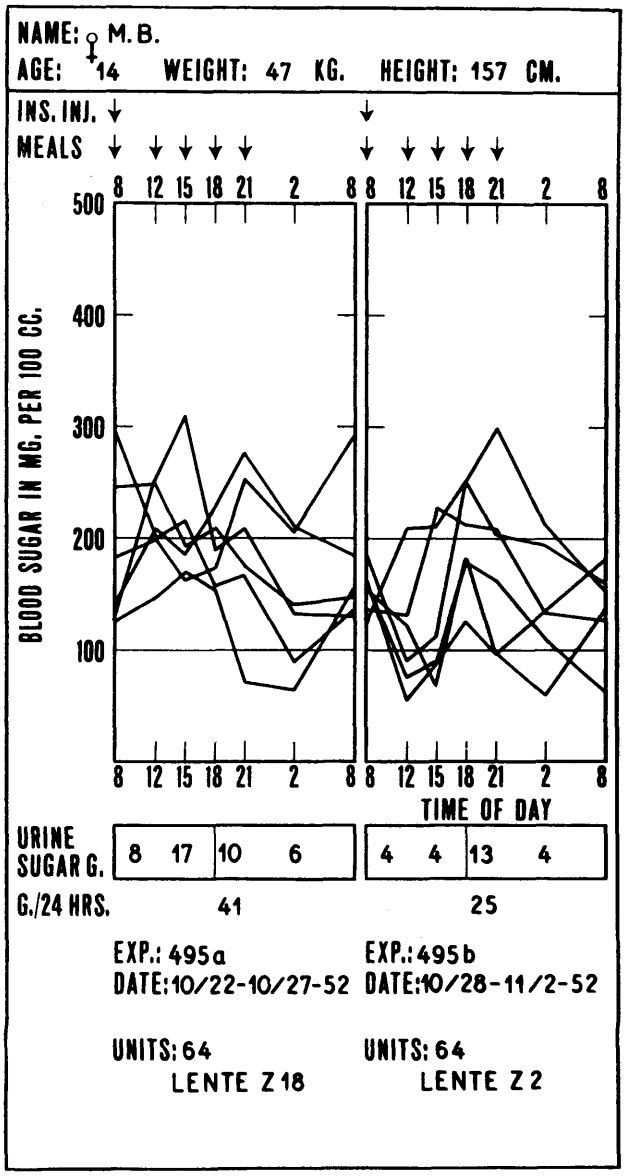

FIG. 3. Comparison of actions of Lente suspensions containing 2 mg. and 18 mg. of zinc per 1,000 international units in diabetic patient.

from ox insulin as well as from pig insulin. It is surprising to see that Ultralente made from pig insulin has exactly the same effect as the Semilente insulins, whereas Ultralente made from ox insulin has the characteristic slow action. In other words, the physical state of pig insulin in the preparations does not affect the degree of retardation in rabbits. This striking result indicates an important fallacy inherent in tests on rabbits, because in diabetics we do not find the same phenomenon. Clinical experiments clearly indicate that the species variation is normally unimportant. It does happen, however, that in a few cases we observe a less pronounced degree of

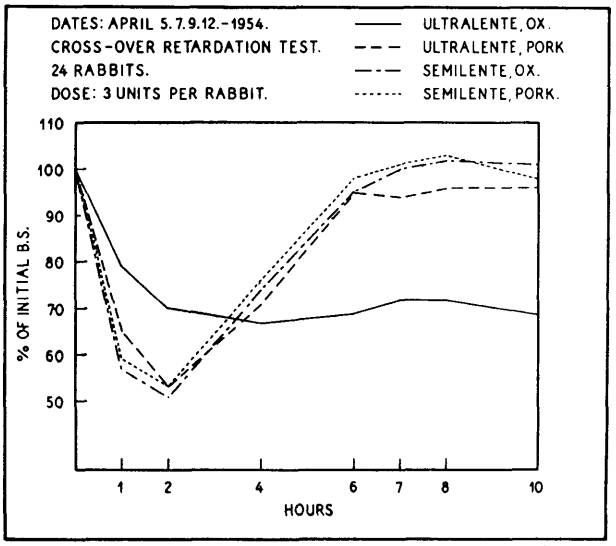

FIG. 4. Means of results obtained in 24 rabbits each given 3 international units of Semilente and Ultralente suspensions derived from pig insulin and from ox insulin.

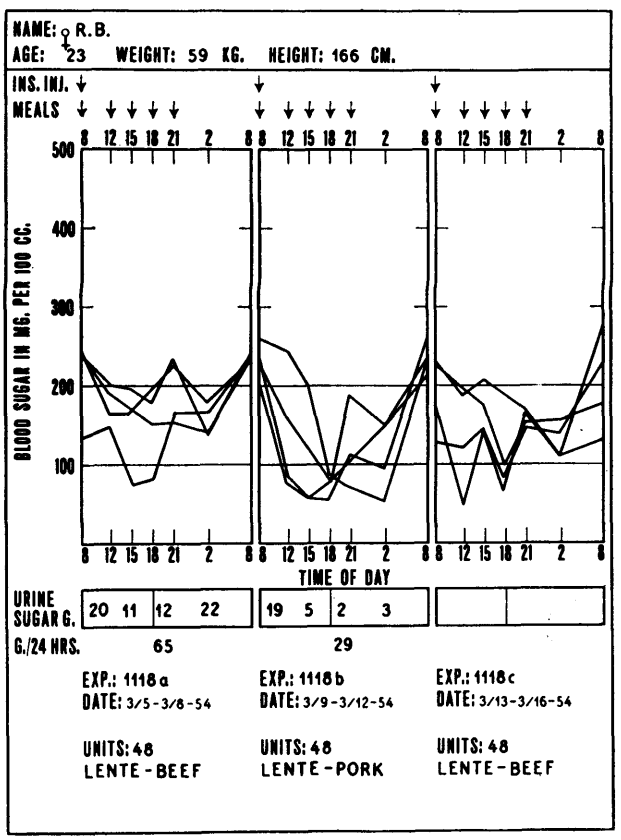

FIG. 5. Comparison of actions of Lente suspensions in which the crystalline fractions were derived from pig insulin and from ox insulin, in diabetic patient.

retardation with pig insulin, which can be seen in figure 5.

The factors which have an influence on the action of insulin-zinc suspensions are easy to control, so that in practice one obtains two well defined, stable insulins, Semilente and Ultralente, with a constant effect. The difference in the action of these insulins is conditioned solely by a physical difference, and they are miscible while retaining the particular effect of the components. Accordingly, a number of mixed insulins can be prepared with varying degrees of retardation.

In recognition of the fact that the action of an insulin is a function of the properties of both insulin and patient, a special clinical test technic has been used for characterizing the different preparations. Figure 6 illustrates the effect of exactly the same depot insulin on three patients with diabetes of almost the same degree. The first patient reacted quickly to the insulin. This type of reaction we call the A reaction. The third patient reacted slowly, and this we call the C reaction. The middle patient reacted satisfactorily to the insulin, there being merely slight 24-hour fluctuations. This we call the B reaction. If an insulin is to be regarded as suitable for administration in one injection during the 24 hours, it must give the highest possible number of B reactions. A large number of patients—excluding those with mild diabetes—are necessary in making such an evaluation.

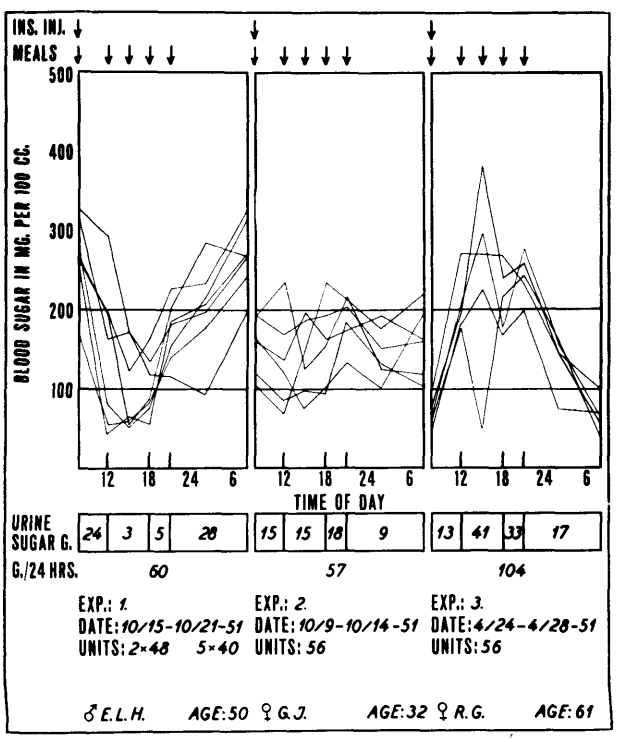

FIG. 6. Results of clinical trials of same depot insulin in 3 diabetic patients showing A, B, and C reactions, respectively. Reproduced by courtesy of "Journal of the American Medical Association."

When a patient has been adjusted to a test preparation of about five to seven days it is generally possible to plot a mean blood sugar curve expressing the patient's adjustment. The upper left half of figure 7 represents five days' treatment of a patient with NPH insulin. Below is the mean curve, which shows an A reaction. The difference between the maximum and minimum blood sugar of the curve—△ BS—indicates the fluctuation. The right half of the figure is a diagram which at the top shows the △ BS, and below the mean blood sugar in 33 cases adjusted on the same insulin. The △ BS columns are drawn below the zero line when there is an A reaction, that is, a fast action, and above it in the case of a C reaction, which means slow action. The individual case illustrated in the left half of the figure recurs in the diagram in the form of the solid columns. The B reaction, the slight blood sugar fluctuations, is identical with only slightly pronounced A and C reactions and therefore corresponds to the small columns.

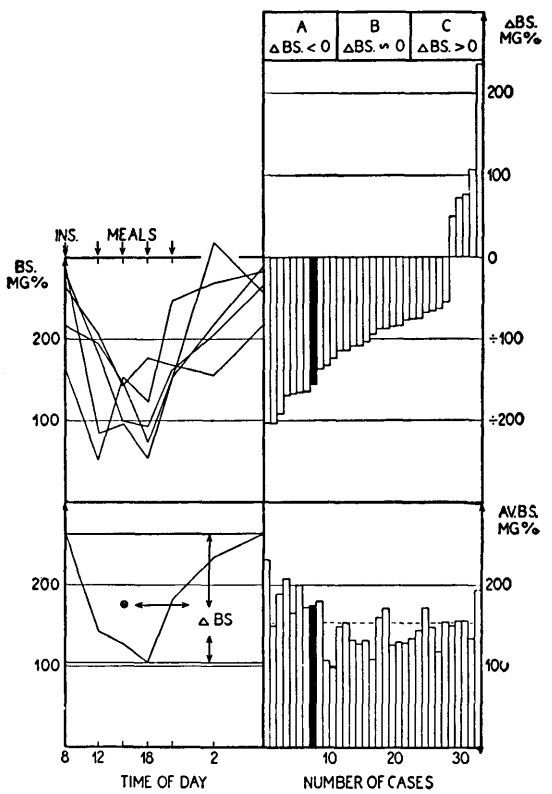

FIG. 7. Diagram for a depot insulin, 33 cases and a descriptive individual case: J. K., age 25, dose 60 units.

It appears from the figure that there is a preponderance of A reactions, which in other words means that the NPH insulin tested here is of a more rapidly acting type of insulin preparation.

In accordance with the technic described here the evaluation was carried out with Semilente (figure 8). As a whole it gives A reactions owing to its relatively short

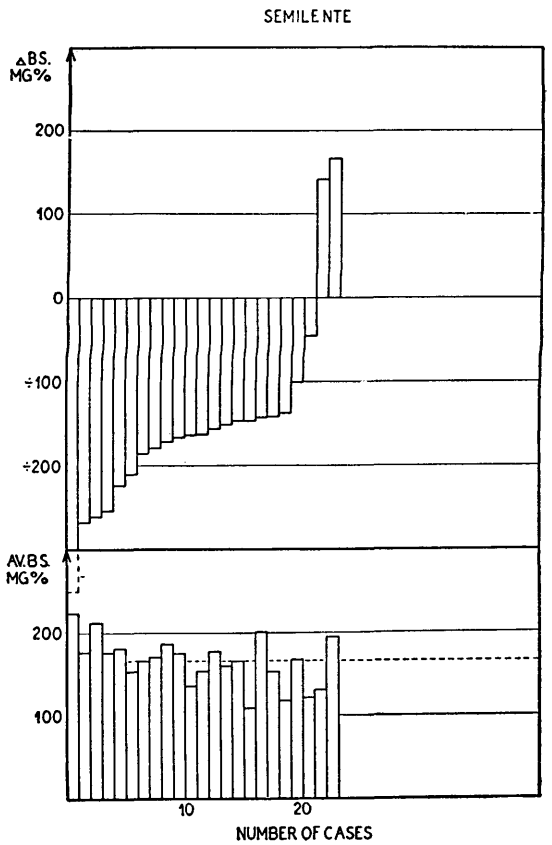

FIG. 8. Insulin Novo Semilente: 23 cases.

range of action. The picture is reversed when Ultralente is employed (figure 9) as this gives mainly C reactions. Figure 10 illustrates the adjustment of 218 patients with Lente, which is a mixture of three parts Semilente and seven parts Ultralente. The material reveals approximately equal amounts of A and C reactions, and a relatively large number of adjustments with small blood sugar fluctuations—B reactions. This must be a prerequisite for the suitability of the insulin as a one-injection preparation. If its degree of retardation were less there would be a larger number of A reactions, and if it were greater the tendency would be to give a larger number of C reactions.

At the Second International Diabetes Congress in Cambridge, England, July 4-8, 1955, J. Schlichtkrull presented a paper dealing with the results of a more elaborate statistical evaluation technic which applies to the patient material upon which this diagram is based. His findings fully confirm the results shown on the diagram. Among other things, he is working with the ratio be-

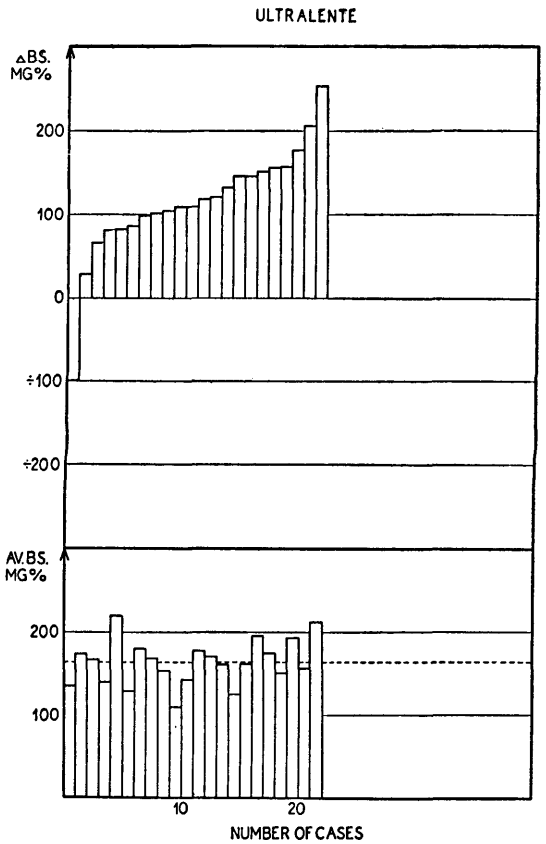

FIG. 9. Insulin Novo Ultralente: 22 cases.

tween the night blood sugar level and the 24-hour level. With a normal physiologic blood sugar curve this ratio will naturally be 1. A low day blood sugar level and a high night level will give a ratio which is greater than 1, corresponding to the A reaction, whereas a high day level and a relatively low night level will give a ratio which is less than 1, corresponding to the C reaction. In figure 11 these ratios—f—are given for different preparations. Lente shows an even share of cases on either side of the unity line, the f value 1. Protamine-zinc insulin and Ultralente show the f value mainly below 1—C reactions. Semilente tends toward A reactions with large f values. NPH likewise tends toward A reactions, as we also saw from the diagram in figure 7.

Here it should be mentioned that we are partly in agreement with Peck[5] when he writes that NPH and the Lente insulin are interchangeable, but we should like to emphasize that Lente has a more marked carry-over effect in the majority of cases. It is a fact, however, that in some cases the action of Lente will be too rapid or too slow, as will be seen from the extreme A and C reactions in figure 10. For such patients Ultralente and Semilente may be mixed with the Lente preparation in order

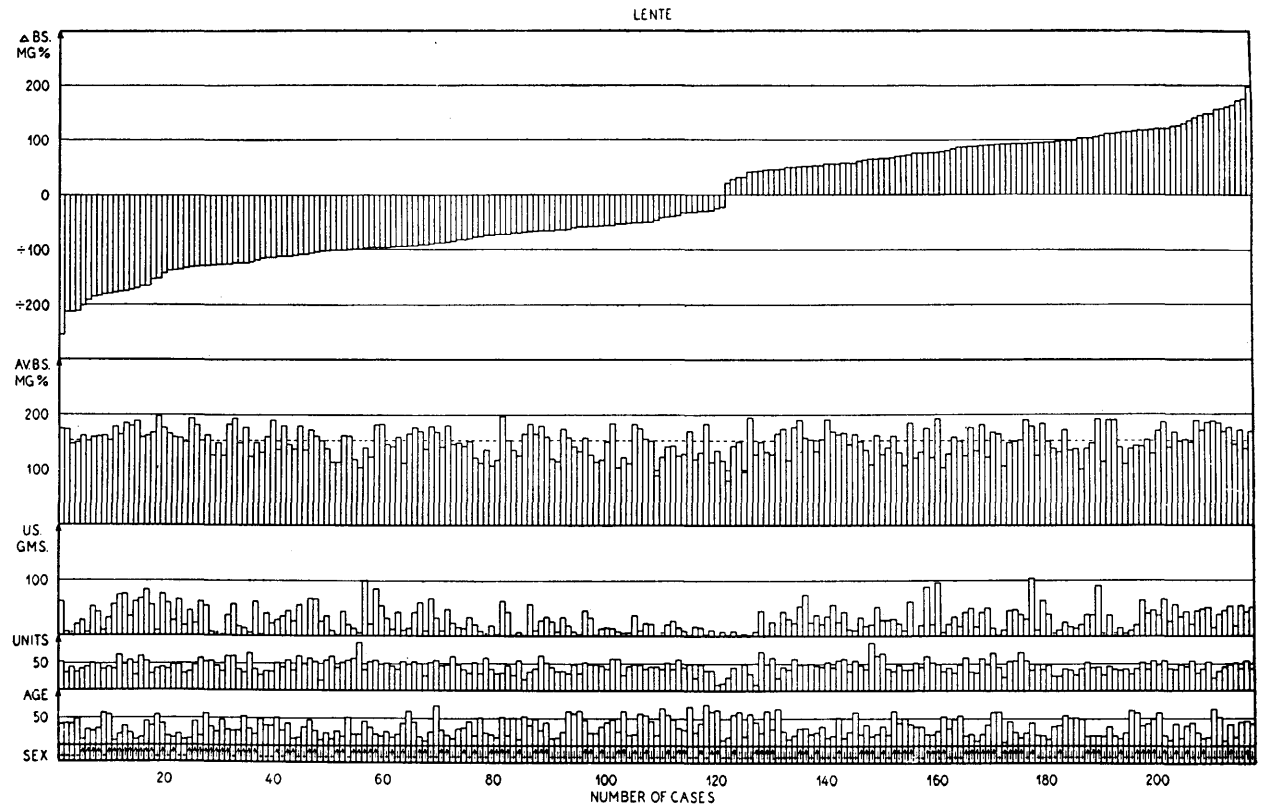

FIG. 10. Insulin Novo Lente: 218 cases.

to prolong or shorten the latter's range of action.

This is the background of the introduction in Europe of the whole Lente trilogy. Through this it is possible for the physician to carry out individualized treatment in difficult cases. In the United States there have been warnings against the advisability of supplementing the number of existing insulin preparations by a further three, as it is feared confusion might arise. We should, however, like to stress that the Lente trilogy is a distinct little family, the members of which can supplement one another in such a simple way that it must be an easy matter to inform the doctors of their right use.

The latest report compiled by Jersild of the Hvidøre Hospital, Copenhagen, states that the number of diabetic patients stabilized on the Lente insulins with an average dose of 40 units daily was 1,030, of whom 990 (96 per cent) were discharged on one injection daily, and 40 (4 per cent) on two injections daily. Of the 990 discharged on one injection daily, the Lente insulins used were Lente-Semilente mixtures in 93 (9 per cent), Lente alone in 790 (80 per cent), Lente-Ultralente mixtures in 100 (10 per cent), and Ultralente alone in 7 (1 per cent).

During the past three years more than 50 publications on the Lente insulins have appeared. Mention should be made of two of the latest, both of which are based on a considerable number of patients. Gurling, Robertson, Whittaker, Oakley, and Lawrence[6] give the results obtained with the use of Lente in the treatment of 479 diabetic patients. They claim that in less than 7 per cent of cases Lente was a failure, whereas 31 per cent of adults and 37 per cent of children previously treated with insulin were found to be improved.

Even more encouraging results were obtained by Stowers and Nabarro,[7] who selected patients for trial with the Lente preparations only if the previous treatment had proved to be unsatisfactory. They clearly demonstrate that a large percentage of these diabetics benefited from the transfer to Lente. Furthermore, the authors state that in the majority of patients Lente—in the ratio of three parts Semilente to seven parts Ultralente—proved satisfactory. Fourteen per cent needed a larger proportion of the Ultralente insulin and 2.5 per cent a larger proportion of the Semilente insulin.

In general, the many clinical publications confirm that our insulin group made the right choice of the Lente composition, and we expect that similar results may be achieved in the United States.

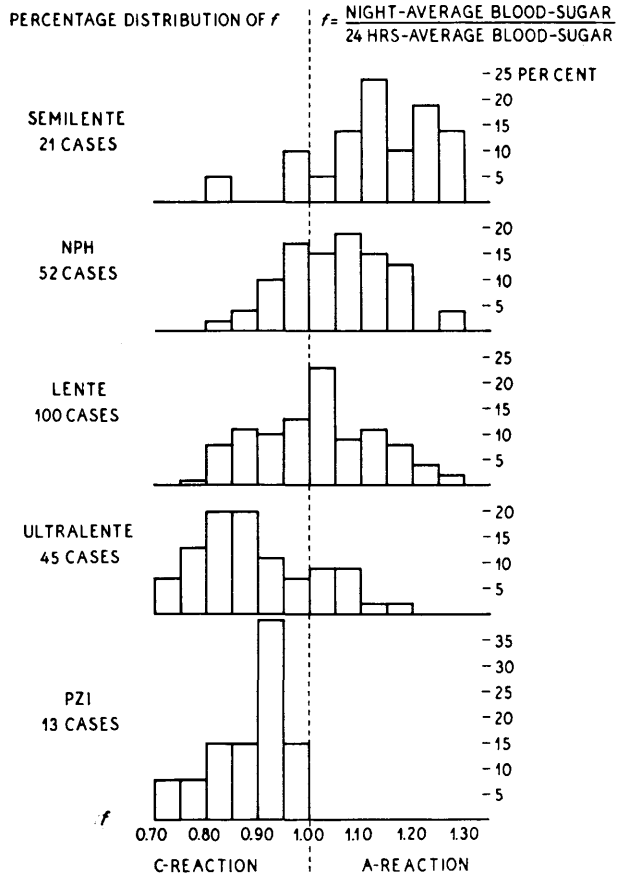

FIG. 11. Comparison between the action of different insulin preparations.

SUMMARY

1. The interaction between insulin and zinc is described with special reference to the physical state and the origin of insulin and the concentration of zinc.

2. A special technic of clinical evaluation and its application to the effects of Lente, Semilente and Ultralente insulins is reported.

3. The treatment of more than 1,000 diabetics at the Hvidøre Hospital, Copenhagen, is reviewed.

4. Results obtained with the Lente insulins in other hospitals are reported.

SUMMARIO IN INTERLINGUA

Le Insulinas Lente

1. Le interaction de insulina e zinc es describite con referentia special al stato physic e al origine de insulina e al concentration de zinc.

2. Es reportate un technica special de evalutation clinic, insimul con su application al effectos de insulinas Lente, Semilente, e Ultralente.

3. Es presentate un revista de plus que 1000 diabeticos al Hospital Hvidør a Copenhagen.

4. Es reportate le resultatos obtenite per insulinas Lente a altere hospitales.

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DISCUSSIONS OF THE ABOVE PAPER BY K. HALLAS-MOLLER, PH.D., AND THE PAPER ENTITLED "LENTE INSULIN: CLINICAL EVALUATION IN 109 DIABETIC PATIENTS" BY EDGAR A. HAUNZ, M.D., GRAND FORKS, NORTH DAKOTA

ALEXANDER MARBLE, M.D., (*Boston*): I think it might be of interest to give a brief summary of our experience with Lente insulin in the last two years during which we have used it in treating sizable groups of patients of various ages.

In general, its action has appeared to be similar to that of NPH insulin and we have used it exactly as we have the NPH type. Substituting it for NPH insulin, unit for unit, we have obtained about the same degree of control of diabetes. In the treatment of patients requiring more rapidity of insulin action than that possessed by Lente insulin alone, we have placed crystalline insulin with it in the syringe just as we have been accustomed to doing with the crystalline and NPH types.

In studies made by Drs. Robert E. Slayton and Ruth E. Burrows of our group with 23 boys at the Elliott P. Joslin Camp, average capillary blood sugar values were obtained every two hours through the day and night with these boys who were leading an active camp life and eating their usual diets. The doses of Lente and NPH insulins in this comparative study were the same in any individual boy. Throughout most of its extent, the composite blood sugar curve following Lente

insulin lay very closely to that following NPH insulin. There was some suggestion that, at least in this group of boys, the Lente insulin did not carry through for quite as long as the NPH variety. However, with other patients not included in this study, the Lente type seemed to act slightly longer than NPH insulin. All told, the effect was about the same.

In 40 cases, crystalline and Lente insulins were given by separate injection on one day and on another day the two types in the same dosage were placed in the same syringe just before injection. The composite blood sugar curves obtained lie very close together. It is true that early in the forenoon following breakfast when the two types were given in the same syringe, there appeared to be not quite as much early, rapid insulin action. Furthermore, later in the day there appeared to be a slightly greater hypoglycemic effect than when the two varieties were given by separate injection. However, the differences in action were small and from a clinical standpoint it is entirely feasible to give crystalline and Lente insulins in the same syringe. It goes without saying that the patient appreciates the convenience of the single injection.

ALVAH L. NEWCOMB, M.D., (*Wilmette, Illinois*): My associates and I have had the opportunity of treating 54 children, and they have all done quite well, except for 9. In nine cases, we had to go back to the former insulin, for different reasons, generally because they were not well controlled; one child developed generalized urticaria, and a second child developed hepatomegaly.

I wonder if Dr. Hallas-Møller has seen hepatomegaly develop. We had not noted it since the days we had been using only regular insulin. The hepatomegaly subsided as soon as the former insulin was prescribed.

We did see some rather severe hypoglycemic reactions under a variety of different situations.

EWEN DOWNIE, M.D., (*Melbourne, Australia*): My experience in using the Lente insulins extends for about 18 months. I do not have any figures with me, but my associates and I have used them in over 200 patients.

I have been interested in the experiences of the previous speaker, in using crystalline insulin with Lente. On occasions when we have experienced difficulty with stabilization, it has been our practice to use extemporaneous mixtures of Lente with Semilente or Ultralente insulins rather than combining regular insulin with Lente.

I should like to direct a question either to Dr. Hallas-Møller or to Dr. Haunz, as to whether they have had any experience in the use of mixtures of Ultralente and Semilente insulins. Has it been their practice to use them in the same way as we use regular and protamine-zinc insulins, varying the proportions according to a patient's needs?

GEORGE W. KOCH, M.D., (*Anaheim, California*): Have you seen any skin reactions after the use of Lente insulin?

LEON S. SMELO, M.D., (*Birmingham, Alabama*): In answer to the question whether Ultralente might be added to Lente insulin, we have added Ultralente to the commercially available Lente insulin and obtained good prolongation of the duration of action of the Lente insulin when this was necessary to secure a normal fasting blood sugar.

THOMAS HODGE MCGAVACK, M.D., (*New York*): Dr. Haunz, with your mixtures of Lente and regular insulin, have you had any difficulty, from day to day or from time to time, in maintaining a smooth, dependable action? In view of the differences in zinc content and *p*H, it would seem to me you could run into considerable trouble. This would be especially true when sufficient amounts of regular insulin are added to bring the *p*H of the mixture to or close to the isoelectric point of insulin.

K. HALLAS-MØLLER, PH.D.: There seems to be a considerable interest in mixing Lente with regular insulin in order to obtain a stronger initial effect.

To tell the truth, as long as Semilente is not available in this country, you are forced to use regular insulin for this purpose. What actually happens is that by mixing Lente with regular insulin, the *p*H will change. Dr. Haunz has told us that, in a mixture of 1:1 of the two insulin preparations, he measured the *p*H to be between 5 and 6. In this *p*H interval, the regular insulin will be converted into an amorphous precipitate identical with Semilente. When this amorphous precipitate is allowed to stand overnight, it will be converted into a crystalline material which means abolition of the desired fast action of the mixture, instead of which you will get a slow-acting preparation comparable to Ultralente.

This is the background for our marketing Semilente in Europe. Semilente has *p*H 7 and can be mixed with either Lente or Ultralente without entailing alterations in the specific action of the components, because no change will take place in the physical state of the insulin. Of course, if regular insulin and Lente are mixed in the syringe and immediately injected as practiced by Dr. Marble, you will undoubtedly get good results. My only comment on this technic is that in the layer between the two kinds of insulin, some crystalline material might be existent in a medium of low *p*H. These crystals might be dissolved and reprecipitated as amorphous material shortening the action of the preparation.

I believe this will explain the difficulties connected with the use of this kind of mixture. On account of our

experience we must strongly advocate that both Semilente and Ultralente should be available.

The foregoing, I think, will also answer the question asked by Dr. Haunz.

I have also been asked about allergy. Of course, there have been a few cases of this nature in the meantime, but I know for certain that there were only 2 patients showing allergy among the 1,030 patients referred to in my paper. Even if the insulin species were changed or the insulin was recrystallized many times, it would be impossible to avoid the rare cases of hypersensitivity reactions indicating true insulin allergy.

In reply to one further question I can say that we have not seen any influence of unknown nature on the diabetic organism which the Lente insulins might induce in comparison with hitherto existing insulin preparations.

Dr. Downie inquired about the use of Semilente and Ultralente. I think his question will be more or less answered by my foregoing statements.

One of the members raised the question of lipo-atrophy. Just before I left Copenhagen, we received the first report of lipo-atrophy in a patient who had been treated with Lente for several years. Generally speaking, I feel that the test period has so far been too short to prove whether the Lente therapy can reduce the frequency of lipo-atrophy observed in previous regimes.

EDGAR A. HAUNZ, M.D., (*Grand Forks, North Dakota*): We have encountered one case of insulin atrophy which occurred in a child eight years old during the administration of Lente insulin.

I think the problem of mixtures of Lente and zinc insulin crystals should be clarified. All our mixtures were made daily and not prepared in advance. Each mixture was made in the syringe. According to what Dr. Marble has stated, we do not mix the preparation after the two insulins are drawn into the syringe. That is unnecessary because they apparently act independently; therefore, it is unnecessary to mix them as you would mix protamine or NPH insulins with unmodified insulin.

Dr. Marble has pointed out in Joslin's textbook that the incidence of skin reactions, as noted by different observers, has varied considerably, and such discrepancies are apparently due to whether or not minor responses are included. We included all responses, I should say, because we kept these patients under very close observation.

In conclusion, it has long been known that the incidence of sensitivity reactions to insulin falls precipitously when the insulin preparation has been recrystallized several times, and for that reason such reactions should be much less frequent when using the new insulin zinc suspensions.

Diabetes and Insurance

Glycosuria has long been a favorite subject for investigation in the insurance field. A current study provides further confirmation of the general benign outlook for mild diabetics. As you all probably know, insurance contracts have been made increasingly available in recent years to well regulated diabetics with no evidence of complications. In the current mortality studies, glycosuria of less than 1 per cent was not attended by any adverse mortality experience, except in older individuals who had some additional impairment such as obesity or elevated blood pressure, etc. Deaths among diabetics were due preponderantly to diabetes itself, diseases of the heart and circulatory system, malignancy and respiratory illness.

From "The Internist and Life Insurance" by Harry E. Ungerleider, M.D., New York, N. Y., *Annals of Internal Medicine* 41:124-30, July 1954.

The Ease and Comfort of Digestion

Psychic factors do not seem to influence the ultimate utilization of food, for Hawk and his associates found that protein prepared in an unpalatable manner was as completely utilized as that which had been more attractively served.

. . . The ease and comfort with which food is disposed of by the stomach and intestine comprise what is easily taken to be digestibility. This depends on many factors, chiefly the secretory and motor response which the food calls forth and a subjective sensation which it produces. The latter is determined in large measure by the former. These several influences in turn are dependent on the physical state of the food, its chemical composition and its appeal to the appetite. In addition to these factors, digestibility is often covered by idiosyncrasy. This follows no law; it is often psychic, sometimes allergic, and not infrequently of unknown nature. . . .

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., pp. 136-37.