A New Diagnostic Procedure for Mild Diabetes Mellitus

Evaluation of an Intravenous Tolbutamide Response Test

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A new parameter for the diagnosis of mild diabetes mellitus would be a valuable supplement to the various types of glucose loading tests which constitute the usual method for the estimation of pancreatic beta-cell function. The most commonly used of these diagnostic procedures is the standard oral glucose tolerance test, which, although sensitive[1] when interpreted by criteria of the American Diabetes Association,[2] is considered by many to be variable and diagnostically unreliable.[1,3-8] In a recent study[1] the prevalence of "abnormal" oral glucose tolerance curves in a random population sample was found to exceed by at least fifteen times the estimated prevalence of diabetes in the general population.[9] This evidence of nonspecificity is supported by the results of long-term follow-up of individuals with "abnormal" curves[8] and indicates that rigid adherence to these criteria can lead to over-diagnosis of diabetes.

Since the nonspecificity of the oral glucose tolerance test has been attributed, at least in part, to variable rates of glucose entry from the gastrointestinal tract,[3,10,11] a variety of intravenous glucose tolerance tests, differing from each other in respect to rate of glucose injection, have been employed,[11-18] and appear to offer greater accuracy and reproducibility. Those procedures requiring slow infusion of glucose solution at a constant rate[11,16] are not widely used for routine purposes. Rapid intravenous glucose tolerance tests[13,14,17,18] are simpler to perform and, according to Amatuzio, Stutzman, Vanderbilt and Nesbitt, provide a high degree of accuracy in the differentiation of the nondiabetic and the mildly diabetic state.[18] In an attempt to reduce the number of blood specimens required for the time-disappearance curves employed in such tests, Lozner, Winkler, Taylor and Peters recommended a diagnostic criterion for a single blood glucose determination two hours after injection.[17] Unfortunately the test, when interpreted according to this standard, has been found relatively insensitive, most diabetics with normal fasting blood glucose levels falling within the normal zone.[19] The need for additional accurate but practical diagnostic parameters for mild diabetes mellitus is therefore apparent.

In 1956 Mirsky, Diengott, and Dolger[20] reported that moderately severe diabetic and nondiabetic subjects differ strikingly in their hypoglycemic response to orally administered tolbutamide. Unger and Madison[21] observed similar differences in response to intravenously administered sodium tolbutamide in mild diabetics and nondiabetics, and suggested that these differences might provide the basis for a new diagnostic test for mild diabetes. A tentative rationale for the use of this compound in differentiating diabetics from nondiabetics stems from evidence,[22-26] as yet not incontrovertible, that the sulfonylureas, like glucose[27-29] induce the release of endogenous insulin.

The purpose of the following report is to evaluate the previously published data referred to above[21] in order to determine the merits of a standardized intravenous tolbutamide response test as a diagnostic procedure for mild diabetes mellitus.

MATERIALS AND METHODS

Seventy-nine mild, stable diabetic patients were chosen from the wards of the Veterans Hospital, from the rosters of the Parkland Memorial Hospital Metabolic Clinic and the Diabetes Detection Unit of the City Health Department, Dallas, Texas. None of these patients was receiving insulin or therapy other than dietary restriction at the time of their selection. They were subclassified according to their pretest fasting blood glucose concentration: Thirty-four subjects had diagnostic

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elevations (115 to 184 mg. per cent); forty-five had normal or near-normal levels (below 115 mg. per cent), including twenty-five patients with values of less than 100 mg. per cent. The diagnosis of diabetes in the latter group had been established by a three-hour oral glucose tolerance test interpreted according to the following criteria: peak blood glucose level of 200 mg. per cent or more; two-hour level of 170 mg. per cent or above; three-hour level of 135 mg. per cent or more. These stringent diagnostic criteria were applied in order to exclude from the diabetic group any nondiabetics with borderline abnormalities in glucose tolerance curve.

A control group of 100 subjects was selected from among medical, surgical, and otolaryngological patients at the Dallas Veterans Hospital (eighty-five persons) and from among medical students (fifteen persons). None of these control subjects suffered from any known acute or chronic disease of consequence and in all the oral glucose tolerance test was normal by the criteria of the American Diabetes Association.[2]

A standard preparatory diet containing 300 gm. of carbohydrate per day was prescribed for at least three days prior to testing. After an overnight fast a blood specimen was obtained and a gram of sodium tolbutamide* in 11 cc. of distilled water was administered by vein over a two-minute period. Blood specimens were obtained at various intervals after the mid-point of the injection. Blood glucose determinations were performed in duplicate by the Somogyi-Nelson technic.[29]

RESULTS

The typical blood glucose response curves of each group are illustrated in figure 1.

Comparison of nondiabetic controls and diabetic subjects. After the intravenous injection of sodium tolbutamide nondiabetic subjects exhibited a rapid decline in blood glucose concentration, not unlike that which normally follows the intravenous injection of insulin. At twenty minutes after injection the mean level of the nondiabetic group had fallen to 60 per cent of the pretest value (S.D.±14.2), with a range of 85 to 9 per cent. At thirty minutes the mean glucose concentration reached a nadir of 51 per cent of the pretest level (S.D.±14.8) and the range was from 82 to 6 per cent. The forty-minute value of 55.6 per cent (S.D.±11.9) reflected an increasing prevalence of rebounding glucose levels and at sixty minutes the mean glucose concentration was 72 per cent (S.D.±12.1)

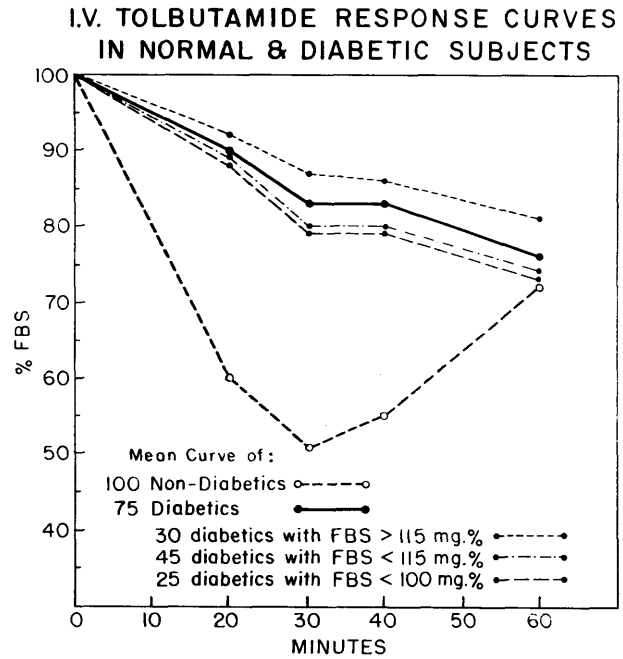

FIG. 1. The mean blood glucose response curves of nondiabetic and diabetic subjects. (The omission of four members of the diabetic group does not appreciably alter the appearance of these curves.) The diabetic group is subdivided according to the level of FBS. The forty-five diabetics with FBS below 115 mg. per cent include those twenty-five patients with FBS below 100 mg. per cent. (Reprinted with the permission of "The Journal of Clinical Investigation," Volume 37, 1958.)

of pretest value.

In contrast, diabetic subjects exhibited a far less rapid decline toward a more distant nadir (figure 1). The mean glucose concentration at twenty minutes fell to only 90 per cent of the pretest value (S.D.±7.4) and ranged from 108 to 61 per cent. Thirty minutes after injection the mean level was 83 per cent (S.D.±8.7), and ranged from 105 to 49 per cent. The forty-minute value was 83 per cent (S.D.±9.8), and the sixty-minute value was 77 per cent (S.D.±10.9).

Forty-five members of the diabetic group had fasting blood glucose levels of below 115 mg. per cent and twenty-five of these patients had normal levels (below 100 mg. per cent). It will be noted in figure 1 that the mean tolbutamide response curve of each of these two subgroups parallels that of the more severely diabetic group and is strikingly different from that of the nondiabetic group.

This point is further emphasized in figure 2 which compares the tolbutamide response curves of thirteen nondiabetic controls with those of thirteen mild diabetic patients whose fasting blood glucose concentration was in the same normal range. Despite the similarity of the

*Sodium tolbutamide was generously supplied by Dr. C. J. O'Donovan, The Upjohn Company, Kalamazoo, Michigan.

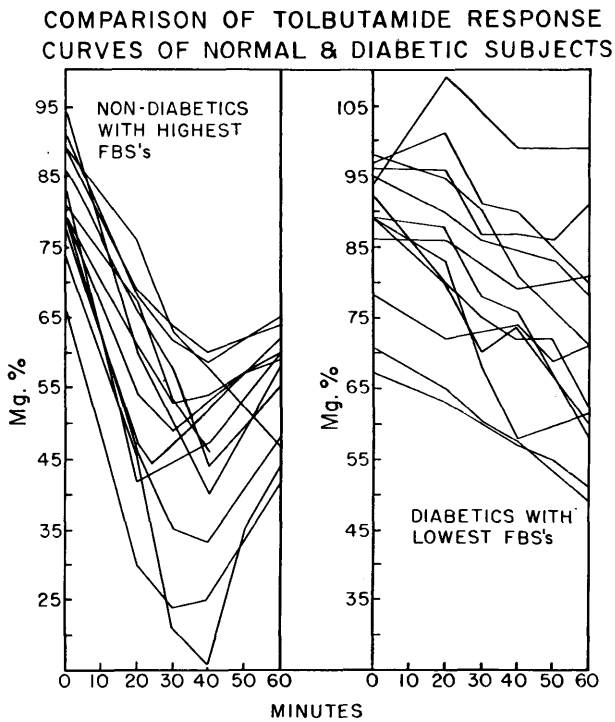

FIG. 2. Tolbutamide response curves of thirteen nondiabetic and thirteen diabetic subjects whose pretest blood glucose levels were in a similar range. The rapid fall characteristic of nondiabetic subjects is in distinct contrast to the more gradual decline typical of the diabetics, and illustrates the ability of the test to detect very mild forms of the disease. (Reprinted with the permission of "The Journal of Clinical Investigation," Volume 37, 1958.)

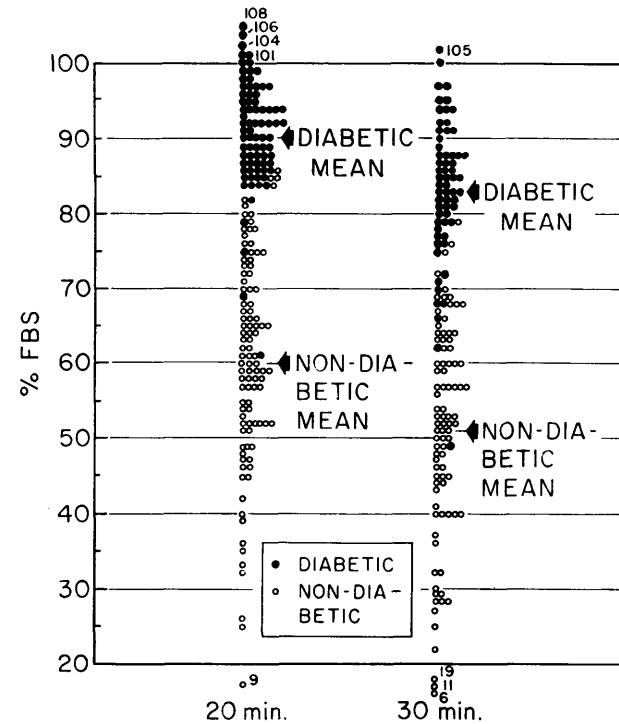

FIG. 3. The blood glucose levels at twenty and at thirty minutes after tolbutamide injection, expressed as per cent of the pretest value, of all diabetic and nondiabetic subjects are recorded.

pretest glucose levels of each group, the precipitous decline of the nondiabetic subjects is in distinct contrast to the more gradually declining curves of the mild diabetics. *Selection of criteria for the differentiation of diabetics and nondiabetics by means of the intravenous tolbutamide response test.* Figure 1 reveals that, of the specimens analyzed, maximum separation of diabetic and nondiabetic response curves took place at twenty and at thirty minutes after tolbutamide injection. These points have, therefore, been selected for closer examination. In figure 3 all twenty- and thirty-minute blood glucose values, expressed as per cent of pretest level, are recorded. It will be noted that at twenty minutes, the glucose level of 96 per cent of nondiabetic subjects had fallen below 84 per cent of pretest level, and to below 80 per cent in 94 per cent of the group. However, the glucose level of 94 per cent of diabetic patients was at 84 per cent of the pretest value or above, and was at 80 per cent or above in 95 per cent of the group.

At thirty minutes after injection, blood glucose concentration of 99 per cent of nondiabetic controls was less than 77 per cent of the pretest level (figure 3). This lower prevalence of "false positive" results at thirty minutes is offset by the observations in the diabetic group. In only 82 per cent of the diabetic subjects did the blood glucose level remain at 77 per cent of the pretest value or above. This increased number of false negative results among the diabetics indicates a seriously diminished degree of sensitivity at this time.

These data indicate that the arbitrary selection of 84 per cent and above as the diabetic zone for the twenty-minute specimen provides a diagnostic standard which has been correct in 95 per cent of the subjects in this study. Similarly, the selection of 80 per cent of the pretest level as the upper limit of the nondiabetic zone for the twenty-minute specimen provides a standard which was accurate in 96 per cent of subjects tested. The zone between 80 and 84 per cent of the pretest level is to be considered to be presumptively abnormal though nondiagnostic.

The blood glucose level at thirty minutes seems far more specific but much less sensitive than that of the twenty-minute specimen. Only the diabetic zone is of importance here, since negative values have little sig-

nificance in excluding the disease. The interpretation of blood glucose levels of 77 per cent and above as diabetic provided 99 per cent accuracy in this series.

In the interpretation of results falling within the zone of overlap, which at twenty minutes extends from 75 to 89 per cent of pretest level and includes 10 per cent of each group, rigid adherence to the recommended criteria can lead to diagnostic errors. Instead, within this zone diagnostic probability must be taken into consideration. According to these limited data persons whose blood glucose level at twenty minutes falls within the 75 to 79 percentage range have a 21 per cent probability of diabetes; those whose level falls between 80 to 84 per cent have a 56 per cent chance of being diabetic; and between 85 to 89 per cent, the diagnostic probability is 91 per cent. Below and above the zone of overlap diagnostic accuracy approaches 100 per cent.

The probability of normality or abnormality of each range of blood glucose response for the twenty- and thirty-minute specimens can be estimated more readily in the frequency distribution charts provided in figures 4 and 5.

Side reactions. Side reactions, due either to drug toxicity or to hypoglycemia, were unusual. Several patients complained of hunger and weakness during the tolbutamide test, but nervousness, trembling, sweating and headache were uncommon. Such symptoms were noted only among nondiabetics, since the blood glucose concentrations of diabetics seldom reached hypoglycemic levels during the test period. Blood glucose concentrations below 25 mg. per cent were recorded in 23 per cent of the nondiabetic subjects, few of whom complained of hypoglycemic symptoms. In several of the patients who reported hypoglycemic symptoms, blood sugar levels ranged well above 25 mg. per cent. In none of these cases was it necessary to terminate the test.

A few patients complained of transitory shoulder pain during the intravenous injection and this was attributed to venospasm. In one individual with a history of drug sensitivity manifested by generalized chronic urticaria, the onset of nausea, vomiting, abdominal pain and an acute exacerbation of urticaria followed within two minutes of the tolbutamide injection and subsided spontaneously within six hours.

DISCUSSION

The foregoing data indicate that the intravenous tolbutamide response test correctly differentiates known diabetic subjects from nondiabetic controls in 95 per cent of instances and appears, therefore, to qualify as a diagnostic test for diabetes. Furthermore, the mean

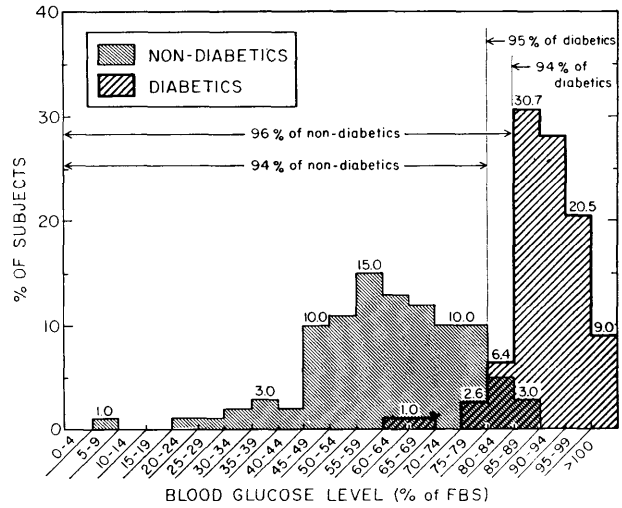

FIG. 4. Frequency distribution of blood glucose levels twenty minutes after tolbutamide injection in 100 nondiabetic and seventy-nine mild diabetic subjects.

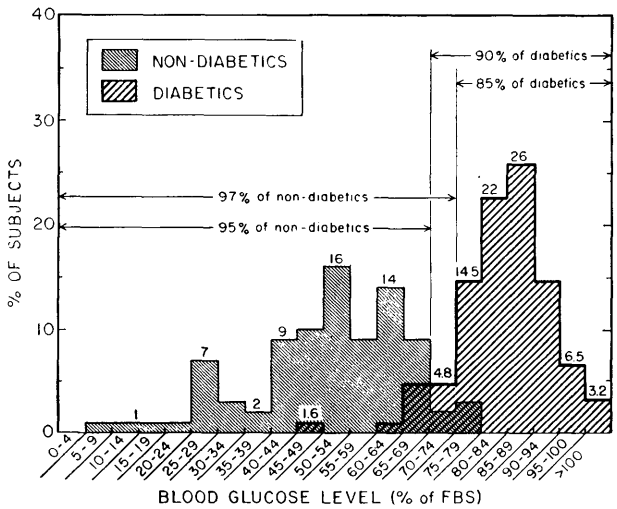

FIG. 5. Frequency distribution of blood glucose levels thirty minutes after tolbutamide injection in 100 nondiabetic and seventy-nine mild diabetic subjects.

tolbutamide response curve of the forty-five mild diabetics with a normal (<100 mg. per cent) or slightly elevated (100 to 115 mg. per cent) fasting blood sugar level closely parallels that of the thirty-four diabetics with fasting hyperglycemia (116 to 184 mg. per cent) of diagnostic proportions, and differs strikingly from that of the nondiabetics. This would indicate a degree of sensitivity sufficient to identify correctly milder forms of the disease.

Diagnostic criteria have been based on the data recorded in figure 3 at the twenty- and thirty-minute specimens, at which time separation of the groups was

maximal. On the basis of the above it is suggested that failure of the blood glucose level to fall below 84 per cent of the pretest level at twenty minutes after injection be considered strong diagnostic evidence of diabetes mellitus. A fall in blood glucose concentration to 80 per cent of the pretest value or below would appear to be strong evidence against diabetes since 96 per cent of such results occurred in nondiabetics. However, a negative result does not entirely exclude diabetes mellitus since the blood glucose level of 5 per cent of diabetics fell below this level. At thirty minutes, failure of the blood glucose level to decline below 77 per cent of the pretest value constitutes even more specific evidence of diabetes. Although of little value in exclusion, this specimen is useful when abnormal, giving added significance to an abnormality at twenty minutes.

The results of an evaluation of a diagnostic test for diabetes will depend to a large degree on the composition of the normal and diabetic groups studied. Our data suggest that if, as has often been done in evaluating other tests, comparison had been restricted to medical student controls (or any similar young population sample) and to overt diabetics, complete separation of the groups would have resulted. However, since the individuals for whom such a test is designed differ markedly from both these categories, evaluations of this type are unrealistic and the standards derived therefrom misleading. For this reason in the selection of the two groups an attempt was made to simulate the population segment most apt to require such a test. In the control group the number of medical students was limited in favor of older nondiabetics, while more than half of the diabetic group were mild cases who, without treatment, maintained normal or near-normal fasting blood glucose levels despite a high-carbohydrate diet.

In any quantitative biologic measurement subjected to large-scale evaluation of this type, a certain amount of overlap between normals and abnormals is likely to appear, the result of skew in the frequency distribution curve of each group. Hence, a zone of overlap between nondiabetics and diabetics is to be expected. Diagnostic errors in this borderline area can be minimized by interpretation in terms of probability of normality or of disease, as has been recommended. Application of these principles to the interpretation of the oral glucose tolerance test, in which overlap between diabetics and nondiabetics appears to be even more extensive,[1] might resolve the controversy[1-8] which now surrounds its diagnostic validity and standards.

In an attempt to confine the evaluation of the tolbutamide test to definite nondiabetics and unequivocal but mild diabetics, stringent and widely separated standards for the interpretation of the oral glucose tolerance test were employed in classification. Unaccounted for, therefore, in these data are those borderline individuals whose oral glucose tolerance curves fall between the criteria used in this study. Because of the uncertain status of this intermediate group, composed, as it appears to be,[6] of both very mild diabetics and false-positive nondiabetics, a separate study has been underway to determine whether or not the tolbutamide response test can contribute to its proper classification.

Evaluation of the test in the presence of liver disease, endocrinopathies, infection, and carbohydrate restriction remains to be completed. Preliminary data suggest that carbohydrate restriction may result in a "diabetic" tolbutamide response curve. This has also been observed in starved rats,[31] and is consonant with the hypothesis that tolbutamide stimulates endogenous insulin secretion, since it has been shown that fasting reduces pancreatic insulin content.[32] Persons in this study were, therefore, instructed to consume at least 300 gm. of carbohydrate daily during the week before the test.

Among the assets of the intravenous tolbutamide response test is the fact that it is complete within thirty minutes and requires only three blood specimens. Since hypoglycemia of considerable magnitude may occur in certain of the nondiabetics, it is recommended that the test be terminated as soon as the thirty-minute specimen is obtained with the administration of carbohydrate. Although no untoward effects have occurred so far, caution is advisable in the testing of persons with atherosclerosis.

It is tempting to attribute the striking similarity of the normal tolbutamide and insulin response curves to a rapid release of insulin stored in the beta cells. If this were true, the more gradual decline characteristic of mild diabetes might then be ascribed to diminished release of insulin from the beta cells, due either to a deficiency of stored insulin or to a slower rate of release. However, extrapancreatic factors in the serum or at the cellular level might result in a similarly diminished responsiveness to the drug.

SUMMARY AND CONCLUSIONS

Intravenous tolbutamide response tests were performed in 100 nondiabetic controls and in seventy-nine diabetic patients, and highly significant differences in the blood glucose responses of the two groups were observed. Whereas in nondiabetic subjects the blood glucose con-

centration fell sharply to a nadir between twenty and forty minutes after the tolbutamide injection, that of diabetic patients, including those with a normal and near-normal fasting blood glucose level, declined more gradually. Separation of the two groups was maximal at twenty and thirty minutes after the injection. At twenty minutes the blood glucose level of 94 per cent of diabetic patients remained at 84 per cent or more of pretest values, whereas in 96 per cent of nondiabetic subjects it had fallen to 80 per cent or less of the pretest level. These levels have been arbitrarily selected as the standards by which the test can be interpreted with maximum accuracy. The zone between 80 and 84 per cent of the pretest blood sugar level is to be considered as suspiciously abnormal though nondiagnostic. Failure of the blood sugar concentration to decline to below 77 per cent of the pretest value at thirty minutes gives additional weight to abnormalities at the twenty-minute specimen. The use of these criteria has permitted proper identification of diabetics and nondiabetics in the vast majority of subjects tested.

The intravenous tolbutamide response test appears to qualify as a diagnostic test for mild diabetes mellitus and should provide a useful supplement to the various glucose loading tests now used for this purpose. It has been found to be safe, simple, not unpleasant for the patient and has the advantage of requiring only thirty minutes for completion.

SUMMARIO IN INTERLINGUA

Evalutation De Un Test Del Responsa A Tolbutamido Intravenose Como Procedimento Diagnostic In Casos Leve De Diabete Mellite

Tests del responsa a tolbutamido intravenose esseva effectuate in 100 non-diabetic subjectos de controlo e in septanta-nove patientes diabetic. Differentias altemente significative esseva observate inter le duo gruppos in le responsas de lor glucosa sanguinee. In non-diabeticos, le concentration de glucosa sanguinee descendeva abruptemente verso su nadir que esseva attingite inter vinti e quaranta minutas post le injection de tolbutamido. In le caso de patientes diabetic—incluse illes con normal e quasi normal nivellos de glucosa sanguinee in stato jejun—le concentration descendeva plus gradualmente. Le separation del duo gruppos esseva maximal a periodos de vinti e trenta minutas post le injection. Post vinti minutas, le nivello del glucosa de sanguine de 94 pro cento del patientes diabetic remaneva a 84 pro cento o plus del valor pre-experimental, durante que in 96 pro cento del non-diabeticos illo habeva descendite a 80 pro cento o minus del valor pre-experimental. Iste nivellos ha essite seligite arbitrarimente como standards per le quales le test pote esser interpretate con un maximo de accuratia. Le zona inter 80 e 84 pro cento del nivello de sucro de sanguine de ante le experimento debe esser considerate como suspiciosemente anormal ben que non como diagnostic. Si le valor trenta minutas post le injection non es inferior a 77 pro cento del valor pre-experimental, un anormalitate in le valor vinti minutas post le injection gania in signification. Per medio de iste criterios il ha essite possibile identificar diabeticos e non-diabeticos correctemente in le vaste majoritate del subjectos studiate.

Le test del responsa a tolbutamido intravenose es apparentemente qualificate a servir como test diagnostic in leve casos de diabete mellite e promitte devenir un utile supplemento pro le varie tests de cargation con glucosa que es nunc usate pro iste objectivo. Illo se ha monstrate salve, simple, non disagradabile pro le patiente, e distinguite per le avantage que illo require solmente trenta minutas pro su completion.

ACKNOWLEDGMENT

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Since 1942 there has accumulated an increasingly impressive body of scientific evidence indicating that the sulfonylurea compounds are extremely effective hypoglycemic agents in both human and animal subjects. The potential usefulness of these drugs in the management of patients with diabetes has provided the stimulus for innumerable clinical trials. However, the fundamental question regarding the mechanism of this hypoglycemic action has not yet been answered. It is obvious that a full understanding of this mechanism is of more than academic interest. Although many classes of drugs may produce hypoglycemia, the usefulness of such drugs as therapeutic agents in diabetes must be dependent upon more than a hypoglycemic action. There must be, in addition, an enhancement of the over-all metabolism of carbohydrate. In order to evaluate the potential therapeutic benefits that may be derived from the sulfonylureas, it becomes important, first to understand the mechanisms by which hypoglycemia is produced and, second, to measure the certain parameters that might reflect alterations in metabolic processes known to be deranged as a consequence of impaired carbohydrate utilization.

Lillian Recant and George L. Fischer in *Annals of the New York Academy of Sciences,* Vol. 71, p. 62.

Many diabetic patients require dosages of insulin far in excess of what is generally considered the production of the normal pancreas, and in various situations, most strikingly in severe ketosis, the insulin tolerance may increase enormously. Under these circumstances, one must suppose that an "antagonist" to insulin is present in undue amounts in the blood or tissues. Whether this antagonist is in the nature of a pituitary hormone, an antibody, or a specific destructive enzyme (insulinase) remains to be determined.

DeWitt Stetten, Jr., in *Currents in Biochemical Research,* p. 171. Edited by David E. Green. Interscience Publishers, Inc., New York, 1956.