A Comparison of the Oral Sodium Tolbutamide Test and the Oral Glucose Tolerance Test in Selected Hospital Patients

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SUMMARY

Increasing use of the two-hour postprandial blood glucose test in screening for diabetes detection has resulted in an increased number of borderline oral glucose tolerance tests, and the dilemma of their proper interpretation. In spite of controlled pretest precautions, the two-hour-lag oral glucose tolerance test with fasting normoglycemia may lack specificity as an index of latent diabetes. The intravenous tolbutamide test as a supplemental test may offer greater specificity in the diagnosis of early diabetes, and a recent oral modification of this test offers added convenience and safety without sacrificing reliability.

This is a report based upon the oral test performed on a group of 105 hospital patients selected because each had an elevated second-hour blood sugar level with fasting normoglycemia on a standard oral glucose tolerance test. An abnormal oral sodium tolbutamide test was elicited in fifty-two of this group of 105, and the abnormal tolbutamide test correlated significantly with a positive family history of diabetes, an obstetrical history suggestive of diabetes, or those patients with an elevated third-hour blood sugar level on oral glucose tolerance. In only six of the 105 patients studied were the results of the oral sodium tolbutamide tests classified as borderline between normal and abnormal by the criteria of Boshell and Vecchio.

We conclude that the oral sodium tolbutamide test seems to be a valuable additional study in the appraisal of *minimally abnormal oral glucose tolerance results at least in the presence of obesity, liver disease, hyperthyroidism,* uremia, myocardial infarction, chronic pancreatitis, spontaneous hypoglycemia, and lymphomas and related neoplasia representing the major disease categories in our study group. DIABETES *15*:212-19, March, 1966.

Postprandial blood glucose levels are being employed with increasing frequency as a screening procedure for diabetes detection.[1] Indeed, in many hospitals a blood glucose determination two hours after a standard test meal is an integral part of the routine evaluation.[2] This type of screening procedure has resulted in a marked increase in standard oral glucose tolerance testing, and a resurrection of the dilemma of the proper interpretation of "minimally" impaired oral glucose tolerance, especially in patients with normoglycemia in the fasting state. Because it has been stated repeatedly[3] that such abnormalities lack specificity in the diagnosis of diabetes mellitus, the intravenous tolbutamide tolerance test has been introduced as an additional method of assaying minimal aberrations in carbohydrate metabolism which may prove to be more specific, although admittedly less sensitive, than the oral glucose tolerance test.[4] Recently an oral sodium tolbutamide diagnostic test for diabetes has produced results comparable to the intravenous technic with greater convenience and less hazard of hypoglycemia.[5]

This report is based upon our experience with this test performed upon 105 hospitalized nonsurgical, nonpregnant adult patients, none of whom was overtly diabetic. All were selected by criteria herein described designed to minimize the extraneous physiologic and pharmacologic variables capable of influencing the oral glucose tolerance test. Each had an *abnormal two-hour oral glucose tolerance unaccompanied by fasting hyperglycemia.*

METHODS

The patients were selected from the adult medical ward population of two general hospitals, excluding pregnant, postoperative, and unconscious subjects, and their ages ranged from twenty-five to seventy-five (average fifty-five) years. Overt diabetics were not eligible, but patients were accepted with a past medical history of transient glycosuria or an obstetrical history suggestive of asymptomatic diabetes. Acute gastrointestinal disease which would affect the usual diet pattern eliminated candidates, and all selectees were afebrile for at least one week. Patients recovering from acute myocar-

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dial infarction were included in this study, but tolerance tests were not performed until at least two weeks after the onset of the attack in an effort to minimize the stressful effect of the acute episode. Patients who had been receiving drugs capable of disturbing glucose tolerance, especially chlorothiazide diuretic or an analog, and adrenal steroid or analogous medication within a month of hospitalization were likewise not selected for this study, although this decision resulted in the elimination of hypertensives, congestive circulatory failure cases, rheumatoid arthritics, and patients with bronchial asthma.

Blood glucose determinations were performed on venous blood, measuring the "true" blood glucose on the AutoAnalyzer by a modification of the Hoffman method,[6] the range of normal values for fasting blood glucose by this method being 65 to 90 mg. per 100 ml. The patients were initially screened by a blood sugar determination two hours after a standard test breakfast containing approximately 100 gm. of carbohydrate.[7] If this "true" blood glucose value was 110 mg. per 100 ml. or higher, the patient had a fasting blood sugar determination on two or more successive days. The patient was considered diabetic, at least for exclusion from this study, if the fasting true blood glucose was greater than 110 mg. per 100 ml. on two or more occasions. Those cases with a fasting blood glucose of 110 mg. per 100 ml. or less on repeated testing were given a standard three-hour oral glucose tolerance test. In patients with histories suspicious of spontaneous hypoglycemia, the oral glucose tolerance test was conducted for a period of five hours. If the glucose tolerance test revealed a two-hour value of 120 or above, such patients were accepted for further study with the oral sodium tolbutamide test* as described by Vecchio and co-workers[8] as an adjunct in the diagnosis of diabetes mellitus.

The normal and abnormal ranges for this test in diabetic versus nondiabetic subjects were tentatively established by Boshell and co-workers[5] and confirmed by Vecchio's group, the results obtained appearing comparable to those with the intravenous test, with a lag of about ten minutes (table 1). The results are expressed as percentage of the fasting blood sugar thirty minutes and forty minutes after a test dose of 2 gm. of sodium tolbutamide combined with 2 gm. of sodium bicarbonate given orally in a multiple tablet form. In eight cases, five of whom had chronic liver disease, significant hypoglycemia occurred at forty minutes, but in no case was symptomatic hypoglycemia encountered at the time of the thirty-minute specimen. All tests were terminated with sweetened fruit juice, followed by breakfast. Results of oral sodium tolbutamide tests classified as borderline between normal and abnormal were obtained in only six of the 105 patients studied. Coincidentally, six of the total group with fasting normoglycemia and an elevated two-hour blood glucose value were classified as having "borderline" abnormal glucose tolerance tests in that the timed glucose values did not quite fulfill Fajans and Conn's[9] criteria of a diabetic oral glucose tolerance curve, i.e., true blood sugar values of at least 160, 140, and 120 at one, one and one-half, and two hours.

RESULTS

Comparative test results in the total group (table 2):

Fifty-two of the total selected group with minimally abnormal oral glucose tolerance tests as defined above had abnormal oral sodium tolbutamide tests by the criteria defined in table 1. Our data showed an interesting correlation between abnormal tolbutamide test responders and the results of the third-hour value of the oral glucose tolerance test. Thirty-two of the 105 patients in the total group had an abnormally elevated

*Oral sodium tolbutamide for these tests was generously supplied by Dr. Thomas Vecchio from The Upjohn Company, Kalamazoo, Michigan.

TABLE 1

Criteria for interpretation of oral sodium tolbutamide test*

	30 Min. per cent FBS	40 Min. per cent FBS	Total patients	Positive family history	PMH Positive (a) Glycosuria (b) Obstetric	Abnormal Third hr. BS on SGTT (110+)
Normal	78 or below	73 or below	47	5	0	3
Borderline abnormal	79-84	Even if below 73	6	1	0	0
Abnormal	85 or above	77 or above	52	35	21	29

*Adapted from data of Boshell et al.,[5] and Vecchio et al.[8]

TABLE 2
Comparative test results in total group

Group	Number of patients	Mean age	Mean weight	"Diabetic" SGTT	Abnormal Third hour BS on SGTT (110+)	Abnormal OTTT	Comment
Total	105	55	153	99	32	52	Normal fasting BS & abnormal 2-hr. oral glucose tolerance in all cases. Six patients had borderline abnormal oral glucose tolerance with abnormal 2-hr. blood sugar.[7]
Age (60+)	43	67	154	41	18	23	
Obesity	19	50	193	18	6	10	20 per cent or more above ideal weight.
Family history positive	41	56	158	39	19	35	
PMH positive a) Glycosuria b) Obstetric	21	54	163	21	10	21	No overt diabetics included in study. Positive PMH limited to obstetric history or glycosuria.
Liver disease	25	52	153	23	7	11	All had 10 per cent or more BSP retention.
Spontaneous hypoglycemia	10	49	155	8	5	8	None had fasting hypoglycemia. No obvious endocrinopathy. All responded to appropriate diet.
Pancreatitis, chronic recurrent	4	52	152	4	2	4	None studied during an acute episode.
Hyperthyroidism	5	55	131	5	0	0	All regained normal oral glucose tolerance after hyperthyroidism controlled.
Uremia	6	63	142	6	1	2	BUN 30+ in each case.
Myocardial infarction	15	57	164	15	9	12	Studies performed at least two weeks after acute attack.
Lymphomas and related chronic blood dyscrasias	16	58	142	15	4	4	Lymphoma, lymphatic leukemia, myeloma, polycythemia.

third-hour blood glucose value, i.e., 100+, on oral glucose tolerance, and twenty-nine of these had an abnormal oral tolbutamide test. If we accept the thesis that the percentage of false positive results are less with the tolbutamide tolerance tests than with the oral glucose tolerance test in diabetes diagnosis, our data would support the concept that the third-hour glucose tolerance lag curve is more specific than the two-hour lag curve in early diabetes diagnosis. However, this does *not* imply equivalent sensitivity in that either a normal tolbutamide tolerance test or a normal third-hour glucose tolerance blood sugar value *excludes* the diagnosis of diabetes mellitus.

A positive family history of diabetes, defined as history of the disease in parents, siblings, parental-siblings, or grandparents, was obtained in forty-one of the total group studied. Thirty-five of these patients had an abnormal oral tolbutamide test (85.4 per cent), compared to an incidence of positive family history in 39 per cent of the total group. We conclude, therefore, that a positive family history of diabetes is associated with a significant degree of correlation with an abnormal tolbutamide test in our total group study.

The diagnostic reliability of impaired oral glucose tolerance in the elderly has been a debatable issue.[10] The mean age of our total group was fifty-five years with an abnormal oral tolbutamide test in fifty-two cases (49.5 per cent). In a review of the forty-three patients in the group over the age of sixty, twenty-three such cases had an abnormal oral tolbutamide test (53.5 per cent). In a breakdown of our total group into age decades, the subgroups are frequently too small to justify valid conclusions, but the data would seem to indicate that the percentage of abnormal oral tolbutamide tests in our series of patients is not significantly related to age.

Our study group included nineteen patients who were 20 per cent or more above ideal weight, including thirteen females and six males. Abnormal oral tolbutamide tests were obtained in ten of these cases, seven of whom had a positive family history of diabetes, and six a "diabetic" obstetrical history. Further correlation reveals that six of the nineteen obese patients studied had an abnormally elevated third-hour blood sugar on glucose tolerance, each of whom had an abnormal oral tolbutamide test. In summary, each of the ten obese patients with abnormal oral tolbutamide tests had one or more associated findings at

least suggestive of subclinical diabetes. Surveying the nine obese patients studied with either normal or borderline oral tolbutamide tests revealed no similar evidence suggestive of the diabetic state in any case.

Liver disease:

This study included twenty-five patients classified as having liver disease of various etiologies, all of whom had bromsulphalein retention of 10 per cent or more on a forty-five minute intravenous test plus other laboratory and clinical evidence of liver dysfunction, but no evidence of hepatic coma. An abnormal oral sodium tolbutamide was found in eleven of these twenty-five patients, ten of whom had a positive family history of diabetes, and seven of these eleven cases were the only patients in the liver disease group with an elevated third-hour oral glucose tolerance. A past medical history of glycosuria was elicited in three of the twenty-five liver cases, all of whom had an abnormal oral sodium tolbutamide test. Incidentally, hypoglycemia at forty minutes during this test, with a true blood glucose below 40 mg. per 100 ml., was encountered in eight cases in the liver disease group, with symptomatic hypoglycemia in five; similar symptoms were presented in only three other patients in the entire study group.

Chronic recurrent pancreatitis:

Four patients in our study group had a primary diagnosis of chronic relapsing pancreatitis. None was studied during an acute symptomatic episode. There was a past history of documented pancreatitis in each case, a chronic alcoholic history was elicited in all, and there was associated significant liver dysfunction in two of these patients. None had steatorrhea, but pancreatic calcification was demonstrable in three of the four patients, and two cases had a past history of glycosuria during attacks. A positive diabetic family history was present in three of the four patients. All four cases in this disease category had abnormal oral sodium tolbutamide tests.

Azotemic patients:

Included are six patients with blood urea nitrogen values ranging from 32 mg. per 100 ml. to 84 mg. per 100 ml. with proportionate elevations of the serum creatinine level in each of these cases. The primary diagnoses in these patients were hypertension, bronchogenic carcinoma, and two cases of multiple myeloma. An abnormal oral sodium tolbutamide test was elicited in two of our six cases in this group, but both of these patients had a positive family history of diabetes.

Hyperthyroidism:

Five cases of thyrotoxicosis were studied, four due to diffuse toxic goiter and one classified as toxic nodular goiter. Four patients were female, one male, and none had a past history or family history suggestive of diabetes. None had an abnormal third-hour blood sugar with their abnormal two-hour oral glucose tolerance during the thyrotoxic state, and all regained normal oral glucose tolerance after they became euthyroid. The oral sodium tolbutamide test was normal in each case in which it was performed during the thyrotoxic state.

Spontaneous hypoglycemia (*table 3*):

It was somewhat surprising that ten patients in the group selected for study had symptomatic reactive hypoglycemia. None had a low blood sugar in the fasting state; all were included in the study because they had an elevated blood sugar level at the second hour of the oral glucose tolerance test, and each patient had hypoglycemic blood glucose levels at the third to fifth hour of the same test. The bromsulphalein liver function test was normal in each case, and there was no obvious evidence of an associated endocrinopathy. One patient referred by the neurologic service had a past history of subtotal gastrectomy for peptic ulcer ten years previously, and this patient had a normal intravenous glucose tolerance test as well as a normal oral sodium tolbutamide test. The other nine cases in this group presented with a variety of concomitant diseases (table 3), and either a seventy-two-hour fast test or a three-hour intravenous sodium tolbutamide test was done in each patient, all of which were negative for evidence of insulinoma. An abnormal oral sodium tolbutamide test was elicited in eight of the ten cases in this hypoglycemic group, five of whom had a positive family history of diabetes, and five of these positive tolbutamide reactors also had a past medical history of either glycosuria or obstetrical history suggestive of diabetes. Since it is well known that stimulative hypoglycemia is not an uncommon symptom of latent diabetes,[11] we conclude from our brief experience that an abnormal oral sodium tolbutamide test should be of supplemental diagnostic value in such patients.

Carbohydrate intolerance after recovery from myocardial infarction (table 4):

In collecting our group for this study we found twenty-three of forty patients with acute myocardial infarction, and not previously diagnosed as overtly diabetic, to have an initial elevation of their two-hour postprandial screening blood glucose level when tested as soon as possible after hospital admission. Subsequent repeated fasting blood glucose determinations revealed two overt diabetics, and fifteen patients had normal fast-

TABLE 3

Spontaneous hypoglycemia

Age	Sex	Concomitant disease	Positive diabetic history	PMH positive (a) glycosuria (b) obstetric	BSP Liver function	OGTT (FBS = 110 or less) 1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	Oral sodium tolbutamide test
62	M	Post-gastrectomy	0	0	Normal	239	149	56	47	65	Normal
46	M	0	+	0	Normal	156	138	78	43	78	Abnormal
68	M	Hypercholesterolemia	0	0	Normal	186	151	118	41	68	Abnormal
60	M	Hypercholesterolemia	0	0	Normal	185	148	128	48	56	Abnormal
34	F	0	+	+	Normal	168	132	112	42	64	Abnormal
53	F	Peripheral neuropathy	+	+	Normal	156	138	118	52	58	Abnormal
34	F	Obesity	0	+	Normal	162	132	48	32	68	Abnormal
32	M	Obesity	+	+	Normal	200	168	112	49	58	Abnormal
34	M	Obesity	+	+	Normal	227	156	68	52	78	Abnormal
58	F	Depression; arteriosclerosis	+	0	Normal	178	156	63	48	76	Normal

TABLE 4

Carbohydrate intolerance after recovery from myocardial infarction*

Age	Sex	PMH (diabetic)	FH (diabetic)	Oral GTT 1 hr.	2 hr.	3 hr.	Oral sodium tolbutamide test (per cent of FBS) 30 min.	40 min.	Normal or abnormal OTTT
51	M	Neg.	Pos.	186	160	134	93	75	Abnormal
62	M	Neg.	Neg.	204	180	168	92	85	Abnormal
55	F	Neg.	Pos.	162	142	96	84	69	Abnormal
45	M	Neg.	Pos.	162	132	98	93	78	Abnormal
62	F	Obs. +	Pos.	180	158	132	92	87	Abnormal
50	M	Neg.	Neg.	174	153	94	86	78	Abnormal
46	M	Neg.	Neg.	164	136	87	53	42	Normal
62	M	Neg.	Pos.	170	153	122	91	85	Abnormal
53	F	Obs. +	Neg.	222	158	128	92	78	Abnormal
71	M	Neg.	Pos.	178	151	115	88	79	Abnormal
55	F	Neg.	Neg.	178	142	102	63	53	Normal
64	F	Neg.	Pos.	186	142	112	84	78	Abnormal
42	M	Neg.	Neg.	184	142	122	90	84	Abnormal
70	M	Glyco. +	Pos.	178	138	112	89	81	Abnormal
73	M	Neg.	Neg.	164	138	92	72	58	Normal

*Fasting blood sugar within normal limits in each case. Hypercholesterolemia (250 mg. per 100 ml.) in each case. Tests performed at least two weeks after acute attack.

ing blood sugars but impaired two-hour glucose levels when subjected to the oral glucose tolerance test at least two weeks after the acute attack. These fifteen cases, ranging in age from forty-two to seventy-three, including ten males and five females, were additionally screened with the oral sodium tolbutamide test. An abnormal tolbutamide test was found in twelve of these fifteen cases, all of whom also had persistent hypercholesterolemia at least two weeks after the onset of acute myocardial infarction.

Correlation of the abnormal sodium tolbutamide test results with other clues to diabetes detection revealed a positive family history of diabetes in eight of the fifteen patients in this group, and each of these eight had an abnormal oral sodium tolbutamide test. The third-hour blood glucose level on tolerance testing was elevated in nine of the fifteen cases, and all of these had abnormal oral sodium tolbutamide tests. A past "diabetic" obstetrical history was elicited in two patients, and a history of glycosuria during a previous infarction was present in one male. Each of these three patients also had an abnormal oral sodium tolbutamide test. Conversely, four of the fifteen patients surveyed in this group revealed none of the above clues to a preexisting asymptomatic diabetic state, and only one of these had an abnormal oral sodium tolbutamide test.

Carbohydrate intolerance in lymphomas and related diseases (table 5):

Unexpectedly, among the group in our study which was chosen on the basis of preliminary selection as described above, sixteen patients had a primary diagnosis of a lymphoma or a related potentially neoplastic disease, and therefore these cases are summarized separately. The only other neoplasm which was present in multiple frequency in this series was bronchogenic carcinoma which was the ultimate diagnosis in four of our

TABLE 5

Carbohydrate intolerance in lymphomas and related diseases.*

Diagnosis	Age	Sex	Wgt.	FH diabetic	PMH diabetic	BSP	BUN	Third hr. BS on SGTT	Oral Sod. Tolbu. Test
Myeloma	66	M	146	Neg.	Neg.	N	42	62	Normal
Lymphatic leukemia	60	F	129	Neg.	Neg.	N	N	93	Normal
Myeloma	65	M	145	Neg.	Neg.	N	N	102	Normal
Lymphatic leukemia	67	M	138	Pos.	Neg.	N	N	102	Normal
Lymphosarcoma	50	M	146	Pos.	Neg.	N	N	47	Normal
Polycythemia vera	53	F	131	Neg.	Neg.	N	N	61	Normal
Myeloma	63	F	138	Neg.	Neg.	15 per cent	N	56	Normal
Lymphosarcoma	58	F	142	Pos.	Obs.+	N	N	172	Abnormal
Lymphatic leukemia	55	F	136	Neg.	Neg.	16 per cent	N	65	Normal
Lymphosarcoma	69	M	138	Neg.	Neg.	18 per cent	N	88	Normal
Lymphoma	38	M	144	Pos.	Neg.	18 per cent	N	79	Normal
Lymphatic leukemia	41	M	148	Pos.	Neg.	N	N	48	Normal
Myeloma	71	M	148	Pos.	Neg.	N	42	118	Abnormal
Lymphoma	58	M	148	Neg.	Neg.	N	N	132	Abnormal
Polycythemia vera	65	F	132	Pos.	Obs. +	N	N	118	Abnormal
Lymphosarcoma	47	F	132	Neg.	Neg.	N	N	68	Normal

*Fasting blood sugar normal and abnormal two-hour oral glucose tolerance in all cases.

total group of 105 cases. Gastrointestinal malignancies were eliminated from the study group by the method of our initial selection of patients. The lymphomas and related diseases as summarized in table 5 include cases diagnosed as lymphoma, lymphosarcoma, lymphatic leukemia, myeloma, and polycythemia vera. All the patients were tolerating an adequate diet at the time of study, and none was receiving steroids or other medication liable to interfere with glucose tolerance. The mean age of this group was fifty-eight years, compared to a mean age of fifty-five years in the total group. Their mean weight, however, was 142 pounds compared to a mean weight of the total group of 153 pounds. Significant azotemia was present in two cases, one of whom had an abnormal oral tolbutamide test, and the bromsulphalein liver function test was significantly abnormal in four cases, each of whom had a normal oral sodium tolbutamide test. Only four of the sixteen patients in this lymphoma group with abnormal oral glucose tolerance had abnormal oral sodium tolbutamide tests, and each of these had at least one additional clue suggestive of an occult diabetic state (table 5).

DISCUSSION

The possibility of prevention of symptomatic diabetes depends largely upon the earliest possible detection of its asymptomatic stage, and newer diagnostic technics are quite properly designed to enhance earlier recognition of a relative or absolute lack of effective insulin. Our data records the application of an oral modification of the sodium tolbutamide test to a group of hospitalized patients selected on the basis of a minimally abnormal oral glucose tolerance test, performed after an attempt to control pretest conditions. In the opinion of others,[4] the tolbutamide response test is more specific but less sensitive than the glucose tolerance test as an indicator of the presence of mild diabetes. Therefore, the reliability of the diagnosis of a minimal diabetic state should be enhanced when both tests are positive. This does not imply, however, that a normal tolbutamide response test positively rules out the diagnosis of diabetes in a patient with impaired glucose tolerance.

Interesting correlations were discovered by us between the abnormal tolbutamide test when compared with other concomitant evidence suggestive of a minimal diabetic state, including an elevated third-hour blood sugar level on oral glucose tolerance test, a past medical history suggestive of early diabetes, or a positive family history of diabetes. There was a significant correlation with each of these additional clues to early diabetes detection and the abnormal oral sodium tolbutamide test. Perhaps the application of this information may improve the diagnostic significance of both the standard oral glucose tolerance test and the oral sodium tolbutamide test.

Unlike the data of Kaplan,[12] we found no significant difference in the incidence of abnormal oral sodium tolbutamide tests with advanced age. However, West[13] reports that the fasting blood glucose levels of apparently normal older subjects are significantly higher than a comparable younger age group. Therefore, the effect of advanced age per se on our test figures may

be somewhat neutralized because we discarded from the study all patients with repeated fasting true blood glucose levels of 110 mg. per 100 ml. or higher.

Creutzfeldt et al.[14] and Kaplan,[12] among other authors, have recommended tolbutamide tolerance as a more specific test than the glucose tolerance in distinguishing abnormalities of carbohydrate metabolism present in liver disease from those due to insulin deficiency. Comparative glucose tolerance and oral sodium tolbutamide testing in our chronic liver disease group confirmed this opinion that the tolbutamide test may be of greatest differential diagnostic value in the impaired glucose tolerance accompanying hepatic disease.

The carbohydrate intolerance of uremic patients has previously been studied by intravenous sodium tolbutamide testing and believed to be distinguishable from that due to the diabetic state by a normal blood sugar response to such tests.[15] Our scanty experience with the oral sodium tolbutamide test in six azotemic patients with minimally abnormal oral glucose tolerance is compatible with this opinion.

The effect of thyrotoxicosis on glucose tolerance lends itself well to study because of the greater opportunity to re-evaluate this test after control of the hyperthyroid state. Our results with the oral sodium tolbutamide test in thyrotoxic patients with abnormal glucose tolerance are similar to the results of others[16] who found the intravenous tolbutamide tests normal during thyrotoxicosis in those patients who regained normal glucose tolerance after becoming euthyroid.

It is not surprising that twelve of fifteen patients with impaired carbohydrate tolerance after recovery from the acute phase of a myocardial infarction had an associated abnormal oral sodium tolbutamide test. The normal tolbutamide reactors had no concomitant clues suggestive of a latent diabetic state. It has been stated that coronary artery occlusion is currently the largest single cause of death in diabetic patients,[17] and it is well known that coronary artery disease is a fertile clinical field for the detection of previously unrecognized diabetes.[18,19] Perhaps the oral sodium tolbutamide test may prove to be an aid in establishing greater specificity to this diagnosis during a period when the standard glucose tolerance test may be impaired nonspecifically by a variety of factors.

Altered carbohydrate tolerance in patients with neoplastic diseases is well known whether the patient is tested orally or intravenously.[20,21] It is believed by some that cachexia may be responsible for this abnormality. The intravenous tolbutamide test has been reported as a more specific diagnostic aid than glucose tolerance testing in carcinoma of the pancreas.[22] Possibly because the criteria for selecting patients for our group study excluded postoperative cases and also cases with gastrointestinal symptoms affecting their usual diet pattern, the only groups of neoplasia found in our selective study were a small number of patients with bronchogenic carcinoma and sixteen patients with lymphomas, lymphosarcoma, lymphatic leukemia, and related diseases. Clinical evidence of cachexia did not seem to be a dominant factor in these cases, and, by selection, they were receiving no drugs known to interfere with glucose tolerance. Azotemia and abnormal liver function were present in a small number of these cases, but the positive tolbutamide reactors usually had concomitant evidence suggestive of pre-existing diabetes.

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BRIEF NOTES AND COMMENTS

Combined Use of Regular and Crystalline Protamine (NPH) Insulins in the Treatment of Severe Diabetes

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SUMMARY

The use of twice daily injections of regular and extended action insulin mixtures, originally described in 1937, is revived and Crystalline Protamine Insulin (NPH) is proposed as the most suitable extended action insulin at present available for use in conjunction with Regular Insulin.

It is suggested that, in severe diabetes, the physician should aim at achieving a blood glucose of below 150 mg. per 100 ml. before breakfast, lunch and supper, and at bed time. This standard of control has been sought in ten pregnant diabetics treated in hospital with twice daily injections of regular + NPH insulin mixtures, and blood sugar results are reported. Experience with the same regimen in 162 diabetic clinic outpatients is also described.

Practical aspects of treatment by twice daily Regular + NPH Insulin mixtures are discussed; it is concluded that this regimen provides a good, and probably the most widely applicable, method at present available for the treatment of severe diabetes. It is sometimes possible to omit one or more of the four insulin dose components of the regimen. DIABETES *15*:219-22, March, 1966.

Diabetes mellitus may usefully be described as severe when withdrawal of insulin is rapidly followed by hyperglycemia and ketosis. The first effective treatment for this condition was by frequent injections of Regular Insulin (RI). Although twice daily administration usually achieved satisfactory symptomatic control, this method of routine treatment fell into disuse in many centers with the development of long-acting preparations which halved the number of injections required. Yet it has always been thought that frequent RI injections mimic more closely the pattern of endogenous insulin secretion in response to carbohydrate intake. Considerations relevant to this form of treatment have recently been reviewed by Lukens[1] in his 1964 Joslin Memorial Lecture. It is, however, usually impossible to maintain the blood sugar close to normal throughout the whole twenty-four hours using two injections of RI alone, and it is certain that late diabetic complications may develop on such a regime.[2,3] Moreover, there is much evidence both from studies of diabetic pregnancy[4,5] and of diabetic complications[6-10] to suggest that it is desirable to keep the blood sugar as closely as possible within physiological limits at all times. These considerations led us in 1958 to start treating most of our severe diabetics with twice daily injections of RI and Crystalline Protamine Insulin (NPH) mixtures. This paper explains the rational basis for this method of treatment and reports our clinical experience.*

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*The three main meals are described throughout as "Breakfast," "Lunch," and "Supper"; "Tea" is used to describe a buffer feed between lunch and supper. Twice daily insulin regimens are expressed as fractions, the numerator being the morning and the denominator the evening treatment. Blood sugars have been performed by a modified Somogyi-Nelson technic giving results only very slightly higher than true glucose values.