Oral Sodium Tolbutamide in the Diagnosis of Diabetes Mellitus

Thomas J. Vecchio, M.D., David L. Smith, Ph.D., Harold L. Oster, M.D., and Richard Brill, M.D., Kalamazoo, Michigan

SUMMARY

The oral sodium tolbutamide test (OSTT) for diabetes was significantly different in 102 *normal*, twenty-one *borderline*, and twenty-nine *diabetic* subjects as classified by the oral glucose tolerance test (OGTT). Mean thirty-minute values, in per cent of FBS, were 57.0, 72.3, and 86.2, and mean forty-minute values were 44.1, 60.3, and 79.4 in the three groups, respectively.

Individual agreement between the OSTT and OGTT was generally good, though with some conflicts.

Effective blood levels were attained ten minutes after oral administration of sodium tolbutamide, 2.0 gm., and at twenty minutes and beyond levels exceeded those after intravenous administration of 1.0 gram. Hypoglycemic response to the intravenous and oral tests appeared comparable except for a lag of about ten minutes and attainment of lower blood sugar levels at forty and sixty minutes after oral administration. Reproducibility was good, except in those subjects with initial conflict between the OSTT and OGTT.

A test for diabetes mellitus has been described by Unger and Madison,[1] based on the relative delay in development of hypoglycemia in diabetics as compared to normals,[2] following the acute administration of tolbutamide. In this test one gram of sodium tolbutamide is administered intravenously and the "true" blood glucose determined before, and twenty and thirty minutes after, the midpoint of the injection. More recently, Boshell[5] has described a modification of this test using sodium tolbutamide orally in a dose of 2 gm. given as four tablets, accompanied by sodium bicarbonate, which is given to neutralize gastric acidity and preserve the tolbutamide as its more soluble sodium salt. The results obtained appeared comparable to those with the intravenous test, with a lag of about ten minutes.

We have compared the blood glucose response and serum concentration of tolbutamide during the oral and intravenous tests, have studied the oral test in an additional group of normals and diabetics, as determined by the standard oral glucose tolerance test, and have examined the reproducibility of the oral test.

Presented in part at the Twenty-third Annual Meeting of the American Diabetes Association in Atlantic City on June 16, 1963.

From The Upjohn Company, Kalamazoo, Michigan; Jackson and Grand Rapids, Michigan.

METHODS

The subjects were presumed nondiabetic, and known mild diabetic, males at the Jackson Prison and the Michigan Veterans' Facility. A two-hour oral glucose tolerance test was performed on all subjects at least one week before or after the tolbutamide test, employing a dose of 100 gm. of glucose by mouth. All subjects received a diet containing 300 gm. of carbohydrate for three days prior to each test.

Subjects were redivided into three groups on the basis of their response to the two-hour oral glucose tolerance test, according to the criteria of Fajans and Conn.[4] Those with a peak value of 160 or above and a two-hour value of 120 or above were called *diabetic*, whereas those with values below these levels were called *normal*. Subjects whose tests exceeded one but not both of these levels were designated *borderline*, for the purposes of this study. Average ages and body weights of these three groups are shown in table 1.

Sodium tolbutamide was administered orally as four 0.5-gm. tablets, immediately preceded by four tablets of sodium bicarbonate, 0.5 gm. Intravenous sodium tolbutamide was administered in a dose of 1.0 gm. in 20 cc. of sterile water over three minutes. Venous blood was drawn for glucose determination fasting and at intervals up to sixty minutes. The tests were terminated by sweetened fruit juice, followed by a good breakfast.

Two to 2.5 cc. of blood were collected in AutoAnalyzer vials containing sodium fluoride, 0.5 mg., and heparin, 40 U, frozen immediately and transported to The Upjohn Company laboratories in dry ice. They remained frozen until run, within two weeks after collection (previously it had been determined that blood glucose values remain constant for at least six months under these conditions). Whole blood glucose determinations were performed on the AutoAnalyzer by a modification of the Hoffman method, utilizing quality control procedures. Serum tolbutamide levels were

TABLE 1
Responses to the oral sodium tolbutamide test in subjects divided according to their glucose tolerance

Subjects	Number	Age (±S.D.)	Body weight (±S.D.)	F.B.S. (mg./100 ml.)	Test results (±S.D.) 30 min. (per cent F.B.S.)	P	40 min. (per cent F.B.S.)	P
Normal	102	38.7 ±9.3	169.9 ±24.8	79.4 ±7.0	57.0 ±13.0	<0.001	44.1 ±12.0	<0.001
Borderline	21	48.1 ±11.2	162.4 ±37.0	83.4 ±8.0	72.3 ±10.1	<0.01	60.3 ±12.0	<0.01
Diabetic	29	56.9 ±11.1	169.3 ±35.2	110.7 ±39.5	86.2 ±10.7		79.4 ±13.3	

performed by a modification of the Toolan-Wagner method.[5]

RESULTS

Comparison between the oral and intravenous sodium tolbutamide tests

Both tests were performed in twenty *normal* and six *diabetic* subjects one week apart, each test being done first in one half of the subjects. In the *normals* there was a relative delay in the response to the oral as compared to the intravenous test, but results were almost identical at thirty minutes. After this, the hypoglycemic response to oral administration was greater, probably because of continued absorption and the use of a higher dose (figure 1). The same differences were seen to a lesser degree in the less responsive *diabetics*, though they were not of statistical significance in the small group studied.

Hypoglycemic symptoms were commonly seen between the forty- and sixty-minute specimens during the oral test, so that the sixty-minute specimen was later abandoned and the test terminated at forty minutes.

The mean serum tolbutamide concentrations during both tests in five normal subjects are shown in figure 2. Although much lower at ten minutes, at twenty minutes the concentrations are higher during the oral test, and the differences become more marked thereafter. The basis for the initial delay and subsequent increase in blood glucose response during the oral test noted above becomes apparent.

The variability of individual serum tolbutamide concentrations is greater after oral than after intravenous administration for the first thirty minutes (table 2). However, effective levels were reached after oral administration at ten minutes in all five subjects, showing the extremely rapid absorption of this preparation.

Response to the oral sodium tolbutamide test (OSTT)

The test was performed on 102 *normal*, twenty-one *borderline*, and twenty-nine *diabetic* subjects as defined above. Mean ages and body weights of these groups and

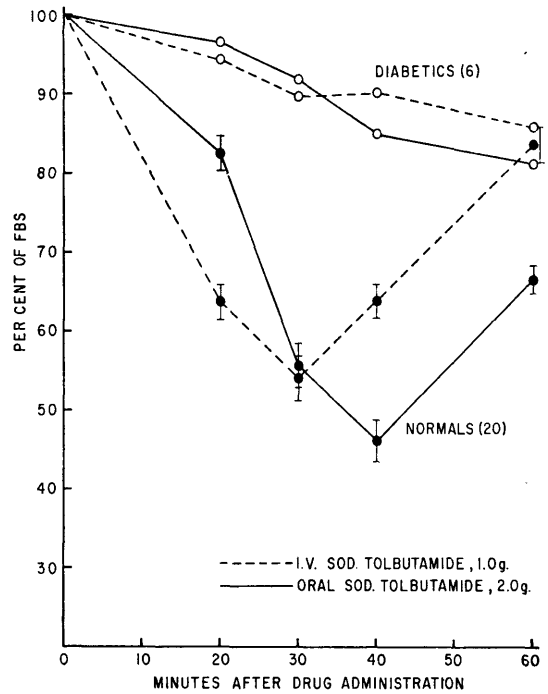

FIG. 1. Comparison of blood glucose response to oral and I.V. sodium tolbutamide in normals and diabetics (S.E.M. in normals shown by brackets; overlap occurs for all values in diabetics and is not shown.)

their responses to the test are shown in table 1. These responses are depicted graphically in figure 3, which shows also a breakdown of the twenty-nine *diabetic* subjects, fifteen of whom had fasting blood glucose values under 100 mg. per 100 ml., while fourteen had fasting values over this level. The former showed greater responsiveness, with mean thirty- and forty-minute values of 80.1 ± 10.3 (S.D.) and 71.9 ± 11.8, in contrast to the latter, whose corresponding values were 93.1 ± 4.8 and 88.5 ± 7.6 ($p < 0.001$).

The individual responses at thirty and forty minutes in each of the three groups of subjects, expressed in per cent of the initial fasting blood glucose, are shown

TABLE 2

Individual serum tolbutamide concentrations (mg. per 100 ml.) after administration of sodium tolbutamide intravenously (1.0 gm.) and orally (2.0 gm.)

Min.	Subject 1	2	3	4	5	Mean	S.D. (mg./ 100 ml.)	S.D. (per cent of mean)
	Intravenous							
0	0	0	0	0	0	0	0	0
10	20	17	17	18	17	18.0	1.4	7.8
20	16	15	14	16	17	15.7	1.3	8.3
30	15	13	13	16	15	14.5	1.5	10.4
40	15	13	12	16	15	14.3	1.6	11.2
	Oral							
0	0	0	0	0	0	0	0	0
10	14	16	5	7	10	10.3	4.4	42.7
20	21	24	13	18	21	19.4	4.3	22.2
30	22	22	16	23	25	21.7	3.3	15.2
40	22	23	21	19	26	22.3	2.4	10.8

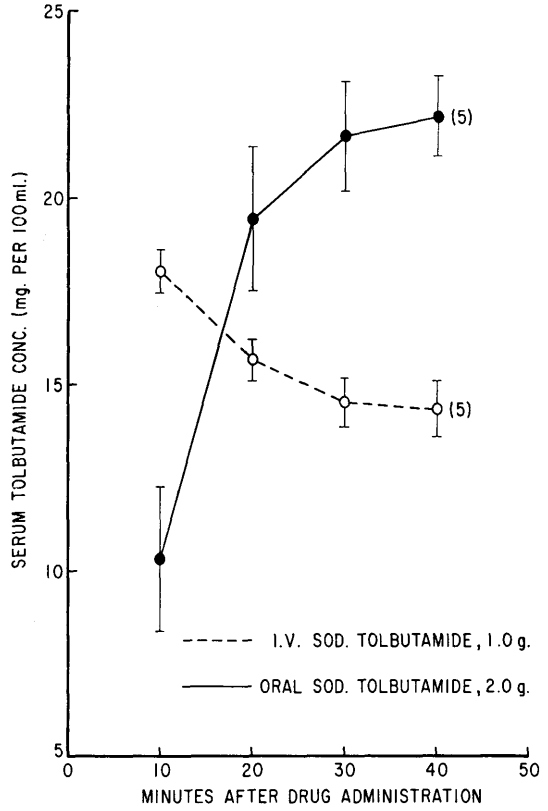

FIG. 2. Mean serum tolbutamide levels during the oral and I.V. sodium tolbutamide tests (S.E.M. shown by brackets).

in figure 4, with the mean values represented by short horizontal lines. Dotted lines are drawn at the cut-off values of 78 per cent at thirty minutes, and 72 per cent at forty minutes, as tentatively established by Boshell. At thirty minutes, three *normals*, or 2.9 per cent, lie above this line, and four *diabetics*, or 13.8 per cent, are below it, with the *borderline* subjects on both

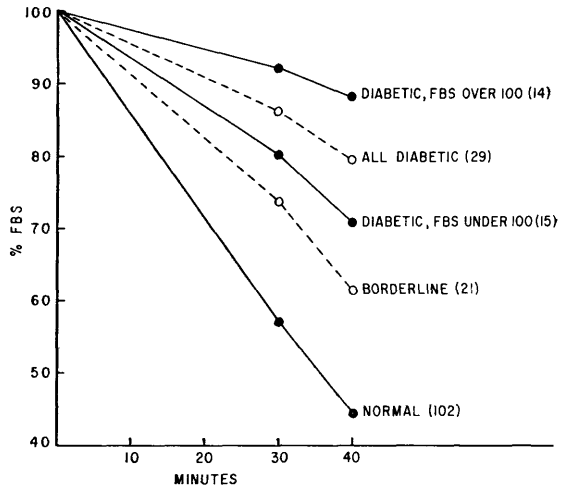

FIG. 3. Oral sodium tolbutamide response curves in subjects with normal, borderline, and diabetic oral glucose tolerance.

sides. At forty minutes three *normals*, or 2.9 per cent, lie above the line and seven *diabetics*, or 24.1 per cent, are below. The thirty-minute value, therefore, appears to be more discriminatory at the proposed levels in this limited group of subjects. However, only one *diabetic* in this group and one *diabetic* in Boshell's group fell below 56 per cent at forty minutes (a total of

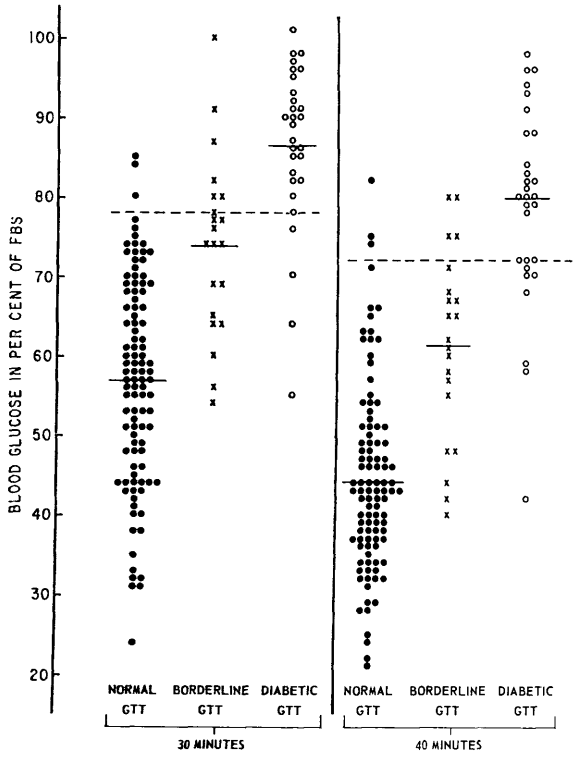

FIG. 4. Individual responses to oral sodium tolbutamide (in per cent of FBS).

2/73 or 2.7 per cent). Therefore, values below 56 per cent at forty minutes appear to diminish markedly the likelihood of diabetes.

Effect of body weight on response

Since a fixed dose of sodium tolbutamide of 2.0 gm. was employed in all subjects, heavier subjects received a smaller dose per unit of body weight. However, there was no significant trend noted in the response at thirty minutes when the *normal* subjects were divided according to body weight (table 3).

Reproducibility

The reproducibility of the OSTT was examined by repetition of the test after intervals of one to six months under similar conditions. Results are shown in table 4.

TABLE 3

Thirty-minute values of *normals* of various body weight groups

Body weight (pounds)	Number of subjects	Mean 30-min. value (per cent F.B.S.)	Standard error of mean
100 - 119	1	61.1	—
120 - 139	16	58.3	3.51
140 - 159	15	61.6	3.17
160 - 179	34	56.8	2.23
180 - 199	25	52.8	2.74
200 - 219	6	62.9	3.85
220 - 239	3	49.5	4.33
240 - 259	1	59.7	—

Those thirty-two subjects in which both the standard GTT and OSTT were *normal* initially showed good reproducibility, the mean values on repeat testing being almost identical at thirty minutes, and only one subject showing a change in diagnostic category. Mean difference between the two OSTT tests was 11.8 (per cent FBS), without regard for sign. In those six subjects in whom there was initial conflict between the OSTT and GTT, greater variability was seen on repeat of the OSTT, changes in diagnosis, using the cut-off point of 78 (per cent FBS) at thirty minutes, occurring in five out of the six subjects. These subjects may well be in an unstable phase of the disease, in which variability of the test from time to time may be expected.

In the eleven diabetics who showed initial agreement between the OSTT and the GTT reproducibility was again good. The one diabetic whose OSTT changed from *diabetic* to *normal* on repeat had initially shown a GTT which barely satisfied the criteria for diabetes, with a peak of 164 and a two-hour value of 120.

DISCUSSION

In the absence of specific clinical, pathological, and pathophysiological findings for comparison, standards for a new test for mild diabetes mellitus can only be tentative. Recognizing this, we have studied the oral

TABLE 4

Reproducibility of the oral sodium tolbutamide test (see text)

Initial tests (OSTT and GTT)	Number of subjects	Changes in diagnosis	Mean 30-min. values (per cent of F.B.S.) Initial	Repeat	Mean difference between tests
Both *normal*	32	1	54.7	54.9	11.8
Conflict	6	5	82.8	69.5	13.3
Both *diabetic*	11	1	90.1	91.1	3.8

sodium tolbutamide test in presumed normal and diabetic subjects, using the oral glucose tolerance test as a frame of reference. However, the latter test, though of great usefulness in the diagnosis of diabetes mellitus, cannot be regarded as a completely reliable criterion of the disease, when positive, in view of the numerous other disease states in which high prevalences of positive tests have been reported,[8-19] as well as the effect of factors, such as aging[20,21] and physical inactivity,[22] in decreasing glucose tolerance. Moreover, results on repeated examination are inconstant.[23,24] In some cases, other abnormalities characteristic of diabetes have been noted prior to the development of an abnormal test.[25] Accordingly, results obtained as in this study by using the GTT as a norm must be regarded as provisional, and should be checked in the future by long-term follow-up studies, random surveys of large populations, and, perhaps, by comparison with other possible indicators of diabetes mellitus, such as the presence of a synalbumin antagonist,[26] serum insulin response to glucose,[27] kinetics of insulin complexing,[28] and tissue changes.

Further studies of the intravenous sodium tolbutamide test,[29-32] on which the oral test is based, have confirmed the original report of Unger and Madison.[1] Kaplan[29] has presented evidence suggesting that the test may be more specific than the oral glucose tolerance test in certain patients with advanced age, obesity, liver disease, steroid therapy, and thyrotoxicosis, though more recently a high incidence of positive tests has been noted in aged males.[33] Creutzfeldt has recommended the test as a means of distinguishing carbohydrate abnormalities resulting from hepatic disease from those due to insulin deficiency.[31] It has also been reported to be of value in the diagnosis of carcinoma of the pancreas,[34] and as a means of distinguishing azotemic pseudodiabetic patients from those with true diabetes and azotemia.[8] Bastenie[35] has used the change in the

rate of glucose disposal when tolbutamide and glucose are given successively by vein as an index of pancreatic insulin reserve, and oral tolbutamide has been used to estimate the insulin-producing capacity of the pancreas in juvenile diabetics.[36] In preliminary studies in ten patients with normal glucose tolerance believed to be prediabetic on varied grounds, Jackson[37] found mean values resembling those seen in mild diabetics, though with marked individual variation. However, the finding of normal tolbutamide tests in certain patients with abnormal glucose tolerance has been interpreted to signify that the tolbutamide test is a less sensitive indicator of mild diabetes than the oral glucose tolerance test.[38]

Several studies have shown that the acute response to intravenous tolbutamide diminishes in late pregnancy,[29,39-41] and the test then loses its value because of the high incidence of positives. It has also been shown that the test is of little value in predicting eventual therapeutic response to tolbutamide.[42]

The data we have presented support Boshell's suggestion that the oral sodium tolbutamide test will be comparable to the intravenous test currently in use, while offering the advantages of convenience and possibly of safety. Absorption of sodium tolbutamide is extremely rapid, effective blood levels being obtained at ten minutes. This is probably dependent on two factors. First, the formulation of sodium tolbutamide employed is rapidly soluble, with a dissolution half time of 2.7 minutes, as determined by a standardized automated technic.[43] Secondly, the drug is probably absorbed in part through the stomach wall; Miller has shown that blood levels are obtained promptly in the rat after administration of sodium tolbutamide despite prior ligation of the pylorus.[44]

The forty-minute value does not appear to contribute appreciably to the interpretation of the test, so that it may be possible to dispense with it, except in problem cases. This would reduce the number of glucose determinations to two, at zero and thirty minutes. Hypoglycemic symptoms are common after the forty-minute specimen, infrequent between the thirty- and forty-minute specimens, and rare before thirty minutes. Terminating the test after the thirty-minute specimen should minimize the likelihood of their occurrence.

The mean results of this test were significantly different in groups of subjects already separated by the oral glucose tolerance test, though with some conflicts. The meaning of these conflicts is not clear and will require further study. In the case of the twenty-one *borderline* subjects, who would have been called normal by the usual criteria of the oral glucose tolerance test, positive OSTTs were found in six, one of whom had previously been told he had diabetes. This group is especially interesting in indicating that subjects with isolated elevation of the peak or two-hour value on GTT may be abnormal when investigated by another method.

The reproducibility of the test is good except in those individuals who show conflicts between it and the glucose tolerance test and who are probably in an unstable, borderline state.

It appears that this test should be of value as a convenient means of screening for mild diabetes, and as a supplement to the standard glucose tolerance test.

The diagnosis of diabetes mellitus in asymptomatic individuals involves serious implications, including a lifetime of treatment and reduced life expectancy, insurability and employability, as well as limitations in selection of a marriage partner. It is doubtful that such a diagnosis should ever be made on the basis of a single glucose tolerance test or tolbutamide test. Careful follow-up and repeated performance of both tests would seem to be indicated in questionable cases.

ACKNOWLEDGMENT

We are indebted to Dr. John H. Flokstra, Ralph F. Willy, and William C. Bell for technical assistance and to Dr. James A. Hagans for the statistical analyses.

SUMMARIO IN INTERLINGUA

Oral Tolbutamida a Natrium in le Diagnose de Diabete Mellite

Le resultatos del oral test con tolbutamida a natrium (OTTN) pro diabete esseva significativemente differente in le tres gruppos de subjectos in qui le resultatos del oral test de tolerantia pro glucosa (OTTG) esseva designate como normal (102 casos), marginal (vinti-un casos), e indicative de diabete (vinti-novem casos). Le valores medie obtenite per le OTTN esseva in le tres gruppos, exprimite in pro cento del sucro sanguinee in stato jejun, 57,0, 72,3, e 86,2 post trenta minutas e 44,1, 60,3, e 79,4 post quaranta minutas.

Le accordo inter le resultatos del OTTN e illos del OTTG in le casos individual esseva bon, a generalmente parlar. Conflictos inter le duo non esseva absente.

Efficace nivellos sanguinee del pharmaco esseva obtenite intra dece minutas post le administration oral de tolbutamida a natrium in un dosage de 2,0 g. Post vinti minutas e plus, le nivellos excedeva illos attingite per le administration intravenose de 1,0 g del pharmaco. Responsas hypoglycemic in le intravenose e oral tests pareva esser comparabile, excepte que le administration oral esseva sequite de un retardo de circa dece minutas e del attingimento de plus basse nivellos de sucro sanguinee post quaranta e sexanta minutas. Le repro-

ducibilitate esseva bon, excepte in le caso del subjectos con conflictos initial inter le OTTN e le OTTG.

REFERENCES

[1] Unger, Roger H., and Madison, Leonard L.: A new diagnostic procedure for mild diabetes mellitus. Diabetes 7:455-61, 1958.

[2] Mirsky, I. Arthur, Diengott, Daniel, and Dolger, Henry: The relation of various variables to the hypoglycemic action of 1-butyl-3-p-tolylsulfonylurea in patients with diabetes mellitus. Metabolism 5:875-93, 1956.

[3] Boshell, Buris R., Wilenski, Allan S., Wayland, James, and Carr, James H., Jr.: A new oral diagnostic test for diabetes mellitus. Metabolism *12*:108-16, Feb. 1963.

[4] Fajans, Stefan S.: in Diabetes. Ed. R. H. Williams, New York, Paul B. Hoeber, Inc., 1960.

[5-7] Toolan, Thomas J., and Wagner, Richard L.: The physical properties of chlorpropamide and its determination in human serum. Ann. N.Y. Acad. Sci. *74*:449-58, 1959.

[8] Westervelt, Fred B., Jr., and Schreiner, George E.: The carbohydrate intolerance of uremic patients. Ann. Int. Med., *57*:266-76, Aug. 1962.

[9] Reaven, Gerald, Calciano, Anthony J., Cody, Robert M.: Glucose tolerance in patients with myocardial infarction. Circulation *26*:775, Oct. (Part 2), 1962.

[10] Waddell, William R., and Field, Richard A.: Carbohydrate metabolism in atherosclerosis. Metabolism 9:800-06, Sept. 1960.

[11] Aleksandrow, D.; Ciswicka-Sznajderman, M., Ignatowska, H.: Studies on disturbances of carbohydrate metabolism in atherosclerosis. J. Artherosclerosis Res. 2:171-80.

[12] Rankin, Thomas J., Jenson, Robert L., and Delp, Mahlon: Oral glucose tolerance as a test of liver function. Gastroenterology *25*:548-52, 1953.

[13] Zollinger, Robert M., and Hoerr, Stanley O.: Gastric operations: Troublesome postoperative symptoms with special reference to carbohydrate ingestion. JAMA. *134*:575-79, June 14, 1947.

[14] Glicksman, Arvin S., and Rawson, Rulon W.: Diabetes and altered carbohydrate metabolism in patients with cancer. Cancer 9:1127-34, Nov.-Dec. 1956.

[15] Crawford, T.: Carbohydrate metabolism in hypothyroidism and hyperthyroidism. Arch. Dis. Child. *15*:184, 1940.

[16] Beardwood, Joseph T., Jr.: Dextrose tolerance test: Its uses and dangers. Med. Clinics N. Amer. *12*:1121-25, 1929.

[17] Sowton, Edgar: Cardiac infarction and the glucose-tolerance test. Brit. Med. J., *1*:84-86, Jan. 13, 1962.

[18] Waddell, William R., Geyer, Robert P.; Hurley, Nancy, and Stare, Frederick J.: Abnormal carbohydrate metabolism in patients with hypercholesterolemia and hyperlipemia. Metabolism 7:707-16, 1958.

[19] Howard, J. M.: Studies of the absorption and metabolism in glucose following injury. Ann. Surg. *141*:321, 1955.

[20] Gottfried, Sidney P., Pelz, Kurt S., and Clifford, Ruth C.: Carbohydrate metabolism in healthy old men and women over 70 years of age. Amer. J. Med. Sci. 131/475, 136/480, Oct. 1961.

[21] Wagner, Arnold: The fallibility of the glucose tolerance test in the aged. Geriatrics 588-94, Dec. 1955.

[22] Blotner, Harry: Effect of prolonged physical inactivity on tolerance of sugar. Arch. Int. Med. 75:39-44, 1945.

[23] Unger, Roger H.: The standard two-hour oral glucose tolerance test in the diagnosis of diabetes mellitus in subjects without fasting hyperglycemia. Ann. Int. Med. *47*:1138-53, Dec. 1957.

[24] Freeman, Harry, Looney, Joseph M., and Hoskins, Roy G.: "Spontaneous" variability of oral glucose tolerance. J. Clin. Endocr. 2:431-34, July 1942.

[25] Daysog, Alberto, Jr., Dobson, Harold L., and Brennan, James C.: Renal glomerular and vascular lesions in prediabetes and in diabetes mellitus: A study based on renal biopsies. Ann. Int. Med. *54*:672-84, April 1961.

[26] Vallance-Owen, J., and Lilley, M. D.: An insulin antagonist associated with plasma-albumin. Lancet *1*:804-06, April 15, 1961.

[27] Yalow, Rosalyn S., and Berson, Solomon A.: Plasma insulin concentrations in nondiabetic and early diabetic subjects; determinations by a new sensitive immuno-assay technic. Diabetes 9:254-60, July-Aug. 1960.

[28] Antoniades, Harry N., Bougas, James A., Pyle, Hugh M.: Studies of the state of insulin in blood; the regulation of "free" insulin and insulin complexes in the blood of diabetic and nondiabetic subjects. New Eng. J. Med. *267*:953-57, Nov. 8, 1962.

[29] Kaplan, Norman M.: Tolbutamide tolerance test in carbohydrate metabolism evaluation. Arch. Int. Med. *107*:212-24, Feb. 1961.

[30] Whitehouse, Fred W., and Lowrie, William L.: The intravenous tolbutamide response test; initial observations. J. Mich. Med. Soc. 59:1540-42, Oct. 1960.

[31] Creutzfeldt, W., Willie, K., and Kaup, H.: Intravenöse Belastungen mit Glucose, Insulin und Tolbutamid bei Gesunden, Diabetikern, Leberzirrhotikern und Insulomträgern. Deutsch. Med. Wschr. *87*:2189-95, Oct. 26, 1962.

[32] Zarowitz, Harold, and Eis, Bejamin: The role of a tolbutamide tolerance test in the detection of the mild diabetic state: A preliminary report. Ann. N.Y. Acad. Sci. *74*:662-66, March 30, 1959.

[33] Kauchtschischwili, G. M.: The blood sugar curve after tolbutamide in the aged. Giornale di Geront. (Florence) 9:293-99, 1961.

[34] Berkowitz, Donald, Greenberg, Leonard, and Glassman, Sol: The intravenous tolbutamide test as a diagnostic aid in carcinoma of the pancreas. Amer. J. Med. Sci. *243*:228-32, Feb. 1962.

[35] Bastenie, P. A., Bellens, R., Ooms, H. A., Franckson, J. M. M., and Conard, V.: Measurement of the insulin reserve by the acute intravenous test using tolbutamide (D 860). Ann. d'endocrinologie. *21*, 1960.

[36] Klein, R., Marks, J., and Mirsky, I. A.: Insulin-producing capacity of the pancreas of children with diabetes mellitus. Pediatrics *22*:289-96, Aug. 1958.

[37] Jackson, W. P. U., and Keller, P.: Intravenous tolbutamide and plasma insulin-like activity in probable "prediabetics": A preliminary report. Diabetes. (Supplement) *11*: 138, 1962.

[38] Fajans, Stefan S.: Discussion XII. Diabetes. (Supplement) *11*:139, 1962.

[39] Chesley, Leon C., Kaufmann, Peter, and Pauerstein, Carl: Progressive resistance to intravenous tolbutamide in pregnancy. Metabolism 10:454-63, June 1961.

[40] Burt, Richard L.: Reactivity to tolbutamide in normal pregnancy. Obst. and Gynec. *12*:447-53, Oct. 1958.

[41] Dolger, Henry, Bookman, John J., and Nechemias, Charles: The diagnostic and therapeutic value of tolbutamide in pregnant diabetics. Diabetes (Supplement) 11:97-98.

[42] Sherry, Sol, Zeffren, J. Lester, Braverman, Abe E., and Drey, Norman W.: The use of tolbutamide in the management of adult diabetes. Ann. N.Y. Acad. Sci. 71:249-55, July 10, 1957.

[43] Schroeter, Louis C., and Wagner, John G.: Automated dissolution rate studies of capsules and tablets. J. Pharm. Sci. 51:957-62, Oct. 1962.

[44] Miller, W. L., Jr., Krake, J. J., Vander Brook, M. J., and Reineke, L. M.: Studies on the absorption, mechanism of action, and excretion of tolbutamide in the rat. Ann. N.Y. Acad. Sci. 71:118-24, July 10, 1957.

Recent Trends in Diabetes Mortality

(*Continued from page 29*)

the trends in diabetes mortality for white men and women at these ages parallels, in large measure, the trend in mortality from heart and circulatory disorders; the same underlying factors manifest themselves in both instances. Thus, women may be benefiting by earlier and more consistent medical supervision and by closer adherence to prescribed treatment. Also, in view of the well-established association between overweight and diabetes, benefits may be accruing to women from more effective weight control. It was noted in the Build and Blood Pressure Study, 1959,* that the average weights of women in recent years were less than those of a generation ago, whereas among men they tended to be higher.

As a result of the increased longevity of diabetics, the disease is being reported with increasing frequency as a cause of death at the older ages. Also, mild diabetes is being discovered more frequently in older persons, traceable in some degree to the nation-wide detection campaigns. Both of these factors may be responsible for the fact that only relatively small reductions in mortality from diabetes were recorded among white persons at the more advanced ages.

Nonwhite persons at ages forty-five to fifty-four years showed contrary trends in diabetes mortality for the two sexes during the 1950's, but at the higher ages the record consistently worsened. A number of factors may account for this unfavorable trend. Among them are the migration of Negroes from the rural areas of the South to urban centers and the increased employment of nonwhites in industries which provide health insurance coverage; these developments have given nonwhites greater access to better medical care, and hence have increased the chances of having the disease diagnosed.

Reprinted with permission from *Statistical Bulletin*, Metropolitan Life Insurance Company, August 1962, Vol. 43, pp.1-3.

*See "New Weight Standards for Men and Women," Statistical Bulletin, November-December 1959.

DEATH RATES PER 100,000 FROM DIABETES MELLITUS
By color, sex and age. United States, 1958-59 and 1950-51

Age Period (years)	Males: Average Annual Death Rate 1958-59	Males: Average Annual Death Rate 1950-51	Males: Per Cent Change	Females: Average Annual Death Rate 1958-59	Females: Average Annual Death Rate 1950-51	Females: Per Cent Change
			White			
All Ages						
Crude	13.1	12.8	+ 2	18.5	20.2	− 8
Age-adjusted*	11.3	11.3	0	13.8	16.4	−16
Under 25	0.5	0.6	−17	0.6	0.9	−33
25-34	2.8	2.1	+33	1.9	2.0	− 5
35-44	4.3	3.8	+13	2.7	2.8	− 4
45-54	10.0	9.7	+ 3	8.7	11.4	−24
55-64	29.4	30.8	− 5	38.1	51.8	−26
65-74	76.4	76.4	0	110.9	125.1	−11
75 and over	141.0	140.4	†	173.7	188.2	− 8
			Nonwhite			
All Ages						
Crude	11.6	10.1	+15	21.2	18.3	+16
Age-adjusted*	14.6	12.0	+22	25.9	22.2	+17
Under 25	0.5	0.9	−44	0.8	1.3	−38
25-34	4.0	2.9	+38	3.7	4.0	− 8
35-44	7.2	7.5	− 4	10.8	13.8	−22
45-54	20.2	17.9	+13	36.8	42.1	−13
55-64	45.0	36.1	+25	101.1	77.7	+30
65-74	98.4	69.5	+42	166.5	114.7	+45
75 and over	93.3	78.9	+18	137.8	110.9	+24

*On basis of total population, United States, 1940.
†Less than 5.
Source of basic data: Reports of the National Vital Statistics Division, National Center for Health Statistics.