Unknown Diabetes Mellitus Among Apparently Healthy Men With "Nonspecific" T Wave Abnormalities—in a Mental Hospital

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SUMMARY

A group of 117 psychiatric male inpatients under age fifty, physically healthy, without known diabetes or manifest heart disease or electrocardiographic evidence of myocardial infarction, were given a 100-gm., two-hour oral glucose tolerance test because their electrocardiograms showed inverted or isoelectric T waves. These men were compared with a similarly studied control group of 303 who did not have such nonspecific abnormalities. Significantly more diabetes was discovered in the former group among those aged forty to forty-nine. At that age, then, abnormal T waves were significantly associated with previously unknown diabetes. Results suggest there is an unusually high prevalence of undetected diabetes among apparently healthy men in their forties who have these nonspecific T wave abnormalities. DIABETES *16*:722-27, October, 1967.

Among apparently healthy North American adults whose electrocardiograms showed flat or inverted T waves, overt coronary heart disease has been reported to develop with significant frequency. This suggested that such nonspecific T wave changes, though they can be due to a variety of causes, may often reflect subclinical coronary heart disease.[1-4] The foregoing, coupled with reports of high yields of previously unknown diabetics among persons with manifest coronary heart disease,[5,6] encouraged a search for diabetes among men under age fifty who seemed physically healthy but whose routine electrocardiograms showed isoelectric or inverted T waves.

METHOD

On Dec. 1, 1961, in the U.S. Veterans Administration Neuropsychiatric Hospital, Brockton, Mass., all ambulatory male inpatients under age fifty were listed for a diabetic survey. Those with any of the following clinical histories were then eliminated: known diabetes, disorders of the thyroid, pituitary or adrenal glands, active pulmonary tuberculosis or other chronic debilitating illness, gastrectomy or gastroenterostomy. Others were discharged before they were studied. As a result, 359 patients were investigated and the findings published.[7]

For the study presented here, those 359 men had complete medical evaluations. Electrocardiograms were taken; and initial glucose tolerance tests were made within the following four weeks. In rare exceptions the interval was six weeks. Thirteen rejected the electrocardiographic procedure and so were excluded from this study. A standard twelve-lead electrocardiogram was taken during the morning, at least one hour after breakfast, on a direct-writing, single-channel Sanborn 500 Viso-Cardiette at a paper speed of 25 mm. per second, and a 1-mv. standardization current was applied on each tracing. Smoking was not permitted after the subject entered the electrocardiographic laboratory. All tracings in this investigation were taken by the same technician with the subject supine and resting, and were read by the author. Chest roentgenograms, taken of every patient routinely on hospitalization and then annually, were interpreted by the hospital's certified radiologist.

Patients were excluded from this study if they had valvular or congenital heart disease, radiologic evidence of cardiac enlargement, an unequivocal history of angina pectoris, Q or QS items falling into Category I-1 or I-2 of Blackburn and associates,[8] or marked pulmonary emphysema. Of the patients remaining, those with any of the following electrocardiographic abnormalities—in the absence of intraventricular or bundle branch block—were termed the abnormal group and all others the control group: T wave isoelectric in any of leads I, II, V3-V6; T wave inverted in any of leads I, II, V2-V6.

In addition, all ambulatory men under age fifty, admitted after Dec. 1, 1961, until June 1966 (approximately 3,100 in number) routinely had a standard 12-lead electrocardiogram taken during the early weeks of their hospitalization. Of these, approximately 2.5 per cent had isoelectric or inverted T waves as listed above.

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Unless they were excluded by the criteria described before, they were assigned to the abnormal group of the present study.

At the investigation's close, the tracings of all subjects in the abnormal and control groups were independently read by a consulting cardiologist without knowledge of the author's original electrocardiographic classification of the subjects or their glucose tolerance results. Four cases originally judged to have isoelectric T waves in a single lead as the sole abnormality were classified by the consultant as having low T waves. Disagreement was due to reading difficulties caused by sloping or swinging baselines. Those cases were eliminated from the study. Two subjects in the abnormal and one in the control group were placed in Category I-2[8] by the consultant and excluded from the study. Here, disagreement was based upon differing measurements of Q duration. As the final result, classifications coincided for 117 men in the abnormal group and 303 in the control group. No instance of atrioventricular conduction disturbance (Category V1),[8] auricular fibrillation or flutter was encountered among these men.

In the abnormal group, nine men had an isoelectric T wave in Lead I as the sole abnormality. In only two of them was the QRS axis more positive than +50°, and in these two it did not exceed +80°. None in the group had an isoelectric T wave in V3 or V4 as the sole abnormality. Although definitive criteria for the electrocardiographic diagnosis of left ventricular hypertrophy have yet to be established, that condition was judged present in five men because they had the following items: inverted T waves in leads I, II, V4, V5 or V6, together with the voltage of R in aVL exceeding 1.1 mv. and/or SV1 plus RV5 or RV6 exceeding 3.5 m.v.

Two men in the abnormal group were classified as hypertensive because their blood pressure, at medical evaluation, exceeded 150/90 mm. Hg. Both men were among the five who had an electrocardiographic pattern of left ventricular hypertrophy as defined above.

Seventy-seven per cent of the abnormal group and 84 per cent of the control had been hospitalized for chronic schizophrenia; the remainder, for other chronic psychiatric disorders. Everyone received the regular hospital diet, which averaged 2,700 calories daily and contained 100 gm. of protein and 300 gm. of carbohydrates. The hospital regimen routinely permitted additional helpings and unrestricted purchase of food, refreshment and candy from hospital canteens and vending machines.

The customary eating habits of the patients were not investigated. There was no special dietary supervision to determine how much of the daily ration was eaten during the days immediately preceding the preliminary tolerance tests. However, for the three days preceding all subsequent glucose tolerance tests, the food intake of test subjects was closely observed and recorded at every meal and they drank 100 to 150 gm. of glucose in orange juice daily. Thus it was established that every subject tested had an adequate daily food intake throughout this period, including 300 gm. or more of carbohydrate a day.

A preliminary glucose tolerance test was done in each patient after an overnight fast. Venous blood specimens were collected in the morning before ingestion of 100 gm. of glucose and one hour and two hours afterwards. Blood glucose was determined by the Somogyi-Nelson method.[9] Patients with a combination of 160 mg. per 100 ml. or above at one hour and 120 mg. per 100 ml. or above at two hours were classified as positive. Those not meeting these criteria were said to be negative.

A subsequent glucose tolerance test was administered to those with positive results. This was similar to the preliminary test except that a blood glucose determination was added one and one-half hours after glucose ingestion. Those with a combination of 160 mg. per 100 ml. or above at one hour, 140 mg. per 100 ml. or above at one and one-half hours, and 120 mg. per 100 ml. or above at two hours were regarded as confirmed positive. If, instead, the level at two hours was 110 to 119 mg. per 100 ml., the combination was called probable confirmed positive.[10]

Cases whose results on second glucose tolerance tests were not compatible with confirmed or probable confirmed positive were given a cortisone-glucose tolerance test. This was done and interpreted according to Fajans and Conn. A combination of 160 mg. or above at one hour, 150 mg. or above at one and one-half hours, and 140 mg. or above at two hours was called a positive response.[10]

During all tolerance tests, subjects were cooperative, remained in a comfortable lounge equipped with magazines and television, and did not smoke. A hospital aide was in constant attendance. None was tested if febrile or acutely ill. Shock therapy, rarely employed, preceded any tolerance test by at least two months. None received digitalis or quinidine or drugs known to affect glucose tolerance in man.

Although serum cholesterol levels were not deter-

mined in the opening phase of the study, they were subsequently done routinely at each glucose tolerance test. In this manner, 91 per cent of the abnormal group and 72 per cent of the control group had serum cholesterol levels determined.[11]

From a majority of subjects it was possible to obtain urine specimens one to two hours after meals or after ingestion of a test dose of 100 gm. of glucose. Urine was examined for sugar by Clinitest.*

Weight was recorded at every tolerance test and the Metropolitan Life Insurance Company's "Table of Desirable Weights for Men" was used for classification.[12] A patient's weight was "desirable" if it was in the desirable range, "underweight" if below this range and "overweight" if above. Percentage of deviation from desirable weight was computed from these figures.

An individual's family history for diabetes was positive if the disease were known to have occurred among his grandparents, parents, siblings, aunts, uncles, or first cousins.

Statistical significance of data was tested as follows: 2×2 and 2×3 contingency tables of chi square were used to test for association of variables, with Yates's correction applied where necessary; mean values were compared by Student's t test.

RESULTS

Initial glucose tolerance results were positive in thirty-eight (32.5 per cent) of the abnormal group and fifty (16.5 per cent) of the control (table 1). Positive results were significantly more frequent in the former group ($p < .001$). Only two of the abnormal subjects had fasting blood glucose levels above 110 mg. per 100 ml. The thirty-eight positive in the abnormal group were retested, with thirty-one confirmed positive and one probably confirmed positive. These thirty-two were classified diabetic. Time lapse between their initial and latest confirmatory glucose tolerance tests ranged from one-half to fifty-one months, with a mean duration of 13.6 months and a median of 3.5. The mean, median and range of their initial and confirmatory blood glucose levels (mg./100 ml.) follow. On initial tests, the range was: at one hour, 160 to 338; at two hours, 120 to 384. Mean was: at one hour, 204; at two hours, 179. Median was: at one hour, 194: at two hours, 161. On confirmatory tests, the range was: at one hour, 160 to 290; at one and one-half hours, 143 to 310; at two hours, 110 to 348. Mean was: at one hour, 200; at one and one-half hours, 198; at two hours, 181. Median was: at one hour, 192; at one and one-half hours, 194; at two hours, 169.

Six of the thirty-eight initially positive were negative on second tolerance test. Three of them were in the fourth age decade and three were in the fifth. Based on the presence of one or more of the following factors, all were classified diabetics: glycosuria on initial tolerance test, minimum weight loss of eight pounds before the second test in an overweight subject, positive response to the cortisone-glucose tolerance test, and diabetic relatives.

All thirty-eight men, then, initially positive in the abnormal group were judged to have diabetes. Glycosuria of 0.5 to 2 per cent was demonstrable in twenty-five cases (65.8 per cent).

Forty-five men of the fifty initially positive in the control group were retested. Thirty-four were confirmed positive and classified diabetic. Negative results occurred in eleven, of whom seven were in the fourth age decade and four in the fifth decade. Based on the same factors used in the abnormal group, eight of the eleven men were judged to have diabetes—four in the fourth age decade and four in the fifth. Early hospital discharges prevented second glucose tolerance tests of three men in the thirties and two in the forties. One man from each of those age groups was classified diabetic: one because of 2 per cent glycosuria and the other because he had 0.75 per cent glycosuria and a diabetic parent. Thus, forty-four of fifty men initially positive in the control group were classified diabetic.

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TABLE 1

Number and per cent of men classified positive and diabetic, by age group

Age group (years)	Abnormal group			Control group				
	Number studied	Positive and diabetic Number	Per cent	Number studied	Positive Number	Positive Per cent	Diabetic Number	Diabetic Per cent
Total	117	38	32.5	303	50	16.5	44	14.5
40-49	59	28	47.5	117	27	23.1	26	22.2
30-39	48	9	18.8	157	21	13.4	16	10.2
20-29	10	1	10.0	29	2	6.9	2	6.9

Prevalence of new-found diabetes in both abnormal and control groups resembled that of known diabetes in the general population,[13] being higher among the older ($p < .001$; table 1) and the overweight ($p < .05$; table 2). Cholesterol levels, as in the general population,[14] were significantly higher among the diabetics than among the nondiabetics (table 3). In neither abnormal nor control group, however, did the prevalence of new-found diabetes among those with a history of diabetic relatives differ significantly from that among men without such a family history. In the abnormal group, 39.5 per cent of those with and 28.6 per cent of those without diabetic relatives had diabetes. In the control groups, 21.3 per cent of those with and 14.6 per cent without such relatives were diabetics. The prevalence of a diabetic family history in each group did not differ significantly: abnormal, 34.9 per cent; control, 28.1 per cent.

Upon comparison of the two groups by age decades, the percentage of new-found diabetes was higher in the abnormal group within the fifth decade ($p < .001$; table 1). Weight distribution within the two groups at this decade was not significantly different (table 4). It was concluded that a significant association existed at this age between inverted or isoelectric T waves and diabetes ($p < .001$; table 5).

Here it is relevant to mention that the majority of subjects in this study were on phenothiazine therapy. It has been reported that thioridazine (Mellaril) sometimes, and chlorpromazine (Thorazine) far less often, may cause broadening and blunting of an upright T wave in man. Thioridazine may also produce notching and decreased amplitude of an upright T and, in daily

TABLE 4

Weight distribution of men in fifth age decade: abnormal and control groups

Weight status	Abnormal group Number	Abnormal group Per cent	Control group Number	Control group Per cent
Per cent overweight:				
20 or more	21	35.6	34	29.1
10 - 19	17	28.8	27	23.1
9 per cent overweight to 9 per cent underweight	21	35.6	55	47.0
Per cent underweight:				
10 or more	0	0.0	1	0.8

TABLE 5

Men classified diabetic in abnormal group by electrocardiographic abnormalities

	T inverted, with or without T isoelectric			T isoelectric only		
	Number studied	Diabetic Number	Diabetic Per cent	Number studied	Diabetic Number	Diabetic Per cent
Total group	94	27	28.7	23	11	47.8
40-49 yrs.	45	19	42.2	14	9	64.3
30-39 yrs.	40	7	17.5	8	2	25.0
20-29 yrs.	9	1	11.1	1	0	0.0

TABLE 2

Number and per cent of men classified positive and diabetic, by weight status

Weight status	Abnormal group Number studied	Abnormal group Positive and diabetic Number	Abnormal group Positive and diabetic Per cent	Control group Number studied	Control group Positive Number	Control group Positive Per cent	Control group Diabetic Number	Control group Diabetic Per cent
Per cent overweight:								
20 or more	49	21	42.9	91	24	26.4	23	25.3
10 - 19	32	9	28.1	70	13	18.6	12	17.1
9 per cent overweight to 9 per cent underweight	36	8	22.2	135	13	9.6	9	6.7
Per cent underweight:								
10 or more	0	0	0.0	7	0	0.0	0	0.0

TABLE 3

Mean cholesterol levels (mg. per 100 ml.) of diabetics and nondiabetics: abnormal and control groups

	Abnormal group Number studied	Abnormal group Cholesterol Mean	Abnormal group Cholesterol S.D.		Control group Number studied	Control group Cholesterol Mean	Control group Cholesterol S.D.	
Diabetic	38	256	45	$p < .05$	37	278	61	$p < .001$
Nondiabetic	69	234	51		181	228	44	

TABLE 6

Number and per cent of men classified positive and diabetic, after excluding those on Mellaril within one week preceding their electrocardiogram

Age group (years)	Abnormal group			Control group				
	Number studied	Positive and diabetic Number	Per cent	Number studied	Positive Number	Per cent	Diabetic Number	Per cent
Total	74	25	33.8	157	18	11.5	16	10.2
40-49	42	20	47.6	55	8	14.5	8	14.5

doses of 800 mg. or more, is alleged to cause occasional T wave inversion.[15-20] Therefore, the data in this study were re-examined after each of the following changes: exclusion of all men with inverted T waves while on thioridazine (a) 800 mg. or more daily, (b) 600 mg. or more daily; exclusion of all men with inverted and/or isoelectric T waves while on thioridazine (a) 800 mg. or more daily, (b) 600 mg. or more daily. None of these four changes altered the significant prevalence of newfound diabetes in the fifth decade of the abnormal group and the association at this age of inverted or isoelectric T waves and diabetes ($p < .001$ altered to $p < .005$). Finally, from both the abnormal and control groups, all were excluded who had received thioridazine within one week preceding their electrocardiograms. Examination of the residual data revealed that the original significant prevalence of new-found diabetes in the fifth decade of the abnormal group remained unchanged ($p < .001$; table 6).

In the previously mentioned survey for unknown diabetes by the author, the question of carbohydrate metabolism during chlorpromazine therapy was discussed.[7] Published results of studies in both animals and man were noted to conflict. In that survey, no significant differences were found between nondiabetic and newly detected diabetic groups in the prevalence, duration, or dosage of phenothiazine therapy. Nor was there a significant difference between the prevalences of positive results on initial glucose tolerance tests among those on prolonged chlorpromazine therapy and among those in other forms of prolonged phenothiazine therapy or on no phenothiazines.[7] After that survey, glucose tolerance was studied in twelve diabetic and twelve nondiabetic men who had never received phenothiazines or had been off the drugs for periods ranging from five weeks to several years. After oral administration of at least 200 mg. of chlorpromazine daily for three weeks or longer, the glucose tolerance test was repeated. Neither diabetic nor nondiabetic group, compared with similarly tested groups of twelve diabetics and twelve nondiabetics not on phenothiazines, showed statistically significant changes in mean glucose levels. In addition, remissions of untreated diabetes were observed in some men of constant weight while being maintained on unchanged regimens of chlorpromazine.[21] These findings make it appear that chlorpromazine therapy does not alter man's carbohydrate tolerance. Indirectly, of course, through promoting overweight,[22] phenothiazine therapy may contribute to the clinical emergence of diabetes in those predisposed to this disease and aggravate the course of known diabetes. There is no sound evidence that chronic schizophrenia impairs glucose tolerance.[23]

An investigator has reported an unusual frequency of "T-wave malformations" among schizophrenics without clinical evidence of organic heart disease.[24,25] However, the T-wave malformations ranged from simple blunting of the apex to notching and inversion, and their reported frequency of 15 per cent was based upon including the electrocardiograms of patients given Mellaril or other phenothiazines with those of patients not on phenothiazine therapy.[26] As a result, the observation about an unusual frequency of T-wave malformations in schizophrenics is clouded and cannot be made germane to this present report.

COMMENT

Flat or inverted T waves in the electrocardiograms of apparently healthy North American adults often portend overt coronary heart disease and therefore may reflect the subclinical phase of that disorder.[1-4]

A recent study reported "hyperglycemia" to be an independent risk factor among persons with coronary heart disease.[27-29] An individual was "hyperglycemic" if his blood glucose level was above the eightieth percentile of his age group one hour after ingestion of 100 gm. of glucose.

T-wave inversion was found significantly associated with "hyperglycemia" in eighteen (37.5 per cent) of forty-eight men past age forty who were without known diabetes or manifest heart disease. The explanation was offered that this association might mean many individuals with such electrocardiographic changes were mild

or latent diabetics. The present study supports that suggestion because nineteen (42.2 per cent) of forty-five apparently healthy men in the fifth decade of life were found to have T-wave inversions significantly associated with previously unknown diabetes ($p < .025$; table 5).

This investigation suggests there is an unusual prevalence of undetected diabetes among apparently healthy men in their forties who have nonspecific T-wave abnormalities.

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