Bimodality of Fasting and Two-hour Glucose Tolerance Distributions in a Micronesian Population

P. Zimmet, M.B., Ph.D., F.R.A.C.P., and S. Whitehouse, Melbourne

SUMMARY

While frequency distributions of glucose concentrations in Caucasian populations are unimodal, bimodality has been described in the Pima Indians, a population with an extremely high prevalence of diabetes.

Venous plasma glucose concentrations at fasting and after a 75-gm. oral glucose load were determined in 596 Nauruans, a Micronesian population with a diabetes prevalence of the same order as the Pima Indians. In both sexes and in subjects 10 to 19 years, the frequency distributions of the logarithms of the fasting and two-hour glucose values were clearly unimodal. In most sex and age groups of 20 years and older, the frequency distributions of fasting and two-hour glucose values were bimodal and consistent with a model of two overlapping Gaussian distributions.

This population is characterized by marked obesity. However, there was no significant difference in the degree of obesity between subjects in the first and second curves of the bimodal distribution. This makes it unlikely that the bimodality is a consequence of the marked obesity seen in both the Pima and Nauru populations.

The data show that among Nauruans, as with the Pimas, the frequency distribution of glucose concentrations can be used to separate the population into normal and hyperglycemic groups. DIABETES 27:793-800, August, 1978.

INTRODUCTION

Considerable controversy exists as regards the criteria for the diagnosis of diabetes. Different sets of diagnostic criteria may produce twofold differences in prevalence rates.[1] Views as to what represents normal and abnormal glucose tolerance vary widely from country to country.[2] In addition, the problem arises as to where the line should be drawn between diabetes and normality.[3] All of these points become relevant when one realizes that none of the recommended criteria is derived from long-term studies of the further development of different degrees of glucose intolerance.[3]

The frequency distributions of glucose levels in Caucasian populations are continuous and unimodal.[4,5] As a consequence, there is no clear point of separation between normal individuals and diabetics. In contrast to this, bimodality in glucose tolerance distributions has been reported in the American Pima Indians.[6] These people have the highest prevalence of diabetes yet recorded.[7] It has been suggested that the presence of the bimodal distribution allows the separation of the Pima population into two groups—normal and hyperglycemic.[6] This separation may have important implications in the understanding of what degree of glucose intolerance actually represents diabetes. It is important, therefore, to find and study other high diabetes-prevalence groups to see if the bimodal phenomenon seen in the Pimas can be confirmed.

Recently, the Micronesian inhabitants of a Central Pacific island have been shown to have a diabetes prevalence similar to that reported in the Pima Indians.[8] This paper is a report of the findings related to glucose tolerance distributions in this population, where the prevalence of diabetes is 34.4 per cent in subjects 15 years and older.

MATERIAL AND METHODS

These data were collected as part of a continuing diabetes epidemiologic survey among the Micronesian population of the island of Nauru. Nauru is a small island, 8½ square miles in area, situated in the central Pacific Ocean just south of the equator. Details relating to its history, geography, and people have been

From the Department of Metabolic Medicine and Epidemiology, Southern Memorial Hospital, Melbourne, 3162, Australia.

Address reprint requests to Dr. Paul Zimmet, Southern Memorial Hospital, Box 185, Caulfield South, 3162, Melbourne, Australia.

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reported elsewhere.[8,9] The life style of the inhabitants is almost completely Western and virtually all food is imported.

Glucose tolerance tests were performed in the morning. The subjects were not prepared for the test with a formal carbohydrate diet, and all were on unrestricted diets; the average Nauruan daily diet contains over 350 gm. carbohydrate.[8]

Venous blood samples were taken while fasting and two hours after the ingestion of a 75-gm. carbohydrate load.* The subjects were ambulatory during the test. The venous blood samples were drawn into Vacutainer tubes† containing 30 mg. sodium fluoride. After mixing, the blood was centrifuged, separated, and frozen within two hours. At the conclusion of the study, samples were packed in dry ice and carried in two batches to Melbourne, Australia (3,000 miles distant). The plasma glucose was determined on the SMAC 20 (Technicon) by a glucose-oxidase method.‡

This is a report of the results of this glucose tolerance test done on 596 Nauruan subjects (322 females and 274 males) aged 10 years and older, regardless of whether they were known diabetics. These subjects constitute about one third of the island's population in the stated age range. Because of the small numbers of persons in the older groups, the data for subjects 50 years and older have been pooled into one group. In addition, fasting plasma glucose data were available on 29 known diabetics, on whom glucose tolerance tests were not performed, and this has been included in the results pertaining to the fasting state.

Using the general approach outlined by Rushforth et al.,[6] the distributions of fasting and two-hour glucose and their relationships to sex and age by decade were examined. The histograms of the arithmetical glucose values were similar to those reported for the Pima Indians,[6] i.e. unimodal in the younger groups, with definite bimodality in the older groups.

The model of the two overlapping Gaussian distributions[6] was adopted:

$$f(x) = \frac{\alpha e^{\frac{-(X-\mu_1)^2}{2\sigma_1^2}}}{\sigma_1\sqrt{2\pi}} + \frac{(1-\alpha)e^{\frac{-(X-\mu_2)^2}{2\sigma_2^2}}}{\sigma_2\sqrt{2\pi}}$$

in which μ_1 and μ_2 are the means of the two distributions, σ_1 and σ_2 their respective standard deviations, and α is the proportion of individuals belonging to the first curve.

A computer program was written to determine the best-fitting bimodal distribution and to compare the computed distribution with the actual data using a conventional chi-square test. The parameters of the Gaussian distributions—μ_1, μ_2, σ_1, σ_2, and α—were calculated using a minimum chi-square technique.

RESULTS

The means and standard deviations of the fasting and two-hour glucose values by decade for females and males are shown in table 1. There was a progressive rise in mean fasting and two-hour glucose concentrations with age for both sexes except for one group—fasting females 50 years and older.

TABLE 1

Plasma glucose concentrations (mg./100 ml.) determined at fasting and two hours after an oral 75-gm. glucose load

Age group	Fasting			2-Hour		
	No. exam'd	Mean	S.D.*	No. exam'd	Mean	S.D.*
Females						
10-19	98	88.9	13.4	97	109.6	30.3
20-29	96	107.1	56.1	95	144.3	72.5
30-39	46	133.2	75.8	40	177.3	98.6
40-49	43	158.5	91.6	43	221.7	129.1
50+	48	149.1	67.6	47	237.8	114.3
Total	331			322		
Males						
10-19	82	93.4	9.1	79	106.2	23.2
20-29	72	112.2	49.9	69	128.3	52.8
30-39	44	128.5	65.7	42	162.8	93.7
40-49	52	164.7	81.8	46	192.9	123.3
50+	44	172.2	89.7	38	231.2	130.0
Total	294			274		

*Standard deviation.

Bennett et al.[10] proposed a hypothesis that the distribution of glucose tolerance in natural populations consists of two components that are distributed to form overlapping Gaussian curves. To examine the applicability of this hypothesis, we used the method described above to estimate the parameters of the two component distributions. As with the Pima study,[6] the logarithmic values of plasma glucose gave a closer fit to the observed distributions than the arithmetical values. For this reason, only the results for logarithmic glucose values are reported here.

*Trutol, Sherwood Medical, St. Louis, Missouri.

†Vacutainer, no. 4752, Becton Dickinson, Rutherford, New Jersey.

‡Technicon Instruments, Tarrytown, New York, method no. SG4-0021.

Figures 1a and 1b are diagrams of the logarithms of the fasting plasma glucose values for females and males plotted as histograms. The predicted composite curve is represented as a continuous line and the two component curves (seen only where the component curves overlap) as interrupted lines. For both females and males aged 10 to 19 years, the frequency histogram is unimodal. Only a single Gaussian curve could be fitted to these distributions.

In all older groups there was evidence of bimodality. Chi-square goodness-of-fit tests showed satisfactory agreement between the observed frequency distributions and those predicted by the model for all of the other age groups ($p > 0.1$) except females and males 20 to 29 years ($p < 0.05$) and males 30 to 39 years ($0.01 < p < 0.025$). These deviations from the model were possibly due to the small numbers in these particular age groups.

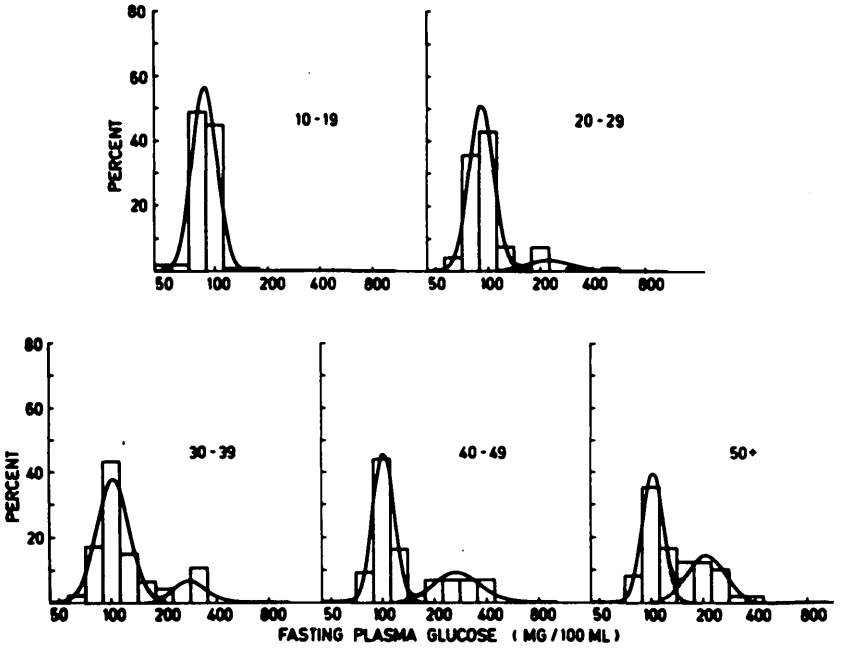

FIGURE 1a

Histograms and superimposed composite curve and component curves of fasting glucose values for females by decade.

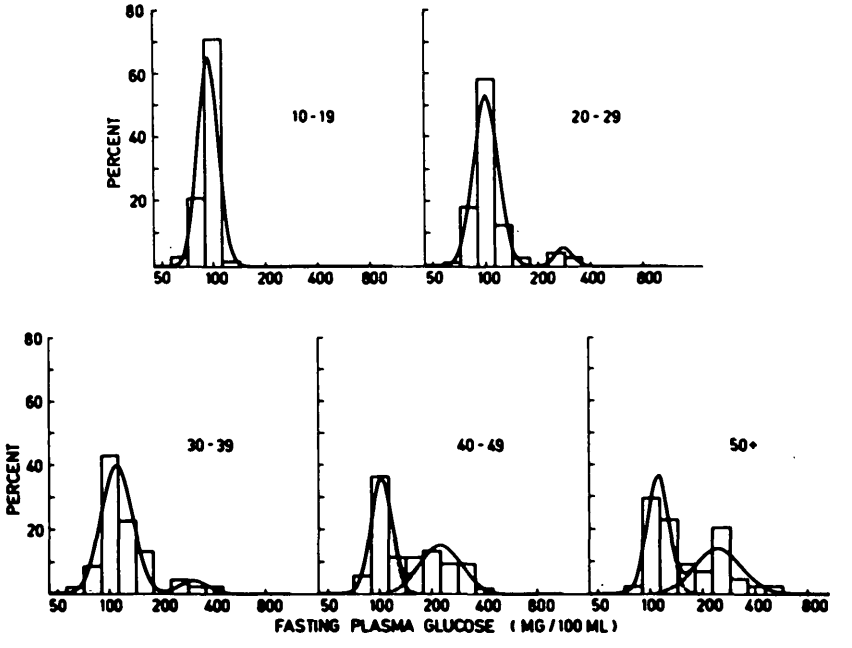

FIGURE 1b

Histograms and superimposed composite curve and component curves of fasting glucose values for males by decade.

Figures 2a and 2b are diagrams of the logarithms of the two-hour plasma glucose values for females and males plotted as histograms. For both females and males aged 10 to 19 years, the distributions fitted that of a single Gaussian curve. There was satisfactory agreement between the observed and predicted distributions on the basis of chi-square tests for most of the other age groups in both sexes ($p > 0.10$). However, disagreement with the model existed in females 30 to 39 and 40 to 49 years ($0.025 < p < 0.05$). The results in these groups just failed to reach statistical significance.

Table 2 is the estimated means (μ_1, μ_2), the standard deviations (σ_1, σ_2) of the two curves, and the percentage of individuals in the first ("normal") component ($100 \times \alpha$) (for both the fasting and two-hour glucose values) determined by the maximum likelihood procedure. Figures 3 and 4 are the percentage of subjects in the second component for each age group both for fasting and for two-hour glucose values. The percentage of fasting subjects in the second component rose steeply in both sexes from 0 per cent below age 19 to a maximum of 39.6 per cent in females over 50 years and 50 per cent in males 40 to 49 years. At two hours, there was again a steep increase from 0 per cent in both sexes to a maximum of 42.6 per cent in females and 39.5 per cent in males, both of which were in the age groups 50 years and older.

The means and standard error of mean of body mass index and triceps skinfold thickness of subjects—female and male—in the first and second component are in table 3. For all age groups, there was no significant difference in body mass index or triceps skinfold thickness between the first and second components. Therefore, the degree of obesity in subjects in both components was similar for both female and male groups.

DISCUSSION

Bimodality in the frequency distribution of the one-hour and two-hour postload glucose levels has

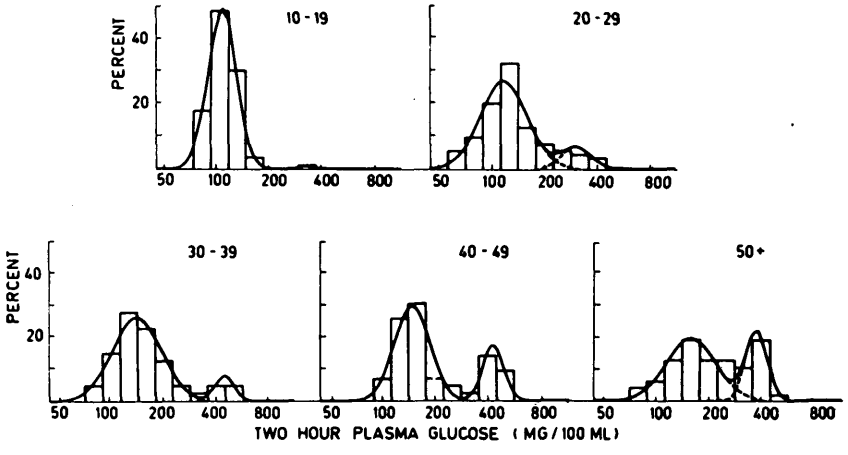

FIGURE 2a

Frequency distribution of two-hour glucose values for Nauruan females by decade.

FIGURE 2b

Two-hour plasma glucose in males by decade.

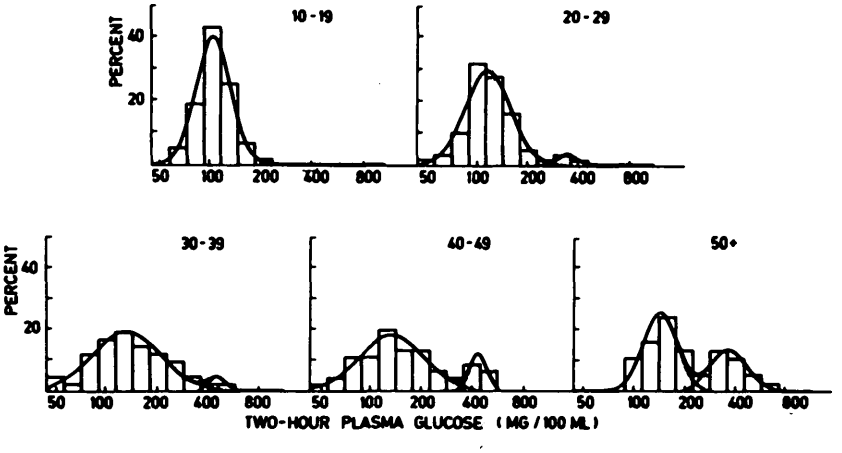

TABLE 2

Maximum likelihood estimates of the parameters of the frequency distributions in log glucose units with arithmetical values in mg./100 ml. in parentheses*

Sex-Age	Number examined	First Component Mean μ_1	First Component Standard error of mean S.E.μ_1	First Component Standard deviation σ_1	Per cent of subjects in first component (100 × α)	Second Component Mean μ_2	Second Component Standard error of mean S.E.μ_2	Second Component Standard deviation σ_2
Females (fasting)								
10-19	98	1.94(87)	0.007	0.066	100	—	—	—
20-29	96	1.95(89)	0.001	0.001	83.3	2.26(182)	0.042	0.170
30-39	46	1.98(95)	0.012	0.069	73.9	2.34(219)	0.048	0.166
40-49	43	2.02(105)	0.011	0.063	69.8	2.43(269)	0.032	0.117
50+	48	2.02(105)	0.011	0.057	60.1	2.32(209)	0.027	0.117
Males (fasting)								
10-19	82	1.97(93)	0.001	0.001	100	—	—	—
20-29	72	1.98(95)	0.007	0.054	87.5	2.33(214)	0.051	0.152
30-39	44	2.03(107)	0.015	0.093	88.6	2.44(275)	0.062	0.139
40-49	52	2.00(100)	0.012	0.059	50.0	2.34(219)	0.027	0.135
50+	44	2.05(112)	0.015	0.078	63.6	2.42(263)	0.023	0.093
Females (2-hour)								
10-19	97	2.03(107)	0.010	0.095	100	—	—	—
20-29	95	2.07(117)	0.013	0.118	87.4	2.47(295)	0.025	0.087
30-39	40	2.12(132)	0.019	0.108	82.5	2.54(347)	0.035	0.093
40-49	43	2.17(148)	0.015	0.086	72.1	2.60(398)	0.030	0.102
50+	47	2.17(148)	0.021	0.111	57.4	2.55(355)	0.019	0.083
Males (2-hour)								
10-19	79	2.02(105)	0.011	0.096	100	—	—	—
20-29	69	2.06(115)	0.014	0.112	94.2	2.46(288)	0.043	0.085
30-39	42	2.12(132)	0.030	0.185	92.3	2.60(398)	0.058	0.100
40-49	46	2.11(129)	0.029	0.176	80.4	2.61(407)	0.023	0.068
50+	38	2.15(141)	0.020	0.095	60.5	2.53(339)	0.031	0.122

*See text for explanation of symbols.

previously been reported in the Pima Indians.[6,11] These findings suggested that the Pima population could be divided into two subgroups—the nondiabetic normal population and a hyperglycemic group. As the two-hour glucose levels of this latter group were mainly in excess of 200 mg./100 ml., it was assumed to represent subjects with diabetes. If a single measure of glucose tolerance is to be chosen for the diagnosis of diabetes in the Pima Indians, the one- and two-hour bimodality data provide a mathematic rationale for preferring the two-hour level. Misclassification of a normal as "hyperglycemic" is almost twice as common if the one-hour plasma glucose level is used!

This study of a Micronesian population confirms the Pima findings and, as was found in the Pimas, the phenomenon was not present in the younger groups but became more evident with increasing age. To our knowledge, this is the first report of bimodality in fasting plasma glucose distributions in a population. In subgroups below the age of 20 years, the frequency distribution was clearly unimodal. However, beyond this age there was clear evidence of bimodality. These data suggest that, as with the Pima Indians, this Micronesian population consists of at least two subgroups—the first component representing the normal population and the second component the diabetics. As with the Pima findings, we found incomplete separation between the upper end of the first component and the lower end of the second component, and this could result in a minor degree of misclassification of certain individuals.[6]

A comparison of the data of this Micronesian population with the Pima findings is clearly of importance. In this context, we are able to report that preliminary data on this point are available.[12] There was no significant difference either in the parameter of the two components or in the per cent of the population lying within the two components. This indicates a close similarity in the mean and variance of the first and second components of both Pimas and Nauruans, and that the prevalence of hyperglycemia (diabetes) is not significantly different in the two populations.

It could be argued that the bimodal phenomenon occurs as a result of the extreme obesity seen in the Pimas and Nauruans as compared with other populations. The major effect of obesity on the form of glucose distribution appears to be that the mean of the first component of the glucose distribution is shifted

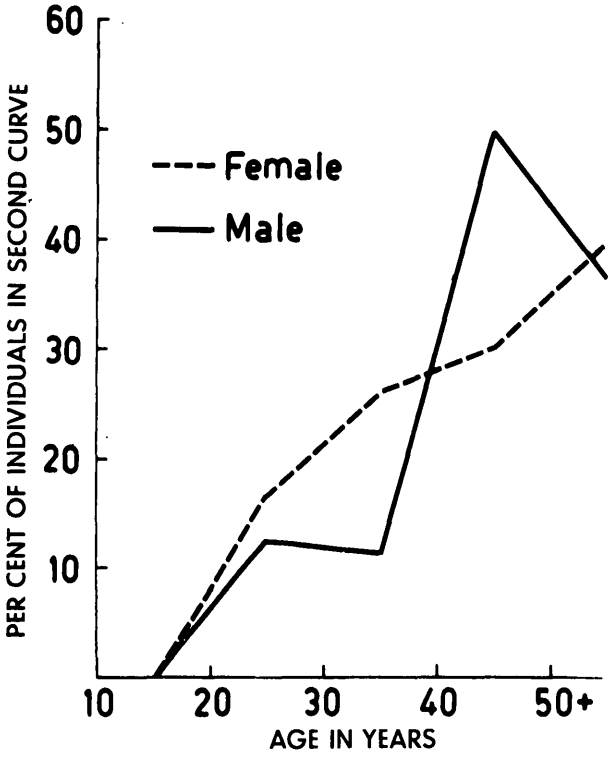

FIG. 3. Fasting data showing percentage of individuals lying in the second component as a function of age for females and males.

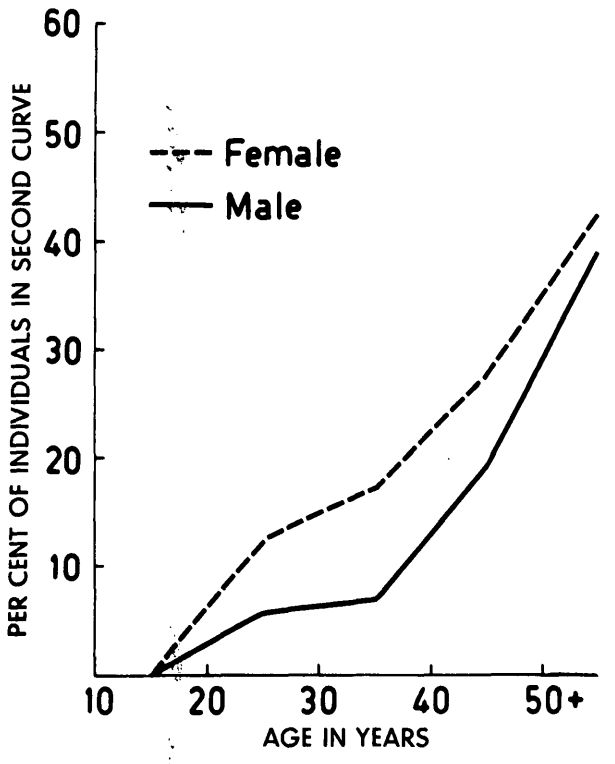

FIG. 4. Two-hour data showing percentage of individuals lying in the second component as a function of age for females and males.

to a higher level in the more obese subjects.[13] However, as the degree of obesity was similar in subjects in the normal and diabetic components in our study population, there is no evidence to suggest that a difference in the degree of obesity per se produces the separation of the population into these two components.

It has been suggested that 10 per cent of a population would need to fall into the second component before bimodality became evident in frequency distribution of their glucose levels.[6] This might explain why the phenomenon has not been demonstrated in other racial groups, including Caucasians. We have recently reported on an urbanized Polynesian popula-

TABLE 3

Mean and standard error of mean of body mass index and triceps skinfold for males and females in first and second component

Age group	Number examined	Cut-off point* plasma glucose (mg./100 ml.)	Body mass index† First	Body mass index† Second	Triceps skinfold (mm.) First	Triceps skinfold (mm.) Second
Females						
10-19	97	—	24.0±0.7	—	22.9±1.0	—
20-29	95	200	34.1±0.9	37.7±1.9	33.7±1.1	38.3±3.2
30-39	40	251	34.7±1.0	36.4±1.7	37.4±1.4	42.7±2.2
40-49	43	224	34.4±1.1	37.8±1.9	34.5±1.7	36.8±3.6
50+	47	224	33.2±1.7	31.9±0.9	31.2±2.2	28.8±1.6
Males						
10-19	79	—	24.0±0.7	—	18.8±1.5	—
20-29	69	200	32.6±0.6	41.7±6.1	25.2±1.9	32.5±10.5
30-39	42	282	31.9±0.9	36.0±4.5	24.0±2.6	28.7±7.0
40-49	46	282	32.3±1.1	30.4±1.0	22.8±1.7	19.7±2.4
50+	38‡	200	29.7±1.2	28.7±0.9	20.1±2.1	16.3±1.8

*This plasma glucose level represents cut-off point for separation of first and second component for each age group.
†Body mass index = weight (kg.)/height (cm.^{2})×100.
‡One subject was an amputee, and data on weight and height were not obtained.

tion with a diabetes prevalence of 8 per cent in subjects 10 years and older.[14] We were unable to demonstrate bimodality in either fasting or two-hour glucose frequency distributions (Zimmet—unpublished observations). However, the model has been tested among Asiatic Indians living in South Africa, and it has been shown to be applicable.[6]

The presence of bimodality in these populations has great importance with respect to the classification between normal and diabetic subjects. Thus, Rushforth et al.[6] have noted that the two-hour plasma glucose levels of the hyperglycemic group were, for the most part, in excess of 200 mg./100 ml. and by conventional standards the group contained subjects with diabetes mellitus. The second component was assumed, therefore, to represent subjects with diabetes.

The applicability of these findings to other populations (especially lower diabetes-prevalence groups) must still be established. The incidences of diabetic retinopathy and nephropathy, however, are much higher in the Piman second component group as compared with the normal population.[13]

In addition, Jarrett and Keen[3] have provided information that diabetic retinopathy is much more common in Caucasian subjects with a two-hour capillary blood sugar of 200 mg./100 ml. or over. Similar data exist as to the risk of developing lens opacities.[3] If the diagnosis of diabetes is based on the premise of subjects who have substantial glucose intolerance and an appreciable risk of specific diabetic complications, then a two-hour plasma glucose of 200 mg./100 ml. would also seem to be a reasonable value for diagnosis in a Caucasian population.

The evidence reported above does suggest that the Piman and Nauruan findings may have more general applicability to the question of the actual degree of glucose intolerance that represents true diabetes. As suggested by others,[3] the present criteria for diagnosis of diabetes may require revision on the basis of the above-mentioned studies.

The increasing proportion of subjects lying in the second or "diabetic" component presumably results from increased numbers of subjects who were initially in the first component and who have developed glucose intolerance as they aged.[6] The actual mechanism as to why this occurs is not clear but we would like to propose a hypothesis in relation to this.

Savage and his co-workers[15] have reported on patterns of insulin secretion with varying degrees of glucose tolerance in the Pima Indians. While it may be coincidental that the tendency towards development of hypoinsulinemia in these subjects occurs at two-hour postload glucose levels of 200 to 239 mg./100 ml., it is interesting to note that this is in the region of the cut-off point of the first and second components. At two-hour glucose values up to 169 mg./100 ml., there is a progressive increase in the two-hour plasma insulin, which then falls as glucose intolerance becomes more overt. It is tempting to suggest that the failure of the endocrine pancreas to respond to the glycemic stimulus at this point may represent the mechanism of the development of further hyperglycemia leading to overt diabetes. This could be the mechanism of the moving of a particular individual from the first ("normal") component into the diabetic group. The patterns of insulin response over a wide range of glucose tolerance in Nauruans are identical to those of the Pimas.[16]

The confirmation of the bimodal phenomenon in another population, other than the Pima Indians, has important ramifications not only for the determination of correct diagnostic criteria for diabetes but also for new approaches to test genetic hypotheses for diabetes in these populations.[17]

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