HYALINIZATION OF THE ISLETS OF LANGERHANS IN NONDIABETIC INDIVIDUALS*

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For many years following Opie's discovery of hyalinized pancreatic islets in diabetic patients,[1,2] this lesion was considered diagnostic of diabetes mellitus. But during the intervening years, there have been several reports of hyaline islets in subjects without clinical evidence of diabetes. Arey[3] found hyaline islets in 19 of 114 nondiabetic persons over 50 years of age. Hartroft[4] stated that the amount of hyaline in the islets increased with age in both diabetic and nondiabetic individuals; but at any given age the extent and severity of hyalinization was greater in those having diabetes than in those without it. However, no extensive studies have been reported on the incidence of hyaline islets in nondiabetic individuals.

In 1952 I reported the frequency and age distribution of hyaline islets in 1,194 diabetic patients.[5] The present study includes 1,661 such patients (Tables I and II). It will be noted that the frequency of hyaline islets in these cases increased with age until about the seventh decade, and that there was no significant difference with respect to sex.

The purpose of this study is to determine the frequency and the age and sex distribution of hyaline islets in the nondiabetic population. It is based upon microscopic examination of the pancreas in 3,959 nondiabetic individuals over 20 years of age. There were 2,413 males and 1,546 females. The age distribution is shown in Tables I and II. It will be noted that 1,906 males and 1,143 females were over 50 years of age. The observations were made on one or two sections of pancreas each, usually about one square centimeter in area. The number of islets seen ranged from 10 to 100 or more, depending upon the part of the pancreas from which the section was taken. Since often only one hyaline islet was observed in a section, it is highly probable that a more extensive study would have revealed a larger number of cases with this feature, but this is a comparison of a diabetic with a nondiabetic population, and the pancreases examined in diabetes are subject to the same error of underestimation.

In Tables I and II the incidence and degree of hyalinization of the islets in diabetes and in the nondiabetic state are compared. The first

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two decades have been omitted since no hyaline islets were found in either group under the age of 20 years. In the diabetic group the incidence of hyaline islets increased with age and attained a maximum at about the age of 60 years; in the nondiabetic patients the incidence continued to increase with advancing age to reach a maximum in the ninth decade. In the nondiabetic individuals the proportion of those with mild or moderate hyalinization (grades 1 and 2) was much

TABLE I

The Incidence of Hyaline Islets in Diabetic and Nondiabetic Males with Respect to Age

Age at death		No. of cases	Extent of hyalinization		Percentage with evidence of hyalinization
			Grades 1 and 2	Grades 3 and 4	
20–30	D	16	1	0	6.3
	ND	101	0	0	0
30–40	D	50	2	0	4.0
	ND	181	1	0	0.6
40–50	D	64	8	8	25.0
	ND	225	2	1	1.3
50–60	D	136	31	21	38.2
	ND	367	12	7	5.2
60–70	D	271	74	46	44.3
	ND	727	64	7	9.8
70–80	D	195	66	40	54.4
	ND	507	61	11	14.2
80–100	D	66	19	16	53.0
	ND	305	45	10	18.0

D = diabetic.
ND = nondiabetic.

TABLE II

The Incidence of Hyaline Islets in Diabetic and Nondiabetic Females with Respect to Age

Age at death		No. of cases	Extent of hyalinization		Percentage with evidence of hyalinization
			Grades 1 and 2	Grades 3 and 4	
20–30	D	32	1	0	3.1
	ND	129	0	0	0
30–40	D	38	4	0	10.5
	ND	124	0	0	0
40–50	D	64	12	3	23.4
	ND	150	1	0	0.7
50–60	D	149	37	25	41.6
	ND	168	8	0	4.8
60–70	D	282	86	49	47.9
	ND	371	21	1	5.9
70–80	D	225	74	39	50.2
	ND	377	40	4	11.7
80–100	D	73	26	12	52.1
	ND	227	29	4	14.5

D = diabetic.
ND = nondiabetic.

TABLE III

The Incidence of Diabetes in the Necropsy Population with Respect to Sex and Age at Death

Age at death (yrs.)	Males			Females		
	No. of necropsies	No. of diabetics	Per cent diabetic	No. of necropsies	No. of diabetics	Per cent diabetic
0–10	7344	9	0.12	5206	2	0.04
10–20	1222	10	0.82	1004	16	1.59
20–30	2211	23	1.04	1889	40	2.12
30–40	3531	69	1.95	2318	53	2.29
40–50	5943	86	1.45	3117	77	2.47
50–60	9211	193	2.10	4039	209	5.17
60–70	10534	360	3.42	4750	361	7.60
70–80	7780	250	3.21	4298	285	6.63
80–93	3122	82	2.65	2145	92	4.29
Total	50898	1082		28766	1135	

TABLE IV

Number of Subjects with Hyaline Islets per Each 1,000 Necropsies with Respect to Age and Sex. (Constructed from Data in Tables I, II and III)

Age at death	Diabetic patients		Nondiabetic patients		Total hyaline islets per 1,000 necropsies	Per cent of hyaline islets attributable to diabetes
	No.	No. with hyaline islets	No.	No. with hyaline islets		
Males						
50–60	21	8	979	51	59	13.6
60–70	34	15	966	95	110	13.6
70–80	32	17	968	137	154	11.0
80–93	26	14	974	175	189	7.4
Females						
50–60	52	22	948	46	68	32.4
60–70	76	36	924	55	91	39.6
70–80	66	33	934	109	142	23.2
80–93	43	22	957	139	161	13.7

greater than in the cases with diabetes, but some nondiabetic patients, especially males, showed severe hyalinization (Table I).

In all decades and in both sexes, hyaline islets were found much more frequently in diabetes than in its absence. In males (Table I) the preponderance was 18 to 1 in the fifth decade but decreased to 3 to 1 in the ninth. In females (Table II) the preponderance in diabetes was even more pronounced since hyaline islets were less frequent in nondiabetic females than in nondiabetic males.

The preponderant occurrence of hyaline islets in diabetic patients is so pronounced that no one can doubt that they are related in some

way to the diabetic state. It is obvious, however, that the observation of hyaline islets at necropsy does not justify a diagnosis of diabetes mellitus.

Table IV is constructed from the data provided in Tables I, II and III. Column 1 is the number of diabetic individuals per each 1,000 necropsies (10 times the percentage in Table III). Column 2 is the number of diabetic patients in whom hyaline islets were encountered (number of diabetic cases times the percentage with hyaline islets). Column 3 is the number of nondiabetic persons per 1,000 necropsies (1,000 less the number with diabetes). Column 4 is obtained by multiplying the number of nondiabetic patients by the percentage of those whose pancreases contained hyaline islets (Tables I and II). When the data are arranged in this way, one may readily determine the percentage of hyaline islets attributable to diabetes in each sex and age group. For example, in males 70 to 80 years old there was only one chance in 9 that a hyaline islet represented clinically detectable diabetes; but in a female 60 to 70 years old there were 2 chances out of 5 that diabetes existed.

The Significance of Hyaline Islets

As noted above, hyaline islets must have some relation to the diabetic state. They are evidently not the cause of diabetes since they were absent in nearly all young persons with diabetes and about one half of older diabetic individuals. In diabetes the hyaline islets are not related to any feature of the disease except the age of the patient.[5] Two theories of their significance may be discussed:

(1) Hyaline islets represent a wear-and-tear process, due to age, which is accentuated by the diabetic state. We know that diabetes does not cause atherosclerosis, but it accelerates and intensifies certain forms of atherosclerosis, viz., renal vascular disease, gangrene, and coronary artery disease. This theory would explain the very high incidence of hyaline islets in nondiabetic individuals over 80 years of age, but it does not account for the greater incidence of hyaline islets in males in the nondiabetic group.

When the nondiabetic patients were arranged in several groups such as those with atherosclerosis, cancer, infections, or trauma, no differences in the incidence of hyaline islets in the several groups were noted except those assignable to age. There was no relation to atherosclerosis. Pancreases which were the seat of atherosclerosis showed no increased incidence of hyaline islets.

(2) Hyaline islets are an expression of unrecognized or potential

diabetes. Since the inheritance of diabetes is not sex-linked, one would expect to find an equal sex distribution; but in the community from which these cases stemmed, clinical diabetes is about twice as frequent in females as in males. This fact justifies the view that unrecognized or potential diabetes is about as frequent as overt diabetes in males, thereby accounting for the higher incidence of hyaline islets in nondiabetic males since more male diabetic patients are unrecognized. Hyaline islets are just as frequent in mild as in severe diabetes.[5] The theory that hyaline islets indicate potential diabetes does not explain their very high incidence in subjects over 80 years of age.

Steinberg and Wilder[6] suggested that the total diabetic population, including undiagnosed and potential diabetic patients, was 5 times as great as the number of recognized instances of diabetes. If this be true, nondiabetic persons with hyaline islets may represent individuals with undiagnosed or potential diabetes.

Summary

In males the incidence of pancreatic hyaline islets in diabetes, in respect to a necropsy population without diabetes, ranges from 18 to 1 in the fifth to 3 to 1 in the ninth decade. In females the preponderance in diabetic individuals is even more pronounced. There is no doubt that hyaline islets are related in some way to the diabetic state.

When hyaline islets are found at necropsy in a male over 50 years of age, the chance is only about 1 in 10 that the patient was recognized to have diabetes in life. In females of corresponding age, the chance is about 1 in 4.

There is some evidence to support the view that nondiabetic individuals with hyaline islets are potential or unrecognized instances of diabetes.

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