Observations on the Pancreatic Islet Tissue of Young Diabetic Subjects

Neil Maclean, M.B.Ch.B., and Robertson F. Ogilvie, M.D., Edinburgh

Little is known of the succession of changes which take place in the pancreas of a young diabetic since direct observation is obviously impossible. Some idea of the alterations which occur may, however, be gained from study of the pancreases of diabetics dying at different stages of the disease. To this end we examined the pancreases of diabetics dying under the age of thirty years, and here summarize our findings and inferences.

MATERIAL AND METHOD OF STUDY

All the available pancreatic sections of diabetic patients who were under thirty years of age at death were examined. Some were too autolyzed for quantitative examination. Five showing acute pancreatitis of varying severity were rejected because of the effect of a primarily exocrine inflammation upon the function of the islets. Two cases with hyalinization and fibrosis of the islets were rejected because of the difficulty in estimating the amount of functioning islet tissue remaining in partly hyalinized islets. Two cases were unacceptable because the date of onset of symptoms could not be ascertained. In the remaining forty-one cases the interval between the known onset of the disease and death varied from two days to nineteen years. In twenty-nine cases, sections from blocks of the head, body and tail of the pancreas were examined, and in twenty-seven of these cases the weight of the pancreas was known. In six cases two blocks were available and in a further six cases only one block was available for examination. The weight of the pancreas was known in only two of these twelve cases. The pancreases of twenty-two nondiabetic patients of similar age were used for comparison. Quantitative estimations by a method previously described[1] were made without knowledge of the age of the patient or of the duration of the disease.

The decision to use the six cases in which only a single block of the pancreas was available was made in light of previously unpublished observations. In a former investigation,[1] no constant variation in the distribution of islets in either the anteroposterior or vertical axes of the pancreas was noted. In contrast, the frequency distribution of islets in twelve transverse sections taken at equidistant intervals along the whole length of the pancreases of two diabetic and three nondiabetic subjects followed a fairly characteristic pattern in each pancreas (figure 1). It will be seen that sampling of a single block taken from the neck or the tail of the pancreas might yield unduly low or high results respectively. These, however, are not the usual sites from which a single routine histologic block is taken. Examination of a single block taken from the body of a pancreas with normal exocrine tissue will probably give a fair repre-

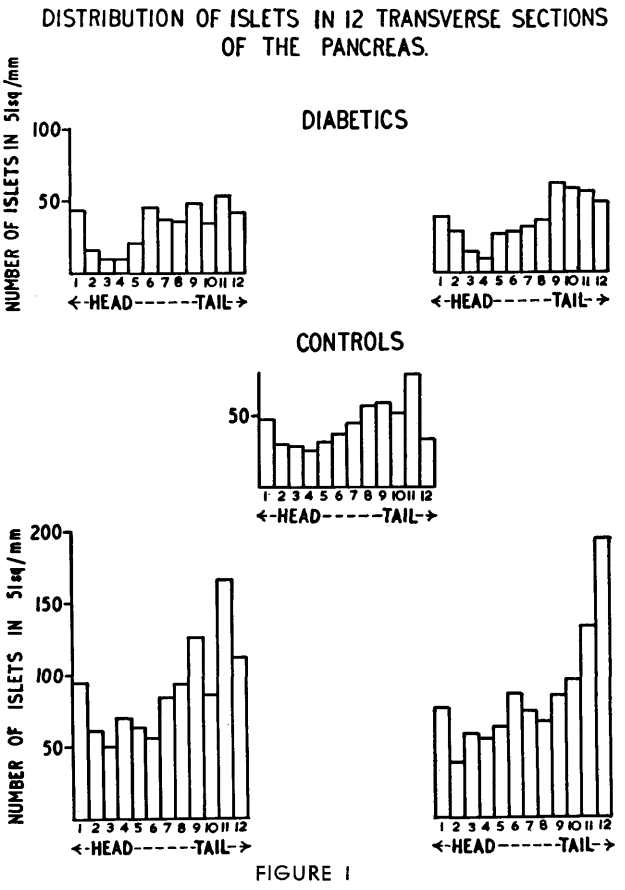


FIGURE 1

From the Departments of Pathology, The Western General Hospital, Edinburgh, Scotland, and the University of Edinburgh.

sentation of the proportion of islet tissue in the pancreas as a whole. Obviously this does not apply to pancreases which are fibrotic or grossly infiltrated by fat.

Measurement under low magnification of the size of the islets in twelve sections of the pancreases of each of three nondiabetic subjects suggested that there was no consistent variation in the size of islets in different parts of the pancreas. The validity of applying this observation to diabetic material was determined by estimating the area size of fifty islets at the magnification subsequently used in the investigation.[1] The results (table 1) suggested that the mean size of fifty randomly selected islets was fairly constant in all portions of the pancreas. For the purpose of the subsequent investigation[1] the mean size of one hundred islets distributed evenly between the sections available was estimated. Such an estimate performed on sections from different levels of a single block is unlikely to deviate significantly from the true mean islet size of the whole pancreas.

These considerations prompted us to use the six cases (cases 10, 19, 29, 37, 38, 41—tables 2 and 3) in which only one block was available. Analysis of the findings on completion of the investigation has shown that the results obtained from them were similar to those in which sections of the head, body and tail of the pancreas were examined, and that none of the trends exhibited or the conclusions drawn would be affected by their removal from the final results.

RESULTS

The results are detailed in tables 2, 3 and 4. Eighteen patients died within eight weeks of the onset of diabetes and are grouped as "acute" cases. The remaining twenty-three died at intervals varying from nine months to nineteen years after the onset of diabetes and are termed "chronic."

Weight of pancreas. The weight of the pancreas was known in twenty-seven of the diabetic cases and in fifteen of the nondiabetic subjects who served as controls. Because of the wide scatter in the ages of the patients, estimation of the mean weights over the whole range serves no useful purpose. In patients of the age of fourteen years and over, the mean pancreatic weights were: fourteen chronic cases—38.3 gm.; five acute cases—51.6 gm.; ten control cases—63.9 gm. The differences between the chronic and acute diabetics, and between the chronic diabetics and controls are significant, but the difference between the acute diabetics and the controls does not attain statistical significance ($P>0.2$).

Size of pancreatic islets. The size of pancreatic islets was measured in terms of squares (1 square = 0.0024 sq. mm.). It varied quite widely and in each group showed a tendency to increase with age and with the age of onset of the disease (figures 2 and 3). In contrast it tended to diminish in proportion to the duration of the disease, slowly and gradually in the chronic diabetics, and more rapidly in the acute diabetics (figure 4).

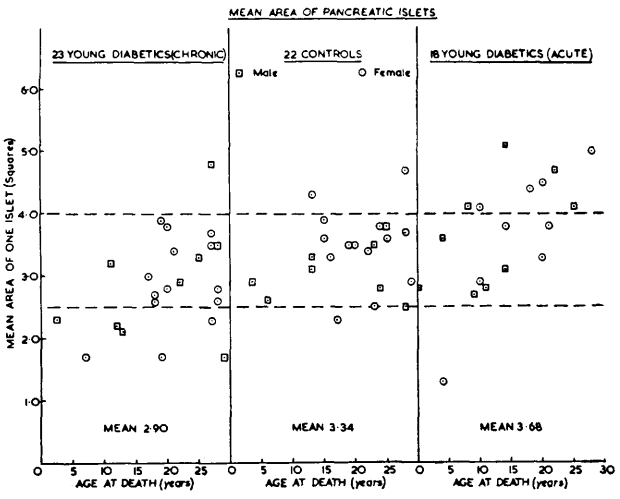


FIGURE 2

The mean size of the islets of the chronic diabetics (2.90) was significantly less than that of the acute diabetics (3.68) and the controls (3.34). The acute diabetic group and the controls were not strictly comparable since they contained three and one children respectively under the age of five. Over the age of five the mean size of the islets of the acute diabetics was significantly greater than that of the controls.

TABLE 1

Mean size of fifty islets (in squares) in each of twelve sections of the pancreases of four diabetic subjects

	1	2	3	4	5	6	7	8	9	10	11	12	Mean of twelve sections
Diabetic	4.50	5.06	4.54	4.72	4.74	5.02	4.20	4.60	4.22	4.44	4.38	4.64	4.58 ± 0.26
Diabetic	2.92	2.80	2.88	2.88	3.08	3.14	2.64	2.86	2.88	2.92	2.78	2.90	2.89 ± 0.13
Diabetic	3.92	4.12	3.98	4.26	3.76	4.64	3.98	3.60	3.82	4.10	3.94	3.80	3.99 ± 0.27
Diabetic	1.98	1.74	2.00	2.16	1.78	1.92	1.72	1.90	2.00	1.96	1.94	1.98	1.92 ± 0.12

TABLE 2

Diabetic cases (chronic)

Case no.	Sex	Age at death (years)	Duration of diabetes (years)	Age at onset	Weight of pancreas gm.	Percentage of islet tissue	Weight of islet tissue gm.	Mean area of one islet (squares)
1	M	2½	9/12	1 9/12	8.4	1.74	0.15	2.3
2	F	7	6	1 5/12	26.1	0.59	0.15	1.7
3	M	11	5	6	28.4	1.46	0.41	3.2
4	M	12	2½	9½	40.0	0.33	0.13	2.2
5	M	13	3	10	26.1	1.18	0.31	2.1
6	F	17	2	15		0.83		3.0
7	F	18	4	14	46.8	0.44	0.22	2.7
8	F	18	2½	16		0.54		2.6
9	F	19	5	14	22.0	0.95	0.21	3.9
10	F	19	6	13		0.15		1.7
11	F	20	7	13	27.8	0.69	0.18	3.8
12	F	20	5	15	32.9	0.58	0.19	2.8
13	F	21	1 5/12	19	40.7	0.81	0.33	3.4
14	M	22	5	17	69.4	0.18	0.12	2.5
15	M	25	10	15	35.9	0.40	0.14	3.3
16	F	27	14	13	20.4	0.23	0.05	2.2
17	F	27	6	21	44.4	0.76	0.34	3.7
18	M	27	2½	24		0.67		4.8
19	F	27	3	24	14.0	1.04	0.14	3.5
20	F	28	14	14	47.2	0.32	0.15	2.6
21	F	28	19	9	21.2	0.42	0.08	2.6
22	M	28	6	22	43.6	0.86	0.38	3.5
23	M	29	12	17	70.0	0.33	0.26	1.7

TABLE 3

Diabetic cases (acute)

Case no.	Sex	Age at death (years)	Duration of diabetes	Age at onset (years)	Weight of pancreas gm.	Percentage of islet tissue	Weight of islet tissue gm.	Mean area of one islet (squares)
24	M	11/52	5 days	11/52		3.94		2.8
25	F	3 11/12	6 weeks	3 10/12		1.50		1.3
26	M	4	2 weeks	4	12.4	2.86	0.37	3.6
27	M	8	12 days	8		2.71		4.1
28	M	9	6 weeks	9	17.7	1.15	0.20	2.7
29	F	9 8/12	3 weeks	9 7/12		0.93		4.1
30	F	10	12 days	10	21.4	1.03	0.22	2.9
31	M	11	5 weeks	11		1.16		2.8
32	M	14	5 days	14		2.33		5.1
33	F	14	8 weeks	14	50.0	0.58	0.29	3.8
34	M	14	4 weeks	14	60.0	1.81	1.09	3.1
35	F	18	7 days	18		1.60		4.4
36	F	20	3 weeks	20	49.2	0.67	0.33	3.3
37	F	20	2 days	20		1.12		4.5
38	F	21	5 weeks	21		0.58		3.8
39	M	22	3 days	22	50.0	1.74	0.87	4.7
40	M	25	7 days	25	48.6	0.93	0.45	4.1
41	F	28	3 days	28		1.12		5.0

Proportion of large islets in the pancreas. The number of pancreatic islets which measured more than ten squares in area in any pancreas tended to be directly related to the mean area of the islets in that pancreas (figure 5). Large islets were most numerous in the acute diabetics and least numerous in the chronic diabetics (figure 6).

Proportion of islet tissue in the pancreas. In each group the proportion of islet tissue in the pancreas was highest in young children and tended to decrease with increasing age of the patient (figure 7). In both groups of diabetics it tended to diminish as the duration of the disease increased (figures 8 and 9).

The mean proportion of islet tissue in the diabetic subjects was significantly less than in the controls (2.45 per cent) and was significantly less in the chronic diabetics (0.67 per cent) than in the acute (1.54 per cent).

Weight of pancreatic islet tissue. The mean weight

TABLE 4

Controls

Sex	Age at death (years)	Weight of pancreas gm.	Percentage of islet tissue	Weight of islet tissue gm.	Mean area of one islet (squares)
M	3½	21.1	3.31	0.70	2.9
M	6	24.0	3.01	0.72	2.6
F	13	28.6	3.23	0.92	4.3
M	13	58.8	1.48	0.87	3.3
M	13	44.6	1.90	0.85	3.1
F	15	78.4	1.88	1.47	3.9
F	15	44.5	2.61	1.10	3.6
F	16	29.8	3.62	1.08	3.3
F	17	47.6	2.88	1.37	2.3
F	19		2.89		3.5
F	20	77.5	2.49	1.92	3.5
F	22		2.95		3.4
F	23	55.6	2.54	0.81	2.5
M	23	73.6	2.96	2.18	3.5
F	24		1.88		3.8
M	24		2.08		2.8
F	25		3.11		3.6
M	25	99.9	1.41	1.40	3.8
F	28	52.9	1.62	0.86	3.7
M	28		1.59		2.5
F	28		2.41		4.7
F	29	81.5	1.91	1.56	2.9

of the islet tissue in the diabetics was less than in the controls (1.19 gm.) and was less in the chronic diabetics (0.21 gm.) than in the eight acute diabetics (0.70 gm.) in which the pancreatic weights were known (figure 10). These differences are statistically significant, but the number of acute cases in which the pancreatic weight was known was unfortunately small. In an attempt to ascertain whether the differences were likely to be present throughout the whole group of acute diabetics, hypothetical weights of islet tissue were calculated. In figure 11 a hypothetical weight, based upon the age of the patient, was allotted to those pancreases in which the real weight was not known. In patients fourteen years of age and older, the pancreatic weight in both acute and chronic diabetics was assumed to be 40 gm.—an assumption which probably results in an underestimate of the weight of islet tissue in these acute cases. The distribution of values obtained is similar to that of the known weights of islet tissue, and suggests that in the acute diabetic group the known weights of islet tissue are representative of the group as a whole.

The weight of islet tissue tended to decrease as the duration of the disease increased (figure 12). This trend affected not only the long-established diabetics but also, with one exception, the acute diabetics (figure 13). (In figure 13, the eleven-weeks-old infant is omitted since the weight of pancreatic tissue at this age is not comparable with that of older children.)

Proportion of β cells in pancreatic islets. Estimation

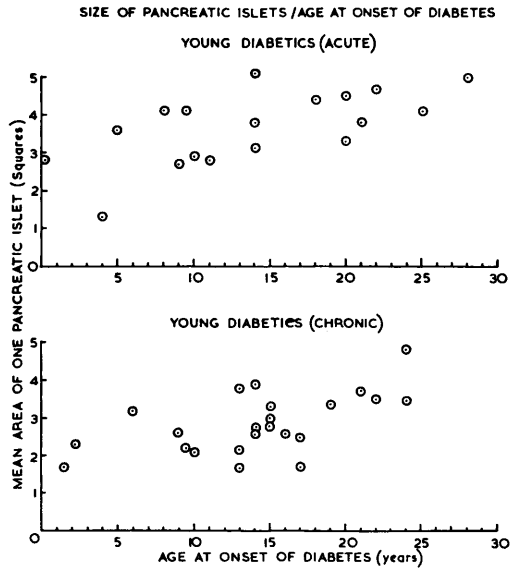


FIGURE 3

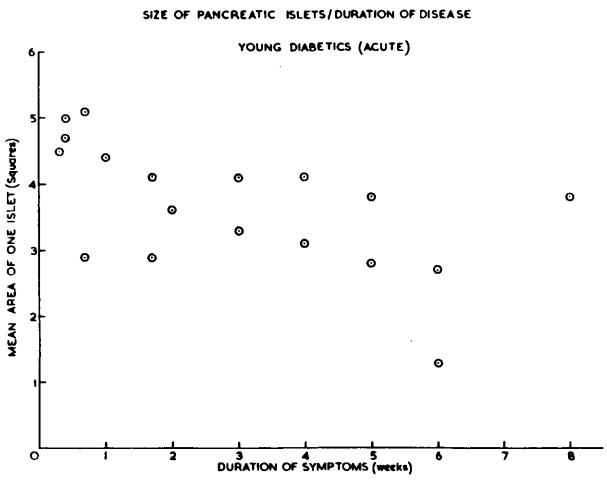


FIGURE 4

of the proportion of β cells was outside the scope of the present investigation, but observations had been made in a previous investigation on four of the present series, and differential counts were made in two additional cases. In these six cases the proportion of β cells was lower in the chronic than in the acute cases (table 5).

Other changes in the pancreatic islets. The islets of the diabetic subjects commonly showed degranulation of the β cells which was usually more severe in the acute than in the chronic diabetic cases. Hydropic change was less frequent in both groups. Slight lymphocytic infiltration of some of the islets was noted in three of the acute cases. The regeneration of islets described by Weichselbaum[2] was obvious in all of the acute and in ten of the chronic diabetic subjects.

TABLE 5

Proportion of α and β cells in pancreatic islets

Sex of patient	Age of patient (years)	Duration of diabetes	Mean area of one islet (squares)	Proportions of islet cells α	β	Mean α:β cells proportions
F	20	2 days	4.5	24	76	
M	8	12 days	4.1	25	75	1 : 2.7
F	14	8 weeks	4.8	33	67	
M	22	5 years	2.5	35	65	
F	27	14 years	2.2	46	54	1 : 1.1
F	28	19 years	2.6	54	46	

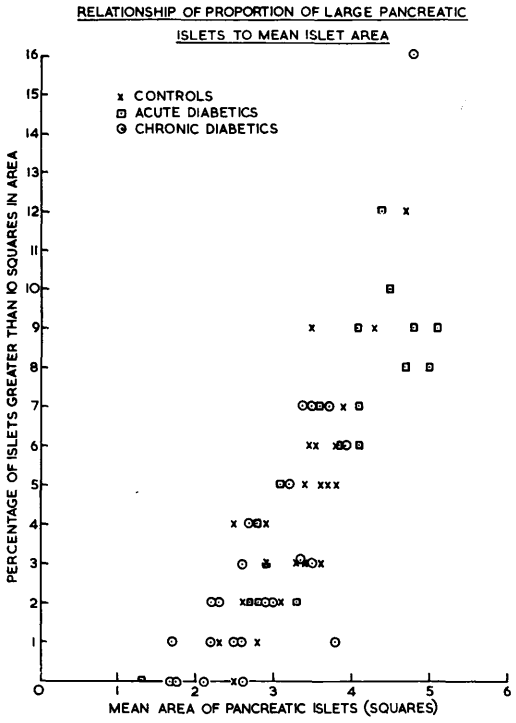
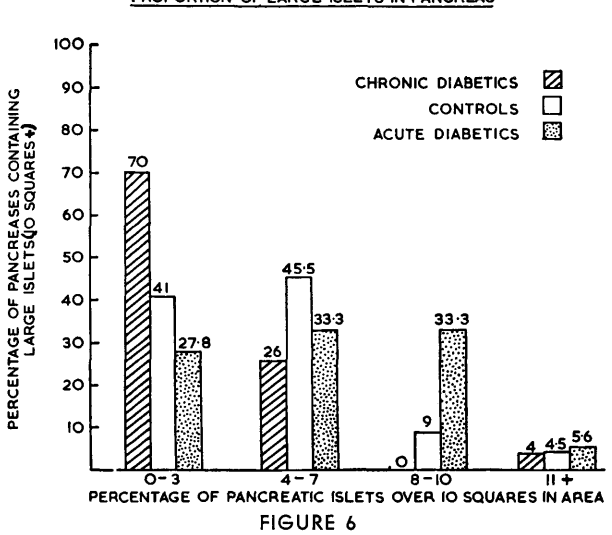


FIGURE 5



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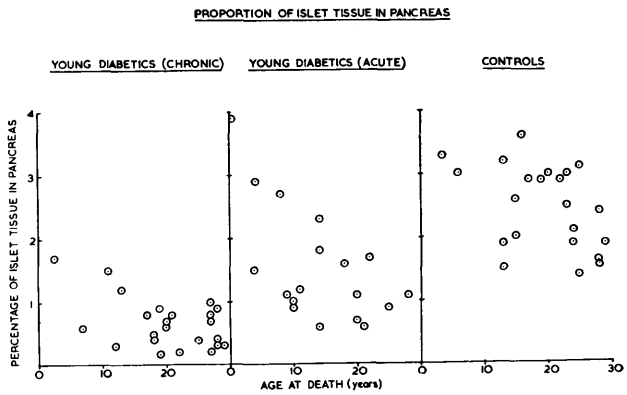

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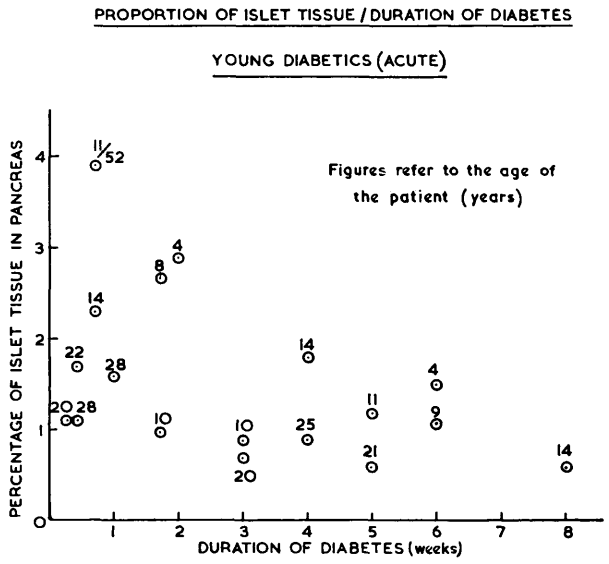

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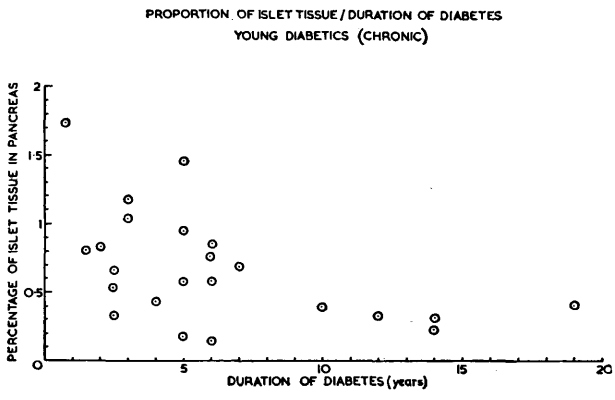

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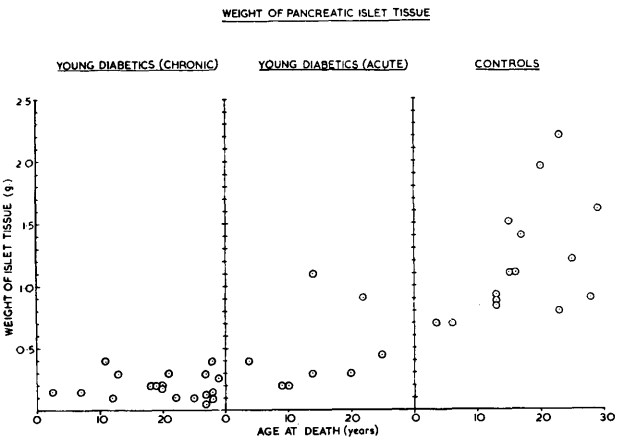

FIGURE 10

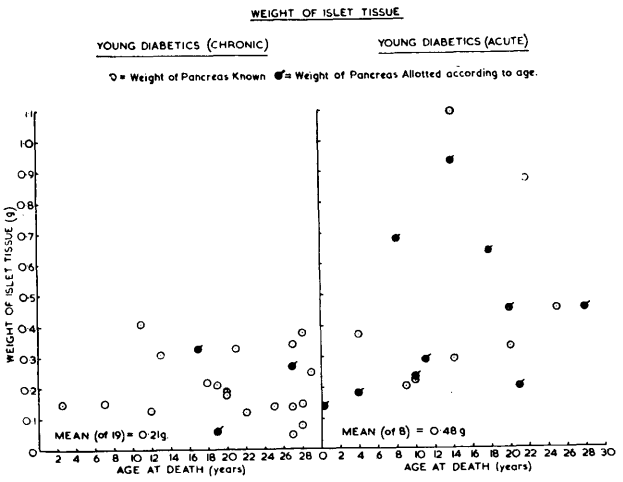

FIGURE 11

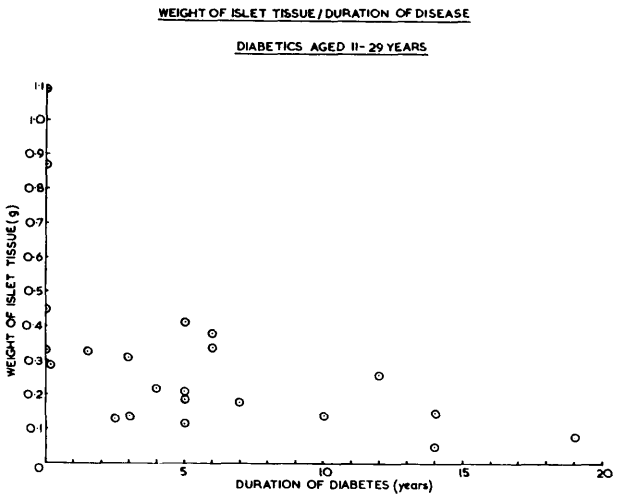

FIGURE 12

DISCUSSION

Experimental investigation has done much to clarify the pathogenesis of diabetes mellitus, but the causation of "essential diabetes" remains obscure.[3] In some cases, impaired function of the β cells may be associated with fibrosis or hyalinization of the islets. In others, where the islets appear normal in sections stained by hematoxylin and eosin, reduction in the amount of β cell tissue[1] and degranulation of the β cells[4] are probably responsible for the reduced insulin content of the pancreas. For these reasons, the pancreatic insulin content may be extremely low in diabetics who develop the disease during the growing period.[5] Abnormalities such as these suffice to account for the loss of control of carbohydrate metabolism, but they do not explain why the disease occurs. Any such explanation must take into account the hereditary nature of the disease.[6–8]

Diabetes can be produced experimentally either by (a) the effects of normal metabolic stress upon a subnormal amount of islet tissue, or (b) by excessive metabolic strain or by toxins acting upon a normal quantity of islet tissue. It is possible that one or both of these processes may be concerned in the hereditary influence in diabetes. If initiation of the diabetic syndrome is dependent upon hypoplasia of the islets, then the amount of islet tissue should be abnormally low at the time of onset of the disease. Opportunities to demonstrate that this is so seldom or never occur in man. If, however, the amount of islet tissue can be shown to be within normal limits shortly after the development of symptoms, it is probably safe to infer that it was not abnormally low at the time of onset of the disease. In the present series, the weight of islet tissue in three of the acute diabetics (numbers 26, 34 and 39), and the proportion of islet tissue in three additional acute cases (numbers 27, 33 and 35) in which the weight of the pancreas was not known, were within the control limits. There are other reasons to believe that, in some cases, the development of the pancreas may be normal. For example, the mean weight of the pancreases of the acute diabetics at the ages of fourteen and older was not significantly different from that of the controls, suggesting that the growth of the pancreas during childhood and early adult life was not grossly abnormal. Moreover, in the pancreas of infants born of diabetic and prediabetic mothers, the islet tissue is hyperplastic rather than hypoplastic.[9] It would therefore appear that the onset of diabetes cannot be attributed in all cases to faulty development of the pancreas.

Hyperplasia of the islet tissue was a recognized finding in some diabetic subjects even in the days when

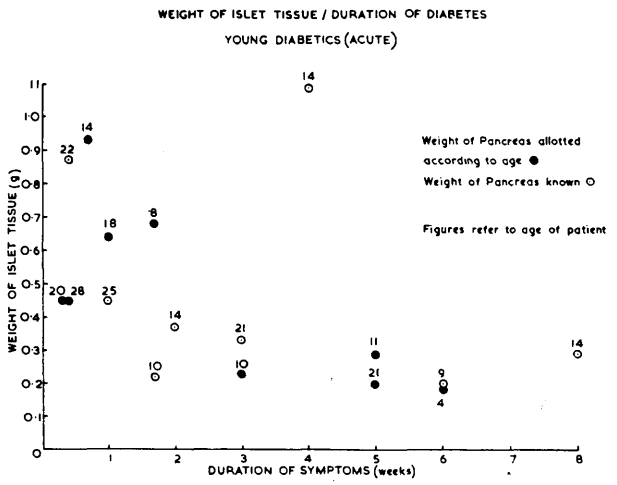

FIGURE 13

the function of the islets of Langerhans was still a matter of dispute. It would seem to be inconsistent with an illness which results from insulin deficiency, but it is nonetheless a well-substantiated phenomenon. In 1907, MacCallum[10] noted its occurrence in two children who died in diabetic coma after an illness of short duration, and suggested that it was compensatory for some extrapancreatic disturbance of carbohydrate metabolism which imposed an excessive strain upon the islets. Islet hypertrophy has since been reported in a variety of circumstances. It has been observed in the obese,[11] in rats force-fed high carbohydrate diets,[12] after perfusion of the pancreas of the dog with hyperglycemic blood,[13] in familial obese diabetic mice,[14] in rats and rabbits treated with pituitary extracts,[15,16] in rats injected with growth hormone,[17] and in rats treated with cortisone.[18] Under these circumstances, hyperplasia of the islets sometimes may be succeeded by degeneration of the β cells and glycosuria. Young[19,20] has suggested that hypersecretion of pituitary hormone, particularly growth hormone, by causing excessive stimulation and later exhaustion of the pancreatic islets, may be responsible for the diabetic syndrome in man.

Stimuli acting upon the islets may excite growth of already existing islets (hypertrophy), or formation of new islets from ducts or ductules. Weichselbaum[2] termed the latter process "regeneration," and found evidence of it in fifty-eight of 183 diabetic pancreases. Cecil[21] observed either regeneration or hypertrophy of the islets in thirty-four of 100 diabetics. In the present investigation, similar changes were seen in all of the acute and in ten of the twenty-three chronic diabetics, and were most pronounced in those cases dying shortly after the commencement of the disease. Measurement confirmed the observation that the islets were larger in the acute than in the chronic diabetics and the controls (figure 2) and that they were largest in those diabetics who died within a week of the onset of their symptoms (figure 4). The subsequent decrease in islet size suggests either that the hyperplastic stimulus may wane or that the islets may degenerate. Hydrops and degranulation of β cells, and the progressive decline in the proportion of β cells in the few cases which we examined, are both compatible with the latter possibility. Moreover, differences in percentage of islet tissue at the beginning and end of the two-month period after the commencement of the disease are proportionately greater than differences in islet size (figures 8 and 4). If our estimates are correct, therefore, some factor other than mere reduction in islet size must operate; some of the islets must have been destroyed or undergone atrophy. This does not exclude the possibility that the hyperplastic stimulus is subject to periods of remission. If, however, the remission was abrupt, temporary diabetes similar to that induced by pituitary and adrenal hormones in experimental animals might be expected to occur more often than it appears to do. The two possibilities are not mutually exclusive and both may operate; for example, hyperglycemia may produce continued islet damage after the hyperplastic stimulus which induced the diabetes has diminished in intensity.

The pattern which appears to emerge from the present observations is that diabetes in the young may be accompanied by initial hyperplasia of the islets, may occur in some patients who have a normal quantity of pancreatic islet tissue, and may result within a few weeks in diminution of islet tissue to levels which are usually met with in young chronic diabetics (figure 13); thereafter, there is a very gradual decline in the proportion and weight of islet tissue (figures 9 and 12). This succession of changes in the pancreas of young diabetics recalls the sequence of events in mature dogs treated with pituitary extracts.[22,23] The dogs are insulin-insensitive during the period of administration of the hormone, but after becoming permanently diabetic, they regain their insulin sensitivity on withdrawal of the hormone. Their islets are permanently damaged, and the pancreas has a low insulin content. The metahypophyseal diabetic dogs, therefore, resemble the insulin-sensitive diabetics of Himsworth,[24] the growth-onset diabetics of Wrenshall and his associates,[5] and the young chronic diabetics of the present series. In both groups of the young diabetics of this investigation, the pancreatic findings are not inconsistent with Young's concept

of the causation of diabetes in man. They also suggest that young diabetics dying in coma shortly after the onset of the disease resemble in some respects elderly obese diabetics. Both may exhibit insulin resistance and may possess large islets and relatively normal quantities of islet tissue.[1] These similarities are of some interest since Young attributes the clinical differences and end results of diabetes in the young and old to differences in intensity and duration of pituitary stimulation.

The part played by stress in the causation of diabetes has been reviewed so recently[25] that it is unnecessary for us to make any general comment on it, but we can hardly conclude this consideration of diabetes in the young without mention of infectious illness as a possible islet injuring or stimulating factor, since it commonly precedes clinical manifestations of the disease and may quadruple the insulin requirements in established diabetes.[7] It might exert its effect either by a direct toxic action upon the pancreatic islets, or indirectly by increasing the metabolic needs of the patient. In such a manner, toxic infection might prove to be the last straw to islets under stress from a constitutional metabolic disorder. Our results merely suggest that a metabolic disorder which causes initial hyperplasia of the pancreatic islets and later degeneration of the β cells may exist, and that it may be a factor in the causation of diabetes even in patients with normal amounts of islet tissue.

SUMMARY

Quantitative observations on the pancreatic islet tissue were made on forty-one young diabetics and twenty-two control subjects. Eighteen of the diabetic patients died within eight weeks of the onset of symptoms ("acute"), and twenty-three died at intervals ranging from nine months to nineteen years after the commencement of the disease ("chronic").

The size of the islets, and the proportion and weight of islet tissue were greater in the acute than in the chronic diabetic cases. In both groups these values tended to decline with increasing duration of the disease, rapidly in acute and slowly in chronic subjects.

In acute diabetics the islets were larger than in the control patients, and in some of them the proportion and weight of islet tissue were normal.

The bearing of these observations on the diabetic syndrome in man is discussed.

SUMMARIO IN INTERLINGUA

Observationes Relative Al Histo Del Insulas Pancreatic In Juvene Diabeticos

Observationes quantitative relative al histos del insulas pancreatic esseva effectuate in quaranta-un juvene diabeticos e vinti-duo subjectos de controlo. Dece-octo del diabeticos moriva intra octo septimanas post le declaration del symptomas (lor casos esseva "acute"), e vinti-tres moriva post intervallos de inter nove menses e dece-nove annos a partir del comenciamento del morbo (lor casos esseva "chronic").

Le dimensiones del insulas e le proportion e le peso del histo insular esseva plus grande in le acute que in le chronic casos de diabete. In ambe gruppos, ille valores tendeva a declinar in le curso del morbo—rapidemente in le casos acute e lentemente in le casos chronic.

In le subjectos con diabete acute le insulas esseva plus grande que in le subjectos de controlo. In certe subjectos con diabete acute le proportion e le peso de histo insular esseva normal.

Es discutite le signification de iste factos pro le syndrome diabetic in humanos.

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A. S. Earle, G. F. Cahill and Hoar (*Ann. Surg. 146*: 124, 1957), by employing the determination of blood pepsinogen levels, endeavored to determine whether or not glucagon played a role in gastric secretory activity. Mongrel dogs weighing 8 to 15 kg. were fed a standard ration until eighteen hours before the beginning of each experiment. Amorphous glucagon was administered intravenously during pentobarbital anesthesia and femoral vein blood was analyzed at intervals for glucose and pepsinogen levels. The rapid injection of 200 μg. of glucagon resulted in glucose values between 184 and 232 mg. per cent, reached between fifteen and thirty minutes after injection. The simultaneous decrease in blood pepsinogen level from 300 to 260 units, though probably significant, indicated the necessity for testing the effects of glucagon administered by continuous drip.

Infusions lasting from two to four hours, with dose rates ranging between 2.5 and 3.3 μg. per minute, resulted in significant decreases in blood pepsinogen levels during the induced hyperglycemia. The average control level for blood pepsinogen of 420 units fell to 320 and 250 units after one half and two hours of glucagon infusion, respectively. During the hour after the completion of infusion the blood sugar values returned to normal, but the blood pepsinogen levels remained low. The fact that no significant alteration of normal blood glucose or pepsinogen level occurred during anesthesia alone eliminated the possibility that pentobarbital was responsible for depressing gastric activity. In order to learn whether the vagi influenced gastric activity after glucagon, the infusion was repeated in animals that had undergone vagotomies one week before. Although the blood pepsinogen level dropped following vagisection, a further significant drop was observed following the infusion of glucagon over a two-hour period. Intravenous infusion of glucose was used in an additional experiment to determine whether the hyperglycemia was responsible for the drop in pepsinogen level. The animals showed significant decreases in blood pepsinogen levels comparable to those seen following glucagon injection.

The injection of glucagon into human subjects showed results essentially similar to those seen in the experimental animals. The rapid injection of 0.8 mg. elicited a moderate rise in blood glucose (74 mg. per cent to 134 mg. per cent) and a decrease in blood pepsinogen from 360 units per milliliter to 335 units per milliliter. Subjects 2 and 3 received infusions over a two-hour period and the gastric acid collections were evaluated for hourly volume and acidity. Subject 2, a normal volunteer, was given 1.75 mg. of glucagon during two hours and subject 3 with duodenal ulcer, associated hyperacidity, and elevated blood pepsinogen was given 2.5 mg. of glucagon during two hours. The blood pepsinogen levels of both subjects dropped more than 50 units and the milliequivalents of total acid decreased.

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