FAMILIAL DIABETES MELLITUS IN MICE, ASSOCIATED WITH INSULIN RESISTANCE, OBESITY, AND HYPERPLASIA OF THE ISLANDS OF LANGERHANS *

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Over a half century has elapsed since von Mering and Minkowski[1] reported the production of diabetes mellitus in dogs by extirpation of the pancreas, but the cause and nature of the naturally occurring disease remain obscure. Warren[2] has expressed the pathologist's difficulties in attempting to explain this disease process: "Few diseases definitely associated with any one function, metabolic or otherwise, show as wide a range of concomitant pathological change as does diabetes—or as frequent absence of demonstrable pathological change." Bell[3] was able to demonstrate marked reduction, or even absence, of beta granules in the pancreatic islands in only 63 per cent of patients with diabetes mellitus. Warren[2] found no demonstrable pathologic changes in the islands of Langerhans in 20 per cent of 842 patients with diabetes. In the remainder, however, he was able to demonstrate hyalinization of islands, hypertrophy of islands, fibrosis or lymphocytic infiltration of islands, hydropic degeneration of cells, pyknosis of the nuclei, sometimes hemochromatosis, as well as an occasional distinct reduction in the number of islands. Recent experiments summarized by Cori[4] indicate the importance of an antagonistic pituitary factor in carbohydrate metabolism. However, Eisenhardt and Warren[2] found no consistent lesions in the pituitary glands of 17 diabetic patients, although 4 exhibited focal necrosis; one, basophilic adenomata; one, variation in cell size; and one, vacuolation of chromophobe cells.

While it is established that there is a hereditary factor in the occurrence of diabetes,[5] the importance of this factor is not clear. Similarly, the etiologic significance of the association of diabetes with obesity[6] is not established.

A small group of mice with familial diabetes mellitus and associated defects has recently been established. These diabetic animals constantly exhibit a striking insulin resistance, centripetal obesity, and certain tissue changes. It is the purpose of this report to describe the characteristic morphologic abnormalities in these mice and to compare

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them with their non-obese, non-diabetic siblings and parents, and with normal Swiss mice. A number of important correlations with pancreatic, pituitary-adrenal, and metabolic factors will be made.

Material and Methods

Mayer and co-workers[7,8] have recently reported the appearance in V strain mice, and in a hybrid group of mice derived from a cross of V strain and fuzzy animals, of a form of obesity inherited as a simple mendelian recessive. These obese mice have blood sugar values generally exceeding 300 mg. per cent in the non-fasting state, and glycosuria on the order of 3 per cent. They are hyperglycemic even after the administration of 400 units of insulin per kg. Fasting causes 40 to 50 per cent reduction in blood sugar. Adrenalin causes marked rise in blood sugar values. These mice choose a high fat diet on free selection of nutrients. Non-obese siblings of the obese animals are consistently killed by small doses (0.5 unit) of insulin and have normal blood sugar levels, which can be markedly elevated by adrenalin. Whether these non-obese sibs are heterozygous for the gene for obesity is unknown. Parent fuzzy mice are non-obese and normoglycemic.

Eleven obese mice and 13 non-obese siblings were available for study. Together with 8 mice of the parent, fuzzy strain and 7 Swiss mice controls, the animals were killed by jar etherization or by decapitation, generally at the ages of 3 to 5 months. Tissues were generally fixed within a few minutes. One obese animal died at the age of 7 months but was not received for dissection until 2 days later. Portions of skin, heart, lung, mediastinum, spleen, stomach, small and large intestine, pancreas, liver, adrenal gland, kidney, bladder, uterus, ovary, testis, epididymis, aorta, salivary gland, tongue, skeletal muscle, bone, thyroid and pituitary glands, mid-brain, spinal column, and bone marrow of representative animals were fixed in 4 per cent formaldehyde solution or Zenker's acetic fixative, sectioned at 6 μ after paraffin embedding, and stained with hematoxylin and eosin. Pancreas, liver, kidney, skeletal muscle, tongue, and skin were fixed in absolute alcohol and in Gendre's alcoholic acetic picroformalin fluid for Best's carmine and Schiff's periodic acid leukofuchsin stains for glycogen. Pancreases were fixed in Bouin's fluid, in Zenker-formol, or mordanted in Zenker's fluid after formalin fixation for Gomori's chrome alum hematoxylin stain and azocarmine-aniline blue-orange G stain, with and without permanganate oxidation, for pancreatic island cells. Adrenal glands were stained for fat with Sudan IV after frozen sectioning of formalin-fixed tissue. Pituitary bodies were stained with Mallory's phosphotungstic acid hematoxylin for demonstration of basophile granules.

Gross Findings

The obese animals, excepting one immature animal, ranged from 35 to 56 gm. in weight (Table I). A weight of 90 gm. was attained by one

Table I

Comparative Size and Number of Islands of Langerhans

Animal		Age	Weight	Number of islands		Size of islands in μ	
				Maximum per 100× field	Total of 10 fields	Maximum	Average of 10
		days	gm.				
Obese	067	53	29	6	32	171	77
	020	91	42	5	25	266	235
	080	97	35	6	16	320	160
	026	101	56	12	26	380	233
	030	103	40	4	9	256	154
	032	114	49	7	35	600	225
	031	115	51	6	30	450	213
	002	124	51	5	32	425	225
	057	160	48	6	32	550	243
	055	160	47	10	45	400	175
	088	175	49	7	44	400	214
Siblings	NoY	33	16	3	7	190	84
	440	53	19	6	18	500	182
	50	71	22	6	34	250	120
	N32	78	25	4	17	300	82
	760	84	21	6	25	247	152
	90	85	21	6	21	615	247
	790	91	22	5	11	513	184
	N31	114	23	5	25	300	115
	N71	115	26	4	13	235	120
	450	120	21	8	18	303	250
	090	126	24	10	16	247	152
	N23	180	31	3	9	225	123
	N77	268	29	2	4	675	341
Parents	BA	153-167	25	2	6	175	105
	BHr		25	2	6	225	116
	BAc		26	8	30	200	135
	BHa		25	3	7	200	95
Swiss	31	90-130	22	2	9	50	35
	23		20	3	14	95	55
	21		23	2	3	171	56
	24		21	2	3	143	80
	32		20	2	6	175	95
	22		20	3	15	200	99
	1		21	2	5	226	177

mouse which was not dissected. The non-obese siblings weighed from 21 to 26 gm., excepting 2 immature and 2 aged animals, as did the normal parents and Swiss mouse controls. The mice were all of similar length. The non-obese animals were well proportioned, but the obese mice exhibited striking central localization of fat, causing approximately 50 per cent increase of abdominal girth over normal, 25 per cent increase in thoracic girth, and 20 per cent increase of neck circumference. The size of extremities and facies did not appear abnormal. The testes of obese animals did not descend into the scrotum on

abdominal pressure, as they did in non-obese and control mice.

The hair of the non-obese animals was luxuriant. That of the obese mice exhibited inconstant thinning over the dorsal trunk. Two obese animals had actual cephalic baldness. A number of obese animals developed striking focal alopecia during the use of the feeding cannisters. These lesions were irregularly demarcated and extended over most or all of the squatting surface of the buttock and over wide expanses of body wall. The areas of denuded skin were lightly wrinkled, inelastic, parchment-thin in some portions, and covered with thin, adherent, gray-tan crusts or with dried blood in others. The central portions of many exhibited punched-out ulcers with bases of lobular, glistening, yellow-white subcutaneous fat crusted with blood, and ragged margins of thin skin (Fig. 1).

The subcutaneous fat of the obese animals was greatly increased in thickness. It measured as much as 0.6 cm. in thickness on the abdomen, 0.5 cm. on the chest, 0.3 cm. on the neck, and 0.3 cm. on the dorsal trunk, as compared with less than 0.1 to 0.2 cm. for non-obese and normal animals. The properitoneal fat was 0.7 cm. thick in obese mice. The fat was pale yellow to almost white, and was coarsely lobulated by thin, fibrous septa. The peritoneal and mesenteric depots were correspondingly large, but those around the heart and in the mediastinum were not remarkable.

The dispersal of the pancreatic tissue within the mesentery made measurements of the size of this organ inaccurate. But, with one exception, no gross difference between the pancreases of obese, non-obese, sibling and parent, and normal Swiss mice was noted. The exception was an obese mouse with definite translucence and whitening of the pancreas. Microscopically, the islands of Langerhans were preserved in this animal, but most of the acini had been replaced by fatty tissue and clusters of lymphocytes and histiocytes. No bile stones nor a probable cause of pancreatic duct obstruction was found in this animal.

In a few obese animals the livers were yellow-brown, compared to the usual chestnut brown. No evidence of renal scarring, infection, or contracture was noted. The large arteries did not appear sclerotic. The adrenal, thyroid, and pituitary glands of all mice were of similar weight and appearance. Other viscera contained no gross abnormalities.

Microscopic Examination

The skin and dermal appendages were generally well formed, but at the margins of the bald and ulcerated areas in the obese mice there was a gradual transition to thin epidermis with few or absent rete pegs and absence of dermal appendages. At the sites of crusting and ulcer-

ation there was abrupt transition to necrotic plaques of epidermis, or of epidermis and corium, or to complete loss of epidermis and necrosis of corium and subjacent fat and muscle. Some of the necrotic areas and many of the septa of the subjacent fibro-fatty and muscular tissue contained nests of polymorphonuclear neutrophils, eosinophils, and rare lymphocytes. Cutaneous blood vessel walls were of normal thickness. There was scattered neutrophilic infiltration of some of the cutaneous nerves, but no apparent fragmentation of nerve fibers was seen. In the necrotic, superficial tissues beneath the deep ulcers there were masses of moderately large cocci in great clusters; but at the area of transition from normal skin, no organisms could be seen. There was a surprising lack of epithelial, fibroblastic, or angioblastic proliferation near the ulcers.

The heart and lungs were not remarkable. No arteriosclerotic lesions were detected in these young animals. The livers of 2 obese animals contained a moderately large amount of lipid in small vacuoles within slightly enlarged cells throughout the hepatic lobules. No fibrosis or necrosis was noted in the livers of these, or of any other mice.

The islands of Langerhans were increased in number and in size in obese animals as compared with non-obese siblings, in non-obese siblings as compared with members of the parent strain, and in parents as compared with Swiss mice (Tables I and II). This was not a straight-line relationship. The differences of island size and number between obese and Swiss mice were statistically highly significant. The difference of island size between obese and parent mice was also statistically highly significant, but difference of island number between obese and parents was slightly significant. Differences of island size and number between obese and sibling mice were not statistically significant in these small series. With one exception, obese mouse 67, which was less than 2 months old and weighed only 29 gm., there were islands greater than 250 μ in diameter in the pancreases of all obese animals. In 6 of the 11 adult obese mice the maximum island diameter was 400 μ or more. In only 7 of the 12 adult non-obese siblings was the maximum islet diameter greater than 250 μ, and in only 4 was it greater than 400 μ. Conversely, in none of the parent or Swiss mice was an island with a diameter greater than 200 μ measured. Similarly, the average of ten island diameters was greater than 150 μ in all obese mice except obese mouse 67, and greater than 200 μ in 7 of 11. In only 7 of 12 adult non-obese siblings was the islet diameter more than 150 μ; in only 3 was it greater than 200 μ. Conversely, in the parent and Swiss mice, with one exception, the island diameters averaged less

TABLE II
Comparison of Size and Number of Islands of Langerhans

	I Obese (N = 10) Mean	Em	II Siblings (N = 12) Mean	Em	III Parents (N = 5) Mean	Em	IV Swiss (N = 7) Mean	Em	P values
Maximum number of islands per field at 100×	6.8	±.75	5.4	.62	3.8	1.44	2.3	.18	I vs II >.05 I vs III >.05 I vs IV <.01 II vs III >.05 II vs IV <.01
Total number of islands in 10 fields	29.4	3.6	17.6	2.0	12.2	6.3	7.9	1.9	I vs II <.01 I vs III <.05 I vs IV <.01 II vs III >.05 II vs IV <.01
Maximum diameter of islands, in μ	405	31.8	368	46.8	200	10.2	151	23.5	I vs II >.05 I vs III <.01 I vs IV <.01 II vs III <.01 II vs IV <.01
Average of 10 island diameters, in μ	208	10.3	172	21.5	113	8.6	85.3	17.6	I vs II >.05 I vs III <.01 I vs IV <.01 II vs III <.05 II vs IV <.01

N = number of animals in series.
Em = standard error of the mean.
P = probability value of difference between means (<.05 is significant; <.01 is highly significant).

than 150 μ. There was greater variation in size of islands in the obese mice. Many were located near pancreatic ducts. Occasional mitotic figures were found in islets of obese mice, and rare ones in non-obese siblings. Three of the obese mice had a definite trabecular pattern of island cells (Fig. 5) similar to that described in regenerating islets by Cecil.[9] That pattern was the only manifest cytologic difference between the islands of Langerhans of obese mice and of non-obese siblings (Figs. 5, 6, and 7). The alpha and beta cells of the pancreatic islets were similar in numerical proportion, granularity, size, character, and distribution in the obese, non-obese sibling, parent, and Swiss mice. Hyalinization, fibrosis, hydropic degeneration, or necrosis was not observed in the islands of Langerhans. The pancreatic acini and ducts in all but one animal were intact.

No glomerulosclerosis, vacuolation of renal tubular epithelium, or pyelonephritis was observed. The adrenal glands were examined carefully under survey and fat stains. With these basic technics the secretory zones were all similar to those in the Swiss mice. No cortical nodules were found. The adrenal medullae were not manifestly hypertrophied. Apparently normal, active spermatogenesis was found in both obese mice and non-obese siblings. The ovaries of both contained many well formed graafian follicles. The pituitary bodies of the obese mice, of siblings, parents, and Swiss mice contained basophils and acidophils in comparable numbers. No adenomatoid collections of cells, necrosis of cells, Crooke's changes of the basophils, variations in cell size, basophilic "invasion" of the posterior lobe, nor hyaline plaques could be found in the pituitary glands of these animals. The central nervous system presented normal structure and well preserved neurons at the hypothalamic, spinal cervical, and low dorsal levels.

There were characteristic deviations of glycogen content in the experimental animals. Sections of liver, stained for glycogen, permitted accurate differentiation of obese mice from all non-obese animals (Figs. 2, 3, and 4). The obese mice consistently exhibited much less hepatic glycogen than did all the others, although they showed a small to moderate amount. On the other hand, the non-obese siblings and parents showed slight to moderate increase of hepatic glycogen when compared with Swiss mice. In no cases were excessive amounts of glycogen, or abnormal amounts of nuclear glycogen observed. The glycogen was scattered throughout the lobules, occasionally concentrated in centrolobular and peripheral areas. Pilot chemical assays confirmed these quantitative abnormalities in hepatic glycogen. Skeletal muscle contained quite variable amounts of carminophilic glycogen. Very little glycogen could be stained in the skin of any of the animals.

No significant amount of glycogen was stained in the kidneys of the experimental or control mice.

Peripheral eosinophile cell counts were comparable in obese, sibling, parent, and control mice and revealed similar reduction after ACTH administration.

Comments

By the usual definition of diabetes, including hyperglycemia and glycosuria, the obese mice were diabetic. Although the blood sugar levels usually were taken in the non-fasting state, they indicated definite hyperglycemia as compared with the levels of control animals on diets with an even higher carbohydrate content.

Clinically we were dealing with two groups of animals: one group was obese and diabetic, and insulin resistant; the other group, including siblings, parents, and Swiss mice, was clinically normal. Morphologically, however, there were three groups of animals, in addition to controls: (1) obese, diabetic, insulin-resistant mice which had a marked increase in pancreatic island size and number and manifested marked decrease in liver glycogen content; (2) siblings, which were non-obese, normoglycemic, sensitive to insulin, revealed moderate increase of pancreatic island size and number, and had large amounts of liver glycogen; and (3) parents, which were non-obese, sensitive to insulin, normoglycemic, revealed slight increase of pancreatic island size and number in comparison with Swiss mice, and had large amounts of liver glycogen. It is not evident from this study just what interaction of hereditary and environmental factors produced these three types of animals; but clinically and morphologically the obese animals were in a group apart.

The obese animals manifested marked, statistically highly significant, increase in size and number of islands of Langerhans when compared with non-obese parents and Swiss mice. The numerical increase of islets was significant when compared with non-obese siblings, but the differences in islet size were only suggestive in these small series (Table II).

The islands of Langerhans in the obese mice, and to a less extent in the non-obese sibling and parent animals, exhibited many of the characteristics of islands reacting to a growth stimulus. They were enlarged and increased in number, mitotic figures were present, and many were clustered adjacent to ducts from which they are known to arise throughout life in other species of rodents.[10] Some of these islets had the trabecular pattern described by Cecil in regenerating islands.[9] The growth stimulus could conceivably be a primary pancreatotrophic principle; a secondary growth-stimulating factor, for example, a de-

mand for more insulin in the insulin-resistant organism; or a factor releasing inhibition of growth. We know too little of the checks and balances of island growth to delve deeply into the last possibility. The association of insulin resistance with marked island hypertrophy in the obese mice suggests a growth stimulus associated with insulin resistance. The correlation of marked island hypertrophy with hyperglycemia in the obese mice may indicate that the growth stimulus is related to hyperglycemia. Our methods were not sensitive enough to rule out slight insulin resistance and transient hyperglycemia or "glucose tolerance test diabetes" in the non-obese siblings and parents which also manifested evidence of some stimulation of growth of islands.

There is no histologic explanation of the cause of insulin resistance in these mice. Experimentally and clinically, apparent insulin resistance can sometimes be correlated with insulin hypersensitivity, acidosis, infection, toxemia, circulatory failure, renal glycosuria, liver disease, hemochromatosis, or pituitary-adrenal hyperfunction.[2,11] The syndrome of centripetal obesity, insulin resistance, diabetes, and skin changes associated with pituitary or adrenal hyperactivity in humans is comparable to the state in the obese mice. No pituitary or adrenal pathologic changes have yet been found in these mice to support such a possibility, but it has been shown that the insulin antagonistic effect of pituitary extract is mediated in an enzymatic, metabolic reaction.[4] Possibly insulin resistance in these animals is associated with such an enzymatic effect.

Association of abnormalities of fat distribution with peculiarities in glycogen deposition is indicated. The low levels of liver glycogen of obese animals are contrasted with the high levels in non-obese siblings and parents. The hyperglycemia and lability of blood sugar levels of the obese mice are quite different from the stability of blood sugar of non-obese siblings. According to the glycostatic theory of the regulation of appetite, the metabolic defect of the obese animals may be such that they store less liver glycogen, are less able to maintain stable blood glucose levels, and, hence, have great appetites.[12] Whether the resultant excess food intake causes damage to pancreatic beta cells, as Wilder[13] suggested, and whether diabetes occurs as a consequent effect in the obese animals, cannot be determined from the present study. The hypothesis that inability to store liver glycogen increases the appetite in these animals does not, however, explain the peculiar distribution of fat in the obese mice. Although many of the defects in these mice resemble the results of pituitary-adrenal hyperfunction, the low levels of liver glycogen in obese mice are at variance with the

effect of pituitary extracts and corticosterones, which increase gluconeogenesis and promote the deposition of liver glycogen.[14,15] The apparent inability of the obese animals to store liver glycogen may be part of an "inborn error of metabolism" which in turn is not necessarily an endocrine abnormality.

The slow rate of healing of the skin ulcers, some of which were of weeks' duration, may be related to an unfavorable metabolic milieu for tissue growth. Conceivably, of course, it could be related to pituitary or adrenal hyperactivity.[16] The skin ulcers, on smear and culture, revealed enterococci, alpha streptococci, and proteus bacilli, all skin contaminants. The cocci seen microscopically in the ulcer site probably did not cause the skin breakdown, for there was little exudation or inflammatory reaction, and the organisms were scarce at the margin of ulceration but numerous in the centers. Occlusion of vessels was not demonstrated, and there was no evidence of neurogenic atrophy of skin or underlying tissues. These skin changes resemble the "dermatitis gangrenosa" described by Riven[17] in a human patient in diabetic coma. The ulcerations he described arose at sites of pressure: the flank, posterior portions of thighs, and legs. The consistent gluteal or shoulder localization of the ulcers in the mice, at the regions of marked fat accumulation and of pressure during squatting or feeding, indicates a decubital factor in the causation of these ulcerations.

Complications of diabetes were rare in these animals. None of the mice became comatose and no acetone or diacetic acid could be detected in the urine of obese mice; but infection, trauma, change or marked restriction of diet, and physiologic hardships such as pregnancy were avoided. A few obese, diabetic animals did develop fatty livers. The absence of glycogen nephrosis seems surprising in consideration of the large amounts of glucose excreted in the urine of the obese animals.[18] However, the blood sugar level at which glycogen nephrosis develops in mice is not known. Arteriosclerosis, glomerulosclerosis, hepatic cirrhosis, xanthomata, and fatty macrophage accumulation in the spleen were not found; however, none of the animals lived longer than 7 months. The tissues of the obese animal which died at the end of that time were too poorly preserved for accurate diagnosis.

It is hoped that further studies will better indicate the cause of the abnormalities of blood sugar content, of hepatic glycogen distribution, of fat deposition, of pancreatic islet size, and of insulin response. The supply of mice is still limited, but studies of the effect of ACTH administration, alloxan therapy, ageing, and endocrine organ extirpations are being pursued. A number of physiologic, chemical, and histochemical studies are indicated.

SUMMARY

A strain of obese mice with constantly associated diabetes and insulin resistance has been studied in comparison with clinically normal siblings and parents, and Swiss mice. The obesity is inherited as a simple mendelian recessive.

The obese mice exhibit larger, more numerous islands of Langerhans and other evidences of a stimulus to island growth. The siblings manifest slight evidence of a similar stimulus. Structural changes of other endocrine organs have not yet been demonstrated. The obese mice have less than normal amounts of hepatic glycogen. Cutaneous atrophy and ulcers which did not heal were found in some of the obese animals.

The association of changes in the islands of Langerhans with insulin resistance and hyperglycemia suggests the existence of an insulin antagonistic factor which results in island growth primarily or secondarily. This may be an inherent metabolic antagonist.

The low liver glycogen content in obese mice and the lability of blood sugar levels implicates the glycostatic theory of the regulation of appetite in the causation of the obesity, and possibly of the diabetes, in these experimental animals.

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ADDENDUM

Subsequent studies by Guggenheim, Mayer, and Dickie (in preparation) indicate that obese animals do not oxidize administered radioacetate to the same extent as non-obese animals. Other studies by Mayer, Russell, Bates, and Dickie (in preparation) show that the diabetes occurs at the ninth week, is precipitated by growth hormone administration, and that the blood sugar of obese animals is strikingly increased by growth hormone, while that of non-obese animals is not affected.

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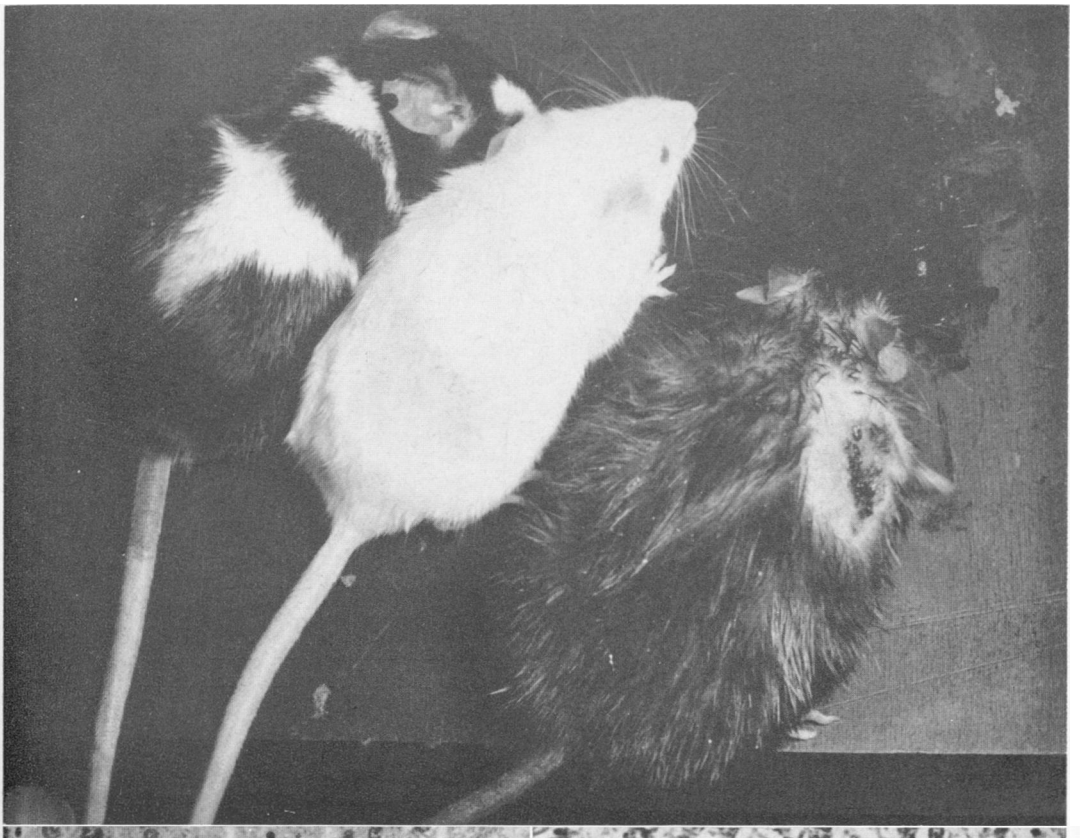
DESCRIPTION OF PLATES

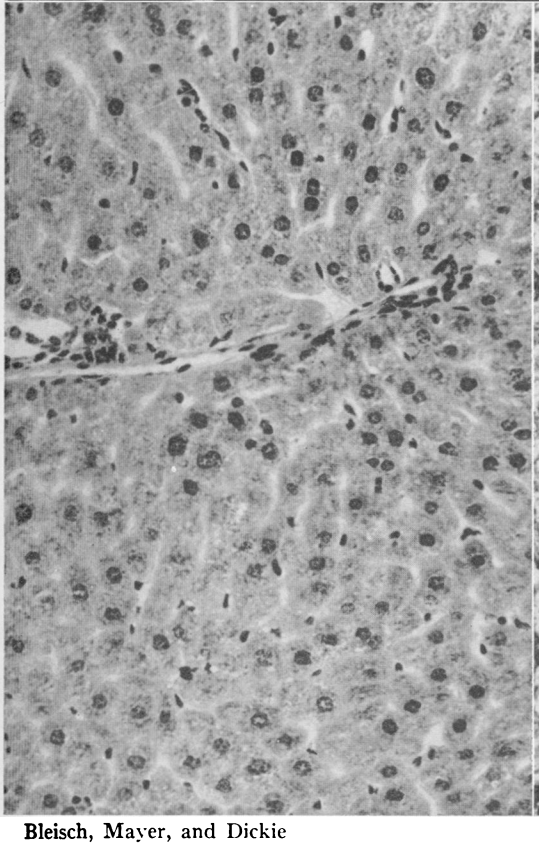
Plate 60

Fig. 1. Obese mouse (gray), non-obese sibling (black and white), and normal control (white). The obese animal has large ulcers of the right shoulder and of the squatting surface of the trunk (not shown).

Fig. 2. From a section of liver of an obese, diabetic, insulin-resistant mouse stained with Best's carmine stain for glycogen. Of note are the small number of granules of stained glycogen. × 180.

Fig. 3. Liver of non-obese, non-diabetic sibling, stained with Best's carmine for glycogen. There are many granules of stained glycogen. × 180.





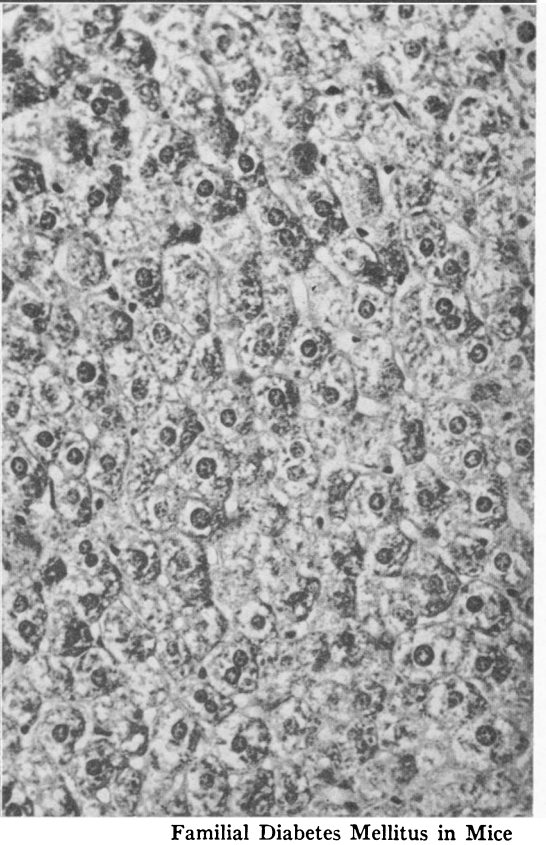
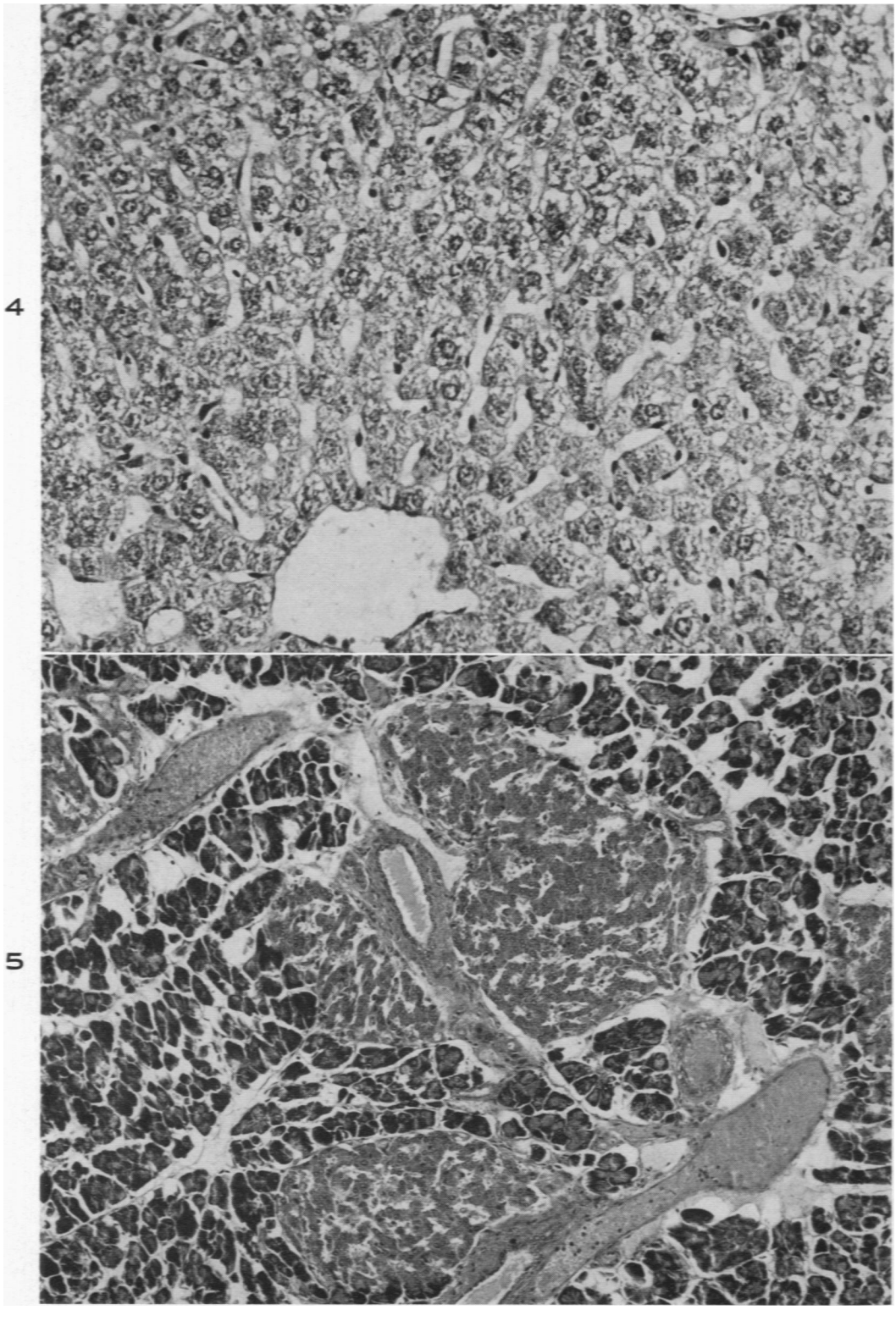


PLATE 61

FIG. 4. Liver of control Swiss mouse stained for glycogen. Moderate numbers of granules of carmine-stained glycogen may be seen. × 180.

FIG. 5. Pancreas of obese, diabetic, insulin-resistant mouse. The islets are large, numerous, and composed of cells arranged in a distinctive trabecular pattern. Hematoxylin and eosin stain. × 80.

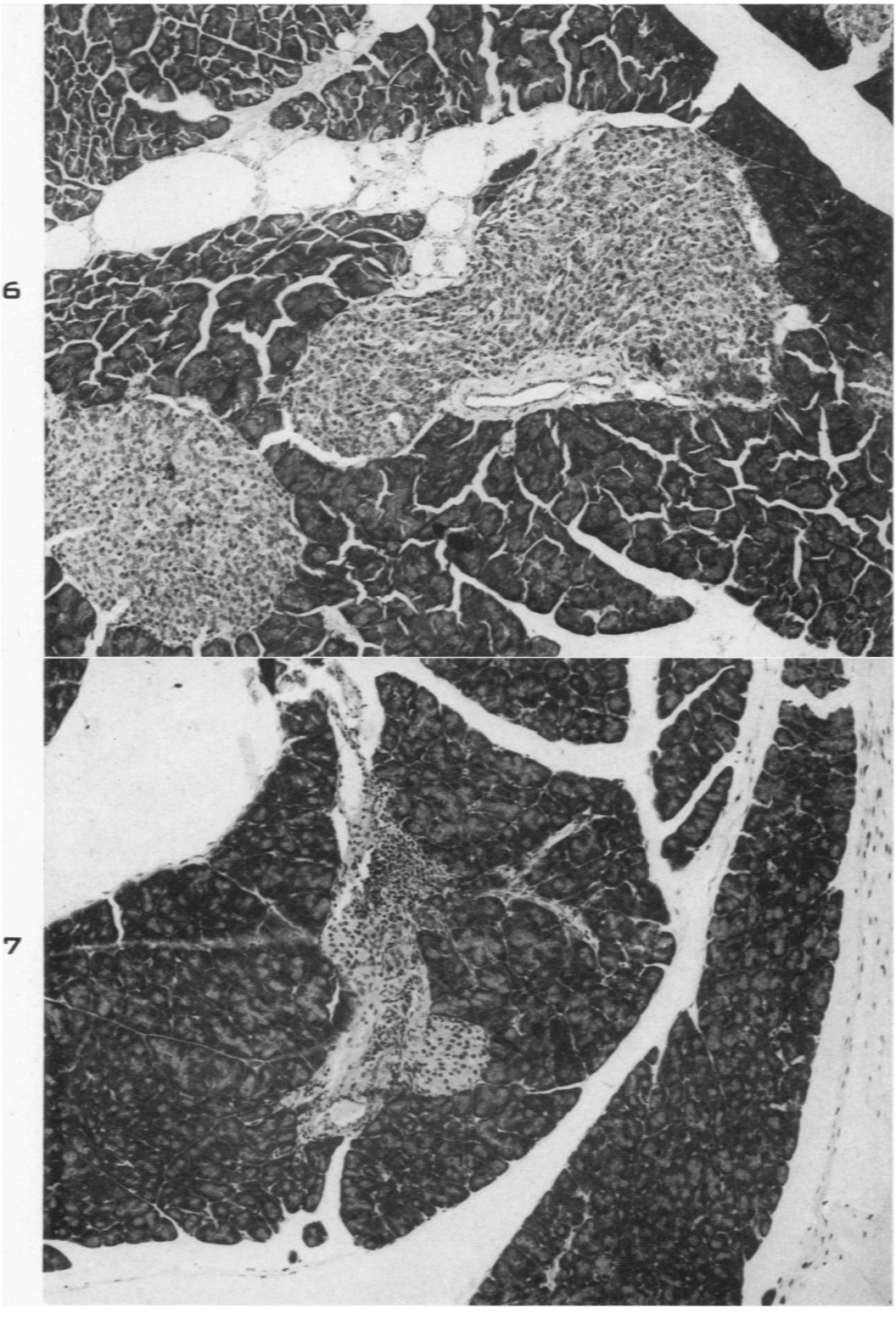


Bleisch, Mayer, and Dickie Familial Diabetes Mellitus in Mice

PLATE 62

FIG. 6. Pancreas of non-obese, non-diabetic sibling. The islands of Langerhans are large and numerous. Hematoxylin and eosin stain. × 80.

FIG. 7. Pancreas from control normal Swiss mouse. The two small islets are characteristic of the normal animals. Hematoxylin and eosin stain. × 80.



Bleisch, Mayer, and Dickie Familial Diabetes Mellitus in Mice