HYPERTROPHY OF THE ISLANDS OF LANGERHANS IN DIABETES MELLITUS.

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Since the publications of Opie and Ssobolew much attention has been directed to the role of the islands of Langerhans in connection with carbohydrate metabolism and particularly to the changes which are found in them in cases of diabetes mellitus. These changes consist for the most part, as is well known, in degeneration and sclerosis, in which the strands of cells composing the islands are replaced hy hyaline-pink staining material. From the frequency of this change and its isolated occurrence in certain cases of diabetes the idea arose that the islands constitute an organ whose duty it is to maintain in some way the ordinary course of carbohydrate metabolism and whose destruction gives rise to such disturbances of this metabolism as are seen in diabetes when sugar is excreted in the urine. Certain observers, however, among whom Hansemann is prominent, think that lesions of the islands are of little importance in the causation of diabetes, and lay more stress upon changes occurring in the pancreatic tissue in general, and Hansemann claims for a type of granular atrophy of the pancreas, which he has described, the chief place in the pathological anatomy of the disease.

There are, however, as Sauerbeck points out in his review of the literature, many cases in which no such definite lesions of the pancreas are to be found and in which the cause of the diabetes must be regarded as extrapancreatic.

Various attempts have been made to give some definite outline to a theory of diabetes without as yet, it is true, arriving at any very lucid working hypothesis. Even if the islands of Langerhans are quite essential to the furtherance of carbohydrate metabolism, as the upholders of that theory believe them to be, we are still at a loss to know the nature of their activities and just where in the chain of events which constitute carbohydrate metabolism their influence is felt. It seemed for a time that with Cohnheim's experiments upon the effect of the interaction of muscle extract and pancreatic extract upon carbohydrates some light had appeared, hut more recent work seems to have invalidated to a great extent these results, tempting as they were.

It was with these facts in view that the present case aroused interest, inasmuch as it shows alterations in the islands of Langerhans in the course of diabetes, but alterations which can hardly be interpreted as degenerative changes, nor, indeed, as changes which might hring about their functional insufficiency; on the other hand, they are changes which seem to indicate an actual increase

in the bulk and functional capahilities of these islands. The case is as follows:

L. H., a boy, aged ten years, was brought to the Johns Hopkins Hospital on December 14, 1905, complaining of headache, frequent micturition, and extreme thirst. His family and personal history were unimportant. The condition of which he complained had begun three weeks previously with very intense headache. His appetite was not excessive. On entry it was found that he was a somewhat emaciated boy, hut physical examination was practically negative. The blood showed approximately normal conditions, except that a little fat was observed in the centrifugalized specimen.

On entry the urine was found to contain 6.6 per cent. of dextrorotatory sugar as estimated hy the aid of the polariscope. On December 30, this had decreased to 5.3 per cent. (by Pavy's titration method 5.1 per cent.). Later the amount decreased gradually, being 2.5 per cent. on January 5, and 3.2 per cent. on January 11. No β-oxyhutyric acid was present, but acetone and diacetic acid were found in all the more recent examinations.

On February 4 he began to be drowsy and very dull, but physical examination was then quite negative. On February 5 he was still very dull and was given intravenous injections of sodium carbonate. The stupor was such that it was unnecessary to use a local anesthetic in exposing the vein. Very deep respirations with pallor and cyanosis were present at this time. On February 6 air-hunger continued, and, although the patient became brighter after the sodium injection, he lapsed again into coma which did not yield to further injections of alkali. During the injection he suddenly vomited a quantity of fluid, some of which was aspirated into the lungs, with immediate death.

At the autopsy, which was performed a few hours after death, the body was found to be that of an emaciated boy, with dry scaly skin. Examination of the internal organs failed to reveal any gross change whatever, except the presence of food materials in the bronchi. No examination of the central nervous system was permitted.

The pancreas weighed 35 grams. It was normal in color and consistence; on section the ducts appeared normal, and the lohulation and general character of the cut surface could not be said to present any abnormalities.

Microscopically, too, it may be stated briefly, careful examination of the organs, other than the pancreas, failed to reveal any histological abnormality, except for the presence in the liver and renal epithelium of vacuoles containing glycogen.

Chemical examination of portions of the pancreas, which were submitted to Dr. Amberg, showed that the fermentative activities of extracts of the gland were those of a normal gland.

For the rest, portions of the gland were taken from the head, the

middle portion, and the tail, and examined in serial section after fixation in Zenker's fluid or in alcohol.

It was found that, in a general way, the pancreas is not much altered, there being no great destruction of parenchyma nor any overgrowth of connective tissue; the lobulation is practically normal, and, for the most part, the acini which make up the lobules cannot be distinguished by any alteration from the normal. The islands of Langerhans, however, which are far more numerous toward the tail than in other portions of the pancreas, are very conspicuous, and seem larger and much more deeply stained than normal. So striking is their appearance that they seem to stand out very prominently throughout the section. Each lobule has such an island in its central portion, and frequently the islands are more numerous and seem to lie close together or even to be almost continuous with one another. Probably these are points in which the somewhat eccentric islands of adjacent lobules approach one another. In size they vary greatly, as seen in serial sections, where the equatorial section may be found, as well as in single sections, where, of course, the smaller areas may always represent merely tangential sections of an island. On the average they are apparently distinctly larger than the normal islands, a basis for which statement may be found in the following table of comparative measurements in which islands were measured in five normal glands:

Autopsy.	No. of islands measured.	Average size.
2685	0	0.132 x 0.156
2662	8	0.104 x 0.100
2670	10	0.200 x 0.168
2693	7	0.172 x 0.128
2698	8	0.180 x 0.180
		average 0.157 x 0.146
2670 (diabetes)	22	0.240 x 0.188

In their histological structure, these islands are quite different from the normal in several respects (Fig. 1). They are far less sharply outlined, having indeed nowhere such a clear contour formed by a membrane or a layer of connective tissue as may often, if not always, seem to encircle the normal island. Instead of this the strands of cells which compose them are almost everywhere distinctly continuous with the cells of the adjacent acini. The transition is perfectly definite and by no means difficult to find or observe (Fig. 2). As one passes from the secreting cells into those of the island, however, a very marked qualitative alteration is observed, as well as the conspicuous change in their arrangement. The cells in the island are quite different in form from those of the acini, being elongated with square ends; they are arranged in long, tortuous, and anastomosing columns, which twist into a sort of knot,

and are kept apart by spaces in which lie bloodvessels. Usually only a single row of cells forms these strands, their long axis being

FIG. 1.—Islands of Langerhans of the hypertrophied type, continuous with and probably differentiated from the adjacent parenchyma.

FIG. 2.—Margin of one of the enlarged islands more highly magnified, showing the continuity of the cells of the island with those of the adjacent acini.

arranged transversely to the strand, and their nuclei lying in the middle, so that the whole forms a band of cells with a central row

of nuclei. The protoplasm of these cells is less granular than that of the parenchyma in general. The nuclei are large and vesicular and contain coarse chromatin particles, which stain deeply. A large, deeply-stained nucleolus is especially conspicuous, and renders it easy to distinguish these cells from those of the acini.

Such islands, therefore, do not resemble with any precision the normal island of Langerhans. They are not sharply outlined; their columns of cells are long and tortuous and independent, being seldom more than one layer of cells wide; they are everywhere directly continuous at their ends with the adjacent parenchyma; and they stand out prominently by reason of the abundant chromatin content and conspicuous nucleoli of their nuclei.

In many places such strands of cells are intercalated in an isolated way in the general parenchyma, where they are easily recognized; but it is probable, if not certain, that these are always outposts of an island approached tangentially by the knife. They are not found in any connection with the ducts, but lie, as a rule, toward the centre of the lobule. From this mode of occurrence and their general appearance there seems little doubt that they represent the islands of Langerhans.

With few exceptions all the structures found throughout the pancreas, which could be regarded as islands, have these characters. It must be stated, of course, that toward the head of the pancreas there seem to be many lobules without any such bodies. There are also in that part of the pancreas, lobules, in the central portion of which there are no well-defined islands, but in which the parenchyma gives place throughout a relatively small area to a compactly arranged mass of cells, exactly like those forming the islands, but no longer arranged in single rows. In places these cells, less regular and columnar in form than in the above-mentioned islands, are closely applied to one another in such a way that they form irregular radiating masses in which any capillaries present are separated by the thickness of several rows of cells. Such masses resemble only faintly the normal islands of Langerhans. They have neither their arrangement nor their characteristic cells, but are simply radiate masses directly continuous with the adjacent acinar cells, or cells distinguishable by the character of their protoplasm and their deeply stained nuclei.

But there are other lobules which have a quite different look. Chiefly in the tail of the pancreas there are large lobules, few in number and collected closely together, in which the islands of Langerhans are much more like the normal and do not exceed the normal in size. These are sharply and smoothly outlined by a thread of fibrous tissue (Figs. 3 and 4), which separates them clearly from the surrounding acini, at least at most points. In their structure and in the appearance of these cells, on closer inspection, however, they too are very different from the normal; they are made up of

rather large columns of cells separated from one another, not by spaces, but merely by the capillaries to whose walls they are closely

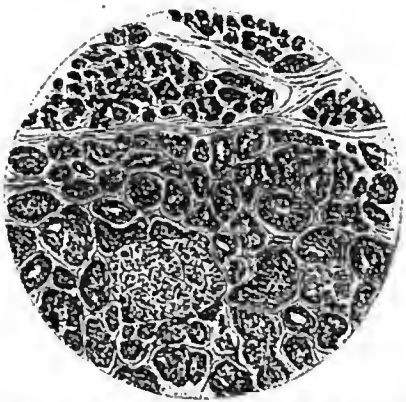

FIG. 3.—Portion of an enlarged lobule, showing enlarged acini and an island of Langerhans more closely approaching the normal. In the adjacent lobule the parenchyma is normal.

FIG. 4.—Margin of the island shown in Fig. 3. The adjacent acini of the parenchyma are larger than normal. The drawing shows the character of the cells of the island with the peculiar small bodies at the nuclear pole.

applied. Were it not for the great transparency of the cells themselves, such islands would appear very compact, hut the cells seem to consist of only the merest ragged outline of protoplasm. The nuclei stain rather palely and do not present so distinct a nucleolus as in the cells of the other islands. They are often accompanied by peculiar small, rounded, bodies which lie near their poles and which take a faint nuclear stain. The nature of these small bodies is not clear.

The acinar tissue which makes up the lohules in which this type of island lies, is different from that in the other lobules, in that the acini and their component cells are much larger. This may be seen in Figs. 3 and 4; hut it is much more striking when one can compare under a low power the appearance of such lobules with that of the adjacent ones. That there is an actual increase in the bulk of the tissue seems evident from the fact that sometimes not all of the tissue of the lohule has undergone this enlargement, hut only portions of it which then stand out as overgrown masses which push aside and flatten out into concentric rings the adjacent small acini.

Otherwise, however, I can discern no especial change in the character of the cells and no mitotic figures were found.

Another case of a similar character, to which my attention was called by Dr. Opie, occurred also at this Hospital. It was as follows: A child was admitted to the hospital complaining of hunger and thirst, frequent micturition, and excessive loss in weight. The intense symptoms developed suddenly three weeks before entrance. On admission the child was found much emaciated; the skin extremely dry and harsh. Physical examination was negative. The child was semiconscious, and the respiration was labored. The urine contained 2 per cent. of sugar. Acetone was present, as shown by Le Noble's test. There was also a trace of alhumin. The patient died in coma, two days after admission.

The anatomical diagnosis reads as follows: Diabetes mellitus; subserous hemorrhages; hemorrhagic gastroenteritis with ulceration; hemorrhage into the intestine; extreme fatty degeneration of the organs. The organs were practically normal throughout, except for the ulcerative condition of the mucosa of the intestine and for the pallor and accumulations of fat in the kidneys and liver. The blood showed a little free fat. The central nervous system was not examined. The pancreas weighed 25 grams, was soft, and perhaps more opaque looking than normal.

In this case the pancreas presents an appearance almost precisely similar to that described above. Only two sections are at my disposal, but from these it appears that there is not only a change in the islands resembling that first mentioned, but also an increase in the hulk of the secreting tissue in certain lohules. The islands, however, in this case, are fairly sharply outlined as in the normal

and are all of one kind. The swollen parenchyma shows very distinctly a basal layer of darkly stained granular protoplasm, as contrasted with the paler more central part.

On the whole, therefore, we have in these cases of diabetes in children a peculiar condition of the pancreas, in which the islands of Langerhans are apparently increased in size and number, and modified in their general appearance, and in which certain portions of the parenchyma are also increased in bulk. It remains for us to explain the relation of these changes to the diabetes.

This is a difficult problem in view of our ignorance of the nature of diabetes; but even a working hypothesis may be of some value, and it has occurred to me that there is here the result of some disturbance in carbohydrate metabolism from extrapancreatic causes such as impose an excessive amount of work upon the islands of Langerhans, and that these in order that they may maintain their control of their own particular link in the process have undergone the compensatory hypertrophy which has been described. That this explanation of hypertrophy in an organ of internal secretion is not entirely fanciful is shown by the condition of the parathyroids in a case of gastric tetany, in an old man, in which the parathyroids were greatly hypertrophied in the attempt to maintain their function of neutralizing poisons produced in the stomach.[1] In that case, however, the accumulation of poisonous materials in the highly dilated stomach was such that despite the great size of the parathyroids the man died of tetany. So here in spite of the great increase in the bulk of tissue of the islands of Langerhans the children died of diabetes.

It is also possible, and perhaps even probable, that these islands of Langerhans are not only hypertrophied, but indeed actually newly formed from the tissue of the pancreas. It may be that they have appeared in the tissue of the child's pancreas by a differentiation of Langerhans tissue from the ordinary parenchyma which might not be possible at a more advanced age. This view is supported by the very intimate connection which amounts to actual continuity with the cells of the acini. In that case the presence of a few islands of Langerhans much more closely approaching the normal would suggest that they were the only remaining islands of those originally present, and that the others had been destroyed by some specific process, constituting in that case an intra-pancreatic cause of the diabetes. Thus, two rather distinct hypotheses are suggested: the first, that the excess of Langerhans tissue is the response to an extrapancreatic cause of diabetes, and the second that the destruction and disappearance of all but a few of the islands of Langerhans produced diabetes, but also subsequently a regeneration of

[1] MacCallum. Die Beziehung der Parathyroiddrüsen zu Tetanie. Centralbl. f. allg. Path., 1905, xvi, 385.

islands from the parenchyma. There are no remains or scars, it is true, in the position of the destroyed islands and those now in existence occupy their central position fairly accurately, but still the possibility of this mode of genesis of the condition cannot be ruled out; and, indeed, it might explain very well the increase in bulk of some of the secreting parenchyma which could result from the coincident destruction of similar tissue elsewhere in the pancreas. That the islands of Langerhans are now in a degenerated condition and incapable of function might perhaps be suggested as the cause of the diabetes from their altered appearance, but the idea can hardly be entertained, since their cells are not degenerated and have every appearance of functioning actively. Certainly, however, whatever the mechanism of its immediate production, there is an increased bulk of Langerhans tissue with a coincident diabetes, and whether the cause of the diabetes be intrapancreatic or extrapancreatic, it seems clear that the hypertrophy of the Langerhans tissue is compensatory in nature, as far as it goes, even though it were finally inadequate to avert death.

But little in the literature seems to bear directly on the point discussed here. M. B. Schmidt,[2] in describing extensively altered glands in diabetes, found island-like structures similar to those first described, and regarded them as the result of the differentiation of island tissue from the parenchyma. Gütmann,[3] in one case of pernicious anemia and in one case of diabetes, found somewhat similar newly formed islands, which he also regards as being developed from the parenchyma by a process of differentiation. For this process he finds, however, no adequate explanation, since there seems to be no destruction of the pancreas sufficient to call forth such a response.

UNIVERSAL ITCHING WITHOUT SKIN LESION; HEMATOGENOUS UROBILINURIA; MALARIAL POISONING; PECULIAR ERYTHROCYTOLYSIS.

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The case here detailed is believed to be not only unusual but to present a condition not hitherto described, so far as the relation of the cause and its effects are concerned. The innumerable possi-

[2] München. med. Woch., 1901, No. 41.
[3] Virchow's Archiv, vol. clxxvii, Supplementheft.