SIMPLE ADENOMA OF THE PANCREAS ARISING FROM AN ISLAND OF LANGERHANS.

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The tumor that I have the opportunity of describing in the present communication was discovered accidentally by me at autopsy, and I have been moved to place it on record in the belief that it is unique, a somewhat careful study of the literature on the subject failing to reveal any case even approximating to the condition.

One is struck in looking over the overwhelming mass of publications on pancreatic disease with how little attention has been paid to the progressive disturbances of the gland and notably tumor formation. Even yet we have but little information as to the place and mode of origin of carcinomata, the most frequent neoplasm of the pancreas, and still less is known with regard to the simple or benign growths. This is chiefly, I believe, due to the fact that at autopsy the pancreas generally receives but scant attention, so that many conditions that might throw light upon the etiology of gross disease are overlooked. This is the more unfortunate since it is frequently the study of lesions in the earlier stages that gives us the most valuable information. Primary tumors of the pancreas are certainly not common. Thus Remo Segie[1] in eleven thousand five hundred autopsies at Milan found only one hundred and thirty-two instances, a proportion of one and fourteen-hundredths per cent. As may be seen by a reference to any standard text-book on pathology, carcinoma is practically the only tumor that receives consideration, owing of course to its relative frequency. With regard to the ratio of occurrence of the various neoplasms, the only figures I have to refer to are those of Remo Segie just mentioned. In his one hundred and thirty-two cases he found cancer one hundred and twenty-seven times; sarcoma twice; cysts twice;

syphiloma once. Combining the statistics of the Royal Victoria and the Montreal General Hospitals, in fifteen hundred and fourteen autopsies of which I have notes, primary carcinoma occurred six times and adenoma once. With regard to carcinoma alone, Förster in six hundred and thirty-nine post-mortems found eleven cases, a proportion of nine-tenths of one per cent. The only references to benign growths I have been able to find in any continued article on the subject are in Oser's monograph on the Pancreas in Nothnagel's "Specielle Pathologie," where three cases are cited to which I shall refer shortly.

The tumor that I here desire to record was a small, round, and somewhat flattened nodule on the anterior surface of the pancreas, situated about the junction of the middle and terminal thirds. It first attracted attention by its color, which was tawny yellow with a few distended blood-vessels upon the surface, contrasting sharply with the ivory white of the pancreas proper. When cut into, it was well-circumscribed, rather soft, and exuded a little blood. The whole mass was not larger than a marrowfat pea.

MICROSCOPICAL EXAMINATION. — The portion of the pancreas containing the tumor was hardened in five per cent formalin and mounted in paraffin. In spite of great care taken in embedding, the cells of the tumor became somewhat shrunken, but it was nevertheless possible to get a good idea of the original structure of the growth.

The sections were cut on a Minot microtome and stained with hematoxylin, hematoxylin-eosin, thionin-blue, and Mallory's stain for connective-tissue. When mounted the tumor presented as a perfectly oval nodule in the pancreatic substance, measuring three by two and one-half millimeters, and projecting somewhat above the general level.

The tumor was enclosed completely in a delicate capsule composed of wavy laminæ of connective-tissue rather loosely arranged and with relatively few nuclei. In this capsule were narrow elongated cavities lined with flattened cells containing spindle-shaped nuclei. Some of these cavities contained

blood and were clearly blood-sinuses, while others appeared to be lymph-spaces. In addition, in the capsule could be seen small groups of cells resembling those of the pancreatic acini, but flattened, compressed, and atrophic. At one spot outside the main mass was a small nodule enclosed in a separate thin capsule and identical in structure and appearance with the tumor proper. This was possibly due to the existence of a minute subsidiary growth beside the main one or to a slight obliquity in the cutting of the section. It was certainly not an infiltration in the sense of malignity, for the growth was quite regular, the capsule was perfect, and not involved in the extension of the new-growth.

Viewed as a whole with the low power (No. 3 Winckel), the tumor was composed of a great number of cell-masses bounded by more or less completely anastomosing bands of fibrous tissue so that a somewhat alveolar-looking stroma was produced. These fibrous bands did not always join, but some formed isolated irregularly-branching and stellate masses. In the center were what at first sight appeared to be sinuses filled with blood. The cells filling the alveolar spaces had a general resemblance to the cells of the pancreas. They formed rounded, elongated, and irregular clumps, and in some cases a single row which branched freely or followed a sinuous course in close touch with the ramifications of the stroma. In a few places a tendency to form lumina was observed, but this was only apparent, as in the majority of cases a single small mass of connective-tissue could be made out in the center. The cells in question were not in close contact with the supporting stroma, but had shrunk, no doubt in the process of embedding. The general appearance of the growth, which recalls somewhat the tubular adenomata of the kidney, may be gathered very well from the figure (Plate XVIII., Fig. 1).

With the high power (Winckel No. 7), the supporting stroma was found to be composed of a slightly cellular connective-tissue forming irregular masses from which delicate prolongations passed out to meet those of similar masses near by. The nuclei here were round or bluntly spindle,

and the bands contained minute blood-vessels. The "blood-sinuses" mentioned proved not to be true sinuses, inasmuch as there was neither limiting membrane nor endothelium, but were simply areas of blood-extravasation between the cells, which were thereby dislocated, and a false impression of lumina was thus produced. The cells adjoining these extravasations were distinctly compressed. A considerable amount of amorphous blood pigment was here observed.

Coming to the cells proper of the growth, they varied somewhat in shape, some being short columnar, others being polyhedral, depending on the arrangement whether in columns or in masses. The cytoplasm was granular, taking the eosin fairly well. The nuclei were pale, somewhat vesicular, presenting several dots of chromatin much darker than the rest. In some there was a central darker nucleolus from which radiating bands of chromatin passed to the periphery. The peripheral portion was also darker than the rest. The nuclei were for the most part rounded, or irregularly oval, and rather large. As compared with the cells of the pancreatic acini, the cells were smaller, the nuclei relatively larger, and the cytoplasm much looser in texture, staining both more faintly and more irregularly. The strands of the supporting stroma were much coarser in the tumor than those between the acini. In the preparation stained by thionin, the peculiarities mentioned came out with even greater distinctness (Plate XVIII., Fig. 2). The cytoplasm of the epithelial cells of the tumor was faintly tinged with blue and showed numerous dots staining intensely. The reticular arrangement of the chromatin was well brought out.

We have, therefore, briefly, to do with a tumor consisting of a stroma of connective-tissue arranged in the form of imperfect and irregular alveoli, in the interstices of which are situated cells of a glandular type, forming masses and wavy bands. From this structure it is clear that the tumor is adenomatous in character. Again, from the fact that the growth is well encapsulated and shows no tendency to infiltrate or take on aberrant growth, it is clearly benign. Nowhere is the capsule invaded. The term SIMPLE ADENOMA would therefore correctly describe it.

For purposes of comparison I would refer just here to the few cases of adenoma of the pancreas hitherto recorded.

Owing to the kind coöperation of Prof. J. G. Adami, I have been enabled to abstract, I believe, the complete literature on the subject, but find that it throws but little light on it. So far as I am aware, nothing like the above growth has been described.

Thierfelder [I.] found in the otherwise normal head of the pancreas of a young man who died of tuberculosis a firm, relatively bloodless tumor the size of a cherry, which he was able to remove intact from its fibrous capsule. The tumor was composed of much winding and dividing cell-cylinders possessing no lumina. The stroma was in the main firm and poor in cells. Here and there, however, it was looser and more cellular. In the centre of the mass was a small calcified area. According to Thierfelder's description the cells of the new-formation resembled the cubical epithelium of the smaller glands and excretory ducts, and were from their arrangement to be regarded as originating from these. The figure Thierfelder gives is so poor that very little can be made of it. The appearances indicated, however, are those of a somewhat scirrhous carcinoma rather than a simple growth.

Neve [IV.] records under the head of "adenoma" the following case: In a female, aged fifty, a globular tumor was found in the region of the pancreas. This measured two by two and one-half inches, and was somewhat flattened at the poles. The growth was adherent to the duodenum which was narrowed. The bile-duct was also included and contracted. To quote Neve's own description there were "microscopically trabeculæ of nucleated fibrous tissue. Spaces lined by well nucleated cells. In some places fibrous tissue presented scirrhous characters. Here and there were atrophied lobules of glandular tissue. In the center of some of the alveolar spaces there are larger cells, some measuring .025 m.m. These appeared later to lose their nuclei and become granular and yellowish masses, retaining their original shape. In some places glandular tubes (apparently new-formed) were to be seen packed with round cells. Others were older and

full of structureless material." This description does not make it absolutely certain that the tumor in question was an adenoma. It might equally well have been carcinomatous, so that it must be included, like Thierfelder's, with the doubtful cases.

The case reported by A. Cesaris-Demel [V.] may, however, be accepted with considerable certainty as being a true adenoma. His patient was a male, aged sixty, who died of purulent cystitis and pyelonephritis. He presented well-marked evidences of syphilis, such as abundant osteophytes on the inner table of the skull, general atheroma, scars on the liver, and fibrosis of the spleen and pancreas.

The pancreas was notably attenuated and almost completely substituted by compact adipose. The glandular substance was markedly diminished and replaced by hard, compact tissue of connective-tissue type, in which the acinous structure could be distinguished. In the inferior convex border of the organ about the middle was a tumor the size of a pigeon's egg which was free from adhesions. The surface was nodular. The mass was enclosed in a firm fibrous capsule about one millimeter thick. The tumor proper was soft and fleshy, very vascular, the center homogeneous and hyaline, from which passed radiating septa. The lymph-glands in the neighborhood were scarcely recognizable and there were no metastases. Microscopically, the cells of the tumor were for the most part cylindrical, but in some regions irregular as if from pressure, with an imperfect reproduction of an excretory tubule. There were no cell-inclusions and no nuclear degeneration. The author remarks that he could find no other cases in the literature and has no doubt that he had to do with an acinous adenoma. On a reference to his figures it would appear that his view is correct. The structure suggests a growth starting from the excretory ducts.

Biondi [VI.] records a case that he calls a fibro-adenoma. His patient, aged forty-five, had been in good health until six years previously, when she began to suffer with anorexia, nausea, eructations, continuous but not severe epigastric pains, progressive emaciation, and the presence of a tumor.

She was sub-icteric, and a tumor the size of a hen's egg was discovered in the middle of the epigastrium. There were neither hypo- nor hyper-chlorhydria. From the pain and emaciation, tumor of the pancreas was diagnosed. Bronzing of the skin also suggested pressure on the solar plexus.

The tumor was found in the head of the pancreas and was well encapsulated and delimited. The surface had a curious mother-of-pearl appearance. The tumor was removed and the patient remained in excellent health for three years and nine months. The growth was in the main fibrous, but contained spaces or canals having peripheral digitations, lined by a single layer of cylindrical epithelium. Within the canals was a granular material. The more central softer part showed tortuous cylindrical convolutions also lined with a single layer of epithelium, the characteristics of which were those of the pancreatic ducts.

A few other cases may be mentioned, but are with great hesitation to be included in the category of adenomata. Such is that of Baudach, [III.] who describes a hemorrhagic cyst of the pancreas that developed within an adenomatous new-growth with marked overgrowth of the vessels and secondary myxomatous degeneration.

Martin [2] reports a case that was possibly adenomatous.

Another is that of Ruggi, [II.] where in a woman fifty years of age two tumors were found attached by pedicles to the pancreas and removed. One of these weighed six hundred and fifty grams. The diagnosis was "adenosarcoma." From the appearance of the figures given, the tumor is almost certainly not a plain adenoma, but rather an adenocarcinoma.

Cases such as those of Thierfelder, Neve, and Ruggi illustrate the difficulty of drawing a hard and fast line between benign and malignant growths in certain cases. There appear to be certain nodular growths of the pancreas that histologically resemble carcinoma very closely, if indeed they be not identical with it, and yet these are well encapsulated and exhibit no tendency to infiltrate or form metastases. Possibly many of these go on to form true cancer, but so little is known of this subject that it is as yet a matter

of conjecture whether carcinoma of the pancreas takes its origin in a previously existing adenomatous growth or whether it may start immediately from the specific cells of the acini or ducts. In such cases when the tumor is removed during life, probably the only clue we can get to the true state of affairs is in the formation of metastases.

In my own example a point of great interest and importance was to determine its origin.

Glandular tumors of the pancreas, such as those described, must of necessity arise from one of three structures: (1) the epithelium of the ducts, (2) the pancreatic acini, (3) the islands of Langerhans. There is one possible exception that will be referred to shortly.

The adenomata of the pancreas hitherto described appear to have been derived from the ducts, the epithelial elements being composed usually of short columnar cells and having a tendency to form a lumen, as most growths of this type do. In the tumor that I have here described, however, the gland-cells, while in a few instances they are short and columnar, bear no resemblance to those of the ductal epithelium, since they are granular, the cytoplasm staining more deeply, and form no true lumina. They also differ from the lining cells of the finer excretory ducts in which the cytoplasm is relatively small as compared with the nucleus. It only remains to decide whether it originated in the acini or in an island of Langerhans, and I think it possible to determine this with certainty.

In looking over microscopic preparations of the pancreas, no one familiar with the appearance of the organ can have failed to notice the differences both in structure and arrangement of the cells of the islands as compared with those of the acini. The differences are apparent in sections prepared by all methods, but are specially well-marked in those stained by Van Gieson, thionin-blue, and Mallory's connective-tissue stain. The islands invariably appear as more or less rounded collections of cells staining much more lightly than the rest of the pancreas, and sometimes bounded by a thin connective-tissue membrane. The cells composing them are poly-

hedral and flattened rather than pyramidal. The cytoplasm does not take the dye so diffusely and appears pale, almost colorless, with deeper staining granules, whereas the cytoplasm of the acinar secreting cells takes nuclear stains rather deeply. The nuclei also do not stain so intensely or so homogeneously as those of the cells of the acini, but are more vesicular-looking, and contain well-marked nucleoli and numerous dots and threads of chromatin. A further point of distinction, well brought out by Mallory's method, is that while the connective-tissue of the lobules where it surrounds the acini is delicate and thread-like, in the islands much thicker bands can be made out, containing capillaries and showing a tendency to branch. Another difference is that the cells of the island do not form groups about a central minute lumen, but form irregular masses and wavy anastomosing columns between which the connective-tissue stroma appears. In those preparations stained by Mallory's method one notices that the islands are of a pale dull brown color contrasting with the steel-blue of the acini. Again, the nuclei of the acinar cells stain very diffusely and indistinctly, but those of the cells in the islands are clear, vesicular, and take the orange constituent of the stain particularly well. The cytoplasm is a dirty bluish-brown, a fact which explains the brownish color of the islands under the low power. When we study the tumor in question in the light of these facts we see that it resembles an island of Langerhans far more than an acinus. In fact, so far as the arrangement of the glandular cells, their structure and peculiarities of staining, and the appearance of the fibrous stroma, are concerned, the tumor rather suggests an overgrown island. Stained by Mallory's method the tumor stands out as a clearly defined brownish nodule against the blue of the rest of the pancreas. The stroma is in the form of thick branching trabeculæ containing vessels; the specific cells are clear in appearance, the nuclei taking the orange stain rather deeply, and are of a bluish-brown tinge, so that the whole appearance of the structure is identical morphologically and microchemically with that of the cells of the island of Langerhans. To my mind it is impossible to resist

the conclusion that the tumor in question originated in the overgrowth of an island.

How these pancreatic adenomata start is difficult to explain. The case of Cesaris-Demel is interesting as it suggests a clue to the development of some at least of the growths. Here we note atrophy of the glandular tissue of the pancreas with considerable fibrosis and substitution of the specific tissue with fat that were attributed to syphilis. It may be that, as in the parallel case of atrophic cirrhosis of the liver where we have an imperfect replacement of the destroyed lobules in the shape of warts or adenomata, so here the tumor may have had its origin in a compensatory hyperplasia of certain of the specific cells of the pancreatic acini. Such could not have been the explanation, however, in my case, since the pancreas was in other respects normal. Further I could not make out any degeneration or numerical diminution in the islands of Langerhans. It is possible that some at least of the nodular tumors of the pancreas, notably those of angiomatous structure, are derived not from the pancreatic cells proper but from suprarenal "rests" included at some time within the organ. Questions of etiology, however, cannot be settled until more material has accumulated. Unfortunately these tumors are described but seldom, for the smaller ones may be readily overlooked by the pathologist and the larger growths only come under the ken of the clinician when they are of such a size and in such a position as to press upon important structures.

It is however certain that many of the "cysts" of the pancreas are properly to be included in the group of adenomata. This subject is as yet in great confusion. Surgeons are apt to regard every cyst in the neighborhood of the pancreas as of pancreatic origin, and no doubt many conditions differing widely etiologically are brought into the same category. Here again the study of our morbid material is deficient. Retention cysts, of which the so-called "acne pancreatica" and "ranula pancreatica" are examples, as well as hemorrhagic and other degeneration cysts, are not uncommon, but "proliferation" cysts or cystadenomata are

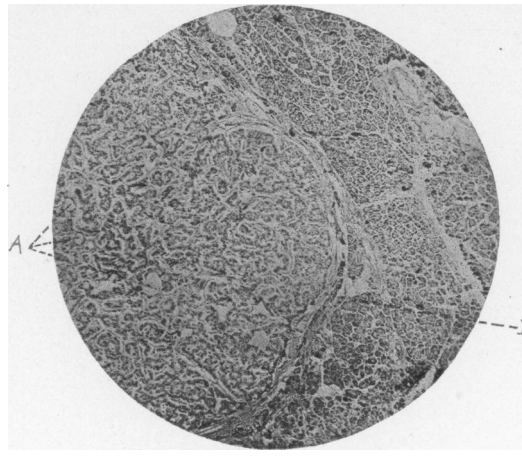

FIG. I. (No. iii. Winckel obj., without eye-piece.)
Tumor to the left; normal pancreas to the right.
A. Blood extravasations. B. Fibrous capsule.

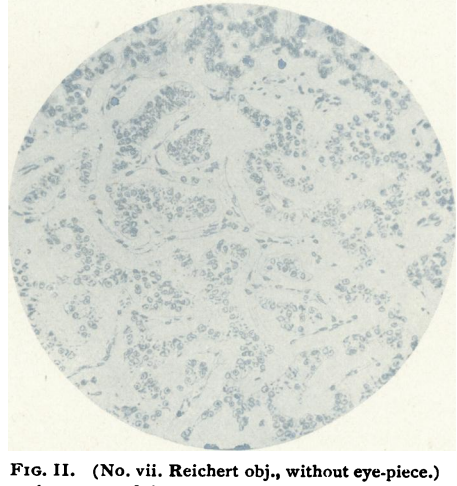

FIG. II. (No. vii. Reichert obj., without eye-piece.)
Taken from near the center of the tumor. Shows well the thick fibrous septa and the glandular cell-masses. Stained with thionin-blue.

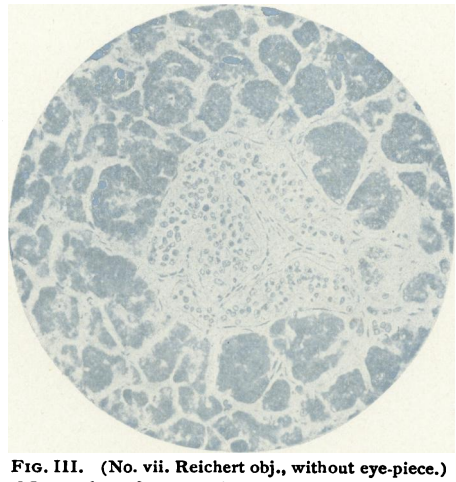

FIG. III. (No. vii. Reichert obj., without eye-piece.)
An "island" of Langerhans for comparison with Fig. II. The resemblance is close.

decidedly rare. Garrigues[3] describes a "cystadenoma" of large size which Birch-Hirschfeld was inclined to regard as a true cystadenoma. The tumor was multiloculated, the principal cyst containing two and a half gallons of fluid. The walls of the cavities showed large holes and were lined by cylindrical or polygonal epithelium. Somewhat similar cases are recorded by Riedel,[4] Salzer and Paltauf,[5] Nimier,[6] and Heaton.[8] Fitz[7] and Moynihan[9] have written lengthy papers on the subject. Judging from the published cases there are two varieties at least of pancreatic cystadenomata: multilocular cystomata and papillomatous cystomata (see Ransohoff[12]). As will be observed, the analogy with the ovary is close. Just as in the case of the solid adenomata so here it is difficult to decide just where malignancy begins. The so-called "cystic epitheliomata" of the pancreas, of which cases have been recorded by Hartmann,[10] Terrier (quoted by Nimier, loc. cit.), Gilbert,[11] appear invariably to be malignant.

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