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Granulomatous pancreatitis – granulomas in chronic pancreatitis*

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Summary. Granulomatous pancreatitis can be described only in infectious granulomas and pancreatic involvement by systemic granulomatosis. The presence of classical chronic tryptic pancreatitis in addition to individual sarcoidosis granulomas in one of our cases of sarcoidosis, shows that pancreatitis in a patient with generalized granulomatosis should not necessarily be considered granulomatous pancreatitis. A variety of foreign-body granulomas found in the pancreas may be explained by previous surgical operations, and other foreign bodies introducted iatrogenically. Occasionally, the pancreas in chronic pancreatitis contains granulomas that must be considered foreign body granulomas, although the causal foreign body cannot be identified. We believe that we can identify inspissated secretion that has passed out of the ductal system into the interstitium as the foreign body responsible. It is not possible to establish whether such iatrogenic measures as manipulations of the duct with back-up of the secretion within the ductal system, has any causative involvement in this secretion oedema. However, the absorption of the individual parenchymal secretions is impaired to such a degree that any extravasated remain "in situ" for a lengthy period. The absorption of the aqueous constituents leads to inspissation, so that it can finally be absorbed only through the formation of foreign body granulomas.

The same granulogenic property in highly scarred pancreatic parenchyma is also recognizable in the abnormal degradation mode of normally absorbable Ethibloc, and in the excessive arterial and periarterial reactions following angiography.

The presence of granulomas within the parenchyma of the pancreas in chronic pancreatitis, many of which have been induced by endogenous and/or exogenous foreign bodies would not lead us to refer to a granulomatous pancreatitis, since the remaining sections of the parenchyma manifest typical necroses and scar foci of chronic pancreatitis. We would characterize these granulomas by the term "granulomas in chronic pancreatitis", and differentiate this from granulomatous pancreatitis.

Key words: Chronic pancreatitis – Granuloma – Formation and Morphology

Introduction

More than 1.000 surgical specimens of pancreas resected for chronic pancreatitis from the material sent to the Pathological Institute at Erlangen between 1972 and 1985 were reviewed with a histological work-up of up to 30 paraffin blocks per case. Granulomas of varying morphology were found in the pancreatic parenchyma in 34 cases of the various stages and variations of chronic pancreatitis according to the morphological and pathogenical classification given by Becker (1984).

Characterization of these granulomas by their localization within the parenchyma, by incidence and by the varying reactions in the surrounding tissue, permitted us to clarify, aetiologically and pathogenically, the difference between granulomatous pancreatitis and the presence of granulomas in chronic pancreatitis.

Materials and methods

An overview of the 34 cases with granulomas in the pancreatic parenchyma is presented in Table 1. Most of the specimens

* Dedicated to Prof. G. Seifert on the occasion of his 65th birthday

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Table 1. Overview of the surgical specimens

Identification No.	Diagnosis	Stage	Granulomas
19482/85	ctP	II	Cryptogenic granulomas
18999/85	ctP	m	Cryptogenic granulomas
18403/85	sctP	m	Foreign body granulomas following subtotal gastric resection
9861/85	sctP	II	Cryptogenic granulomas
3838/85	ctP	II	Cryptogenic granulomas
3454/85	sctP	II	Periarteriitic granulomas
204/85	ctP	II	Cryptogenic granulomas
19735/84	ctP	II	Periarteriitic granulomas
17340/84	ctP	II	Periarteriitic granulomas
17339/84	ctP	II	Periarteriitic granulomas
14724/84	sctP	II	Ethibloc granulomas
12811/84	sctP	II	Cryptogenic granulomas
9465/84	ctP	m	Ethibloc granulomas
9261/84	ctP	m	Cryptogenic granulomas
7345/84	ctP	II	Cryptogenic granulomas
6466/84	ctP	m	Cryptogenic granulomas
20704/83	syphilitic P		Epithelioid- and giant cell granulomas
10392/83	ctP	II	Cryptogenic granulomas
5317/83	ctP	m	Cryptogenic granulomas
1866/83	sctP	II	Periarteriitic granulomas
13945/82	ctP	II	Cryptogenic granulomas
13690/81	ctP	II	Foreign body granulomas following cystojejunostomy
10727/81	ctP	m	Cryptogenic granulomas
2040/81	sarcoidosis		Epithelioid granulomas
15153/80	ctP	II	Cryptogenic granulomas
14110/80	ctP	II	Foreign body granulomas following cystojejunostomy
11953/80	sarcoidosis		Epithelioid granulomas
522/78	ctP	m	Cryptogenic granulomas
15988/77	ctP	II	Cryptogenic granulomas
16299/75	ctP	m	Cryptogenic granulomas
6205/75	ctP	II	Cryptogenic granulomas
3717/74	ctP	m	Foreign body granulomas following subtotal gastric resection
14569/74	ctP	m	Cryptogenic granulomas
10939/72	ctP	m	Cryptogenic granulomas

ctP: chronic tryptic pancreatitis[a]; sctP: segmental chronic tryptic pancreatitis[a]; II: second stage[a]; m: metatryptic stage[a]

[a] According to the morphological classification given by Becker (1984)

comprise the head and body of the pancreas removed during partial duodenopancreatectomy as described by Whipple (22/34) or the entire gland in cases of total pancreatectomy (3/34). 10% formalin was injected at a pressure corresponding to the physiological intraductal pressure (Stolte and Schaffner 1978) via a cannula inserted into the pancreatic and common bile ducts from the resection surface. Of the remaining 9 specimens, 5 were obtained from a body/tail resection of the pancreas (so-called left resection of the pancreas), and these were pressure-fixed, retrograde, via the main pancreatic duct. In the last 4 cases, the material sent to us comprised slices of pancreas, and this was fixed in toto. For the histological examination, the resection surface and the pancreas parenchyma were embedded, selectively in a number of segments (up to 20 slices of 0,5 to 0,7 cm in thickness obtained perpendicularly to the course of the large ducts) and stained with haematoxylin and eosin (H & E), elastic van Gieson (EvG), trichrome Masson-Goldner, PAS alcian blue, or haematoxylin-phloxine-safranin (HPS).

Table 2. Classification of granulomas

1	*Granulomatous pancreatitis*
1.1	Infectious genesis: syphilis
1.2	In generalized granulomatosis: Boeck's disease
2	*Cryptogenic granulomas* "Secretion granulomas" and foam cell granulomas
3	*Granulomas induced by exogenous materials*
3.1	Suture granulomas and other foreign body granulomas following previous surgical operations
3.2	Ethibloc granulomas
3.3	Periarteriitic granulomas

Results

In 34 surgical specimens, granulomas of varying morphology were found which we characterized into three different groups in accordance with morphological and histological criteria (Table 2), as described below:

1. Granulomatous pancreatitis

1.1 Infectious causes. A 36-year-old man with syphilitic pancreatitis had high-grade cholestasis accompanied by recurrent, diffuse upper abdominal pain and severe diarrhoea. An ultrasonic examination of the pancreas revealed an echo-poor space-occupying lesion of 4.5 cm to 5 cm in diameter, the aetiology of which remained unclear despite percutaneous fine needle biopsy. The head of the pancreas was resected because of the high-grade cholestasis. The histological work-up of the specimen obtained from a Whipple's procedure revealed numerous epithelioid cell granulomas in the mucosa of the gastric corpus and the submucosa of the duodenal bulb, some of which contained abundant giant cells. The granulomas contained leukocytes and plasma cells arranged centrally, and were surrounded by a narrow border of leukocytes. The parenchyma of the head of the pancreas contained dense, primarily perilobular, but also intralobular, fibrosis. Numerous granulomas were to be seen, some of which contained abundant giant cells of the Langhans type (Fig. 1). Some older and smaller granulomas were situated isolated, in the broad scar plate; younger granulomas were clustered in large groups. The epithelioid-cell granulomas were

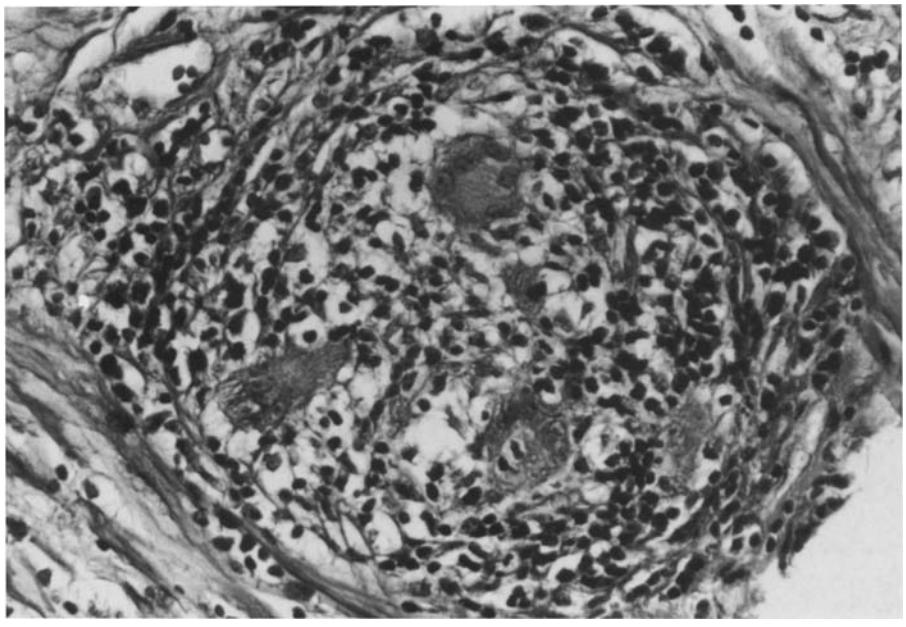

Fig. 1. Epithelioid cell granuloma in syphilis. Numerous epithelioid and plasma cells, individual giant cells of the Langhans type, small patch-like, non-caseating necrosis. Peripheral loose fibrotic "encapsulation". (Ident. No. 20704/83 Masson-Goldner, × 100

often located in the immediate neighbourhood of medium-sized, segmentally narrowed arteries and arterioles. The surrounding, loose, fibre-rich connective tissue contained a sparse round-cell infiltrate with numerous plasma cells and was surrounded by a peripheral margin of densely packed fibroblasts.

After the histological diagnosis of syphilitic pancreatis had been obtained, third stage syphilis was clinically proven by positive specific serological tests.

1.2 Granulomas in the pancreas in cases of generalized granulomatosis. In two cases of sarcoidosis, sarcoid granulomas were found in the pancreatic parenchyma and in the peripancreatic lymph nodes.

In the first of these cases – a 41-year-old woman hospitalized with diffuse joint pain because of bone involvement and decalcifying osteopathy – ultrasonography revealed a solid space-occupying lesion, 2 cm in diameter, located caudally in the tail of the pancreas. Fine-needle aspiration under percutaneous ultrasonic guidance and coeliacography supported the suspicion of a malignant tumour in the tail of the pancreas. A zone of reduced structural density in the liver – against a background of known alcoholic cirrhosis – was interpreted as a metastasis of this tumour, and thus the indication for pancreas resection and hemihepatectomy was established. The body/tail specimen of the pancreas revealed, macroscopically, a low-grade interlobular fibrosis which, in the terminal caudal area, had formed a thick cufflike pseudocapsule. Histological work-up revealed, in the tissue of the capsule, varyingly densely packed granulomas, some with abundant giant cells of the Langhans type, some containing in particular epithelioid cells, but no necroses or caseation; rarely were they accompanied by a lymphocytic reaction in the surroundings. The giant cells were large, contained numerous nuclei, and enclosed shell-like, lamellated calcifications (Schaumann bodies). Other granulomas were older, with incipient fibrous encapsulation, usually with no accompanying lymphocytic reaction. In the parts of the parenchyma close to the resected surface, which are macroscopically unremarkable, miliary, newly formed granulomas were found, in part clustering around vessels, in part disrupting the parenchyma. Adjacent to these were characteristic cholesterol granulomas with multinuclear giant cells of the foreign-body type arranged around the crystals that have been washed out by the embedding procedure. In the second case of sarcoidosis with epithelioid cell granulomas, a metatryptic high-grade calcification chronic pancreatitis with multiple post-pancreatitic pseudocystis presented in a 38-year-old man with a history of chronic drinking. In the surgical specimen obtained after Whipple's procedure, sarcoidosis of the lymph nodes at the ventrolateral aspect of the head of the pancreas was fortuitous finding; the parenchyma revealed only a few granulomas. These latter were very small and usually arranged around blood vessels, the majority containing epithelioid cells and only solitary multinucleate

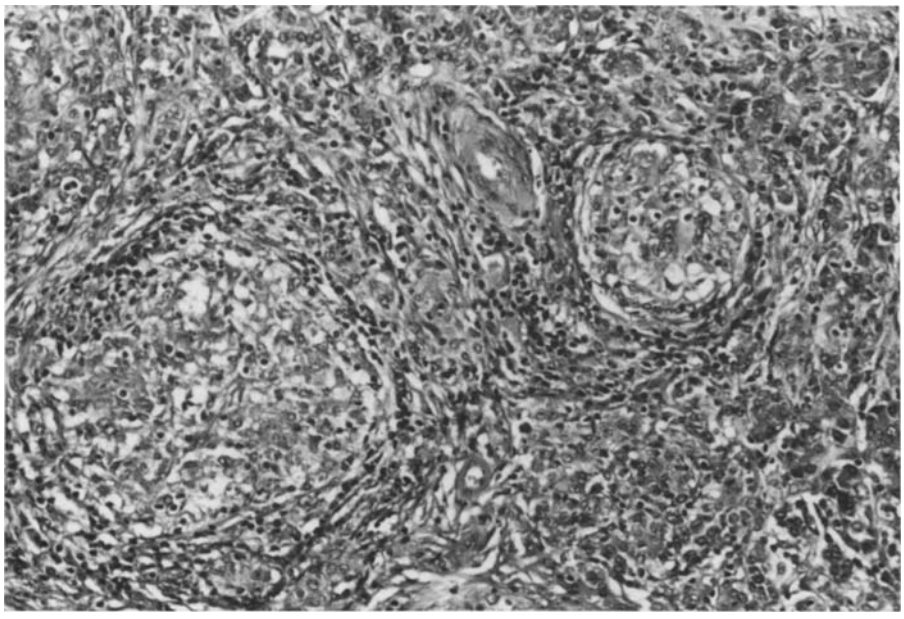

Fig. 2. Secretion granulomas. Two adjacent granulomas, differing in size, almost exclusively made up of epithelioid cells. Peripheral infiltration of round cells. Loose fibrous encapsulation. (Ident. No. 10392/83 Haematoxylin & Eosin, ×40)

giant cells of the Langhans type. No lymphocytic reaction was to be seen, the epithelioid cell granulomas lying, apparently without reaction, in the highly scarred parenchyma. Sarcoidosis had been proven by x-ray examination of the thorax and a positive Kveim-reaction.

2. Cryptogenic granulomas

Granulomas in which all aetiological factors for generalized or intestinal granulomatous or inflammatory disease had been clinically and histologically excluded were found in 20 surgical specimens irrespective of stage and variation of chronic pancreatitis. Granulomas made up of loosely packed connective tissue cells, but occasionally also of giant cells of the foreign-body type, and surrounded by lymphocytes in varying numbers, are seen in these cases (Fig. 2). Some granulomas resemble a tubercle, but caseation is absent. In some places, sparse necroses with collections of cell detritus can be observed in the centre of the granulomas. The appearance of individual granulomas varies considerably with respect to content and arrangement of epithelioid cells, and in the different degrees of water content. The content of giant cells with peripherally located nuclei varies. Relatively small numbers of lymphocytes are to be seen. In some cases, the granulomas have coalesced, then reveal central necrosis with cell detritus, and are surrounded by serveral rows of epithelioid cells arranged "palisade-like", so that the entire region of the granulomas, is reminiscent of rheumatoid structures. Occasionally, bleeding into the centre of the granulomas has occured. In some cases, inert nests of foam cells can be seen in the neighbourhood of the granulomas. The original parenchyma has been completely transformed into a scar plate, in which the individual blood vessels and nerves are embedded. Occasionally, lymphoid follicules are to be seen, adjacent to which are the granulomas. Some of the granulomas contain haemosiderin crystals and huge grotesquely deformed giant cells, in the middle of the clumped cell detritus. Sometimes, in small and larger older epithelioid and giant cell-containing granulomas, delicate flecks of moderately dense calcification can be seen. Small flecks of calcification can also occur in well-organized granulomas, together with needle-like crystals of cholesterol. Granulomas in the scarred fields are sometimes found adjacent to highly dilated small ducts, which manifest epithelial dysplasia, giving the impression that the granulomas have arisen from the content of these dilated ducts. At other places, the small ducts have been completely incorporated into the granuloma (Fig. 3), so that the epithelial layer has become desquamated, or shows a purely lymphocytic infiltration. Sometimes such destroyed ductuli can be identified over a considerable distance. The veins in the immediate neighbourhood are then occasionally thrombotic, and sometimes mural lesions are observed.

In other places there is no longer any recognizable relationship to the ductal or vascular system (Fig. 4). The granulomas delimit the residual portions of the pancreatic parenchyma. Independently of the granulomas just described, there are also

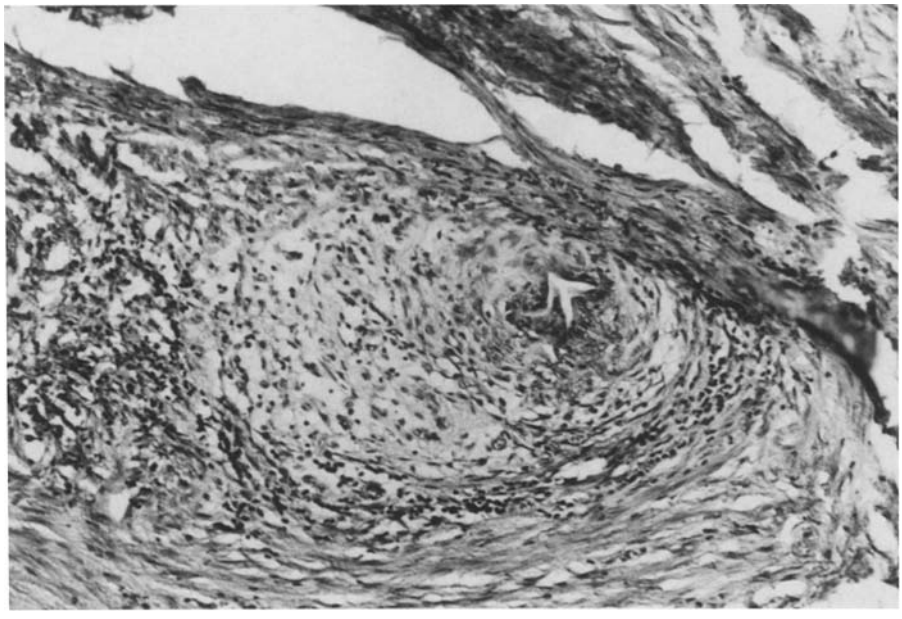

Fig. 3. Granuloma involving a small branch of the pancreatic duct. Loose epithelioid and foam cell granuloma, excentrically located duct, peripheral margin made up of lymphocytes and lamellated fibrosis.
(Ident. No. 13945/82
Haematoxylin & Eosin, ×40)

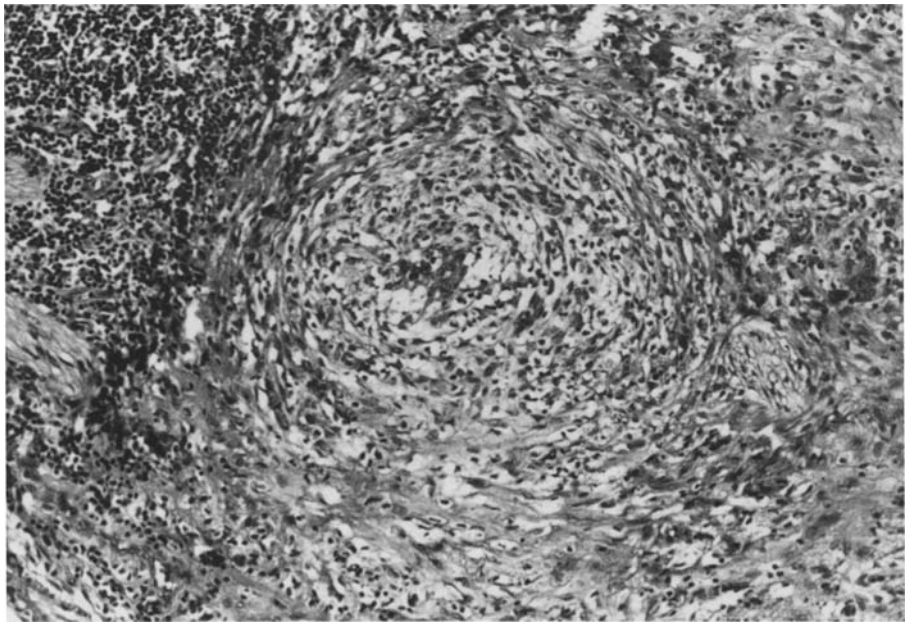

Fig. 4. Secretion granuloma. Old epithelioid cell granuloma with a dense fibrotic margin. No correlation to the vascular or ductal system can be seen. Unilateral, marked lymphocytic reaction in the surroundings.
(Ident. No. 6466/84
Haematoxylin & Eosin, ×40)

more or less extensive foam cell granulomas (Fig. 5). These are dense aggregations of foam cells which, in part, penetrate into the gaps of the lymphocytic infiltrate. Occasionally, the centre of these foam cell granulomas reveal sparse necroses or a foamy material containing only few cells, while, in the surroundings, the same material is present within the foam cells. At the granuloma margins, a thin, fresh, reticular layer containing numerous fibroblasts can be seen. A number of the foam cell reactions are densely infiltrated with poorly organized haematomas which are extensive at the margin. Occasionally, fibrous connective tissue is found growing between the individual foam cells as sign of organization.

3. Granulomas induced by exogenous materials

3.1 Suture granulomas and other foreign-body granulomas occuring after prior surgery. Four resections of the pancreas were preceded by prior surgery, not necessarily involving the pancreas itself (two cases of subtotal (2/3) Billroth II gastric resection), but which had led, in the immediate vicinity

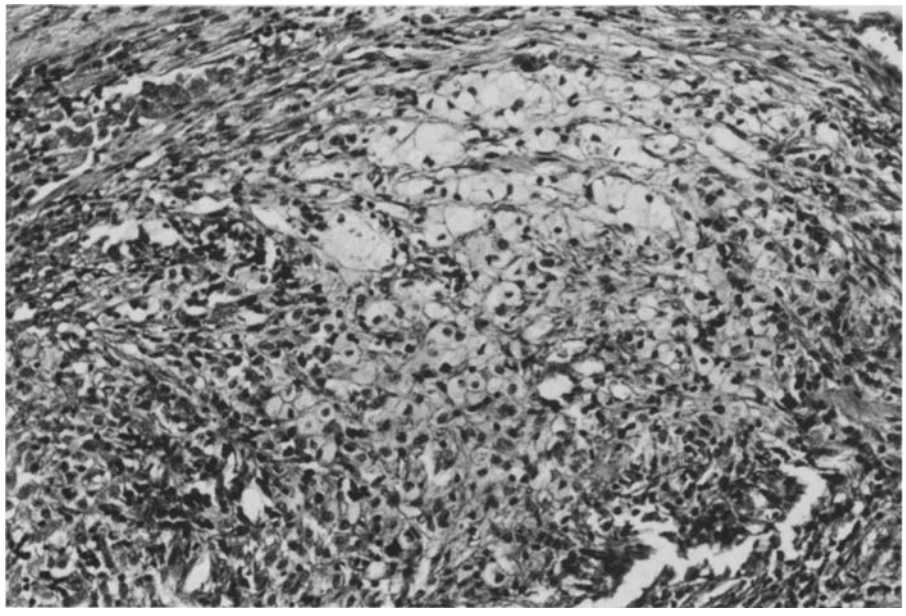

Fig. 5. Foam cell granuloma. Loose granuloma, made up almost exlusively of macrophages with foamy cytoplasm. Dense peripheral fibrosis. (Ident. No. 204/85 Haematoxylin & Eosin, ×40)

of the pancreatic parenchyma and ductal system, to local resorptive inflammation and to intended or accidental implantation of foreign material. Previous operations involving the pancreas itself in our material were 2 cases of cystojejunostomy done with the aim of draining pancreatic pseudocysts. Here, foreign-body granulomas are found in the immediate neighbourhood of the previous surgical area, and in the perilobular fibrosis, which often forms a pseudocapsule. The foreign body granulomas are characterized by multinucleate – often polynucleate – giant cells surrounding the frequently visible, but sometimes washed out (by the embedding procedure) foreign body which, in the latter case is then recognizable only by its "shadow". Small foreign bodies are taken up into the cytoplasm. In polarized light, the foreign bodies appear birefringent and can be identified as suture material.

3.2 Ethibloc granulomas. Our selection of resected pancreas specimens contains 2 cases in which, prior to resection, an attempt was made to obliterate the exocrine parenchyma by occluding the ductal system via the endoscope.

For this purpose, Ethibloc^{R}, a fast-hardening amino acid mixture, was injected, endoscopically, into the papilla of Vater. Ethibloc, as a deliberately injected foreign material, is the cause of various forms of mesenchymal reactions: Under favourable conditions, it is absorbed; however, granulomas with tall palisade-like epithelioid cells can develop around residual material with no relationship to the original ductal system (Fig. 6). The Ethibloc masses are penetrated by lymphocytes and leukocytes. In other sections, largely homogeneous Ethibloc, sometimes also "loosened" by the presence of air or water bubbles, can be observed in the tissue with considerable cellular reaction at the margins, but without granuloma formation.

Within the ductal system, Ethibloc can also remain unabsorbed and unaccompanied by reaction, in these cases the epithelial cells are not involved, the homogeneous mass containing merely a number of leukocytes. In 1 of the 2 cases, non-reaction-evoking deposits of Ethibloc in the ductal sytem, but also fully developed granulomas around Ethibloc masses within the interstitium, were observed.

3.3 Periarteriitic granulomas. In five specimens, granulomas located around vessels are seen, so that the impression given is of local granulomatous arteriitis found only at circumscribed sites. In all of these five cases there had been no other clinical signs of arteriitis or vasculitis and all the vascular pathology was in the form of fortitious findings in the histological work up of pancreatic parenchyma. In 2 cases all forms of arteriitis extending to complete obliteration, can be recognized; some vessel walls are, segmentally, replaced by giant cells. In some cases, the intima of the vessel is thickened concentrically (Fig. 7) and is elevated by an infiltrate which penetrates through the media into the innermost layer of the intima. The media is relatively uninvolved, the lamina elastica interna presents a ruffle-like appearance, and the musculature is preserved circularly. The muscle layers in

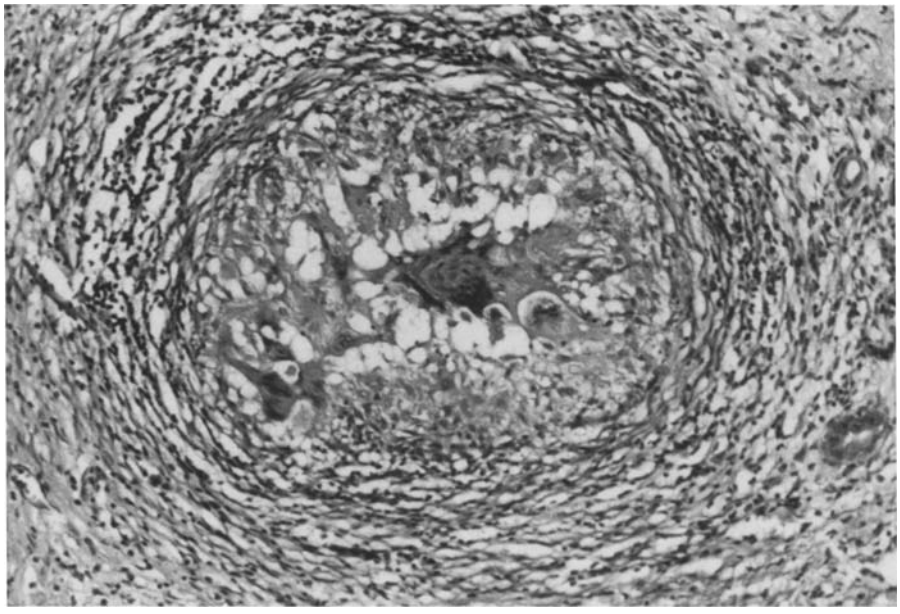

Fig. 6. Ethibloc^{R} granuloma. Tall epithelioid cells showing a pallisade-like arrangement; central multinucleate foreign body giant cell in the midst of Ethibloc remnants, some of which are infiltrated by lymphocytes. Peripheral ring of fibroblasts and lymphocytes. (Ident. No. 9465/84 Haematoxylin & Eosin, ×40)

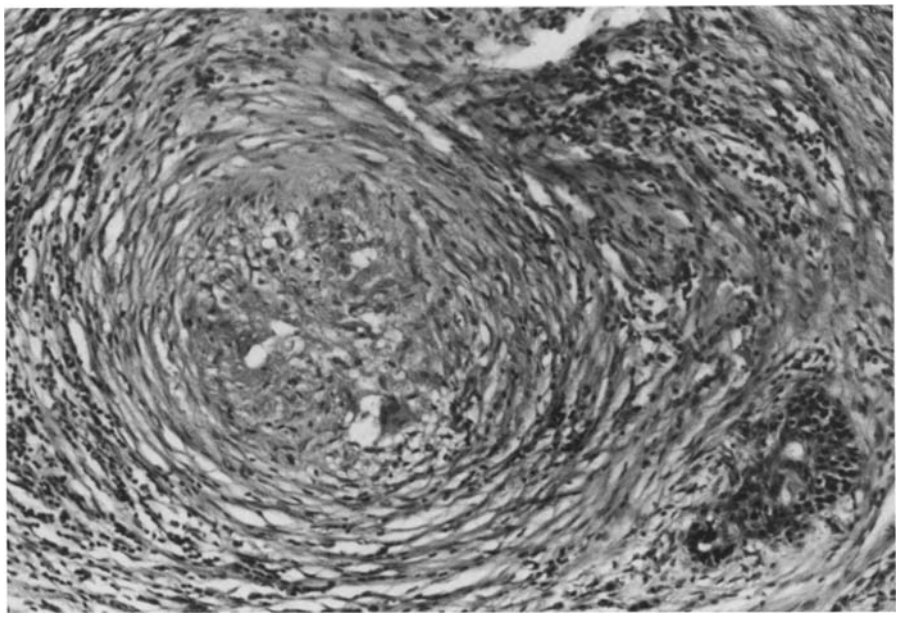

Fig. 7. Periarteriitic granuloma. Complete obliteration of the vascular lumen by dense fibrotic granulomas. Marginal lymphocytic infiltrate. (Ident. No. 19735/84 Haematoxylin & Eosin, ×40)

the outer zone of the media are loosened by cellular infiltrates of plasma cells. The lamina elastica externa is intact. Vessels with thickened fibrotic intima with narrowing of the lumen are also seen. The media, too, is irregular in thickness and its musculature is disordered. At one of the proliferation sites, a new elastica interna can be seen, which is again replaced and interspersed with a renewed intimal plaque. The effect is subtotal occlusion of the vessel. In a third variant, the lumen is completely occluded by granulation tissue, the wall of the vessel remaining virtually unchanged. Presumably, this represents organizing tissue which develops after an arterial thrombosis. Finally, the vessel is completely replaced by granulomas: In the lumen, an intimal "plug" is seen, which is contained within a granulomatous wall of epithelioid cells. Layering of the vessel is only vaguely discernible.

Discussion

In syphilis, granulomas represent the morphological substrate of the specific inflammation. In generalized acquired syphilis – in contrast to congenital syphilis – the pancreas is only rarely involved. Gruber (1929) differentiates three forms of pancre-

atic involvement in acquired syphilis: secondary stage syphilis of the pancreas, gummatous pancreatitis, and scarring of the pancreas or "syphilitic cirrhosis".

In these three forms, gummatous granulomas or diffuse destructive or sclerosing processes develop (Roulet 1956). The nodule-like collections of various round cells, seen predominantly around small vessels are typically embedded within a variably loose network of reticular cells (Roulet 1956). Sometimes, multinucleate giant cells are located around the central non-caseating necroses. Generalized syphilis with involvement of the pancreas is now a rare entity; but syphilitic pseudotumour of the pancreas, in particular when located within the head of the pancreas (Becker 1973) is still important in differential diagnosis (Charif 1958).

The absence of caseation is the leading differential diagnostic criterion vis-a-vis granulomatous pancreatitis with underlying miliary tuberculosis. In the resection specimens we examinated, numerous classical granulomas were found in a highly scarred pancreas, which represented the scarring of the pancreas caused by syphilis, described by Gruber (1929). Here, the obstruction to the flow out of the major papilla had led to chronic pancreatitis with extensive scarring; the few granulomas within the parenchyma cannot, alone, explain the destruction of the organ.

Sarcoidosis of the pancreas is a clinically rarely diagnosed entity, so that only a few clinical case reports are to be found in the literature, in which the sarcoidosis was confirmed by biopsy (Curran and Curren 1950, Ryrie 1954, Chaun et al. 1972, Caldwell and Evans 1978, McCormick et al. 1985).

The clinical symptoms of granulomatous pancreatitis in sarcoidosis are usually uncharacteristic. They can be confused with hypercalcaemia-induced acute pancreatitis following bone involvement. In autopsy material, the incidence of pancreatic involvement in histologically demonstrated sarcoidosis is between 1% (Mayock et al. 1963) and 5.2% (Loncope and Freimann 1952). Although the clinical incidence is much smaller than sarcoidosis of the pancreas confirmed histologically, this entity nevertheless represents an important differential diagnosis of non-epithelial tumours and pseudotumours of the pancreas (Biedermann 1985). The typical isomorphic miliary epithelioid cell granulomas with non-caseating central necroses (Roulet 1956, Gusek 1969) was first discovered in the pancreas by Nickerson (1937).

Our examination material contained two cases of clinically proven sarcoidosis of the pancreas. The first of these – on which Biedermann (1985) reported in detail – was a case of florid Boeck's disease (sarcoidosis) which had led to the development of a pancreatic pseudotumour. The second was a case of metatryptic chronic pancreatitis with high-grade scarring of the head of the pancreas, in particular in the dorsal segments. This scarring and a warren-like system of duodenal wall cysts (Stolte 1984) with post-pancreatitic pseudocysts in the region of the papilla had, together with the granulomatous involvement of the parenchyma and the lymph nodes at the ventro-cranial head of the pancreas, led to a high-grade stenosis. There was additional sub-total obstruction by numerous stones in the pancreatic and common bile ducts. The resulting rapidly progressing jaundice gave such a strong impression of carcinoma of the pancreas that even repeatedly negative needle biopsies failed to deter the surgeon from performing a Whipple resection of the head of the pancreas as palliative procedure (Becker and Lux 1985).

The cryptogenic group of granulomas comprises variously structured granulomas at different locations within the pancreatic parenchyma without any relationship to the vascular or ductal system and in which no other aetiological or pathogenical factor could be found, clinically or histologically. The structure of the granulomas differs both inter- and intra-individually: exlusively epithelioid cell granulomas, granulomas with predominantly epithelioid cells and only few giant cells of the Langhans and foreign-body type, and granulomas made up almost entirely of foreign-body giant cells may be seen. In many cases, these are characteristically structured, so that a search must be made for a responsible foreign-body. A possible granulogenic foreign-body is X-ray contrast material injected for endoscopic retrograde pancreaticography (ERCP). In the smaller branches of the pancreatic duct, this leads to acute reactions with multiple, crater-like epithelial defects (Bürner 1979, Wachhausen 1979, Bub et al. 1983), through which contrast material can escape into the interstitium. In view of the large number of ERCP's, this must occur frequently, but a granulogenic effect of the contrast medium would appear, statistically, unlikely, since out of more than 1.000 pancreas resections for chronic pancreatitis, of which almost certainly more than 500 were submitted to pre-operative pancreatography, cryptogenic granulomas in the parenchyma were found in only 20 cases. Conversely, we also saw three cases in which such granulomas presented despite no prior ERCP. Our findings support our view that ERCP has no aetiological significance for granulomas.

Since, in these cases, other exogenous foreign-bodies can also be excluded, we must consider an endogenous foreign-body as the causal agent. The multiple nature of the granulomas must be due either to various endogenous foreign-bodies, or to differences in the granulomatous reaction on the part of the host. Foreign-bodies can produce granulomas only if they posses properties that make phagocytosis impossible (Heymer and Haferkamp 1980), or if they overwhelm the phagocytic capacity. Possible foreign-bodies in the pancreas are endogenous secretions, or some part of the latter.

When, in the presence of chronic pancreatitis of stone-induced occlusion or other types of obstruction, or as a result of a hindrance of secretion, the pancreatic secretion is dammed back, individual areas of secretion oedema occur (Doerr 1953a, b). Inspissation of the secretion due to deficiency of the canalicular epithelial cells or to exsiccosis, may lead to the formation of "secretion-clumps" and "spheres" within the ductal system, and thus trigger secretion-stasis with consecutive secretion oedema. This latter is a frequently occuring phenomenon, and is normally rapidly absorbed. When these absorption mechanisms no longer function adequately, chronic secretion oedema is the result. The diminshment of absorption due to scarring in chronic pancreatitis appears to be the decisive factor for the development of granulomas in the pancreas. Constant insudation of the secretions are, presumably, a further factor that is responsible for the increase in connective tissue in chronic pancreatitis. The result is a vicious circle involving chronic insudation of secretions and scarring, which continues until the exocrine parenchyma has been completely burnt out. In the individual pancreas, chronic insudation of the secretions does not appear to lead to scarring. Local granulomas are formed, the morphology of which is determined by the re-absorption of individual constituents of the juice.

When only the aqueous, alkaline constituents of the secretion pass through the epithelial cells of the ducts, they give rise to a lymphocytic infiltration in the interstitium which can be rapidly re-absorbed. This absorption process normally takes place in two directions: into the ductal system and via lymph drainage. In chronic pancreatitis, these two cleaning-systems are increasingly blocked by the progressive scarring of the interstitium and the thickening of the ductal walls with periductal fibrosis. Initially the aqueous constituents can still be re-absorbed or removed; the more viscous constitutents of the secretion remain outside the duct and, as a result of further loss of water, become more and more inspissated. Here, the inspissated components of the secretion material that normally does not occur in the interstitium, leads to a foreign-body reaction. With increasing density of the secretion this reaction becomes more marked, but also more ineffectual. First, there is an aggregation of histiocytes, which become activated macrophages that attempt to phagocytose and store the non-toxic material within themselves (Spector 1980). Sometimes, this succeeds completely, but the macrophages can no longer be eliminated and become the classical foam cells. Sometimes they remain within the tissue inducing no major reaction, in other places they form granulomas proper. These represent a form of secretory retention within the interstitium; inspissated secretion can neither be re-absorbed into the ductal system nor removed. This pathogenetic pathway has already been described for mucoid and foam cell granulomas of the salivary glands (Hamperl 1932, Seifert et al. 1980). Sometimes, the centre contains incipient calcific incrustations of aggregated secretion suggesting that it represents the cause of the so-called absorption granulomas. If, as a result of a more rapid re-absorption of aqueous constituents in the presence of a marked disturbance of the removal mechanism, the secretion becomes inspissated, secretion-clumps occur, the size of which overwhelms the phagocytotic capacity of the macrophages (Fig. 8). This leads to a transformation of the histiocytes into epithelioid cells. Since, in addition, the other pre-conditions for the formation of granulomas, such as the persistence of the triggering agent within the tissue (Gusek 1962, Spector et al. 1972, Heymer et al. 1971, Heymer 1972, Gusek 1972, Adams 1976, Oort and Scheper 1977) are also obtained, epithelioid cell granulomas develop as a form of foreign-body reaction (Cottier 1980). In these structures constituents of the secretions become visible in the form of small flecks of calcification.

If inspissation is even more rapid, more dense secretion-clumps occur, which stimulate the fusion of the histiocytes to form multinucleate giant cells. These foreign-body giant cells aggregate around the foreign-body, and thus screen it from the mesenchyme.

Foreign-body granulomas found after surgical operations are often induced by suture material, glove powder, or by constant flooding with endogenous material that is not typical of the region (small bowel contents in cystojejunostomy). Depending upon their size, shape and chemical composition, foreign-bodies induce various defensive reactions (Gedigk and Helpap 1984). Larger bod-

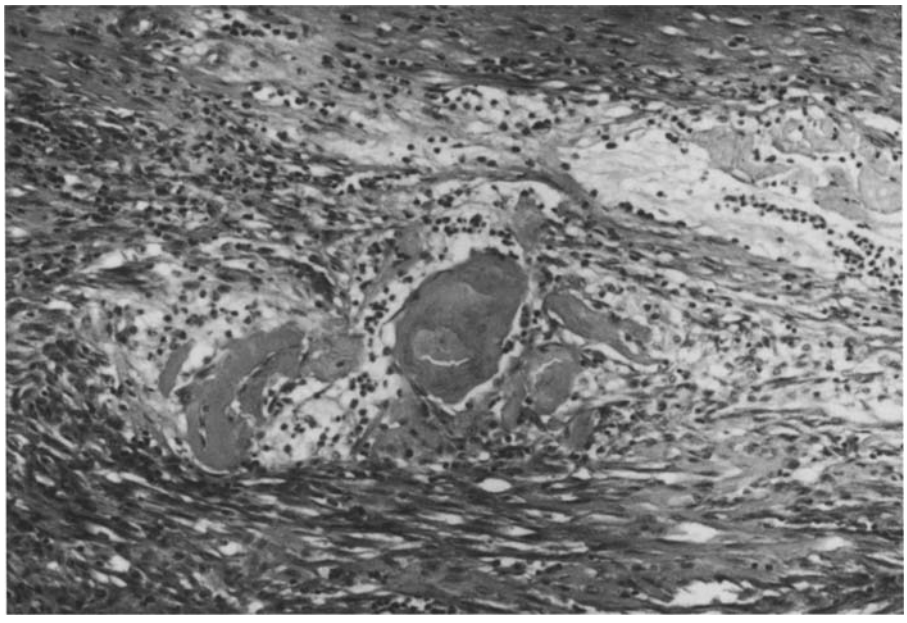

Fig. 8. "Secretion-clumps". "Secretion-clumps" of varying size and density, with loose cellular reaction in marked fibrosis. (Ident. No. 9861/85 Haematoxylin & Eosin, ×40)

ies – in our cases mainly birefringent suture material – induce, via mechanical irritation, an initially exudative inflammation that rapidly develops into granulation tissue with abundant foreign-body giant cells and fibroblasts, so that they block off any contact between the foreign-body and the mesenchyme. In the pancreas, these foreign-body granulomas have no general pathological peculiarities.

Other foreign-body granulomas have developed in response to iatrogenically injected foreign material (Ethibloc^R). Ethibloc is a quick-setting mixture of amino acids which is used for occlusion of the ductal system (Gebhardt and Stolte 1978, 1980, 1982, Ammann et al. 1984). The first observations were made after ligation of the pancreatic duct (Maurer 1965). The procedure was further followed up by the working group headed by Hoffmann (Hoffmann et al. 1977). The simplest means of inducing atrophy is by accomplishing complete filling of the ductal system extending into the acini, a procedure which has been attempted both with an acrylate glue (Little et al. 1977, 1979) and with Ethibloc^R (Gebhardt and Stolte 1978, 1980, 1982). Where a wide, cicatricially distorted ductal system, possible subtotally occluded by stone exists as in underlying chronic pancreatitis, obstruction of the duct often proves impossible. If the procedure is carried out subtotally, intraluminal stenosis of the duct represents an obstruction to the outflow of secretion, and further tryptic necrosis occurs.

The Ethibloc mass is not liquid enough to allow endoscopic injection into the entire ductal system down to the acini within a reasonable time (Rösch et al. 1979, Rösch and Gebhardt 1981). Often, the endoscopist is able to place a "block" only in the vicinity of the papilla, which is subsequently partially broken down. In such cases, partial obstruction is accomplished and is responsible for sustaining the chronic pancreatitis (Becker 1984). Thus, Ethibloc is only used for certain indications (traumatisation, fistula formation, partially digested suture material), for which it is suitable (Gebhardt and Stolte 1978, 1980, 1982, Gall and Gebhardt 1979, Gall et al. 1982, Gebhardt 1981). Endoscopic "burn-out" in chronic pancreatitis is justifiable only in the presence of analgesic-refractory pain and selectively cannulatable pancreatic duct system (Schneider et al. 1985).

In our two cases, an attempt was made, prior to partial resection of the pancreas, to accomplish endoscopic "burn-out", but in neither case was a lasting improvement achieved.

Animal experiments have shown that Ethibloc in the ducts is broken down after two weeks and does not lead to foreign-body reactions (Stolte et al. 1980). In the interstitium, a low-grade periductal oedema is to be observed, which is organized to a fine interstitial fibrosis. Interstitial depots of Ethibloc achieved by deliberate "overinjection" are encapsulated by connective tissue to form a pseudocyst. We had earlier suspected that in chronic pancreatitis, a delay in the absorption of foreign material occures (Becker 1984). At a number of sites, the activation of the mesenchyme leads to the development of foreign-body granulomas. These contain the residue of the polymerized

mixture of amino acids, which is surrounded by a palisade-like arrangement of epithelioid cells; sometimes, individual giant cells can also be seen. Here, the Ethibloc must have entered the interstitium in a compact, highly concentrated form, and, as a result of polymerization, escaped phagocytosis.

In one case, the ductal system contained Ethibloc deposits which have induced no reaction, but also Ethibloc material within the interstitium that led to the formation of fully developed granulomas around the material. The varying reaction is determined by the site of the deposition and by the concentration of the Ethibloc.

At other places at which the Ethibloc is not so dense, it led to a marked cellular reaction, and appeared to be undergoing degradation. In specimens with Ethibloc granulomas, both unilateral and concentric vascular granulomas are seen which we have also observed in other cases. Whether Ethibloc has entered the vascular system, or whether these granulomas have developed independently of the occlusive therapy, cannot be established. In both patients an angiographic examination had been performed prior to endoscopic injection of Ethibloc.

A number of granulomas within the pancreas are unequivocally arranged around blood vessels, or the remains of such vessel, so that they must be termed periarteriitic granulomas. Although the vessels within these granulomas are frequently quite well preserved, they reveal proliferations originating in the intima, which have led to a considerable narrowing of the lumen. In contrast to the so-called Kaiser phenomenon (Kaiser and Hommel 1975), sometimes described as "arteriitis" (Leger et al. 1963), however, the narrowing is not concentric, but an unilateral, nose-like narrowing that has left a small residual lumen (Fig. 7). Here, the progressive scarring of the pancreatic parenchyma with the diminishing perfusion requirement, plays no causal part. Whether these periarteriitic granulomas represent a special granulomatous reaction of the vascular wall, and what triggers such a reaction, we are unable to say. It is, however, quite clear that the vascular granulomas occur only in surgical specimens of patients in whom an angiographic examination of the pancreatic vessels had been carried out preoperatively. It is conceivable that in the highly scarred pancretic parenchyma the normally inert contrast material triggers an abnormal reaction of the arterial wall that leads to non-resorbable extravasates, and to the periarterial activation of the mesenchyme. Another possible explanation for the destruction of the vessel walls is the direct action of the pancreatic secretion's on the vessels. It would appear to be an organ-specific vascular injury which, secondarily, leads to the escape of contrast medium, which in turn induces the formation of granulomas.

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