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Epithelial Dysplasias in Chronic Pancreatitis

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Summary. The present 280 specimens of chronic pancreatitis were examined to determine the type and frequency of epithelial dysplasia of the duct system. The epithelial dysplasias were divided into 3 degrees of severity according to cytological and histological criteria. Dysplasia was demonstrable in 40.1% of the 280 specimens. Of these 32.9% were classified as dysplasia grade I and 7.1% as dysplasia grade II. Dysplasia grade III did not occur.

The epithelial proliferations were correlated with the topography, the stage of the scarring and the degree of obstruction of pancreatic secretion. An increase in dysplasia was evident in relation to the stage of the scarring and to the obstruction of secretory outflow. In correlation with the topography of the chronic pancreatitis there was the highest frequency of epithelial dysplasias in uniformly scarred glands (47.7%). Papillary and pseudopapillary hyperplasias with atypia were demonstrated in 17.9 vs. 4.5% of the cases with epithelial proliferations.

Key words: Chronic pancreatitis – Pancreatic carcinoma – Epithelial dysplasia

In highly industrialised countries a rising incidence in chronic pancreatitis and pancreatic carcinoma has been reported for many years (Krain 1970; Ishi et al. 1973; Levin and Connelly 1973; Pour et al. 1974, 1975; Levitt 1977; Fitzgerald 1976; Takahashi and Pour 1978; Herman and Cooperman 1979; Levison et al. 1979; Reed et al. 1979; Lin and Kessler 1981).

A causative connection between these two illnesses has been repeatedly casuistically communicated (Israels 1953; Bartholomew et al. 1959; Case Records of the Massachussetts Hospital 1972). However there is as yet no statistical or pathogenetic proof (Gambill 1971).

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Because pancreatic carcinoma is mainly an adenocarcinoma of ductal origin (Sommers et al. 1954; Cubilla and Fitzgerald 1975; Fitzgerald 1976, 1980; Becker 1973, 1978 b, c; Moossa 1981) we examined epithelial proliferation of the ductal system in chronic pancreatitis, which could be a potential precursor of pancreatic carcinoma.

Such epithelial proliferation was examined with reference to the topography, the stage of chronic inflammation and possible outflow impedance to pancreatic secretion.

Material and Methods

The 280 operatively obtained specimens of chronic pancreatitis were fixed under pressure with 10% formaldehyde to resemble their natural state. The fixed specimens were examined radiologically-anatomically (Stolte et al. 1977; Stolte and Schaffner 1978).

From each surgical specimen an average of 12 sections from several defined areas of the organ were available for examination under the light microscope. Staining: Haematoxilin-Eosin; Masson-Goldner; Elastica-van Gieson and PAS-Alcianblue at pH 2.5.

The definition of dysplasia was based on the overall impression given by the epithelial lining, therefore the reported values are semiquantitative. The epithelial dysplasias were correlated with the topography, the degree of scarring and the degree of impedance of pancreatic outflow.

a) The Topography of the Scarring. The specimens were divided into 3 groups according to the location of the chronic inflammatory process. It was differentiated between those types of pancreatitis causing a uniform parenchymal destruction of the total gland and that attacking only a local segment. Within the segmental type of chronic pancreatitis a further differentiation was possible between that which was strictly limited to one region of the gland and a second group which resulted in a mainly segmental inflammation of one pancreatic region. These topographically different forms of chronic pancreatitis were examined for the occurence of epithelial dysplasia in the ductal system.

b) The Stage of the Scarring. The stage of scarring of the pancreas was divided into 4 groups. Stage I has been defined as a reduction in parenchyma due to scarring of up to 30%. A parenchymal loss of 30–60% has been defined as stage II scarring. An extensive scarring, which means a marked replacement of parenchyma by fibrosis with a parenchymal loss of 60–90%, has been defined as stage III. Stage IV of the scarring infers the endphase of an autodigestive pancreatitis with a parenchymal loss over 90%.

The incidence and the frequency of epithelial dysplasia of the ducts were related to the stage of parenchymal scarring caused by the chronic inflammation.

c) Impedance to Pancreatic Outflow. Narrowing and displacement of the ductal system with consequential delay in pancreatic secretion results mainly from calculi, which cause a shift in the prepapillary section of the main pancreatic duct. Additional causes of secretory disturbancies are postpancreatic pseudocysts, true cysts of the pancreatic head and cysts of the duodenal wall (Zink 1978), benign papillary stenosis and hyperplasia of the tubular glandular ducts of the prepapillary section of the Wirsung's canal.

Cases with such impedance of secretion were examined for epithelial dysplasia in the ramifications of Wirsung's duct.

Results

I. Definition and Frequency of Epithelial Dysplasia of the Ductal System

We labelled every deviation of the ductal epithelium from the normal cubical to cylindrical epithelium as dysplasia, according to cytological and histologi-

cal criteria as described for other organs (Kleinsasser 1966; Grundmann 1973; Otto and Gebbers 1978, 1979; Koss 1978; Brunner 1979; Oehlert 1980; Park 1980). We divided them into 3 grades of severity.

Of 280 specimens with chronic pancreatitis 112 (40.1%) cases exhibited dysplasias of the ductal epithelium.

I.1 Definition of Epithelial Dysplasia of the Ductal System, Grade I

All forms of epithelial hypertrophy and hyperplasia which did not exhibit signs of atypical cells or disturbancies of stratification within multilayered epithelium were defined as Grade I.

The following types were differenciated:

I.1.1 Simple Extra-Tall Cylindrical Epithelium (Fig. 1). Simple epithelial hypertrophy consists of slim cylindrical epithelium closely packed in rows, with one and a half to twice the height of normal cylindrical epithelium. The cell nucleus is round or oval and polar aligned, the cytoplasm is slender and slightly eosinophilic.

I.1.2 Double Rows of Cylindrical Epithelium (Fig. 2). This epithelial variation consists of several succesive erect cylindrical cell-rows which also exhibit a long thin pulled out cytoplasm and a round basally situated nucleus.

I.1.3 Mucoid Transformation of the Epithelium (Fig. 3). Mucoid transformed cells have a very enlarged round integral cytoplasm due to increased mucus production. The nucleus is pushed to the base of the cell and has a round or sickle shape.

I.1.4 Pseudopapillary Hyperplasia (Fig. 4). Pseudopapillary hyperplasia denotes papillary elevation and folding of the epithelium without connective tissue stalk. The epithelial sheath of the pseudopapillary hyperplasia varies. There often is cubical or cylindrical epithelium which is occasionally replaced by mucoid transformed cells. Beside these there are also pseudopapillary hyperplasias in which the epithelium is totally transformed to mucus producing cells. Isolated areas of pseudopapillary hyperplasia are covered by extra-tall cylindrical epithelium.

I.1.5 Papillary Hyperplasia (Fig. 3). In contrast to pseudopapillary epithelial proliferation papillary hyperplasia has a connective tissue stroma which is dragged, with the proliferating epithelium into the duct lumen. The epithelium of this type of dysplasia shows a morphological variation of the epithelium which is of the same kind as in the pseudopapillary hyperplasia. A villous proliferation is occasionally seen.

I.1.6 Multilayered Epithelial Metaplasia (Fig. 5). Under the term multilayered epithelial metaplasia all forms of stratified epithelium were included.

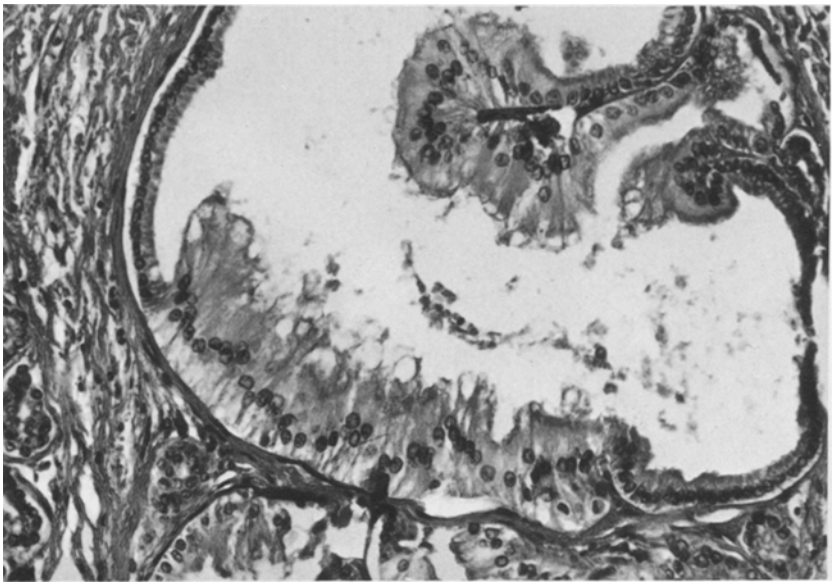

Fig. 1. Simple extra-tall cylindrical epithelium. Normal (left) cuboid epithelium of a small duct changes to a simple-layered extra-tall cylindrical epithelium with twice the height of normal epithelium. The nuclei are round and basally located. The cytoplasm is slender. To the right and above is an area on papillary hyperplasia with a small stalk of connective tissue. HE ×160

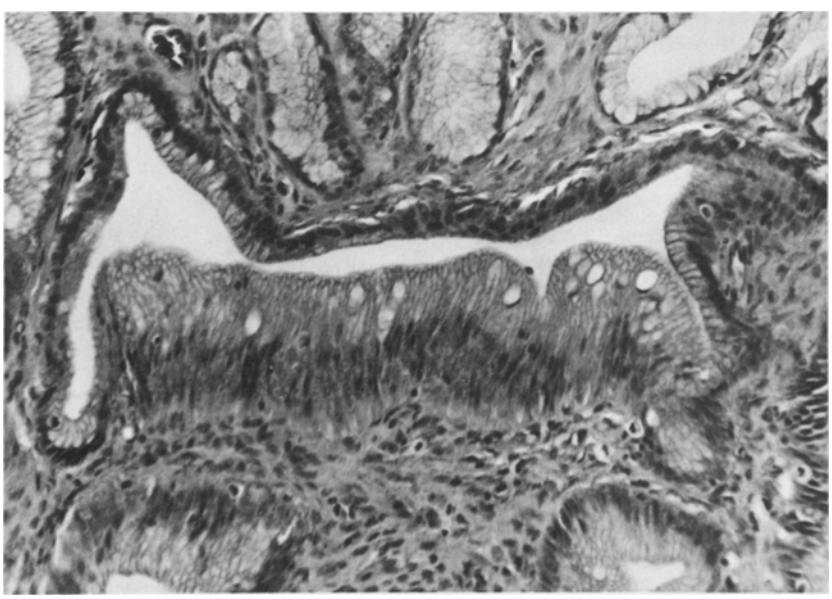

Fig. 2. Double rows of cylindrical epithelium. A focus of densely arranged extra-tall cylindrical epithelium with slender cytoplasm and basally located nuclei, occasionally intermingled with goblet cells. HE ×160

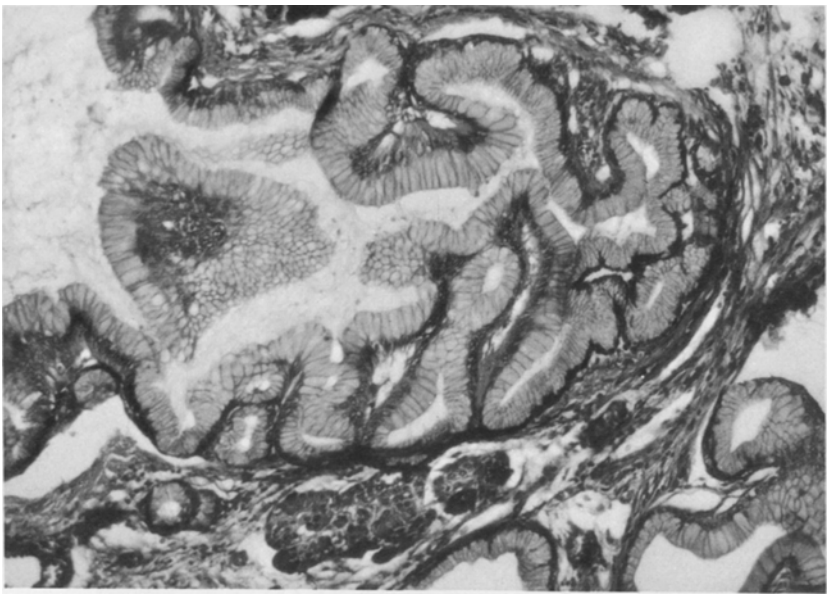

Fig. 3. Mucoid transformation of the epithelium and papillary hyperplasia. Epithelium of a larger duct dragged into the lumen with papillary folds showing small stalks of connective tissue. The epithelial sheet consists totally of mucoid transformed cells which show an enlarged cytoplasm due to mucus-production and small sickle-shaped basally located nuclei. HE $\times 80$

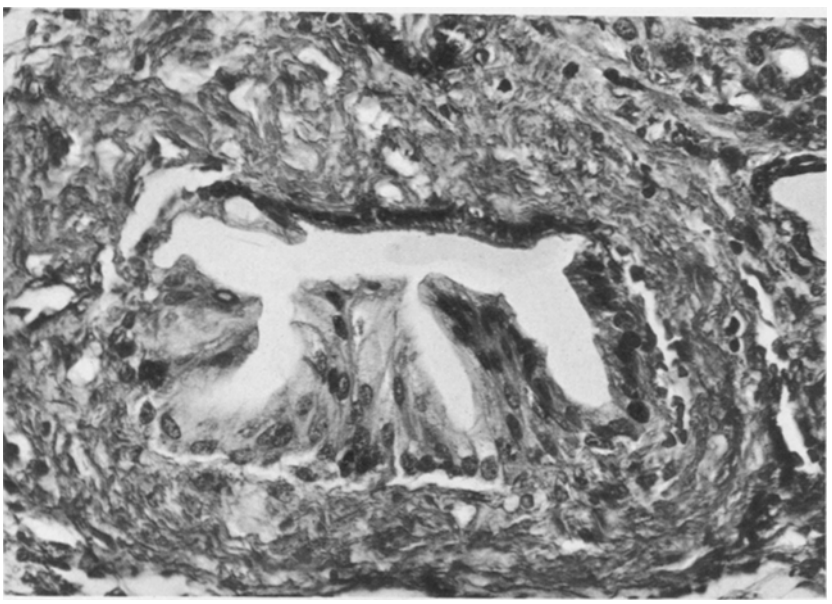

Fig. 4. Pseudopapillary hyperplasia. A small duct showing above and to the right, a slightly flattened and cuboid epithelium. There are three small pseudopapillary projections of the epithelium into the lumen. They consist of densely packed cylindrical cells. HE $\times 160$

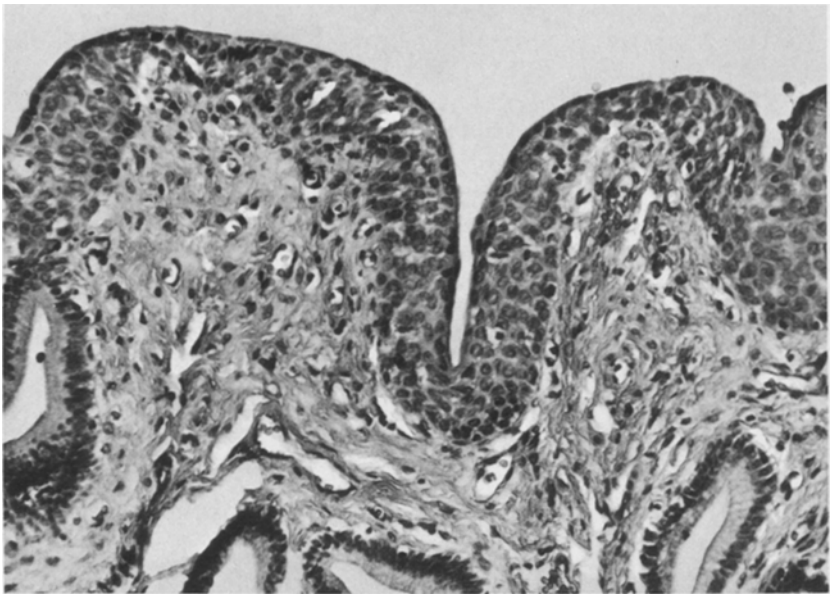

Fig. 5. Multilayered epithelium. Epithelial sheet of a larger duct which consists of several superimposed layers of epithelium showing stratification and flattening of the upper layer. HE ×160

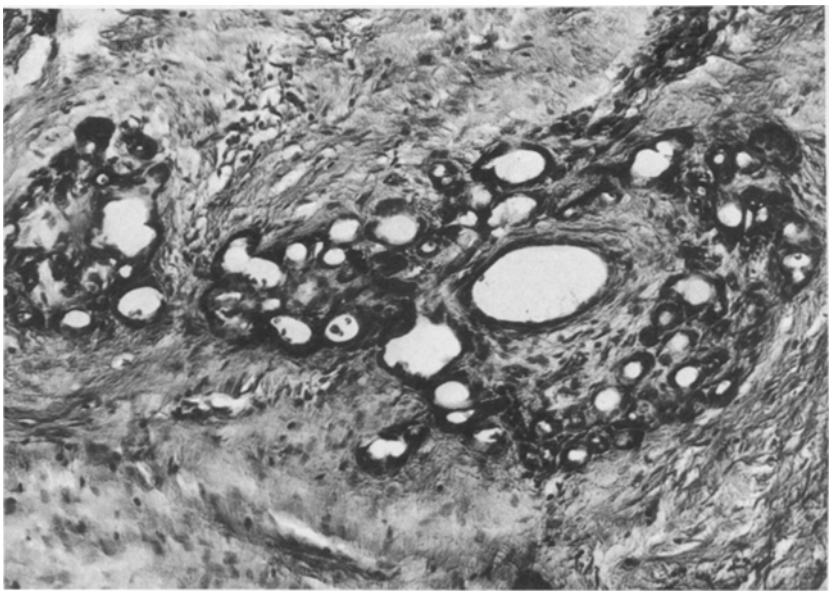

Fig. 6. Tubular accumulation. A focus of very small dilated ducts totally surrounded by fibrosis. The ducts are covered by a endothelial-like flattened epithelium. HE ×240

These show either a fully developed stratified structure, uniformly arranged, or consist of several superimposed cell formations showing a basal-cell like characteristic.

I.1.7 Tubular Accumulation (Fig. 6). Strictly speaking tubular accumulation is not a variation of the epithelium of the ducts but a tissue variant. It consists of closely packed groups of very tiny ducts. The epithelial sheath is almost always flattened, resembling endothelium. Occasionally the flattened epithelium is replaced by mucoid transformed cells. Zymogen granules have not been observed.

Nevertheless we have also included this kind of tissue variation since it seems to be a slight dysplasia and because we are concerned, not only with the simple dysplasia in a single cell but with the whole structure of the pancreatic gland. Just as papillary hyperplasia involves not only individual cells, which can be completely normal, but also the total epithelial structure and stroma that is the complete "mucus membrane". So the tubular accumulation is also a characteristic reaction of the total structure – in this case probably of the smallest secretory ducts.

I.2 The Frequency of Epithelial Dysplasia of the Ductal System, Grade I

From 112 cases of chronic pancreatitis 92 came under the criteria for grade I.

Single rows of extra-tall cylindrical epithelium of the ductal system were demonstrated 19 times (17%) in 112 cases of dysplasia. They occurred only in the side branches (s.b.) and were not correlated with the calibre of the side branches.

Double rows of cylindrical epithelium were found 6 times in the duct of Wirsung (d.W.) and 69 times in the s.b. where this type of dysplasia also demonstrated a calibre independent distribution. With 61.6% of the dysplasia, the double rowed cylindrical epithelium occurred frequently.

Mucoid transformation of the epithelium was seen with a very similar frequency (58.9%). It was found 6 times in d.W. compared with 60 times in the s.b. Most frequently mucoid transformation was found in the small side branches of the intralobular ductal system.

Papillary hyperplasia was found 7 times in d.W. it occurred 23 times in the side branches and here could be seen a similar distribution as to the pseudopapillary hyperplasia. With 26.8% papillary hyperplasia was definitely less often demonstrable compared with pseudopapillary epithelial proliferation (85.5%).

Epithelial dysplasias which were included under multilayered epithelial metaplasia partly regularly stratified partly with a basal-cell like epithelial alteration were the most often observed variation of all dysplasias (94.6%). These were demonstrated 20 times in d.W. and 86 times in the s.b. of all calibres.

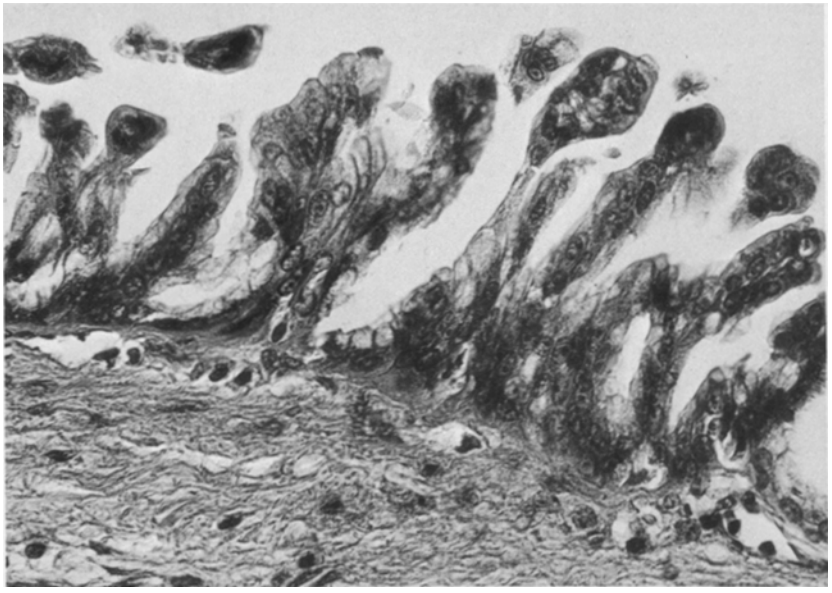

Fig. 7. Pseudopapillary epithelium with atypia. Epithelium of a medium-sized duct showing epithelial projections into the lumen without a stromal stalk. The projected cells are irregular with an enlarged hyperchromatic nucleus and prominent nucleoli. The nucleus-cytoplasm ratio is increased. HE ×160

Ductule accumulation occurred only 18 times. It was mainly in the totally scarred regions of the pancreatic gland, however isolated areas also occurred in the direct vicinity of the main secretory duct. With 16% of all dysplasias, the ductule accumulation was the least common of the dysplasias grade I.

I.3 Definition of the Epithelial Dysplasia of the Ductal System, Grade II

Dysplasia grade II, which we also labelled as atypical hyperplasia, was formally restricted to 3 epithelial variations: the pseudopapillary hyperplasia with atypia (Fig. 7), the papillary hyperplasia with atypia (Fig. 8) and the multi-layered epithelial metaplasia with atypia (Fig. 9).

It differs to dysplasia grade I in that there is a definite displacement of the nucleus-plasma-relationship to the advantage of the nucleus. The nuclei are enlarged, slightly polymorphous and hyperchromatic. The chromatin is loosely structured and 1–2 nucleoli are clearly visible. Isolated mitoses can also be detected. The cytoplasm exhibits basophilia. The basal membrane is intact. The cell nuclei are already enlarged and slightly irregularly situated on the basal membrane.

The multi-layered epithelial metaplasia with atypia shows an additional disturbance of the stratification and a predominance of basal cells.

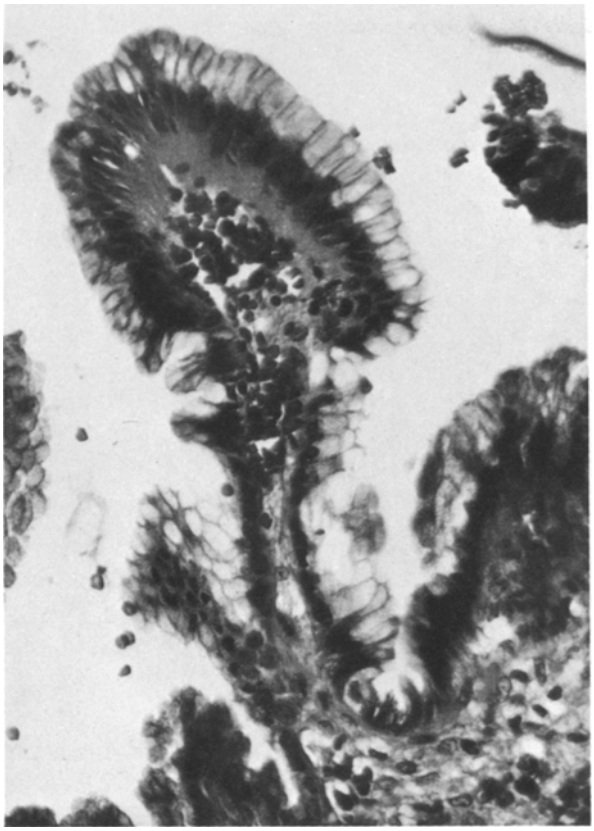

Fig. 8. Papillary hyperplasia with atypia. A papillary fold dragged into the lumen shows an epithelial layer of mucoid transformed cells with irregular enlarged nuclei. Moderate lymphocytic infiltration of the stromal stalk. HE $\times 240$

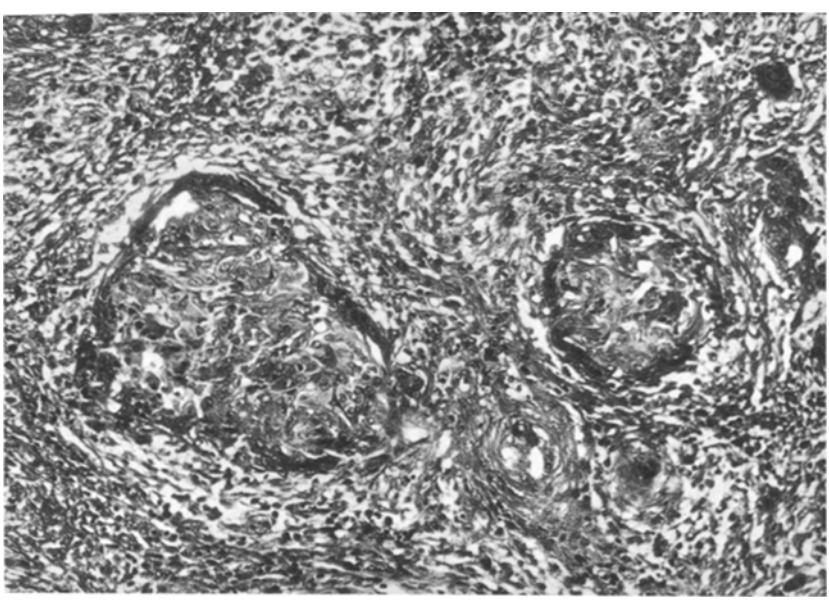

Fig. 9. Multilayered epithelium with atypia. Two small ducts surrounded by fibrosis showing a multilayered epithelium with loss of stratification and slightly irregular cells with enlarged nuclei. HE $\times 240$

I.4 Frequency of Epithelial Dysplasias of the Ductal System, Grade II

Of the 112 cases with dysplasia of the ductal epithelium, 20 cases (7.1%) were classified according to the defined criteria as dysplasia grade II.

Multilayered epithelial dysplasia grade II occurred in 14 of the 112 cases of dysplasia (12.5%), 3 times in the d.W. and 11 times in the side branches.

Papillary hyperplasia with atypia has been observed slightly more often. It was found 3 times in the d.W. and 17 times in the s.b. (17.9%) and here the papillary dysplasia grade II had a similar distribution pattern as the papillary dysplasia grade I.

Atypical pseudopapillary hyperplasia was found in only 5 cases (4.5%) of the 112 cases with epithelial dysplasias. These were exclusively localised in the side branches.

I.5 Definition of the Epithelial Dysplasia of the Ductal System, Grade III

From the morphologically point of view we defined duct epithelial dysplasias grade III exactly as for grade II.

Dysplasia grade III exhibits an high grade nuclear polymorphism the cell nuclei vary in size and are irregularly positioned, the number of nuclei is increased. In comparison to dysplasia grade II the nuclear density is increased and there is also an increased rate of mitoses. The cytoplasm shows a more intense basophilia as in grade II. Moreover there is a loss of cell polarity. The basal membrane is intact but can exhibit localised protrusions so that it simulates an incipient invasion. In addition multilayered epithelial metaplasia grade III shows a complete loss of stratification.

Epithelial dysplasia, defined as for grade III, was not demonstrable in the pancreatic duct epithelium in chronic pancreatitis.

For the type and frequency of epithelial dysplasias of the ductal system see Table 1.

II. The Relationship of Epithelial Dysplasias of the Ductal System to the Topography of the Chronic Inflammation, the Stage of the Scarring and the Impedance of Pancreatic Secretion in Chronic Pancreatitis

II.1 The Relationship of Epithelial Dysplasias of the Ductal System to the Topography of the Chronic Inflammation

In agreement with the differentiation of topographically different forms of chronic pancreatitis the collection of 280 specimens consisted of 40 cases

Table 1. Type and frequency of duct epithelial dysplasias in chronic pancreatitis ($n=280$)

Epithelial proliferation	Dysplasia grade I $n=92$			Dysplasia grade II $n=20$		
	d.W.[a]	s.b.[b]	%	d.W.[a]	s.b.[b]	%
Simple hypertrophy		19	16.9			
Double rowed cylindrical epithelium	6	69	61.6			
Mucoid transformation	6	60	58.9			
Pseudopapillary hyperplasia	7	77	85.7		5	4.5
Papillary hyperplasia	7	23	26.8	3	17	17.9
Multilayered epithelium	20	86	94.6	3	11	12.5
Tubular accumulation		18	16.0			

[a] d.W. = duct of Wirsung; [b] s.b. = side branches

with a strictly segmental scarring 61 cases with a predominantly segmental scarring and 179 cases with a uniform scarring of the total pancreatic gland.

In 179 cases with uniform scarring of the gland epithelial dysplasias grade I and II occurred 85 times (41.1%) of which 70 were dysplasia grade I and 15 dysplasia grade II.

From 61 cases with a predominantly segmental scarring 19 cases (31.7%) had dysplasia grade I and II, 14 times grade I and 5 grade II.

Eight of 40 cases with an exclusively segmental scarring showed epithelial dysplasia grade I representing 20% of this topographical form of the chronic pancreatitis.

Related to the topography of the chronic inflammation epithelial proliferation of the ductal system occurred most frequently in the uniform scarring of the whole parenchyma (47.7%). Epithelial proliferation has been observed less frequent in those cases with a predominantly segmental scarring of the gland (31.7%). Relatively infrequently they occurred in cases with exclusively segmental scarring (see Table 2).

II.2 The Relationship of Epithelial Dysplasia of the Ductal System to the Stage of the Scarring

In accordance with the defined stages of the scarring the 280 specimens were made up of 16 cases with scarring stage I, 75 cases stage II, 96 cases stage III and 34 cases stage IV – the endphase of the autodigestive chronic pancreatitis. Table 3 shows the incidence of dysplasia grade I and II in relationship to the stage of scarring.

A comparison of the frequency of defined epithelial dysplasias shows a definite increase of epithelial proliferation between scarring stage I to II from 18.4% to 42.6%. There is also a definite rise between stage III and IV of scarring from 44.2 to 72.7%. Comparing grade I and II of epithelial dysplasia there is a similar distribution pattern for dysplasias grade I as for all. In contrast to this epithelial dysplasias grade II do not occur

Table 2. Duct epithelial dysplasias related to the topography of chronic pancreatitis ($n=280$)

Dysplasia $n=112$	Topography of the scarring		
	Uniform $n=179$	Segmental $n=40$	Predominantly Segmental $n=61$
Dysplasia grade I $n=92$	70	8	14
Dysplasia grade II $n=20$	15		5
Total	85 (47.7%)	8 (20.0%)	19 (31.7%)

Table 3. Duct epithelial dysplasias related to the stage of the scarring in chronic pancreatitis ($n=280$)

Stage of scarring	I $n=76$	II $n=75$	III $n=95$	IV $n=34$
Dysplasia				
non	62	43	53	10
Grade I	14 (18.4)	25 (33.3)	32 (32.6)	21 (63.3)
Grade II		7 (9.0)	10 (10.5)	3 (9.0)
Total dysplasia grade I and II	14 (18.4)	32 (42.6)	42 (44.2)	24 (72.0)

with scarring stage I. It occurs in scarring grade II to IV with a similar frequency from 9.0 to 10.5% and an average incidence of 9.5%.

II.3 The Relationship of Epithelial Dysplasia of the Ductal System to Impedance of the Pancreatic Secretion

Stenosis of the ductal system with a consequent impedance of the secretory outflow was found in 98 cases of 280 specimens (35%). A list of the causative factors is given in Table 4.

Epithelial dysplasia occurred in cases with secretory impedance of the pancreas more frequently than in those without any obstruction of the ductal system.

The most frequent cause (36 times) of an outflow disturbance was obstruction of the prepapillary segment of Wirsung's duct due to calculi, in chronic calcifying pancreatitis.

Less frequent causes were benign papillary stenosis (11 times) and postpancreatic pseudocysts (19 times).

Only 3 cases out of 280 specimens showed a compression of the Wirsung's duct caused by a displacing scarring of the parenchyma.

All these causative factors of secretory impedance of the gland can be seen to be a result of the chronic inflammatory process.

Table 4. Causes of pancreatic secretion impedance and epithelial dysplasias ($n=98$)

Cause	n	With dysplasia $n=48$	Without dysplasia $n=50$
Papillary stenosis	11	4	7
Pseudocysts	19	6	13
Calculi in the prepapillary d.W.	36	18	18
Displacement scarring	3	2	1
Cysts of the duodenal wall and pancreatic head	13	7	6
Hyperplasia of the tubular glands	10	7	3
Cirsoid aneurysm of the splenic artery	1	–	1
Peripapillary diverticulum of the duodenal wall	1	–	1
Duct stenosis cause unknown	4	3	1
Total	98	48	50

Table 5. Duct epithelial dysplasias related to the impedance of pancreatic secretion in chronic pancreatitis ($n=280$)

Chronic pancreatitis	n	Dysplasia grade I n	Dysplasia grade II n	Total dysplasia	
				n	-4
With impedance	98	38	10	48	49.0
Without impedance	182	54	10	64	35.1
Total	280	92	20	112	

In 13 cases cysts of the duodenal wall and true cysts of the pancreatic head were the relatively cause of the secretory impedance.

In one case the obstruction of pancreatic outflow was due to a peripapillary pseudodiverticulum of the duodenal wall and in a second it was caused by a cirsoid aneurysm of the splenic artery.

In all these cases there was no obvious correlation between the obstruction and the occurence of epithelial dysplasia.

In contrast to these cases there has been found to be a coincidence of epithelial dysplasia with hyperplasia of the small tubular glands in the prepapillary section of the Wirsung's duct. 7 of 10 cases with a hyperplasia of the small tubular glands had developed epithelial dysplasia. In those cases a generalized proliferative stimulus might be suspected.

With regard to correlations between the degree of epithelial dysplasia and secretory impedance, epithelial dysplasia grade II occurred more frequently in association with duct obstruction than dysplasia grade I. In 92 cases with dysplasia grade I only 38 cases correlated with secretory impedance. In contrast 10 of 20 cases with dysplasia grade II did occur in combination with impedance of secretory outflow (see Table 5).

Discussion

The significance of chronic pancreatitis as a possible precursor of pancreatic carcinoma is still not clear. Edmondson et al. 1948; Hienert and Zeitlhofer 1956; Paulino Netto et al. 1960; Johnson and Zintel 1963; Burch and Ansari 1968; Grözinger et al. 1969; Grözinger 1970; Lundh and Nordenstam 1970; Mainz and Webster 1974; Becker 1977, 1978a–c, 1981; Wanke and Baumann 1980 described a possible connection between the two diseases. Tucker and Moore 1963; Creutzfeldt et al. 1970; Fuchs et al. 1972; Sarles and Gerolame-Santandrea 1972 have discussed the chronic calcifying and Friedman and Fialkow 1976 the hereditary pancreatitis as being special risk factors important for the development of pancreatic carcinoma. In contrast to these authors Weinstein 1968; Möhr et al. 1975; Monson and Lyon 1975; Wynder 1975; Ammann et al. 1979; Klöppel et al. 1979, 1980a; Levison 1979 see only a random increased incidence in carcinoma following chronic pancreatitis.

We therefore concentrated on looking for that epithelial proliferation which could be a potential precursor of the carcinoma, in a larger collection of 280 surgical specimens of chronic pancreatitis.

Epithelial dysplasias grade I showed a large morphological variation. In contrast dysplasia grade II consisted of only three morphologically different epithelial variations, these were multilayered epithelial metaplasia, pseudopapillary and papillary hyperplasia, each of them with atypia.

Papillary hyperplasia as a precursor of carcinoma has been demonstrated in animal experiments on cancerogenesis in rabbits by Elkort et al. (1975) and in golden hamsters by Pour and his group (1980). In the human pancreas, papillary hyperplasia has been discussed by several authors as a potential precursor of carcinoma.

Sommers et al. (1954) found 41% of papillary hyperplasia in 58 pancreatic carcinomas, in 6 cases they also noticed a carcinoma in situ. Cubilla and Fitzgerald (1975, 1976) found tumour-associated epithelial changes in 408 non-endocrine pancreatic carcinomas, 19% had simple epithelial hypertrophy, 52% papillary hyperplasia and in 24% of their specimens they observed a carcinoma in situ. Klöppel et al. (1979) found simple epithelial hyperplasia in 50%, papillary hyperplasia without atypical signs in 45% and atypical papillary hyperplasia in 18% of 40 carcinomas. Carcinoma in situ was seen in 5% in this study. Kozuka et al. (1979) reported simple epithelial hyperplasia in 79.2% of 24 pancreatic carcinomas, besides finding 29.2% with atypical epithelial hyperplasia.

Except for carcinoma in situ, therefore, almost all the forms of epithelial duct reaction which we classified as dysplasia grade I and II in our study have been found in the vicinity of pancreatic adenocarcinomas.

Sommers et al. (1954) reported tumour – associated epithelial changes without exactly defining their topographical relationship to the carcinoma but they did find epithelial proliferations mainly in the close neighbourhood of the carcinoma. Klöppel and coworkers (1980a, b) found atypical papillary hyperplasia only up to 3 cm from the tumour and interpreted them as intraductal tumour-spread.

The epithelial dysplasias which we have found to increase with advanced scarring in the ducts of the pancreas are also seen in the vicinity of carcinoma, as shown in the study of Klöppel and coworkers (1980a and b) even when "only in a surrounding zone of 3 cm". As in other carcinomas, there is also in the vicinity of pancreatic carcinomas a "rosette-like" epithelial reaction in the ductal system.

According to current histochemical criteria, Kozuka et al. (1979) drew up a sequence through simple epithelial hypertrophy, papillary hyperplasia and atypical papillary hyperplasia. These could merge into one another and lead, via atypical papillary hyperplasia to carcinoma. Klöppel et al. (1980a, b) in contrast discuss a hypertrophied epithelium with metaplastic mucus-production as the starting point of pancreatic carcinoma, which in the early phase should imitate benign papillary hyperplasia. Hisata (1979) regarded the papillary hyperplasia which he found in 15 of 90 pancreatic carcinomas, basing it on histochemical criteria, more as a non-specific accompanying reaction and did not consider this form of hyperplasia as a true precursor of pancreatic carcinoma.

In their study on the relationship between ductal epithelial proliferation and pancreatic carcinoma, Klöppel et al. 1979, 1980a, b also took into consideration 37 cases of chronic pancreatitis. They found with no difference to a control group without pancreatic disease the exception of simple epithelial hyperplasia (68%).

The total incidence of all proliferations was in 40% in our material, which was lower than that given by Klöppel et al. for chronic pancreatitis. In contrast, however, we found, in 7% of our cases, "atypical epithelial hyperplasias" which we defined as dysplasia grade II. In neither group was severe dysplasia demonstrated.

Klöppel et al. (1979) correlated the occurence of epithelial proliferation with the degree of the scarring in chronic pancreatitis, they differentiated between 3 degrees of severity and found no positive correlation between the degrees of scarring and the frequency of epithelial proliferation. In contrast to this, in our material we observed a definite increase in epithelial dysplasia related to the stage of scarring; there was a percentage increase in dysplasia grade I from slight to moderate scarring and from severe to total scarring of the parenchyma. In contrast dysplasia grade II did not occur with slight scarring of the gland and showed a relatively constant frequency with an average incidence of 9.5% within the scarring – stages II to IV.

Klöppel et al. (1979) also failed to find a positive correlation between ductal obstruction and the occurence of epithelial proliferation. In contrast to this we found, in our material, a marked percentage increase of epithelial dysplasia in cases with obstruction of the secretory outflow. There was also a positive correlation between dysplasias grade II and secretory impedancies. Therewith we can confirm the observation of Grauer (1939) who found more papillary hyperplasias in 34 pancreatic carcinomas when the tumour had caused an obstruction of the main pancreatic duct.

Our observations also confirm the studies of Wanke and Baumann (1980) who discuss chronic pancreatitis as a predisposing factor for pancreatic carcinoma and give an incidence of 75% simple epithelial hypertrophy,

35% papillary hyperplasia and 10% papillary hyperplasia with atypia for the socalled burned out pancreas. In their study they differentiate between fibrosing interstitial pancreatitis apparently identical with burned out pancreas ($n=20$) and lipolytical-proteolytical pancreatitis ($n=30$) for which they give a frequency of 47% epithelial hypertrophy, 37% papillary hyperplasia and 3% papillary hyperplasia with atypia.

To date, in all series of chronic pancreatitis, no high grade dysplasia which might be identical with the carcinoma in situ as defined for other organs (Kleinsasser 1966; Grundmann 1973; Oehlert 1980) has been communicated. However, Kozuka (1979) in a large series of 1100 unselected cases found atypical hyperplasia less often than pancreatic carcinoma and proposed that the phase of atypical hyperplasia possibly passes in a very short time and then quickly appears as carcinoma. Such a hypothesis might also be constructed for papillary and pseudopapillary hyperplasia with atypia in chronic pancreatitis. This ought to be vertified by further observations.

Histochemical examination to differentiate benign and preneoplastic epithelial proliferation has been reported only for carcinoma-associated epithelial changes (Hisata 1979).

The duct epithelial reaction which we saw in chronic pancreatitis is remarkably similar to those which we (Stolte et al. 1979) and others have found in the vicinity of carcinomas. However, whether this is identical or equivalent has not been demonstrated because the reactive possibilities of the duct epithelium are relatively uniform. Such a reaction could be induced by a chronic inflammatory process or by a parablastomatous influence.

Conclusion

In chronic pancreatitis epithelial dysplasia grade I and II of the duct system occur, frequently related to the stage of scarring and the impedance to pancreatic secretion. Taking in to consideration carcinoma-associated epithelial proliferation in the human pancreas and animal experimental findings in carcinoma induction, only papillary and pseudopapillary hyperplasia with atypia are important as potential carcinoma precursors.

Epithelial dysplasia grade II, which includes papillary and pseudopapillary hyperplasia with atypia occurred in 7.1% of 280 cases of chronic pancreatitis. It remains to be discussed whether this kind of dysplasia indicates a benign proliferative change in the epithelium or whether it represents a paraneoplastic transformation of the epithelium.

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