Comparative radiological and morphological study of human pancreas. Pancreatitis like changes in postmortem ductograms and their morphological pattern. Possible implication for ERCP

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SUMMARY A postmortem study by ductography and histology was performed on 69 human pancreata with no clinical or histological signs of chronic pancreatitis. The ductograms, supplemented by five postmortem ductograms of chronic pancreatitis, were independently evaluated by six clinicians, skilled in ERCP; the degree of alteration was estimated by simple rating, forced choice rating, and by determination of the grade of chronic pancreatitis. Histologically, the amount of intraductal epithelial proliferation, periductal, intralobular and perilobular fibrosis, intraductal protein plugs, and fat necrosis was determined by semi-quantitative methods. The six ductographical evaluations significantly differed in the level of their data, but corresponded in the range of distribution. All evaluations were correct regarding judgement of ductograms from patients with chronic pancreatitis. Ductograms of patients without chronic pancreatitis, however, were also frequently classified as chronic pancreatitis; overall 81% (minimal 37%, moderate 33%, severe 11%). This high level of false positive diagnosis indicates the frequency of pancreatitis like lesions in the main duct and its side branches in patients without chronic pancreatitis. Ductal lesions were significantly correlated with perilobular fibrosis. This finding favours the assumption, that in the non-inflamed pancreas, perilobular fibrosis plays a key-role in the development of ductal alterations, as in chronic pancreatitis. Perilobular fibrosis may result from intralobular inflammation caused by age-dependent intraductal epithelial hyperplasia.

Since the first successful endoscopic retrograde pancreatography (ERCP) in 1968,¹ ERCP has become a routine method in the diagnosis of chronic pancreatitis. The ductal alterations, decisive in the diagnosis of chronic pancreatitis, are well known and generally correlate with the clinical and laboratory parameters of chronic pancreatitis.²⁻⁵ Alterations of the pancreatic duct systems are also produced by age-dependent changes⁶⁻⁹ and may ductographically mimic chronic pancreatitis. The

differentiation between these 'physiological' alterations of the pancreatic duct systems and minimal or mild forms of chronic pancreatitis is not yet clear. Moreover, no data are available regarding the relationship between ductograms and histology in age-dependent pancreatic lesions. The material of our comparative radiological and morphological studies of the human pancreas,⁶⁻⁹ enabled us to study the following topics: (1) the specificity of the criteria of ERCP in differentiating between pancreata with and without chronic inflammation, and (2) the relationships between ductographical and histological lesions in age-dependent pancreatic alterations.

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Received for publication 15 June 1984

Methods

MATERIALS

The postmortem study was performed on 75 human pancreata removed within 10 hours of death. Five patients suffered from chronic pancreatitis (ages 33, 40, 48, 75, 79 years; two men, three women; alcoholic three). Seventy patients showed no signs of chronic pancreatitis, neither macroscopically nor microscopically, but only age-dependent alterations, which are clearly distinguishable from chronic pancreatitis. Moreover, no signs of chronic pancreatitis were known from the clinical history. One of these cases was omitted because of incomplete histological data. Twenty nine patients presented bile diseases on necropsy, mostly gallstones. Cirrhosis was seen in one patient, gastric ulcers in four patients and duodenal ulcers in two patients.

After necropsy, a tubule was fixed in the papilla and the pancreatic duct system was filled with a contrast medium, using a pressure of 20 cm H₂O. The contrast medium was a mixture of 40% bovine albumin solution (25%) and 60% Micropaque®. The pancreas was fixed in 4% formalin, the adherent tissue removed and the isolated organ radiographed. The organs were cut into slices of 8 mm thickness, paraffin embedded, and were studied histologically in giant sections.

EVALUATION OF THE DUCTOGRAMS (Fig. 1)

The 75 ductograms were divided into five groups, each of 15 radiograms. The clinical observer had to evaluate each series independent of the other series and the other observers. Three evaluations were performed in each series: (1) simple rating, using a scale from 1–9; (2) forced choice rating – that is, the ductograms of each series were evaluated against a line where the slightest lesions were at one end and the most severe alterations were at the other end; (3) evaluation of the degree of chronic pancreatitis using a scale from 0–3. The criteria of the evaluation was taken from Kasugai *et al.*,³ estimating alterations of the main pancreatic duct and its branches.

HISTOLOGICAL EVALUATION

The histological evaluation covered the variables: proliferation of ductal epithelium, periductal fibrosis, intralobular fibrosis, perilobular fibrosis, intraductal protein plugs, and fat necrosis,⁶ (Figs. 2–4). The number of each lesion was determined in each slice, summed up for head body and tail, and divided by the number of the slices of each region. A mean value of $0 < \bar{x} \leq 0.5$ was valued as grade 1, a mean value of $0.5 < \bar{x} \leq 1$ as grade 2, a mean value of $1 \leq \bar{x}$ as grade 3. The values of head, body and tail

were summed up, thus providing an overall value on a scale from 0–9, with 0 = no, 1–3 = slight, 4–6 = moderate and 7–9 = severe alterations.

STATISTICAL EVALUATION

Frequencies were computed for all variables, both for all patients and for patients without chronic pancreatitis. The influence of age, sex, bile disease and gastroduodenal ulcers on ductograms, and histology was determined by correlation analyses. The statistical comparison between ductography and histology was done with the mean values of each case in the six simple rating evaluations. Moreover, the rating scale of ductographic changes was subdivided in $1 < 2.5$ = normal, $2.5 < 4.0$ = borderline and 4.0 – 9.0 = abnormal.

Results

Evaluation of simple rating of ductograms showed significant differences between some observers (Table 1). A z-transformation, however, revealed that the six observers agreed in the range of their evaluation and were different by the levels only. Similarly, significant differences were seen in the grading of pancreatitis (Table 2). The diagnosis of all observers was correct in their judgment of chronic pancreatitis. Ductograms of patients without chronic pancreatitis were also often classified as chronic pancreatitis (Table 3). Forty two per cent of these ductograms were falsely estimated by all observers. Only one ductogram, was classed as normal by all observers. An overall calculation of the six evaluations revealed the diagnosis of a normal pancreas in 19% only (Table 2). Even the clinician, mostly skilled in ERCP (no. 4) who had evaluated more than 18 000 ERCP, gave false positive results in 42%.

Histologically, most often perilobular fibrosis and ductal epithelial hyperplasia were present, followed by intralobular and perilobular fibrosis (Table 4). Ductal epithelial hyperplasia was significantly correlated with intralobular and perilobular fibrosis as well as with fat necrosis, while perilobular fibrosis was also correlated with intralobular fibrosis, and fat necrosis (Table 4).

The relationships between ductographical and histological lesions are shown in Table 5. A significant correlation was present between ductographical changes and perilobular fibrosis. Significant age dependency existed in ductal epithelial hyperplasia ($p < 0.01$) and intralobular fibrosis ($p < 0.05$) as well as in ductographical changes ($p < 0.05$). No significant correlation was found to bile tract diseases or gastroduodenal ulcers.

Discussion

Each multiple evaluation is complicated by inconsistent handling of the criteria of evaluation by

the different observers. In our study, we hoped to overcome this problem by using the distinct criteria of Kasugai *et al*³ in the estimation of the ductal alterations. Moreover, the six evaluators were

Fig. 1 Postmortem ductograms of human pancreas. (a-c) Organs with no histological signs of chronic pancreatitis.

Fig. 1 (continued) (d) Organ with histologically proved chronic pancreatitis (HPT)

Results of the ductographical evaluations of these four pancreata

Age	Sex	Estimation of degree of chronic pancreatitis					
		1st observer	2nd observer	3rd observer	4th observer	5th observer	6th observer
(a) 40	Man	0	0	2	0	2	2
(b) 72	Man	2	1	1	0	1	2
(c) 67	Man	2	2	2	1	2	2
(d) 35	Woman	3	3	3	2	2	3

obliged to work scrutinously by using forced choice rating as an additional method of evaluation. Nevertheless, the six evaluations differed distinctly. Each evaluator, however, was very stable regarding the criteria, and there was good correlation in the

range of the evaluation of the six observers. Thus, the results are comparable and consistent. Most of the ductograms of the histologically unaffected organs, however, were classified as chronic pancreatitis. Even the most skilled observer

Table 1 Evaluation of simple rating of 74 postmortem ductograms by six observers

Rating scale	Observer					
	No 1 (%)	No 2 (%)	No 3 (%)	No 4 (%)	No 5 (%)	No 6 (%)
1	5.3	6.7	2.7	52.0	1.3	18.7
2	13.3	9.3	10.7	24.0	12.0	12.0
3	16.0	18.7	13.3	12.0	17.3	18.7
4	26.7	25.3	25.3	1.3	12.0	12.0
5	12.0	25.3	32.0	1.3	13.3	10.7
6	12.0	5.3	6.7	—	14.7	10.7
7	8.0	6.7	5.3	5.3	16.0	8.0
8	6.7	2.7	4.0	4.0	12.0	5.3
9	—	—	—	—	1.3	4.0
$\bar{x} \pm s$ of the rating values	4.28 $\pm$ 1.88	4.09 $\pm$ 1.64	4.35 $\pm$ 1.56	2.17 $\pm$ 1.90	5.00 $\pm$ 2.06	3.99 $\pm$ 2.35

Observer no 4 significantly ($p < 0.001$) reduced versus no 1, 2, 3, 5, 6.

Observer no 5 significantly increased versus no 1, 2, 3 ($p < 0.05$), no 6 ($p < 0.01$) and no 4 ($p < 0.001$).

Fig. 2 Age-dependent alterations of the pancreas (HE, $\times 33$ original magnification). (a) Intraductal epithelial proliferation and slight intralobular fibrosis. (b) Periductal fibrosis encroaching the adjacent parenchyma.

presented a false positive diagnosis in nearly 50%. These results clearly elucidate that ductal abnormalities, identical with those of at least minimal chronic pancreatitis, are common in subjects without clinical and anatomical evidence of chronic pancreatitis.

A direct comparison of our ductograms with ERCP is impossible. On the one hand, the use of a contrasting medium, containing barium and the radiographing of the isolated organs result in pictures of extremely high contrast. On the other hand, our method allows an imaging of the smallest

Fig. 3 Age-dependent alterations of the pancreas (HE, $\times 33$ original magnification). (a) Mild intralobular fibrosis. (b) Marked intralobular fibrosis and moderate perilobular fibrosis.

side branches of the duct systems, which can be reached in ERCP only together with parenchymal opacification. Thus, a great deal of ductal alterations, especially of smaller side branches, may be detectable by postmortem ductograms only, and not by ERCP. But these ductal lesions are not

artefacts. Therefore, paradoxically the diagnostic value of small duct alterations in ERCP may decrease with improving quality of the radiograph. This paradoxon is confirmed by the change of the criteria in the diagnosis of chronic pancreatitis during the last decade. In 1972 Kasugai *et al*³

Fig. 4 Age-dependent alterations of the pancreas (HE, $\times 53$ original magnification). Marked intralobular fibrosis. Partly resorbed perilobular fat necrosis (arrow) with slight perilobular fibrosis.

diagnosed mild chronic pancreatitis, if alterations like irregular distribution, dilatation and stenosis were present anywhere in the side branches.

In 1983 the International Workshop on Classification of Pancreatitis in Cambridge¹⁰ recommends a diagnosis of chronic pancreatitis only, if more than three abnormal side branches are present. Perhaps in some years with further improvement of ERCP the diagnostic value of isolated lesions of the small duct system will be still more insignificant, especially in aged patients.

Reports concerning the appearance of the main duct are controversial. According to Schaffner¹¹ and Stole¹² the main duct of the normal pancreas is free of dilatations or stenosis. In contrast, Anacker¹³ and Classen¹⁴ assume slight irregularities of the main duct to be within the normal range. Sarles *et al*¹⁵ found incomplete stenosis of the main duct in 6.6%

of normal controls. Earlier studies of our group⁹ revealed distinct luminal deviations of the main duct in more than 25% of normal controls, older than 45 years. In the present study, the high incidence of false positive diagnosis of moderate chronic pancreatitis, deriving from the presence of slight alterations of the main duct, confirms this finding. Therefore the criteria of moderate pancreatitis in ERCP 'abnormal main duct with or without branch changes'¹⁰ may not be sufficiently specific. The results of our study support the thesis of Reuben *et al*¹⁶ that endoscopic pancreatography provides accurate distinction only when radiographs are interpreted with knowledge of the clinical data.

The significant correlations between ductal epithelial hyperplasia, intralobular fibrosis and perilobular fibrosis, as well as their age-dependency support the hypothesis, presented in a previous study,⁶ that age-dependent pancreatic lesions start with intraductal epithelial proliferation, followed by intralobular and perilobular fibrosis. Two kinds of mechanism may be involved in the development of perilobular fibrosis. On the one hand, the intralobular lesions may produce a perilobular oedema with secondary fibrosis. On the other hand, the intralobular alterations may release lipase, resulting in perilobular fat necrosis, followed by perilobular fibrosis. Statistical correlation analyses support the second hypothesis. Moreover, an obvious coincidence of partly resorbed fat necrosis and perilobular fibrosis was not infrequently visible in our material (Fig. 4). The significant correlation between ductographical lesions and perilobular fibrosis favours the assumption that perilobular fibrosis plays a key role in the development of ductal lesions in patients without chronic pancreatitis. In contrast, in our study protein plugs have no influence on the development of perilobular fibrosis

Table 2 Evaluation of postmortem ductograms of patients without chronic pancreatitis ($n=69$)

Ductographic evaluation	Diagnosis of the observer								Mean grading of all ductograms $\bar{x} \pm s$
			Chronic pancreatitis						
	Normal		Grade 1		Grade 2		Grade 3		
	n	%	n	%	n	%	n	%	
Observer no 1	9	13	21	30	33	48	6	9	1.52±0.83
Observer no 2	6	9	30	43	28	41	5	7	1.43±0.78
Observer no 3	8	12	27	39	30	43	4	6	1.45±0.76
Observer no 4	40	58	25	36	3	4	1	2	0.52±0.66
Observer no 5	1	2	27	39	23	33	18	26	1.87±0.84
Observer no 6	15	22	24	35	21	30	9	13	1.38±0.97
Overall		19.1		37.2		33.3		10.4	

Observer no 4 significantly ($p < 0.001$) reduced versus no 1, 2, 3, 5, 6.

Observer no 5 significantly increased versus no 1 ($p < 0.05$), no 2, 3, 6 ($p < 0.01$) and no 4 ($p < 0.001$).

Table 3 Incorrect evaluated ductograms by the observers in 69 patients without chronic pancreatitis in postmortem ductograms

Observers with correct diagnosis of 'normal' pancreas (no)	Correct evaluated ductograms		Degree of incorrect estimation as chronic pancreatitis		
	No	%	Minimal (%)	Moderate (%)	Severe (%)
No observer	29	42	16	19	7
One observer	19	28	15	11	2
Two observers	12	17	10	5	2
Three observers	5	7	3	4	—
Four observers	2	3	1.5	0.75	0.75
Five observers	1	1.5	1.5	—	—
Six observers	1	1.5	—	—	—
Total	69	100	47.0	39.75	11.75

Table 4 Histological evaluation of 69 pancreata without chronic pancreatitis

Histological alteration	Grading of alteration									
	No		Slight		Moderate		Severe		Alterations (no)	
	n	%	n	%	n	%	n	%	n	%
Hyperplasia of ductal epithelium*	5	7.3	40	58.0	15	21.7	9	13.0	64	92.7
Periductal fibrosis†	19	27.5	33	47.8	11	16.0	6	8.7	50	72.5
Intralobular fibrosis‡	8	11.6	46	66.7	9	13.0	6	8.7	61	88.4
Perilobular fibrosis§	9	13.0	30	43.5	19	27.5	11	16.0	60	87.0
Protein plugs	42	60.9	22	31.9	4	5.8	1	1.4	27	39.1
Fat necrosis¶	38	55.1	27	39.1	4	5.8	0	0	31	44.9

* Significantly correlated to perilobular fibrosis ($p<0.01$), intralobular fibrosis ($p<0.001$) and fat necrosis ($p<0.05$).

† Significantly correlated to intralobular fibrosis ($p<0.01$).

‡ Significantly correlated to epithelial hyperplasia ($p<0.001$) and perilobular fibrosis ($p<0.05$).

§ Significantly correlated to epithelial hyperplasia ($p<0.01$), intralobular fibrosis ($p<0.05$) and fat necrosis ($p<0.05$).

|| No significant correlation at the 5% level.

¶ Significantly correlated to epithelial hyperplasia ($p<0.05$) and perilobular fibrosis ($p<0.05$).

Table 5 Relationships between ductal alterations and histology in 69 patients without chronic pancreatitis

Histological lesion	Degree of ductal alteration											
	Normal Age: 49.9 ± 22.8 years* n=10				Borderline Age: 64.1 ± 9.5 years* n=32				Abnormal Age: 63.1 ± 17.9 years* n=27			
	No	Slight	Moderate	Severe	No	Slight	Moderate	Severe	No	Slight	Moderate	Severe
Ductal epithelial hyperplasia	2	6	0	2	1	20	7	4	2	14	8	3
Periductal fibrosis	4	1	3	2	8	17	5	2	7	15	3	2
Intralobular fibrosis	1	6	2	1	4	21	4	3	3	19	3	2
Perilobular fibrosis†	3	5	0	2	6	14	9	3	0	11	10	6
Intraductal protein plugs	8	2	0	0	20	11	1	0	14	9	3	1
Fat necrosis	7	3	0	0	19	11	2	0	12	13	2	0

* Significant correlation ($p<0.05$) to the degree of ductal alteration in the mean values of rating evaluations of the six observers.

† Significant correlation ($p<0.01$) to the degree of ductal alteration in the mean values of rating evaluations of the six observers.

and ductal lesions. Rather, such protein plugs are produced by ductal stenosis with retention of pancreatic juice.⁶ Ductal lesions in chronic pancreatitis are mainly produced by periductal fibrosis.¹²⁻¹⁷ As shown by the present study, an identical mechanism may produce ductal lesions in the aging pancreas. This identical formal pathogenesis may also explain the identical pattern of minimal chronic pancreatitis and age-dependent ductal lesions in pancreatic ductograms.

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