Gut 1992; **33**: 1566–1571

Minimal change chronic pancreatitis

T N Walsh, J Rode, B A Theis, R C G Russell

Abstract

In patients with severe abdominal pain, of pancreatic origin, there are a few with minimal or equivocal findings on pancreatic investigation and in whom the aetiology of their pancreatic disease is elusive. The findings and outcome in 16 of these patients (four men and 12 women) who underwent resection are reported. Pancreatic imaging showed minimal or equivocal findings in all 16; pancreas divisum was present in five. All were managed conservatively at first but resection was required for progression of symptoms. A drainage procedure was performed initially in five patients but relief of pain was at best transitory before further surgery was required. Partial resection was needed in 12, of whom eight required subsequent completion pancreatectomy and four had a one stage total resection. Nine patients are currently pain free after resection or are very much improved, while six are no better and one patient has died from an unrelated cause. Histology of resected specimens showed chronic inflammatory changes accompanied by subtle non-inflammatory changes in all but one. These changes include duct proliferation, duct complex formation, adenomatous nodules, and acinar cell atrophy, the significance of which is unclear. These findings suggest a syndrome of minimal macroscopic and radiological change chronic pancreatitis with pain as its chief clinical feature and a distinct histology, the aetiology of which is unclear. It seems that there is a distinct syndrome of minimal change pancreatitis, among the group of patients which presents with the clinical features of chronic pancreatitis.

(*Gut* 1992; **33**: 1566–1571)

Established pancreatic pain is characteristic – the pain is deep and gnawing with prolonged and severe exacerbations; it is situated to the left of the midline and when severe passes round or through to the back; it is aggravated by eating; the epigastrium is tender and movement makes the discomfort worse. Analgesics relieve only temporarily and opiates seem to aggravate the pain over a period of time. This pain is often associated with gross morphological disease, which, when removed, cures the pain, but occasionally investigation of the pancreas shows only minor morphological changes. It is accepted that pancreatic pain correlates poorly with morphology, be it by gross inspection, by histological examination, or by imaging.

Ihse has suggested that pain may be associated with the dynamics of the disease rather than with a static situation.[1] Recent investigation has suggested that intraductal pressures are higher[2] in patients with painful chronic pancreatitis. A close correlation has been found between tissue pressure and pain in these patients.[3] A further dynamic concept is that of pancreatitis associated neuritis. Beger *et al* have reported a comparative increase in the number of nerves in inflammatory pancreatic tissue, together with round cell infiltration and striking disintegration of the perineurium.[4] They suggested that loss of function of the perineural barrier allowed an influx of inflammatory mediators or active pancreatic enzymes, and they recently showed an increase in neuropeptidase substance P and calcitonin gene related peptide within sensory nerve fibres in patients with chronic pancreatitis.

In this paper attention has been paid to a group of patients with characteristic pancreatic pain of sufficient severity to necessitate operative intervention, near normal pancreatic ducts, and normal morphology on ultrasound scan and computed tomography, yet who, on histological examination, have the subtle histological changes of duct proliferation, duct complex formation, adenomatous nodules, acinar cell atrophy, and acinar cell vacuolation.

Patients and methods

Between 1976 and 1989, 486 patients with a diagnosis of chronic pancreatitis were referred for a surgical opinion. Forty three had a characteristic history of pancreatic disease, often with acute attacks associated with a rise in serum amylase, and in all respects with a similar clinical presentation to the other patients referred, yet on investigation were found to have minimal morphological changes in the pancreas on the basis of a pancreatogram, and ultrasound or computed tomography. On the basis of clinical criteria, that is failure to improve as a result of outpatient management with analgesics, enzyme replacement, and abstinence from alcohol, and inpatient treatment on at least three occasions with parenteral nutrition and intestinal rest, 16 patients underwent resection of their pancreas.

Resection was performed as a primary procedure in 11 patients and after a duct drainage operation in five (Table), all of whom had pancreas divisum. Drainage was by accessory duct sphincteroplasty in four of the five patients with divisum, the fifth patient had an endoscopic sphincterotomy of the accessory ampulla. Four patients who had a distal pancreatectomy (75%) also had a pancreatojejunostomy Roux en Y to the divided end of the pancreas. In all, 12 patients have had a total pancreatectomy (in eight of whom it was performed as a staged procedure) and four patients have had a partial pancreatectomy (two of whom have had a distal resection and two a resection of the pancreatic head). Of the 14 patients undergoing resection of the head of the pancreas, either as a total pancreatectomy or as a partial resection, 12 had a duodenum preserving resection of the head, one had a

Departments of Surgery and Pathology, The Middlesex Hospital, London
T N Walsh
J Rode
B A Theis
R C G Russell

Correspondence to:
Mr R C G Russell, Consultant Surgeon, The Middlesex Hospital, Mortimer Street, London W1N 8AA.

Accepted for publication 23 March 1992

Operative procedures performed on 16 patients with minimal change pancreatitis

Outcome	*No*	*First procedure*	*Second procedure*	*Third procedure*
One stage total resection	1	Duodenum preserving total pancreatectomy		
	3	Sphincteroplasty	Duodenum preserving total pancreatectomy	
Two stage total resection	4	Distal resection	Duodenum preserving resection of head	
	1	Duodenum preserving resection of head	Distal resection	
	1	Sphincteroplasty	Distal resection	Duodenum preserving resection of head
	1	Sphincterotomy	Duodenum preserving resection of head	Distal resection
	1	Distal resection	Pancreatoduodenectomy	
Partial resection	1	Duodenum preserving resection of head		
	1	Pylorus preserving resection of head		
	2	Distal resection		

pylorus preserving pancreatectomy, and one a pancreatoduodenectomy. All patients have been followed up by the authors in a pancreatic clinic and assessed at six monthly intervals.

HISTOLOGY

After routine formalin fixation, the pancreatic resection specimens were cut serially into approximately 3 mm thick sagittal slices. These were numbered consecutively to facilitate subsequent identification of any area affected by pathological changes. After macroscopic inspection either all or representative slices were paraffin processed. Selected cases were received fresh immediately after the resection at which time the main pancreatic duct was injected with a radio-opaque dye. Assessment of the distribution of the dye after radiography and by macroscopic and microscopic examination allowed the diagnosis of variants of the ductal drainage pattern of the gland. Only paraffin blocks of tissue sampled at random were available from cases early in the series. Paraffin blocks were cut at 4 μm intervals. Sections were stained with haematoxylin and eosin, for the general neural and neuroendocrine marker protein gene product 9·5 (PGP 9·5) for visualisation of ganglion cells, nerves, and neuroendocrine cells including islet cell tissue; for pancreatic polypeptide to highlight the embryological ventral derived portion of the pancreas; and if thought contributory for diagnosis, for the polypeptide hormones and transmitter substances insulin, somatostatin, glucagon, gastrin, calcitonin, calcitonin gene related peptide, and serotonin. The presence or absence of these neuroendocrine markers was noted and differences with the rest of the group documented.

Histology was performed in all cases by a single pathologist (JR) with a special interest in early changes in chronic pancreatitis.

Results

PATIENT DETAILS

There were four men and 12 women. The mean age at onset was 25·5 years (range 14–30) for men and 32 years (range 14–48) for women while the mean age at surgery was 32 years (range 26–36) for men and 40 years (range 19–51) for women. The only potential aetiological factor was the presence of pancreas divisum in five and excessive alcohol intake in one patient. Two patients felt that their symptoms dated from an attack of mumps and one from a flu like illness as a teenager.

Seven patients had a psychiatric assessment before surgery, and all were considered to be normal. Assessment of the other nine by the surgical team was considered to have been normal in seven, while one patient was thought 'depressive' and another 'inadequate.' It was difficult, however, to determine if these traits preceded or followed the onset of symptoms.

PANCREATIC IMAGING

All 16 patients underwent endoscopic retrograde cholangiopancreatography (ERCP). Pancreas divisum was identified in five; one being associated with delayed emptying while another had minor side duct changes. Of the other 11, seven were reported as showing minor or equivocal side branch abnormalities and four as normal studies.

Ultrasound was performed in all 16 patients, six of whom were reported as showing mild changes – confined to the head in three, to the tail in two, and diffuse in one. No abnormality was detected in the remaining 10 patients.

The pancreatic appearances were considered to be within normal limits in the four patients who had a computed tomogram.

RESPONSE TO SURGERY

Sixteen patients underwent pancreatic resection – in 11 as a primary procedure and after unsuccessful drainage in five.

Drainage

No patient who underwent a drainage procedure had lasting relief of their pain and all went on to require resection within two years.

Partial resection

Twelve patients have had a partial pancreatectomy. Recurrence of symptoms necessitated a subsequent completion pancreatectomy in eight, leaving only four currently with partial pancreatectomy. Two of these had a distal pancreatectomy, both of whom had a good response to surgery, while one had a duodenum preserving resection of the head and now has mild symptoms that are easily controlled by occasional analgesics, and one had a pylorus preserving resection of the head without much relief.

Case reports

CASE 1

A 35 year old woman was referred in 1982 with a four year history of intermittent epigastric pain, precipitated by alcohol and fatty foods. Her past medical history was unremarkable and her alcohol intake occasional. An ERCP was normal but ultrasound questioned changes in the head of the pancreas. The pain progressed and in 1983 an 80% distal pancreatectomy was carried out.

Histology showed some mild intralobular inflammation as well as inspissated protein in some ducts. These was marked acinar atrophy with fat vacuolation duct complex formation and adenomatous nodules. These changes were seen in both anlages.

After her operation she was symptom free for one year but then pain that was unresponsive to conservative management recurred. A duodenum preserving completion pancreatectomy was performed; histological changes in the head were identical. She has been completely well and without symptom during her 53 months' follow up.

Total pancreatectomy

Because of the disappointment with staged procedures, four patients had a duodenum preserving total pancreatectomy as a sole resection. This was performed in three patients with pancreas divisum after a previous accessory duct sphincteroplasty and in one non-divisum patient as her only operation.

CASE 2

A 40 year old woman was referred with a two year history of left upper quadrant pain which was constant, with exacerbations radiating to the back, and associated with vomiting, diarrhoea, and weight loss of 6 kg. Her past medical history was significant in that she suffered from the autoimmune diseases of Sjøgren's, hypothyroidism and rheumatoid arthritis. She did not drink alcohol. ERCP showed pancreas divisum but the ducts were grossly normal. Accessory duct sphincteroplasty was carried out in 1984. This was followed by an eight month period of pain relief but symptoms returned and necessitated four inpatient admissions over the next 18 months. In 1986, a duodenum preserving total pancreatectomy was performed. Histology showed foci of fat vacuolation of the acini with acinar atrophy and duct conversion. These changes were confined to the dorsal anlage. She is currently very much better and has not required hospital admission since her operation.

CASE 3

A 29 year old woman was referred with a history of epigastric pain radiating to the back and aggravated by food. This seemed to follow an attack of mumps in childhood. In her past medical history the only feature of note was Gilbert's disease and a family history of diabetes. She initially had a good response to enzyme treatment and to coeliac block but both responses faded after three to six months. The pain became unbearable, and in 1989 a duodenum preserving total pancreatectomy was performed. Histology showed foci of fat vacuolation of the acini with an increase in centro-acinar cells and duct conversion. These foci were not confined to any one region of the pancreas.

She had complete relief of symptoms for the next year but then developed a bile duct stricture at the distal end requiring a choledochoduodenostomy. She is currently working full time and has minimal symptoms.

Pancreas divisum

The five patients with pancreas divisum initially underwent a drainage procedure (sphincteroplasty in four and endoscopic sphincterotomy in one) with variable periods of pain relief. Progression of symptoms, however, necessitated pancreatic resection in all. This was duodenum preserving in three, and a distal resection followed by completion pancreatectomy in two. Current pain status in this subgroup is improved in four and the same in one.

CASE 4

A 42 year old woman was referred with a nine year history of intermittent epigastric pain culminating in a presentation to hospital where a diagnosis of acute pancreatitis was recorded. The pain then became continuous, radiating through to the back and associated with nausea and vomiting. Her alcohol intake was unremarkable. ERCP showed pancreas divisum. Accessory duct sphincterotomy was performed with immediate improvement in symptoms. Her symptoms recurred, however, and one year later a duodenum preserving total pancreatectomy was carried out. Histology showed inflammatory changes of the parenchyma with periductal fibrosis and inspissated protein in the dilated ductules, as well as the subtle changes of the acini such as acinar atrophy and an increase in the centro-acinar cells. These changes were confined to the dorsal anlage.

Her symptoms were well controlled for some time but she has had two subsequent admissions for pain since. She currently works full time, and has regained all her lost weight but requires mild opiates for intermittent pain.

PANCREATIC HISTOLOGY

The histological features of the resected specimens were often subtle and out of proportion to stated clinical case history. Many of these changes did not affect the gland diffusely but rather focally and had to be examined with care.

In a number of cases (7) when the acinar cells appeared atrophied compared with normal glands (Fig 1) the zymogen granule content was reduced and, in addition, the cytoplasm was often finely vacuolated (Fig 2).

Evidence of chronic inflammation, such as lymphocytic cell infiltrate and intralobular or periductal fibrosis, was faint but was detected in 11 cases by careful examination. Focal ductal dilatation was observed in eight cases; in seven cases inspissated protein plugs were identified in the inflammed region of the gland. Areas of aggregated dilated ductules of varying calibre embedded in otherwise unremarkable exocrine pancreatic parenchyma were not uncommon (Fig 3). These foci or 'ductular complexes' give the impression of resulting from ductular proliferation but retention of their lobular configuration belies their origin from transformed acinar cells assuming acinar features.

Acinar cell nodules were observed in four cases (Fig 4). These are well demarcated areas composed of acinar cells possessing a pale eosinophilic cytoplasm devoid of zymogen

granules and small dense nuclei. On close sectioning most of these nodules were found in close association with islet cell tissue. The surrounding exocrine pancreatic tissue is unremarkable. Staining for a range of neurotransmitter substances showed calcitonin gene related peptide in three cases (Fig 5).

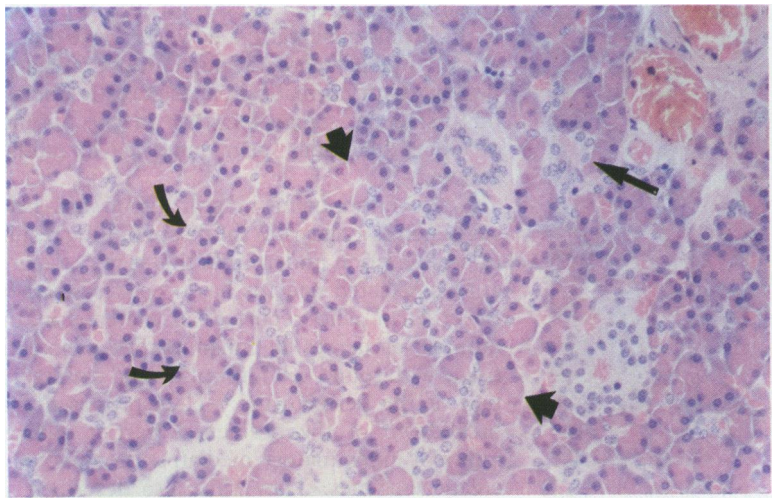

Figure 1: Normal pancreas showing normal acini (short arrows) with centro-acinar cells (curved arrows) and intercollated ductules (arrow).

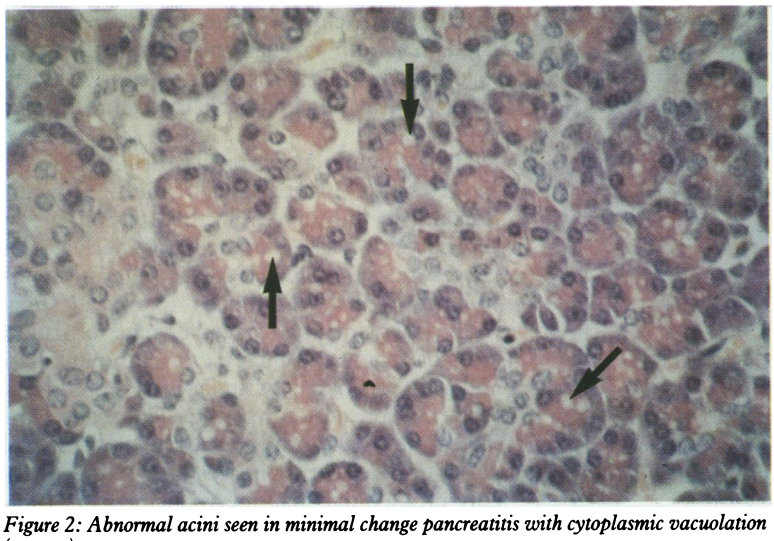

Figure 2: Abnormal acini seen in minimal change pancreatitis with cytoplasmic vacuolation (arrows).

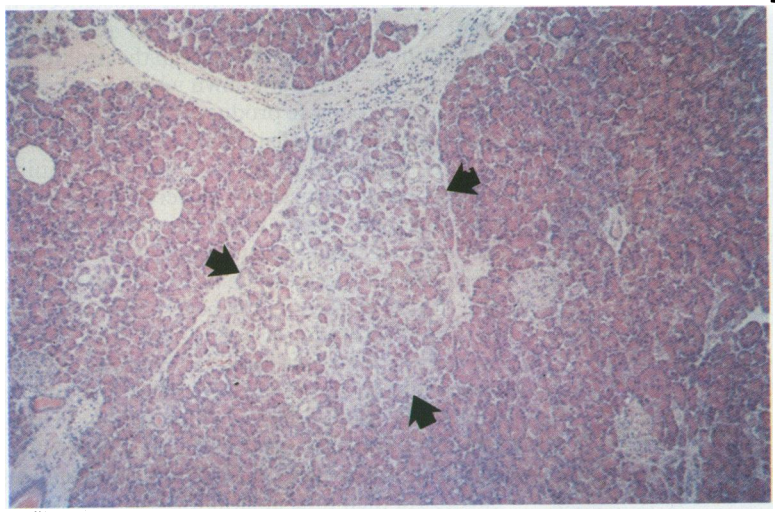

Figure 3: Duct complex formation (arrows) in an otherwise unremarkable pancreas resected for pain.

In eight specimens focal metaplasia of acinar cells to cells with features of ductular or centro-acinar cells was found (Fig 6). These metaplastic cells seem to replace partly the acinar cells and seem to 'take over' the acinus.

Discussion

The presence of a near normal pancreas at operation in conjunction with normal imaging casts doubt on the presence of significant disease, yet this study shows definite histological changes in 15 of the 16 patients in whom histological assessment was undertaken. It is accepted that the earliest changes in chronic pancreatitis are subtle histological findings and normal imaging.[5,6] As the disease progresses, changes may be identified on imaging, although symptoms range from minimal discomfort to severe chronic or relapsing pain.[6,7] In this syndrome, the morphological change is out of proportion to the severity of the pain.

Histological features of the normal pancreas and the severely diseased gland are well described but reports on the earliest changes in chronic pancreatitis are scant. Norohna *et al* described the changes seen in the pancreatic structure of asymptomatic alcoholics and which were considered as presaging chronic pancreatitis.[8] These included cytoplasmic fat inclusions, decreased zymogen granules, nuclear distortion, dilated endoplasmic reticulum, mitochondrial abnormalities, and increased numbers of lysosomes. In symptomatic patients, further changes have been described such as enlargement of acinar cells, osmiophillic bodies, and mitochondrial aberrations while ductule cells show dilated ER and prominent lysosomes.[9]

The most frequent findings in our series of patients were periductal fibrosis, duct dilatation, intralobular inflammation, and diffuse chronic inflammatory changes. Of considerable interest in those cases where there was no evidence of inflammation was the finding of ductular cells 'taking over' the acini (Fig 6). There seemed to be a progression from atrophy of the acini, to an increase in centro-acinar cells, to duct complex formation, and ultimately dilatation of the ductules. This has been described by some as the response of centro-acinar cells to obstruction.[10] In other areas ductular complexes were identified (Fig 3) which have been variously described as the attempt to repair the pancreas by regeneration of the ductal system through hypertrophy and hyperplasia[11] or alternatively, they may represent dedifferentiation of the acinar cell.[12] Similar lesions have been experimentally induced and are thought by some to be forerunners of certain pancreatic cancers.[13]

In some specimens there were circumscribed areas of acinar cells devoid of zymogen granules, changes described as acinar cell nodules or acinar nodular hyperplasia.[14] Similar lesions have been experimentally induced in the rat given azaserine and are thought to develop into acinar cell adenomata and acinar cell carcinomas.[15] Most of these were found in close association with islet cell tissue but we have also seen them in association with islet cell tumours. Hormonal influences may therefore play a role in their genesis. It

is unlikely that these lesions are a forerunner of acinar cell carcinoma in the human, given their frequency in the normal pancreas and the rarity of acinar carcinoma in the pancreas.

The cause of pain in chronic pancreatitis is unclear but it is emerging that several mechanisms are involved. A close correlation has been described between pain and pancreatic tissue pressure.[2] A drop in tissue pressure after surgery corresponded with relief of pain, and a rise in pressure was shown in those with recurrence of symptoms. Intraduct pressures are higher in patients with dilated ducts,[16] and are higher in patients with painful pancreatitis than in those in whom it is painless.[2 3] Less than 50% of patients with chronic pancreatitis, however, have dilated ducts.[17] Furthermore, the outcome of drainage in patients with normal calibre pancreatic ducts is unsatisfactory suggesting that in the absence of duct dilatation, pain must have another aetiology.[18]

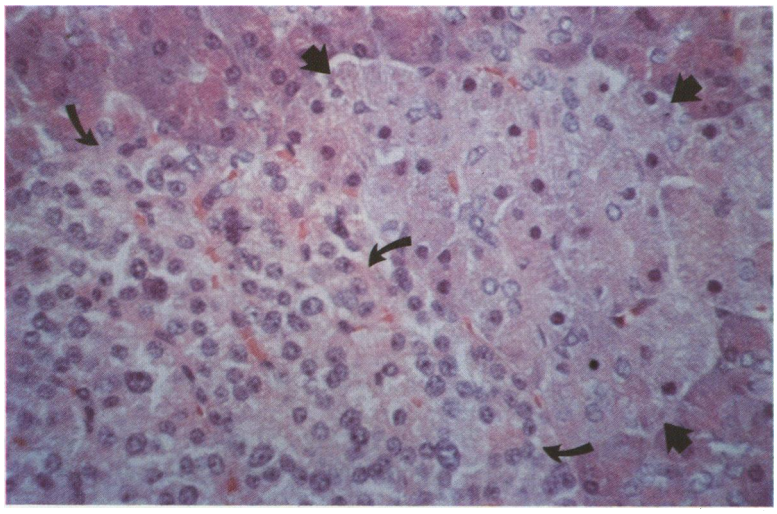

Figure 4: Acinar cell nodule (arrows) in close association with an islet of Langerhan's (curved arrows) in a painful but otherwise unremarkable pancreas.

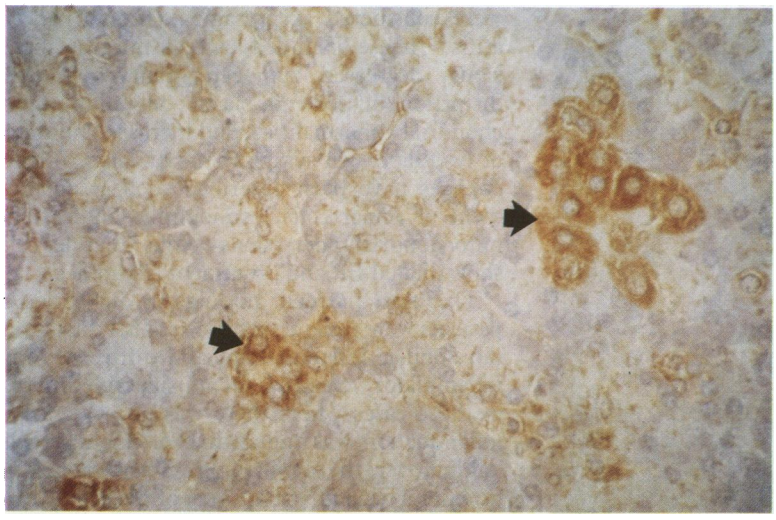

Figure 5: Focal positive staining (arrows) for calcitonin gene-related peptide (CGRP). The immunoreactive cells were identified as metaplastic ductular and centro-acinar cells in adjacent sections stained with (haematoxylin and eosin).

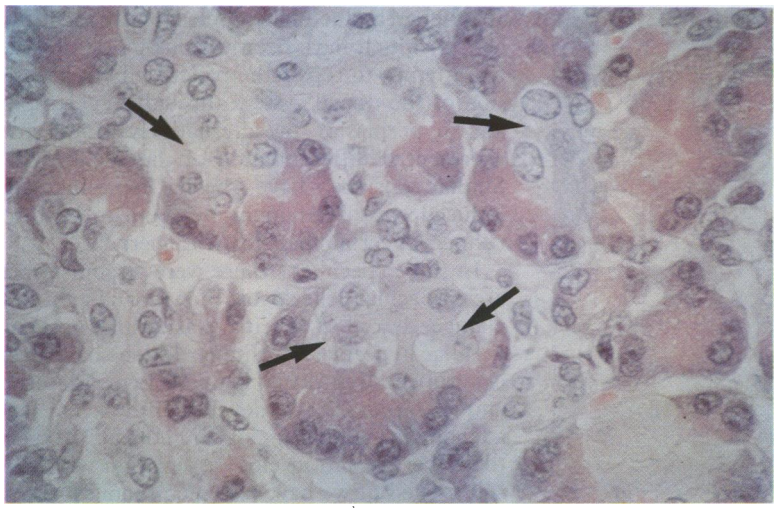

Figure 6: Duct proliferation with partial replacement of the acini by ductular and centro-acinar cell metaplasia (arrows).

Nerve entrapment in scar tissue has been suggested as a cause but the disappointing results of nerve section undermines this view.[19] Pancreatitis associated neuritis has been described by Beger *et al* who reported an increase in the number of nerves in inflammatory pancreatic tissue with round cell infiltration and disintegration of the perineurium.[4] They proposed that breakdown of the perineural barrier allowed influx of inflammatory mediators or active pancreatic enzymes. They have also described an increase in substance P, a powerful mediator of pain and inflammation, and calcitonin gene related peptide within sensory nerve fibres in patients with chronic pancreatitis. Ihse postulated that both mechanisms may in fact work together with high tissue pressures facilitating influx of inflammatory cell mediators into the cell.[1]

More recently attention has been focused on the complex interaction of multiple neurotransmitter substances in the periphery and centrally.[20] A cocktail of mediators derived from nerves, immune cells, fibroblasts etc, is thought to be involved.[21 22] Staining of pancreatic tissue from patients with advanced changes of pancreatitis has shown an increase in both neural and endocrine elements with a marked immunoreactivity for serotonin in the islet tissue, within the epithelium of proliferated ductiles, in single nerve fibres of larger nerves, and within markedly proliferated small nerve elements (J Rode, unpublished observations). When specimens of minimal change pancreatitis were stained for a wide range of neurotransmitter substances, the most significant finding was the presence of calcitonin gene related peptide in the proliferated ductule cells. It is not known whether calcitonin gene related peptide produces pain directly or by inhibiting the degradation of substance P.[23]

It is suggested that patients with minimal change pancreatitis have suffered a significant morphological injury at cellular level such that the pain mechanisms associated with the paracrine and neurocrine systems have been damaged and trigger changes in the nerves which give rise to the pain stimulus. It seems that these changes are diffuse and unrelated to changes in main pancreatic duct pressure as illustrated by the ineffectiveness of drainage procedures in these patients. Similarly, partial resection, especially if the head of the pancreas is retained, seems less successful than total ablation.

The management of these patients is primarily conservative as illustrated by operative interven-

tion in only 16 of the 43, but when operation is indicated surgical resection is preferred to drainage, and logically total resection is preferable to partial resection because of the diffuse changes within the pancreas.

1 Ihse I. Pancreatic pain. *Br J Surg* 1990; **77**: 121–2.
2 Okazaki K, Yamomoto Y, Kagiyama S, Tamura S, Sakamoto Y, Nakazawa Y, *et al.* Pressure of papillary zone and pancreatic main duct in patients with chronic pancreatitis in the early state. *Scand J Gastroenterol* 1988; **23**: 501–6.
3 Ebbohøj N, Borly L, Bülow J, Rasmussen SG, Madsen P. Evaluation of pancreatic tissue fluid pressure and pain in chronic pancreatitis – a longitudinal study. *Scand J Gastroenterol* 1990; **25**: 462–6.
4 Beger HG, Buchler M, Bittner R. The duodenum preserving resection of the head of the pancreas (DPRHP) in patients with chronic pancreatitis and an inflammatory mass in the head – an alternative surgical technique to the Whipple operation. *Acta Chir Scand* 1990; **156**: 309–15.
5 Gyr KE, Singer MV, Sarles H. *Pancreatitis: concepts and classification.* Amsterdam: Excerpta Medica, 1984.
6 Sarner M, Cotton PB. Classification of pancreatitis. *Gut* 1984; **25**: 756–9.
7 Axon ATR. Endoscopic retrograde cholangiopancreatography in chronic pancreatitis. Cambridge classification. *Radiol Clin North Am* 1989; **27**: 39–50.
8 Norohna M, Dreiling DA, Bordalo O. Sequential changes from minimal pancreatic inflammation to advanced alcoholic pancreatitis. *Z Gastroenterol* 1983; **21**: 666–73.
9 Tasso F, Stemmelin N, Searles H, *et al.* Comparative morphometric study of the human pancreas in its normal state and in primary chronic calcifying pancreatitis. *Biomedicine* 1973; **18**: 134–44.
10 Porta EA, Stein AA, Patterson P. Ultrastructural changes of the pancreas and liver in cystic fibrosis. *Am J Clin Pathol* 1964: **42**: 451–65.
11 Norohna M, Bordalo O, Dreiling DA. Alcohol and the pancreas II. Pancreatic morphology of advanced alcoholic pancreatitis. *Am J Gastroenterol* 1981; **76**: 120–4.
12 Bockman DE, Boydston WR, Parsa I. Architecture of human pancreas: implications for early changes in pancreatic disease. *Gastroenterology* 1983; **85**: 55–61.
13 Takahashi M, Arai H, Kokubo T, Furukawa F, Kurata Y, Ito N. An ultrastructural study of precancerous and cancerous lesions of the pancreas in Syrian hamsters induced by N-nitrosobis (2-oxopropyl) amine. *Gan No Rinsho* 1980; **71**: 825–31.
14 Oertel JE. The pancreas: non-neoplastic alterations. *Am J Surg Pathol* 1989; **13** (suppl 10): 50–65.
15 Longnecker DS, Curphey TJ. Adenocarcinoma of the pancreas in azaserine-treated rats. *Cancer Res* 1975; **35**: 2249–58.
16 Bradley EL. Pancreatic duct pressures in chronic pancreatitis. *Am J Surg* 1982; **144**: 313–6.
17 Sato T, Miyashita E, Matsuno S, Yamauchi H. The role of surgical treatment of chronic pancreatitis. *Ann Surg* 1986; **203**: 266–71.
18 Way LW, Gadacz T, Goldman L. Surgical treatment of chronic pancreatitis. *Am J Surg* 1974; **127**: 202–9.
19 White TT, Slavotinek AH. Results of surgical treatment of chronic pancreatitis: report of 142 cases. *Ann Surg* 1979; **189**: 217–24.
20 Buchler M, Weihe E, Friess H, Malfertheiner P, Bockman E, Muller S, *et al.* Changes in peptidergic innervation in chronic pancreatitis. *Pancreas* 1992; **7**: 183–92.
21 Weihe E. Neuropeptides in primary sensory neurones. In: Zenker W, Neuhuber W, eds. *The primary afferent neurone – a survey of recent morpho-functional aspects.* New York: Plenum Press, 1990.
22 Lotz M, Vaughan JH, Carson DA. Effect of neuropeptides on the production of inflammatory cytokines by human monocytes. *Science* 1988; **241**: 1218–21.
23 Nyberg F, Legrevos P, Terenius L. Modulation of endopeptidase activity by calcitonin gene-related peptide: a mechanism affecting substance P action? *Biochimie* 1988; **70**: 65–8.