Hereditary pancreatitis in England and Wales¹

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SUMMARY Information from 72 patients from 7 families in England and Wales confirms that hereditary pancreatitis is inherited as an autosomal dominant condition with limited penetrance. The degree of penetrance is approximately 80%. These patients have had recurrent attacks of abdominal pain starting from childhood or young adult life. The mean age of onset in the 7 families studied was 13.6 years. There were two peaks, with maximum numbers at 5 years and 17 years. The second peak was thought to represent genetically susceptible individuals having pain brought on by alcohol rather than representing evidence of genetic heterogeneity. Five of the 7 families had members with both childhood and adult ages of onset. Only 4 patients out of 72 had life-threatening disease and in the majority of cases the attacks of pain were of nuisance value only. Hereditary pancreatitis was implicated in only 1 patient's death and this was not definite. Patients appear to get better after a period of symptoms usually as they approach middle age, or after a severe attack. In older patients alcohol, emotional upsets, and fatty food appear to precipitate attacks. Pancreatic insufficiency (5.5%), diabetes mellitus (12.5%), pseudocysts (5.5%), and haemorrhagic pleural effusion are uncommon complications. Portal vein thrombosis occurred definitely in 2 patients and was suspected in 3 others. Carcinoma of the pancreas was not found in any of 72 patients studied in detail; however, 2 members from a family not visited personally had chronic pancreatitis and malabsorption going on to carcinoma. They may have suffered from a different disease.

Genetic linkage information was too slight for many definite conclusions. However, there was no suggestion of linkage with any of the markers tested.

Hereditary pancreatitis was first described by Comfort and Steinberg (1952), from the Mayo Clinic. They described a family with 4 definite and 2 suspected cases of chronic relapsing pancreatitis starting in childhood or young adult life. The pattern of inheritance appeared to be an autosomal dominant one with incomplete penetrance. Four other families were described in the ensuing years from the Mayo Clinic (Gross and Comfort, 1957; Gross, 1958; Gross *et al.*, 1962). The findings in those families confirmed the dominant mode of inheritance of the condition and the early age of onset of the attacks of pain. Gross *et al.* (1962) reported in addition that 4 of these 5 families had aminoaciduria. Most of their work on this was confined to one family (the K kindred) who appeared to have a lysine-cystine aminoaciduria.

The first family described outside the Mayo Clinic was reported by Cornet *et al.* in 1962 from Nantes in France. Information on another family from the United States was published soon after (Gerber, 1963) and since then there have been over 35 families reported in the world literature. These families have come from all over the world; however, apart from the Indian family of Choudhry *et al.* (1971) all have come from patients of European ancestry. There have been two relatively recent reviews of the condition from the United States by McElroy and Christiansen (1972) and Kattwinkel *et al.* (1973).

The only reports of hereditary pancreatitis from the United Kingdom have been by Nash (1971) and a large family from Newcastle (Sibert, 1975). A study was made on these and other families in England and Wales to investigate the natural history of the condition, the evidence for genetic heterogeneity, the pattern of inheritance, and the urine amino acids. A

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genetic linkage study using blood and saliva markers was also undertaken.

Patients and methods

Nine families were ascertained in England and Wales (by correspondence with paediatricians, paediatric surgeons, and physicians and surgeons with a known interest in pancreatic disease). Seven of these were studied in depth and visited personally. Two other small families with only 2 affected members were not because most family members were dead.

As many family members were visited as possible, including all the known affected members in the first 7 families in the United Kingdom. Full information was obtained from hospital and general practice records as necessary. A full history was obtained and if clinically indicated the patients were examined. Urine was taken for amino acid chromatography. Blood and saliva was taken for genetic marker studies. Some patients had serum lipoprotein estimations (if Type I or V hyperlipoproteinaemia had not been excluded) and some patients had serum alpha-1-antitrypsin estimated.

The patients were divided into those with definite pancreatitis, and those suspected of having the disease. Those with definite pancreatitis (32 cases) had been diagnosed as such by their doctors on the basis of operation findings, a significantly raised serum amylase level, or radiographic pancreatic calcification. Patients with suspected pancreatitis were at risk genetically of developing the disease and had histories of recurrent abdominal pain typical of the disease in periodicity, site, and age of onset.

FAMILY DETAILS

Brief details of the individual families together with family trees follow. Details of the individual patients have been put together in the Appendix.

Discussion and analysis of results

(A) GENERAL CLINICAL FINDINGS FROM THE FAMILIES

Patients with hereditary pancreatitis have variable attacks of abdominal pain lasting from two days to a week or longer, which are usually associated with vomiting. The pain is epigastric or central and may radiate to the back. A feature is the early age of onset, usually in childhood or young adult life. In 65 patients in this series on whom there is sufficient information the mean age of onset is 13.6 years. This is similar to the families of Kattwinkel *et al.* (1973), and other published series. Some patients start their attacks of pain in early childhood under the age of 5 years, and often go on to have severe disease. Some patients are

free of pain until adult life; perhaps the most striking was II.4 in the K. family (Fig. 1), a woman who did not have pain until she was 60 years old and had pancreatitis diagnosed when she was 82.

An almost constant feature in England and Wales is the improvement of symptoms with increasing age. Indeed if the attacks start in childhood patients have few after the age of 30, and if the attacks start in adult life they get better after about 20 years of symptoms. There is some evidence also that patients who have a very severe attack of pancreatitis may have few attacks afterwards. For instance, III.2 in the Sm. family (Fig. 2) had a severe attack when she was 15 years old and has had no attacks since.

The evidence from the families of McElroy and Christiansen (1972), Kattwinkel *et al.* (1973), and the present study suggests that hereditary pancreatitis is a more benign disease than was apparent from the early reports.

Only a few patients have had serious problems, and the majority have had symptoms which would be best described as a nuisance only. IV.4 in the H. family (Fig. 3) and IV.9 in the Du. family (Fig. 4) have had serious incapacitating disease needing surgical intervention. IV.23 in the H. family (Fig. 3) and III.2 in the Sm. family (Fig. 2) have also had serious disease but have improved as they reached adult life. III.11 in the K. family (Fig. 1) died of what was said to be a perforated duodenal ulcer on coroner's necropsy. Her pancreatitis may have been a factor in her early death. However, apart from this case no patient has died from the disease in the 7 families in this series. Most of the children with hereditary pancreatitis appear to thrive between attacks and have a good appetite. Indeed, some are slightly obese (for example, IV.29 in the H. family).

(B) CLINICAL FINDINGS (EXACERBATING FACTORS AND TREATMENT)

Children with hereditary pancreatitis do not have obvious exacerbating causes for their attacks of pain. However, with adults attacks have been precipitated by alcohol (for example, family Se. III.4 and 7 (Fig. 5)), or worry, or emotional upset (for example, III.1 in the Co. family (Fig. 6) who had a bad attack of pain at the time of his father's death). Occasionally patients have had attacks during reducing diets; however, it may be that stress rather than starvation is the important factor here. Several patients from several families have felt that fatty food has brought on pain and some have limited their fat intake because of this. Some patients have been thought to have had less pain after being either put on low fat diets (family H. IV.23 (Fig. 3) and family B. IV.9 (Fig. 7)) or pancreatic supplements (family B. II.4) by their medical advisers. Sarles and Gerolami-Santandrea (1972) believe that

Fig. 1 K. family. 13 cases (6 males, 7 females). Mean age of onset 18 years. Ascertained by my inquiry of physicians with an interest in pancreatic disease. The proband is a patient of Dr Eric Cox of Reading. This family originates from the Islington area of London. The majority of family members still live in the Greater London area.

regular pancreatic supplementation may prevent attacks of pain in chronic pancreatitis even when there is no frank malabsorption. On the limited evidence available, there is some justification in treating patients with hereditary pancreatitis who are having frequent attacks with pancreatic supplements. Patients should certainly be advised not to take alcohol in anything but small quantities.

(C) CLINICAL FINDINGS (COMPLICATIONS)

Diabetes mellitus appears an uncommon complication of hereditary pancreatitis. Of the 72 patients from the 7 families, only 9 patients had diabetes mellitus. One of these only developed diabetes mellitus

after a total pancreatectomy. The 2 members of the H. family with diabetes had a strong family history of this condition in their paternal family (their mothers having had the pancreatitis gene). Similar considerations apply to the B. family. This supports the work of Kattwinkel *et al.* (1973) that the incidence of diabetes in hereditary pancreatitis is not significantly different from the general population.

Malabsorption also appears to be an uncommon complication of hereditary pancreatitis. Only 4 patients in the 7 families have definite pancreatic insufficiency; one of these had a total pancreatectomy and the other 3 were all from one family (the B. family). The two members of the non-visited Hu. family had pancreatic insufficiency and they may represent a separate disease entity. Calcification of the pancreas was found in 7 patients and was also found in the 2 members of the E. family (Fig. 9) from Liverpool. However, only a minority of patients have had x-rays of the abdomen so a true incidence of calcification cannot be estimated in this series.

Pseudocyst of the pancreas also occurs infrequently from the evidence available, and was only found definitely in 4 patients. Haemorrhagic pleural effusion secondary to the pancreatitis was also found in 4 patients. This complication is less common in British families than in the French family of Bon (1971).

Portal vein thrombosis and gastrointestinal bleeding was found in the 2 most badly affected patients in this series (IV.2 in the H. family and III.9 in the Du. family). In addition 3 other patients had unexplained gastrointestinal bleeding. Longstreth *et al.* (1971) and McElroy and Christiansen (1972) also found portal

Fig. 2 Sm. family. 8 cases (5 males, 3 females), 4 definite, 4 suspected. Mean age of onset 8 years. This family was described by Dr F. Nash of Brighton (1971). They originated from the South London area and there are members in Chelmsford, Crawley, St. Ives, and Exeter.

Fig. 3 H. family: 24 cases (9 males, 15 females), 10 definite cases, 14 suspected. Mean age of onset 11 years. This is the original family studied in Newcastle, with family members in Newcastle, the Midlands, Western Australia, Kent, and Italy. Originated from Bishop Auckland area of County Durham. The proposita is a patient of Dr Christine Cooper described previously (Sibert, 1975).

Fig. 4 *Du. family*. 10 cases (4 males, 6 females), 3 definite, 7 suspected. Mean age of onset 12.5 years. Ascertained by my inquiry of paediatric surgeons. The proband is a patient of the Surgical Unit at the Bristol Royal Infirmary. The majority of the family live in Birmingham and the West Midlands and they originate from there.

Fig. 5 *Se. family*. 7 cases (4 males, 3 females), 3 definite, 4 suspected. Mean age of onset 14.5 years. The proband is a patient of Dr P. T. Bray. Originated from Pontypridd and all family members live there or in the Cardiff area.

Fig. 6 *Co. family*. 3 cases (2 males, 1 female), 2 definite, 1 suspected. Mean age of onset 31 years. The proband is a patient of Mr H. O. Jones. They originate from and live in the Cardiff area.

vein thrombosis in hereditary pancreatitis. It may be that hereditary pancreatitis patients are more liable to this complication than other patients with chronic relapsing disease.

There were no definite cases of carcinoma of the pancreas in the 7 British families with typical hereditary pancreatitis. The only possibility was I.2 in the Co. family who probably had carcinoma of the stomach. II.1 and II.2 in the Hu. family both died from carcinoma of the pancreas; however, it is likely that they had a different disease from the other families studied, with less pain and more pancreatic insufficiency. The evidence available suggests that the risk of carcinoma of the pancreas in typical hereditary pancreatitis is probably small.

(D) CLINICAL FINDINGS (AMINOACIDURIA)

No significant aminoaciduria was found in the 7 families visited personally. Some patients particularly in the Du. and K. families had mild abnormalities of tyrosine or leucine, isoleucine, and valine. However, these changes were never more than slight and many of the patients in these families had normal amino acids. Lysine and cystine, as found in the original Mayo Clinic families, were never found in the urine of patients in the 7 families. Amino acid findings in the urine are notoriously affected by diet and there may also be common mild inherited abnormalities. Experience in paediatrics has shown that many patients have mild abnormalities in their urine amino acids of no significance. II.1 of the E. family is the only British patient I am aware of who has any significant aminoaciduria. These findings support the view taken by

Fig. 7 *B. family*. 7 cases (3 males, 4 females), 6 definite, 1 suspected. Mean age of onset 13 years. Ascertained by my inquiry of paediatricians in England and Wales. The propositus is a patient of Dr R. Hallett. They originate from Gateshead, Co. Durham, and have family members in the North East of England and the Portsmouth area.

Fig. 8 *Hu. family*. Not visited personally. 2 cases, both definite (1 male, 1 female), both dead, who were patients at the Central Middlesex Hospital.

Fig. 9 *Other family not visited personally. E. family*. Two cases, both definite (both male), one of whom has died, from Liverpool. The propositus is a patient of Professor A. Price-Evans and Dr R. B. McConnell.

Kattwinkel *et al.* (1973) and Riccardi *et al.* (1975) that hereditary pancreatitis and aminoaciduria are not associated.

(E) AETIOLOGY

An abnormality in the pancreatic ducts would be an attractive aetiological theory for hereditary

pancreatitis; however, the evidence in the literature and in this study has been conflicting and inclusive. Most of the information comes from those patients who had the severest disease and who came to surgery, and whose changes may well have been secondary to the pancreatitis and not the cause of it. For instance, there was irregular dilatation of the pancreatic ducts in one of the patients of Comfort and Steinberg (1952), and similar changes were found by Gerber (1963) and by other authors. Robeck (1967) found dilated ducts with hypertrophy of the sphincter of Oddi in 2 of his patients. They improved after sphincterotomy; however, 2 of the patients of McElroy and Christiansen (1972) also had apparent hypertrophy of the sphincter but were not improved by the operation. The ducts were normal in 3 of the patients of Gross and Comfort (1957).

The only definite duct abnormality found has been in the family of Cornet *et al.* (1962) (later brought up to date by Bon (1971)). The operative pancreatograms clearly showed dilated pancreatic ducts in all the patients operated on (14 cases). There was no evidence of obstruction and the degree of dilatation makes it unlikely these were secondary changes. The early age of onset, high incidence of malabsorption, and pleural effusion makes this family unusual in several ways.

Three patients had pancreatograms in the present series; one showed normal ducts (H. family IV.2), one a possibility of minor narrowing at the ampulla (H. family IV.23), and one an irregular structure of the duct of Wirsung 4 to 5 cm from the ampulla, probably secondary to inflammation (Du. family III.9). Definite information on the aetiology of hereditary pancreatitis

Fig. 10 Numbers of patients with individual ages of onset.

will probably await endoscopic retrograde pancreatographic studies on patients who have relatively mild symptoms.

There have been two other aetiological theories for hereditary pancreatitis. Moretti and Nusslé (1971) suggested that an abnormally viscous pancreatic juice may be responsible. Adham *et al.* (1968) found a reduced serum trypsin binding activity in some of their patients; however, there were no significant abnormalities of alpha-1-antitrypsin in 16 patients of the present series.

(F) GENERAL GENETIC CONSIDERATIONS

The family trees from the 7 families studied in detail from England and Wales confirm the autosomal dominant mode of inheritance of hereditary pancreatitis. The incomplete penetrance of the gene found in other families throughout the world has also been confirmed. For example in the H. family, III.8, II.7, and II.8 clearly carry the pancreatitis gene but have never had symptoms. Indeed, the disease is extremely variable between family members. In the Du. family, IV.7 has had severe attacks of pain from the age of 4 years; however, her father III.3 has had only attacks of mild discomfort which he felt were hardly worth mentioning. There is no evidence of a sex-linked gene. Males and females are approximately equally represented (males 33, females 39), and there is no difference in the severity of the disease between the sexes. Moreover there are many instances of male-to-male transmission.

The age of onset of symptoms of the patient is diagrammatically represented in Fig. 10. The mean age of onset is 13.6 years though there are clearly two peaks. One peak is between the ages of 3 and 7 years with a maximum of 9 cases with an age of onset at 5 years. There is another smaller peak between 16 and 19 years, with 5 cases with an age of onset at 17 years. This second smaller peak is probably not evidence of genetic heterogeneity but because patients first take alcohol in quantity at about this age. Several of the cases with ages of onset at this time had attacks after alcohol, and alcohol may bring out the inherited tendency that would not have perhaps manifested itself until later in life. Fig. 11 shows that 81% of patients have developed symptoms before 20 years of age. Sarles (1973) stated that with the possible exception of the family of Nash (Sm. family in this series) adult onset cases had not been observed in the same families as the childhood onset cases. The oldest age of onset in the Sm. family is 17 years. Nevertheless, the H. family, the B. family, the Du. family, the K. family, and probably the Se. family all have members with onset in both age groups. Indeed the 7 families studied and the family from Liverpool appear to suffer from the same genetic disorder. There are many similarities and the differences between families are no greater than the within-family variation. There is some evidence of genetic heterogeneity, however, with the family of Dr Sheila Waller of the Central Middlesex Hospital whose members had chronic pancreatitis with relatively little pain, finally dying of carcinoma of the pancreas.

Fig. 11 Percentage of patients with hereditary pancreatitis developing symptoms at individual ages.

In an attempt to find the degree of the penetrance of the hereditary pancreatitis gene, sibships with one or more patients with hereditary pancreatitis were studied to find how many had affected parents. Of 21 sibships with definite information there were 3 with non-affected parents, giving a penetrance of 86%. However, if the 4 parents with only very mild symptoms are added to this total, a penetrance for the gene of 71% is obtained. The exclusion of cases where there was no definite information may have overestimated the penetrance of the gene. For instance, I.1 and I.2 of the H. family, B. family, and Du. family are not remembered as having abdominal pain. If sibships with these parents are included, together with sibships from the Sm., Se., and Co. families where I.1 and I.2 probably did have abdominal pain, there are 27 sibships with 6 non-affected parents. This gives a penetrance of 77% (or 63% if very mildly affected patients are included). Together the evidence suggests the penetrance for the gene is approximately 80%.

Riccardi *et al.* (1975) have suggested that the morphine prostigmine test should be used for genetic counselling, provoking attacks of pain in patients who have the gene but no symptoms. I have no personal experience with this; however, I doubt if it would often be of value and might be potentially dangerous if a severe attack was produced. A full history from the patient and close relatives may reveal mild symptoms in the past and is essential for adequate genetic counselling for patients with this condition. The mild nature of many patients' symptoms, the improvement

of the condition with age, and the relatively low complication rate, make the outlook for a parent with the condition rather brighter than the 4 chances out of 10 risk of a child being affected might make it appear.

It is disappointing not to have found more families in England and Wales with the condition, despite correspondence with many doctors of varying disciplines. However, there is evidence that, though a rare condition, it may be more common than realised. Of the one area searched comprehensively (the South Glamorgan area), two apparently unrelated families were found. This is in the relatively small population of the order of 400 000. Similarly in Newcastle with a less comprehensive search there were two families again apparently unrelated. If this sort of incidence were repeated throughout England and Wales there would be many more than 7 families.

(G) GENETIC LINKAGE STUDIES

Genetic linkage studies were undertaken with the help of Dr Derek Roberts and his staff at the Department of Human Genetics, Newcastle-upon-Tyne. Blood was analysed for standard genetic markers and saliva for secretor status. Similar information on two further patients from the K. family was obtained from Dr Peter Cook at the Galton Laboratory, University College London. The information was too slight for many definite conclusions. However, there was no suggestion of linkage between the hereditary pancreatitis gene and any of the markers tested. Indeed, at recombination scores of 0.05 and 0.1

linkage was disproved with the hereditary pancreatitis gene and the MNSs locus, and at a recombination score of 0.05 linkage was disproved with the hereditary pancreatitis gene and Rhesus, Kidd, acid phosphatase, phosphoglucomutase 1, and haptoglobin loci. Full details are available on request.

I thank all the doctors who have given me information on their patients, particularly those who let me know about the families. I am grateful to Dr Derek Roberts and his staff at the Department of Human Genetics, Newcastle, for performing genetic marker work and for their help, and to Dr Peter Cook of the Galton Laboratory for information on the K. family and help with the genetic marker work. I thank Dr Percy Bray, Dr John Dodge, Professor O. P. Gray, and Dr Peter Harper in Cardiff for their help and advice.

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Appendix

Case	Sex	Definite or suspected	Age of onset (yr)	Improvement with age	?Diabetes	?Calcification
<i>H. Family</i>						
II.1	F	Suspected	*	*	*	*
III.1	M	Suspected	16	Yes; no attacks since 40	No	No
IV.1	F	Suspected	15	Yes; no attacks since 30	No	No
V.2	M	Suspected	8	Too young	No	No
IV.2	M	Definite	20	Yes; no pain since 29	No	Yes
III.2	M	Definite	35	Yes; no pain since 42	Yes	Yes
IV.7	F	Suspected	6	Yes; few pains since 78	No	No
V.9	M	Suspected	10	Too young	No	*
IV.8	F	Definite	16	Yes; no pain since 25	No	No
V.13	F	Definite	6	Too young	No	No
IV.9	F	Suspected	17	Yes; no pain since 25	No	*
IV.10	F	Suspected	17	Yes; pain better since 25	No	*
IV.13	F	Suspected	20	*	No	*
II.5	M	Suspected	10	Better since 50 years	No	*
III.6	M	Suspected	7	Better since twenties	No	No
III.7	M	Definite	5	Yes; no pain since 32	No	No
IV.22	F	Definite	5	Too young	No	No
II.6	F	Suspected	10	Probably	No	*
IV.23	F	Definite	3	Yes but has had surgery	No	No
III.10	F	Suspected	4	Yes; few attacks since 30	Yes	*
III.11	M	Definite	17	Yes; still gets pain but better	No	No
III.12	F	Definite	16	No (but still only 29)	No	No
IV.29	F	Definite	5	Too young	No	No
IV.20	F	Suspected	3	Probably	No	*
<i>Sm. Family</i>						
I.1	M	Suspected	*	Probably none after after middle age	No	*
II.1	M	Suspected	12	Yes; few pains since 28	No	No
III.1	F	Definite	4	Better since 22	No	No
III.2	F	Definite	4	Yes; few attacks since 15	No	No
II.2	M	Definite	6	Yes; no attacks since 50	Yes	Yes
III.4	M	Suspected	17	Not really, but only 27	No	*
IV.2	F	Suspected	9	Too young	No	*
II.3	M	Definite	6	Yes; none since 30	No	Yes
<i>B. Family</i>						
II.1	M	Definite	5	Yes; none since 30	Yes	No
III.3	F	Definite	28	Possibly; none for 1 year	No	No
III.4	F	Definite	6	Yes; no pain since 20	No	No
IV.9	F	Definite	3	Too young	No	No
II.4	M	Definite	43	Pain free last 3 years, and started on Pancrex	Yes	No
III.15	F	Suspected	2	Yes; none since 14	Yes	No
II.6	M	Definite	6	Relatively pain free last 5 years	Yes	No
<i>Se. Family</i>						
I.1	M	Suspected	*	Probably	*	*
II.2	F	Suspected	45	*	*	*
III.4	M	Definite	7	No, but only 25 years	No	No
II.2	M	Suspected	5	Probably	No	No
III.6	F	Suspected	11	Less frequent last 2 years	No	No
III.7	M	Definite	14	Too young	No	No
III.8	F	Definite	5	Too young	No	No
<i>Du. Family</i>						
II.1	F	Suspected	7	Yes; no pains since 20	No	*
III.2	M	Suspected	27	Yes; no pains since 42	No	*
III.3	M	Suspected	25	No	No	*
V.7	F	Definite	4	Yes; no pains for 2 years	No	Yes
II.5	F	Suspected	*	Yes probably	No	*
II.6	M	Definite	5	Yes; no attacks since 13	Yes	No
III.6	F	Suspected	32	No	No	*

Diagnosed by	Exacerbation by	Amino acids	Comment
*	*	*	
*	Worry; ?starvation	*	
*	*	*	
Laparotomy	Alcohol	Normal	Severe pain; portal vein thrombosis; pseudocyst; pleural effusion
Calcification	Worry	Normal	
*	No obvious factor	Normal	
*	*	Normal	
Amylase	Worry	Normal	
Amylase	No obvious factor	Normal	
*	No obvious factor	Normal	
*	No obvious factor	Normal	
*	*	Normal	Little information
*	*	*	
Amylase	Alcohol	Normal	Unexplained gastrointestinal bleeding
*	No obvious factor	Mild amino-aciduria	
Amylase	No obvious factor	Normal	
*	*	*	
Amylase, laparotomy	No obvious factor	Normal	Vague information
*	No obvious factor	Normal	Perhaps better on low fat diet
Amylase, laparotomy	Alcohol	Normal	Pleural effusion
Amylase	Worry perhaps	Normal	
Laparotomy, amylase	?fatty food	Taurine and tyrosine excess	Rather obese
*			Gastrointestinal bleeding, unexplained
*	*	*	
*	Worry and fatty food	Normal	
Amylase	Alcohol and worry	Normal	
Amylase	No obvious factor	Normal	Pleural effusion; very ill once
Calcification	No obvious factor	Normal	Worse attacks 30–50
*	Worry	Normal	
*	No obvious factor	Normal	
Calcification	Fatty food	Normal	
Laparotomy	Alcohol	Normal	
Laparotomy	Emotion and fatty food	Normal	Bad pain at breakup of 1st marriage
Laparotomy	Emotion	Normal	Pancreatic insufficiency
Amylase	No obvious factor	Normal	?Better on low fat
Laparotomy	No obvious factor	Normal	Attacks lasted longer than 1 week; pancreatic insufficiency
*	No obvious factor	Normal	
Pancreatic insufficiency	No obvious factor	Normal	Still gets attacks of pain; pancreatic insufficiency
*	*	*	
*	*	*	
Amylase	Alcohol; ?worry	Normal	No attacks since on low fat diet (6 mths)
*	*	Normal	
*	Worry; ?alcohol	Leucine, iso-leucine slightly raised	
Amylase	Alcohol	Tyrosine and valine slightly raised	
Amylase	No obvious factor	Tyrosine slightly raised	
*		Slightly raised leucine/isoleucine	Mild attacks
*	Worry	Tyrosine slightly raised	Mild attacks
		Tyrosine slightly raised	Mild attacks
Calcification	Emotional upsets and fatty food	Tyrosine slightly raised	Severe attacks
Laparotomy		Normal	Information very vague, died many years ago
*	Dieting	Slightly raised leucine, isoleucine, and tyrosine	1 severe attack; none since Mild attack only

Appendix—continued

Case	Sex	Definite or suspected	Age of onset (yr)	Improvement with age	?Diabetes	?Calcification
IV.10	F	Suspected	4	No, but not old enough	No	*
III.8	F	Suspected	5	Better since 25	No	*
III.9	M	Definite	4	Yes, after total pancreatectomy	Yes	Yes
<i>K. Family</i>						
II.2	M	Suspected	*	*	*	*
III.6	M	Suspected	*	*	*	*
II.4	F	Definite	60	No pain since age 81	No	No
III.9	M	Suspected	25	Yes, less since age 55	No	No
IV.8	F	Definite	11	Yes, better since 28	No	No
V.4	F	Suspected	5	Yes	No	No
V.6	F	Suspected	4	Too young	No	No
IV.9	F	Suspected	26	No	No	*
V.7	M	Suspected	6	Too young	No	*
III.10	F	Definite	31	Yes, none since 41	No	*
V.11	M	Suspected	8	Too young	No	*
III.11	F	Definite	6	Yes probably	No	No
III.12	M	Suspected	18	Yes probably	No	*
<i>Co. Family</i>						
III.1	M	Definite	17	Too young	No	No
II.1	M	Definite	45	No	No	Yes
I.2	F	Suspected	*	*	No	*
<i>E. Family</i>						
I.1	M	Definite	*			Yes
II.1	M	Definite	5	No pain since 46 years	Yes	Yes
<i>Hu. Family</i>						
II.1		Definite	25	No	No	Yes
II.2		Definite	19	No	No	Yes

* Insufficient information.

<i>Diagnosed by</i>	<i>Exacerbation by</i>	<i>Amino acids</i>	<i>Comment</i>
• • Laparotomy	• Worry Worry and fatty food	Normal Normal Normal	Worst between 19–25, quite severe pain Severe pain, total pancreatectomy; pleural effusion; pseudocyst
• • Laparotomy and amylase	• • • Fatty food; worry	• • • Slightly raised leucine, isoleucine, valine, and tyrosine Normal	Pseudocyst
• Amylase • •	Fatty food; worry No Worry	• Slightly raised leucine, isoleucine, valine, and tyrosine Normal	
• • Laparotomy	No • ?Worry	• Normal Slightly raised tyrosine	Only 2 attacks (severe), aged 31 and 41
• Laparotomy and amylase •	No ?Fatty food	• • Normal	Died when aged 34; may have had a peptic ulcer
• Amylase	Emotion, alcohol, and fatty food		Pseudocyst; pain on hearing of father's death
• Calcification and amylase •	Alcohol •	•	Possibility of carcinoma of pancreas
PM Calcification and amylase	• •	• High lysine, cystine, and histidine levels	
• Calcification and pancreatic insufficiency	•	Normal	Both had pancreatic insufficiency and died of carcinoma of pancreas
• Calcification and pancreatic insufficiency	•	Normal	