Does Your Patient Have Pancreatic Disease?

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In the past two decades pancreatic morphology has come of age, sweeping aside the long held dominance of pancreatic secretary tests. New morphographic techniques—isoenzyme scanning, angiography, endoscopic pancreatography, ultrasound and computed tomography—have appeared on the clinical scene in such quick succession that clinicians have been carried along on each new wave of enthusiasm with little time to ponder. In the relative calm of the past five years, a calm interrupted by the emergence of tubeless pancreatic function tests and isoamylase separation techniques, has come the bewildering realisation that the sophisticated imaging techniques may prove, in the context of chronic pancreatic disease, to be Utopian. A recent poem about the pancreas[1] eloquently summed up the frustration frequently experienced by the modern pancreaticologist and his perplexed patient. Of the plethora of existing investigations (Table 1), which test should the clinician use to decide whether or not his patient’s symptoms are due to chronic pancreatitis or pancreatic cancer?

The Problem in Perspective

Published mortality statistics show the incidence of pancreatic cancer to be increasing steadily in the western world—but it remains a rare disease, its current incidence in England and Wales being 0.01 per cent[2]. With increased clinical awareness of patients’ presenting fea-
only when the endoscopic pancreatogram is abnormal[11], since in a few cases both these parameters may remain within normal limits for many years, while in others gross reduction in exocrine secretion may be
remain within normal limits for many years, while in
accompanied by normal duct appearances, or vice versa.
In centres of referral where familiarity with the modes of
presentation and behaviour of these patients generates a
high index of suspicion in the attendant clinicians, laparo-
tomy with removal of the tail of the pancreas for histology
may be seen as the final diagnostic arbiter, an ap-
proach which may be justified because it is important to
identify the disease before the increasing intensity and
duration of pain forces the patient to resort to narcotics.
At Manchester Royal Infirmary, a centre of referral of
patients with suspected pancreatic disease for over 30
years, the number of patients with pancreatic disease
admitted annually is rising steadily (Fig. 1), in keeping
with the recognised trend of increased alcohol-related
pancreatitis[12, 13] and of pancreatic cancer. However,
these cases currently amount to only one per cent of the
total hospital admissions each year and patients with
chronic pancreatitis account for half of these. In peripheral hospitals the figures would be even lower and any
desire for early identification of chronic pancreatitis must
be related to the disproportionately high financial outlay
if an exhaustive approach to diagnosis was routinely
practised. Relapsing acute pancreatitis due to gall-stone
disease or hyperlipidaemia is only exceptionally followed
by permanent pancreatic damage[14]; there is thus no
reason to question the overall validity of the Marseilles
clinico-pathological classification of pancreatitis[8].

The rarity of chronic pancreatic disease is in stark
contrast to the frequency with which its presence is
suspected in patients with a bewildering variety of ab-
dominal and systemic problems, chief amongst which is
non-specific abdominal pain. For this reason a simple
non-invasive test is required to detect the few patients
who probably do have pancreatic disease from among the
vast numbers whose symptoms initially suggest its pre-

cence. The demand for tests to aid in the differential
diagnosis between chronic pancreatitis and pancreatic
cancer or to assist in managing specific pancreatic prob-

elms is easier to meet.

Objectivity in Assessment

In evaluating the available discretionary tests we should
rigorously apply scientific criteria to assess the efficiency
of the test in classifying patients into diseased and non-
diseased categories, the precision of measurement, and

Fig. 1. Annual admission episodes from pancreatic disease compared to total admission episodes at Manchester Royal Infirmary,
1969-1979. Admissions through the Hospital's Programmed Investigation Unit are included in the calculations.
the effectiveness of the test in altering the natural history of the disease[15]. As clinicians, we cannot ignore the more subtle but important factors of test acceptance and risks. Finally, medical innovations that gain a place in practice usually promise some benefit but not without an increase in cost; in Fineberg and Hiatt’s words it ‘behaves clinicians to clarify what we get for what we choose to spend’[16].

Bayes’ theorem[17], a particular method of inductive argument involving a manipulation of probabilities, is the standard method[18-21] of assessing the efficiency of indicators, a word coined by Card and Good[22] for the element of evidence produced by a test result. The idea incorporated in it is summed up in the cliché ‘common things are common’. The first prerequisite is to determine the sensitivity and specificity of each test. Sensitivity indicates the percentage of results that are positive when a test is applied to patients known to have the disease in question; specificity indicates the percentage of results that are negative in the same test when it is applied to subjects free of the disease. The best method of determining sensitivity and specificity is to administer the test to a population representative of the one for which the test is intended and subsequently to establish the true status of all individuals by the most exhaustive and accurate investigations available[15]. In quantitative tests, such as the secretin-pancreozymin test, it is possible to vary positivity or negativity by changing the level at which the test is considered positive. However high these two indices may be, a test’s impact on diagnosis (i.e. the degree of reliance that can be placed on a positive or negative result) is governed by the prevalence of the disease to be diagnosed[17, 20, 21]. If we assume a disease to have a prevalence of 20 per cent (Table 2), of every 100,000 individuals in an unselected population 20,000 have the disease and 80,000 are without it. A test with a sensitivity of 95 per cent will correctly identify 19,000 of the 20,000 diseased patients (correct positives) but will give a negative result in 1,000 patients (incorrect negatives). If the same test has a specificity of 95 per cent, 76,000 of the 80,000 disease-free individuals will be correctly identified (correct negatives) but 4,000 will be incorrectly diagnosed as having the disease (incorrect positives). The predictive value of a positive result, i.e. the percentage of patients who are correctly classified as having the disease, is 82.6 per cent and the false positive rate is 17.4 per cent. The predictive value of negatives is 98.7 per cent and false negatives 1.3 per cent and overall test efficiency, i.e. the percentage of tested patients who have been correctly classified, is 95 per cent. In this setting a hypothetical test with a high sensitivity and high specificity is excellent not only at excluding disease but also at correctly identifying its presence. The same test’s diagnostic impact is very different when disease prevalence is low, 1 per cent (Table 3). In this situation only 1,000 of every 100,000 patients tested have the disease and 99,000 are without it. By an analysis similar to that used previously, the predictive value of positives emerges as only 16.1 per cent, with false positives correspondingly high at 83.9 per cent. The test is useless in making a positive diagnosis, although it retains its value in excluding disease, since the predictive value of negatives is 99.9 per cent. Systematic analysis of predictive values at different prevalence rates, as done by others[20, 21], shows that, at any given sensitivity and specificity, the predictive value of positives is directly related to disease prevalence; in contrast, disease prevalence has little impact on the predictive value of negatives (Table 4). At a fixed prevalence the predictive value of positives is increased by increasing a test’s specificity while the predic-

**Table 2.** The predictive value model [17, 20, 21], given a population of 100,000, disease prevalence of 20 per cent, and test sensitivity and specificity of 95 per cent each.

| Number with positive test | Number with negative test | Totals |
|---------------------------|---------------------------|--------|
| Number with disease       |                           |        |
| 19,000 (correct)          | 1,000 (incorrect)         | 20,000 |
| Number without disease    |                           |        |
| 4,000 (incorrect)         | 76,000 (correct)          | 80,000 |
| Total                     |                           | 100,000|

Predictive value of positives = \( \frac{\text{correct positives}}{\text{total positives}} \times 100 = 82.6\% \)

Predictive value of negatives = \( \frac{\text{correct negatives}}{\text{total negatives}} \times 100 = 98.7\% \)

Efficiency = \( \frac{\text{total correct}}{\text{total tested}} \times 100 \) = 95\%

**Table 3.** Changed impact on diagnosis at reduced disease prevalence (1 per cent), given a population of 100,000 and test sensitivity and specificity of 95 per cent each.

| Number with positive test | Number with negative test | Total |
|---------------------------|---------------------------|-------|
| Number with disease       |                           |       |
| 950 (correct)             | 50 (incorrect)            | 1,000 |
| Number without disease    |                           |       |
| 4,950 (incorrect)         | 94,050 (correct)          | 99,000|
| Total                     |                           | 100,000|

Predictive value of positives = 16.1\%

Efficiency = 95.0\%

Predictive value of negatives = 99.9\%
Table 4. Effect of disease prevalence on the diagnostic value of a test. False positives and false negatives are 100 minus the predictive value of positives or negatives respectively [20, 21].

| Prevalence of disease (%) | Predictive value of a positive test (%) | Predictive value of a negative test (%) |
|---------------------------|-----------------------------------------|----------------------------------------|
| 0.1                       | 1.9                                     | 100                                    |
| 1                         | 16.1                                    | 100                                    |
| 2                         | 27.9                                    | 100                                    |
| 5                         | 50.0                                    | 100                                    |
| 10                        | 68.0                                    | 99                                     |
| 20                        | 83.0                                    | 99                                     |
| 50                        | 95.0                                    | 95                                     |

Sensitivity 95%  Specificity 95%

tive value of negatives is increased by increasing the test's sensitivity[21].

Screening for Pancreatic Disease

An ideal test should correctly establish the presence or absence of pancreatic disease in every individual investigated, but such a goal is impossible to achieve since positivity in disease is inversely coupled to negativity in health[21]. What should we opt for—highest sensitivity, highest specificity or highest efficiency? In general, the highest sensitivity, preferably 100 per cent, is desired when the disease is serious and curable (e.g. phaeochromocytoma) but this does not pertain in the case of either pancreatic cancer or chronic pancreatitis. A test with very high specificity is required when a disease is serious but incurable and when a false positive result would be disastrous; a situation highlighted by pancreatic cancer. Chronic pancreatitis is a serious and treatable disease in which false positives and false negatives are equally serious or damaging (a false positive diagnosis condemns the patient's unemployment and reliance on narcotics, a false negative diagnosis is demoralising since it condemns the patient as a malingerer). This is a situation demanding a test with very high efficiency. The choice of test is governed by the clinician's impression of the local prevalence of chronic pancreatitis and the knowledge that, for any test, sensitivity may equal specificity, sensitivity may be less than specificity, or sensitivity may exceed specificity[23]. If disease prevalence is low, maximal efficiency is achieved by a test with very high specificity when a low sensitivity, even down to 50 per cent, is acceptable (Table 5). Increasing the sensitivity of the test to 99 per cent while dropping the specificity to 50 per cent has the paradoxical effect of drastically reducing efficiency to 50 per cent. When local disease prevalence is high (20 per cent) as in pancreatic referral centres in which prevalence is artificially increased because commoner abdominal diseases have already been excluded by the referring physician, high efficiency ideally requires a test with high sensitivity and specificity, since such a test will not only exclude disease with confidence but will correctly identify its presence (predictive value of positives 83 per cent; Table 5). If a test with these specifications is not available, a small increase in specificity up to 99 per cent will allow a drop in sensitivity down to 50 per cent with relatively little reduction in efficiency or predictive value. The reverse manipulation, i.e. increasing sensitivity while dropping specificity, results in an inefficient test. In an unreal situation in which every alternate patient has chronic pancreatitis high efficiency demands a test with very high sensitivity and specificity.

In an out-patient setting, the less invasive and more accessible a test, the more suitable it will be for a modified screening role. A plain X-ray of the abdomen is mandatory to detect pancreatic calculi but serum amylase analysis, so valuable in diagnosing acute pancreatitis, has proved of little use in detecting either pancreatic cancer or chronic pancreatitis in a remission phase. Our preliminary data suggest that measurement of serum pancreatic and salivary isoenzymes[24] will prove to be insufficiently discriminatory to warrant routine use since the reference ranges for these isoenzymes are so wide[25]. Of the other available tests only three are suitable for screening purposes: isotope scanning, ultrasound scanning and the PABA excretion index. The cost of computed tomography is prohibitively high and is not justified by its low overall efficiency[26], while the tubeless fluorescein di-laurate test is impractical because a minimum of three days is required for its completion[27].

Isotope and ultrasound scanning are familiar tech-

Table 5. Varying requirements for obtaining high efficiency when disease prevalence is very low, intermediate and very high[21]. Se = sensitivity, SP = specificity.

| Disease Prevalence % | Sensitivity % | Specificity % | Predictive value of positives % | Predictive value of negatives % | Efficiency % |
|-----------------------|--------------|---------------|---------------------------------|-------------------------------|--------------|
| 0.1                   |              |               |                                 |                               |              |
| Se = SP               | 95           | 95            | 2                               | 100                           | 95           |
| Se < SP               | 50           | 99            | 5                               | 100                           | 99           |
| Se > SP               | 99           | 50            | 0                               | 100                           | 50           |
| 20                    |              |               |                                 |                               |              |
| Se = SP               | 95           | 95            | 83                              | 99                            | 95           |
| Se < SP               | 50           | 99            | 93                              | 89                            | 89           |
| Se > SP               | 99           | 50            | 33                              | 100                           | 60           |
| 50                    |              |               |                                 |                               |              |
| Se = SP               | 95           | 95            | 95                              | 95                            | 95           |
| Se < SP               | 50           | 99            | 99                              | 66                            | 74           |
| Se > SP               | 99           | 50            | 66                              | 98                            | 74           |

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diagnostic criteria were used[23]. Isotope scanning emerges as a test with very high sensitivity but low specificity[32]; ultrasound carries a very high specificity but low sensitivity, lower with the newer gray-scale machines[33] than with the old-fashioned bistable display units[34]; while the BT PABA/14C test has a very high specificity with moderately good sensitivity[31]. Other factors for consideration are the precision and reproducibility of these tests, the patients' acceptance and risk, operator dependency and cost. With isotope scanning in its present form there are few if any technical failures and the test can be performed by technicians, there is a good reproducibility in reporting by experts but the test cannot be repeated until six months has elapsed in view of the long biological half-life of the isotope. In contrast, ultrasound is harmless but it is more dependent that any other technique on the individual operator's expertise and experience. The pancreas is difficult to visualise in obese patients, or when there is overlying bowel gas or scar tissue from previous abdominal surgery. These factors lead to an overall failure rate of around 25 per cent[33]. The disadvantages of the BT PABA/14C test are its dependence on patient compliance, the requirement for β-counting, and drug interference (particularly by analgesics such as paracetamol which, like PABA, possess a free aromatic amino group). The long physical half life of 14C is not a problem since its biological half-life is short [30, 31] but the test is unsuitable for children, pregnant women or patients in chronic renal failure. On the credit side we find that the test is highly reproducible, well accepted by patients, can be performed when previous gastric or biliary bypass operations preclude other function tests and is cheap (£8 per test).

The diagnostic impact of these tests in a hypothetical population of 100,000 with a disease prevalence rate of 20 per cent can be judged from Table 7. Isotope scanning, which has the highest sensitivity, also has the highest predictive value of negatives but the lowest efficiency—all 48,000 patients who give a positive result will need retesting since the predictive value of positives is only 41 per cent. The BT PABA/14C test is more efficient than ultrasound; its higher specificity ensures a much higher predictive value of positives. If all the patients who give a positive result with the tubeless function test were assessed by ultrasound the resulting predictive value of positives increases to 96 per cent. With the BT PABA/14C ultrasound sequence there are other advantages: the oral test provides a valid index of pancreatic function[23] and the longer time available for ultrasound permits a differential diagnosis between chronic pancreatitis and pancreatic cancer in many cases. When the BT PABA/14C test is not available the ultrasound isotope sequence will yield a high predictive value of positives at around 76 per cent (Table 7). Series testing in this fashion is economical and increases specificity, although sensitivity decreases; this means that a few diseased cases will be missed but those identified as positive will most definitely have chronic pancreatic disease, i.e. there are few false positives.

At a more realistic disease prevalence of 1 per cent the BT PABA/14C and ultrasound sequence generates a low predictive value of positives of only 51 per cent (Table 8)

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Table 6. Comparison of potential screening tests.

|                  | Number of patients | Poor Test | Sensitivity | Specificity |
|------------------|--------------------|-----------|-------------|-------------|
| Isotope          | 185                | 0         | 96          | 64          |
| N 137            |                    |           |             |             |
| A 48             |                    |           |             |             |
| Ultrasound       | 87                 | 11        | 79          | 92          |
| Bistable         |                    |           |             |             |
| N 42             |                    |           |             |             |
| A 45             |                    |           |             |             |
| Gray-scale       | 131                | 25        | 55          | 90          |
| Bistable         |                    |           |             |             |
| N 75             |                    |           |             |             |
| A 56             |                    |           |             |             |
| BT PABA/14C      | 129                | 12        | 74          | 96          |
| N 74             |                    |           |             |             |
| A 55             |                    |           |             |             |

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Table 7. Retesting the positives. Evaluation of three ‘screening tests’ in a pancreatic unit (assuming disease prevalence of 20 per cent).

|                  | Number  | Sensitivity | Specificity | Predictive value of positives | Predictive value of negatives | Efficiency |
|------------------|---------|-------------|-------------|-------------------------------|-------------------------------|------------|
|                  | positive| %           | %           | %                            | %                            | %          |
| Isotope          | 48,000  | 96          | 64          | 41                            | 98                            | 71         |
| Ultrasound       | 19,000  | 55          | 90          | 58                            | 89                            | 83         |
| (Gray-scale)     |         |             |             |                               |                               |            |
| BT PABA/14C      | 18,000  | 74          | 96          | 83                            | 94                            | 93         |
| BT PABA/14C + ultrasound | 40 | 99 | 96 | 91 | 100 | 96 |
| BT PABA/14C + isotope | 71 | 98 | 92 | 73 | 80 | 78 |
| Ultrasound + isotope | 52 | 96 | 78 | 65 | 70 | 65 |

Table 8. Retesting the positives. Impact on diagnosis when the assumed prevalence of chronic pancreatic disease is 1 per cent.

|                  | Number  | Sensitivity | Specificity | Predictive value of positives | Predictive value of negatives | Efficiency |
|------------------|---------|-------------|-------------|-------------------------------|-------------------------------|------------|
|                  | positive| %           | %           | %                            | %                            | %          |
| Isotope          | 36,600  | 96          | 64          | 2                            | 100                           | 65         |
| Ultrasound       | 10,450  | 55          | 90          | 5                            | 99                            | 90         |
| BT PABA/14C      | 4,700   | 74          | 96          | 18                            | 100                           | 96         |
| BT PABA/14C + ultrasound | 41 | 99 | 51 | 13 | 100 | 96 |
| BT PABA/14C + isotope | 71 | 98 | 33 | 13 | 100 | 96 |
| Ultrasound + isotope | 53 | 96 | 13 | 13 | 100 | 96 |
| BT PABA/14C + ultrasound + isotope | 39 | 100 | 73 | 73 | 100 | 73 |
| Ultrasound + isotope + Lundh | 44 | 99 | 58 | 58 | 100 | 58 |

which increases to 73 per cent if isotope scanning is added in series. Where the tubeless function test is not available, the ultrasound-isotope sequence, followed by a Lundh test, the simplest of the invasive tests with sensitivity 83 per cent and specificity 91 per cent[35], will yield a predictive value of positives of 58 per cent. In either sequence invasive tests will be required for further clarification in the selected positive subgroup of patients. Galen and Gambino have clearly set out the assumptions made in this kind of analysis[21]. They point out that series testing is only valid if the tests used are independent of each other. It is assumed that the population selected by the first test redistributes itself entirely to resemble the parent population and although this is unlikely, and despite the statistical difficulties inherent in the analysis, this system does allow for some logic to be introduced in a situation in which many tests are available. The calculated predictive value is always higher than the actual predictive value in a testing situation.

If, instead of using the tests in series, awaiting the result of each before applying another, they were to be used in parallel, the resulting sensitivity would be much higher than that of each individual test because disease would be diagnosed if any test result was abnormal. The disease pick-up rate would be very high with this approach but the financial outlay would be enormous; furthermore, since patients could only be considered free of disease if every test was negative, the specificity of the combination would be considerably reduced, and this would result in a reduced predictive value of positives and a vast increase in false positives. Rang[36] has eloquently described this as the Ulysses syndrome because patients healthy enough at the outset make a long journey through the investigative arts and experience a number of adventures before returning to their point of departure. The syndrome is an adverse effect of investigation and not of therapy; its aetiology is a meritorious desire to investigate a patient fully.

Conclusions

Chronic pancreatic disease is rare but its presence is frequently suspected in patients with abdominal symptoms. Both chronic pancreatitis and pancreatic cancer are incurable. Considering these facts, a non-invasive test with high specificity and efficiency is required to select for the definitive invasive tests the few patients who probably have pancreatic disease from the vast majority of patients who do not. The choice of tests in each centre will be influenced by the available resources but the impact of the tests on diagnosis will be governed by local disease prevalence.

Tests should be applied in series and our own current approach is shown in Fig. 2. To follow the scheme without modification is a waste of resources when the patient presents with an epigastric mass or obstructive jaundice, as, in these circumstances, when clinical suspicion of pancreatic cancer is high, ultrasound followed by endoscopic cholangio-pancreatography is frequently diagnostic. The history and examination of the patient are of paramount importance and the clinical state must be
updated in the light of returning investigations. It is our current practice to give out-patients suspected of having chronic pancreatitis a frozen PABA cocktail to take home after their first clinic attendance (after plain X-ray of the abdomen to detect pancreatic calculi). When the urine samples are returned and analysed, further tests are arranged as necessary, bearing in mind that the results of pancreatic function tests should in the first instance be interpreted in terms of function only and not in terms of structure, which is the second stage in the assessment. A negative result will usually exonerate the pancreas from suspicion (high predictive value of negatives). If, however, the serum amylase is raised and the patient's symptoms persist or are so suggestive as to raise doubt in the physician's mind, an ultrasound scan is arranged which, if normal, implies the presence of non-pancreatic hyperamylasaemia. When the BT PABA/14C test is abnormal, the ultrasound scan not only provides confirmatory evidence (high predictive value of positives) but in many cases will also aid in the differential diagnosis between chronic pancreatitis and pancreatic cancer. If cancer is diagnosed, tissue diagnosis is required in the absence of metastases and this is achieved by cytology of material obtained by ultrasound-guided percutaneous aspiration needle biopsy of the pancreas, provided palliative bypass surgery is not indicated to relieve biliary or pyloric obstruction. If the likely diagnosis is chronic pancreatitis, further function tests are not usually required because the PABA excretion index correlates well with the mean trypsin activity in the Lundh test[35], which in turn correlates with the post-secretin output of bicarbonate in a secretin-pancreozymin test[37], but endoscopic cholangio-pancreatography is invaluable whenever surgery is contemplated. When the distinction between chronic pancreatitis and pancreatic cancer proves to be impossible, a secretin-pancreozymin test (which is routinely combined with cytology of duodenal juice and a serum evocative test) yields big dividends. Endoscopic cholangio-pancreatography, angiography and computed tomography may also be usefully applied, but laparotomy for histology of pancreatic specimens is not infrequently the final investigative tool. Series testing is economical and practical since it generates few false positives; a battery of tests is only necessary in the few patients selected by the screening test sequence.

Future technological developments will inevitably alter the clinical approach. New tests, both morphographic and functional, will emerge and each will need to be carefully evaluated. It has been said that 'diagnosis is not an end in itself but only a mental resting place on the way

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**Fig. 2. A scheme to investigate the pancreas in patients who present with non-specific abdominal symptoms (assuming disease prevalence of 20 per cent).**

| PANCREATIC DISEASE 1981 (Prevalence 20%) |
|------------------------------------------|
| **PABA**                                  |
| **EXCRETION INDEX**                       |
| **(Pred - 94%)**                          |
| **NORMAL**                                |
| No other test                             |
| Amylase †                                 |
| Symptoms persist                         |
| ULTRASOUND SCAN                           |
| **(Pred + 96%)**                          |
| **ABNORMAL**                              |
| **(Pred + 83%)**                          |
| **NORMAL**                                |
| ? HYPERAMYLASAEMIA                       |
| Amylase isoenzymes                       |
| Follow-up                                |
| **CANCER**                                |
| **CHRONIC PANCREATITIS**                  |
| **INDETERMINATE**                         |
| GTT                                      |
| Faecal fat                               |
| Evocative test                           |
| ERCP                                     |
| Splenoportogram                          |
| Chiba needle                             |
| CT                                       |
| S-P test                                 |
| Cytology                                 |
| Lactoferrin                              |
| ERCP                                     |
| Angiography                              |
| Laparotomy                               |

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to treatment ... a new method is good if it helps to classify patients in such a way that we obtain better treatment results, and it is superfluous if that is not the case'[38]. Hitherto, clinicians could claim only modest esoteric gains from early diagnosis of pancreatic cancer and chronic pancreatitis—an explanation of the patient's symptoms, avoidance of the frustration of prolonged investigations, prescription of adequate analgesia, the institution of pancreatic replacement therapy as required, and, most importantly, the ability to offer strong psychological support to the victims of these distressing diseases and their families. Nevertheless, preliminary results from our Department suggest that if patients with chronic pancreatitis are identified early, and particularly when a cause is apparent, there is a chance, given good patient compliance, that the disease can be halted. If this proves to be correct, this attempt to rationalise pancreatic investigations will have been worth the effort involved.

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