CHAPTER 29

Pancreatitis Definitions and Classification

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When I use a word, it means just what I choose it to mean—neither more nor less
—LEWIS CARROLL

If a system of disease definition and classification is to be of maximum value, it must enable practitioners to make precise diagnoses, to give appropriate treatments with accurate prognoses for their patients, and to talk about the same disease with one another. For a clearly defined entity such as acute myocardial infarction this is usually straightforward; but where there is a broad clinical spectrum, with varying etiologies and uncertain outcome, the problem for the classifier is more difficult. All systems of classification merely reflect the state of the art at the time they are promulgated—and so are ephemeral. These points are well illustrated in considering pancreatic inflammatory disease.

Although the effects of inflammation on the pancreas have been known and described for a hundred years or more, prior to the 1960s there were no agreed definitions as to what constituted the acute and chronic forms of the disease, and although various systems of classification could be found, especially in surgical texts, there was no general agreement as to a structure into which the various types of the disease could be fitted. This is hardly surprising; there was little histopathological material—surgical or autopsy specimens coming largely from glands that were severely damaged—and since clinical investigation was limited to plain X-rays, checks of glucose metabolism, or the stool for signs of malabsorption, diagnosis was imprecise or difficult. The use of the serum or urine amylase coming along in the 1930s was a major advance, but agreed criteria for what constituted one or other form of the disease were not available and an understanding as to how the various etiologies affected outcome could not be found. There was no consensus as to what constituted acute pancreatitis, chronic pancreatitis, or pancreatic insufficiency, and so published data could not be compared.

In the early 1960s an initiative was taken to call a meeting on pancreatic disease at which some definitions and a classification were agreed on. This was the Symposium of Marseilles, 1963 (1), and the working classification produced has had a major influence on the study of pancreatic inflammatory disease since then. Its value has been such that only now, 20 years later, has it been felt necessary to review and revise it. Presumably by 1963 diagnostic criteria were agreed on and unequivocal, since no formal clinical definitions of acute and chronic pancreatitis are given. The participants proposed a classification, described pancreatic morphology in the chronic form of the disease, and made some observations about etiology.

At Marseilles (1) it was agreed that pancreatitis was (a) acute, (b) relapsing acute, (c) chronic relapsing, defined as chronic pancreatitis with acute exacerbations, or (d) chronic.

In forms a and b, clinical and biological restitution of the gland takes place if the primary cause or factor is eliminated. It is unusual for acute pancreatitis to develop into chronic pancreatitis, but it may occur. In forms c and d, residual pancreatic damage with anatomical or functional derangement persists even if the primary
cause or factors are eliminated. Chronic pancreatitis may result from chronic relapsing pancreatitis; it may manifest itself from the first as a chronic disease. Sometimes it may follow the acute form.

The distinction between groups c and d is clinical and not morphological.

The Marseilles symposium was primarily concerned with pathological anatomy and with the etiology of the chronic forms of the disease—no attempt was made to explore correlations between anatomical and functional changes. A statement was made relating to the morphology of chronic pancreatitis, characterizing it as irregular sclerosis with destruction and loss of exocrine parenchyma, either focal, segmental, or diffuse. It may be associated with varying degrees of dilatation of the duct system, which may be localized and usually, but not invariably, associated with strictures or stones. All types of inflammatory cells can be found in varying degrees as well as edema, necrosis, or abscess formation. Cysts and pseudocysts, which may or may not communicate with the ducts, are common. The islets of Langerhans may be well preserved. The incidence of calcification is variable and is usually intraductal (stones) or rarely parenchymal (calcification). These histological features can be found irrespective of the etiology of the chronic pancreatitis.

The 1963 symposium focused particularly on the alcohol-induced form of chronic disease, but pointed out that cholelithiasis was commonly associated with the acute form of the disease, although less rarely accompanied the chronic form. Also mentioned was a group of cases where obstruction to the main ducts may lead to chronic pancreatitis, and as examples vaterian stenosis, traumatic stricture, stones, carcinoma, and duodenal obstruction were given. This variety of "obstructive pancreatopathy" presumably was fitted into the chronic pancreatitis group, but no mention is made of potential reversibility of these lesions. Rarer forms of chronic pancreatitis were also mentioned, such as hereditary, metabolic, nutritional, endocrine, vascular, and drug-induced types of disease.

In the 20 years since this classification was produced, there have been major advances in our ability to investigate the pancreas, an accumulation of data from the earlier investigations, new information about etiology and pathogenesis, and, of course, experience with the use of the classification. As a result, it has become clear that the Marseilles classification of 1963 is in need of revision. One problem has been difficulty in defining the intermediate categories; acute relapsing may be very difficult to distinguish from chronic relapsing, a diagnosis that may be dependent on biopsy evidence for which there is rarely material. This makes these categories difficult to use in clinical practice. Moreover, since neither etiology nor severity is included in the Marseilles classification, prognosis is not implied. Thus, in some respects the classification lacks precision, and in the year 1983–1984, two further symposia were held, one in Cambridge (2) and a second one again in Marseilles (3), to review the situation. Many of the participants attended both meetings and so, not surprisingly, there is substantial overlap in what was produced. However, there are some important distinctions and also areas where there is clearly need for further definition—reflecting the current level of our understanding of these disease processes.

This chapter will review both publications in detail and will attempt a synthesis, focusing on areas where more information is required. At both symposia it is clear that the participants had little difficulty in deciding what are the extremes of the clinical spectrum—acute first onset pancreatitis on the one hand, and advanced chronic pancreatitis on the other. Both publications give definitions for acute and chronic pancreatitis. In Cambridge these are entirely clinical, whereas the Marseilles definitions are expanded to include descriptive histopathology:

Acute pancreatitis is defined as an acute condition typically presenting with abdominal pain, and usually associated with elevated pancreatic enzymes in blood or urine, due to inflammatory disease of the pancreas. [Cambridge (2).]

Acute pancreatitis is characterized clinically by acute abdominal pain accompanied by increased pancreatic enzymes in blood or urine. Though it usually runs a benign course, severe attacks may lead to shock with renal and pulmonary insufficiency, which may prove fatal. Acute pancreatitis may be a single episode or may recur.

Morphologically there is a gradation of lesions in acute pancreatitis. In the mild form, peripancreatic fat necrosis and interstitial oedema may be recognised but as a rule pancreatic necrosis is absent. The mild form may develop into a severe form with extensive peri- and intrapancreatic fat necrosis, parenchymal necrosis and haemorrhage. The lesions may be either localised or diffuse. Occasionally there may be little correlation between the severity of the clinical features and the morphological findings.

Both exocrine and endocrine functions of the pancreas are impaired to a variable extent for a variable duration.

If the primary cause and complications such as pseudo-cysts are eliminated in acute pancreatitis, clinical, morphological and functional restitution to normal occurs. In some cases scarring and pseudo-cysts persist. Only rarely does acute pancreatitis lead to chronic pancreatitis. [Marseilles (3).]

Chronic pancreatitis is defined as a continuing inflammatory disease of the pancreas, characterised by irreversible morphological change, and typically causing pain and/or permanent loss of function.

Many patients with chronic pancreatitis may have acute exacerbations but the condition may be completely painless and the only evidence of an inflammatory process may be fibrosis indicating previous inflammation. [Cambridge (2).]

Clinically chronic pancreatitis is characterised by recurrent or persisting abdominal pain, although chronic pan-
creatitis may present without pain. Evidence of pancreatic insufficiency, e.g., steatorrhoea or diabetes, may be present.

Morphologically, chronic pancreatitis is characterised by an irregular sclerosis with destruction and permanent loss of exocrine parenchyma which may be either focal, segmental or diffuse. These changes may be associated with varying degrees of dilatation of segments of the duct system. Thus dilatation of the duct of Wirsung and its small ducts may occur together or independently. No obvious cause for the duct's dilatation may be found, but most often it is associated with strictures of the ducts or intraductal protein plugs and calculi (calcification). All types of inflammatory cells may be present in varying degrees, as well as oedema and focal necrosis. Cysts and pseudo-cysts, with or without infection, which may or may not communicate with the ducts are not uncommon. Compared to the degree of acinar destruction, the islets of Langerhans are relatively well preserved. Based on predominating structural features the following descriptive terms can be used:

Chronic pancreatitis with focal necrosis
Chronic pancreatitis with segmental or diffuse fibrosis
Chronic pancreatitis with or without calculi

A distinct morphological form of chronic pancreatitis is obstructive chronic pancreatitis. It is characterised by dilatation of the ductal system proximal to the occlusion of one of the major ducts (e.g. by tumor or scars), diffuse atrophy of the acinar parenchyma and uniform diffuse fibrosis. Calculi are uncommon.

In chronic pancreatitis (with the exception of obstructive chronic pancreatitis) the irreversible morphological changes of the pancreas may lead to progressive or permanent loss of exocrine and endocrine pancreatic functions. In obstructive chronic pancreatitis both structural and functional changes tend to improve when the obstruction is removed. [Marseilles (3).]

In an addendum to these definitions and classifications, the Marseilles publication stated that the conditions of hemochromatosis and mucoviscidosis should not be classified as chronic pancreatitis and adds that the first manifestation of alcohol-induced chronic pancreatitis may be an episode of clinically acute pancreatitis. In the early phases of alcoholic chronic pancreatitis, exacerbations closely resemble attacks of acute pancreatitis.

As can be seen, both publications now drop the intermediate categories of acute and chronic relapsing pancreatitis. The Cambridge group simply states that acute pancreatitis may recur; it is clear that in ordinary clinical practice it may be impossible to tell whether a patient is having a further attack of acute pancreatitis or simply an exacerbation of chronic pancreatitis. More sophisticated imaging or function testing than is at present available will be required to resolve this problem.

These definitions and this classification were agreed on by a large number of contributing clinicians representing various subspecialties—imaging, surgery, histopathology, etc.—and clearly the best (most precise) definitions of disease and the most accurate classification will combine function, morphology, and histopathology. These data are not always obtainable in any individual case, but since the various subspecialties view pancreatitis from different standpoints, specialists from each field of interest (physicians, surgeons, imagers, pathologists) at Cambridge commented on their contribution to diagnosis and classification.

Physicians felt that, where known, etiology should always be included in diagnosis, since the cause carried implications for management and prognosis, e.g., removal of gallstones will halt the disease in gallstone pancreatitis. The sea of alcohol washing irrevocably over the field of pancreatitis was considered in detail by both groups, especially those in Marseilles. No level of consumption could be stated, above which alcohol-induced pancreatitis is inevitable, and, regretfully, no definite information is available concerning those features that determine whether an individual will or will not develop the disease. Neither group was able to make much of the role of tissue types or the various pancreatic juice proteins such as the stone protein or lactoferrin as markers of sensitivity, although the Marseilles group stated that the significance of the synthesis and origin of the stone protein must be pursued. Although it is certain that alcohol can cause chronic (persisting) disease, its role in acute (reversible) disease is suspect. An addendum to the Marseilles classification states, "the first manifestation of alcohol-induced chronic pancreatitis may be an episode of clinical acute pancreatitis. In the early phase of alcohol in chronic pancreatitis exacerbations closely resembling attacks of acute pancreatitis may occur" (3).

In Cambridge the lack of data relating to the etiologies of "tropical" pancreatitis was noted, and the need for more information on the role of nutrition and diet—especially in early life—in the pathogenesis of this form of the disease was identified.

Routine ductography is now demonstrating congenital anomalies of the pancreatic duct system with increasing frequency, but their role in the causation of disease remains to be adequately defined. Publications relating to pancreas divisum and congenital short pancreas can be found; presumably these anomalies produce an obstructive pancreatopathy, but whether the condition so produced is acute or chronic pancreatitis by definition remains unclear, since we do not know if the lesions regress following surgery.

The list of drugs causing pancreatitis continues to lengthen, but the mechanisms and reversibility of these lesions remain uncertain.

In attempting to assess damage by means of endocrine or exocrine function testing, two main pints emerge. First, following an acute attack, impairment of function may persist for variable lengths of time and in varying degrees of severity, making the diagnosis of possible irreversible damage, i.e., chronic pancreatitis, impossible without sequential testing. Second, available techniques can only detect moderate or marked disease; unfortu-
nately, lesser impairments of function cannot be detected, and as predictors of progress or identifiers of cause, function testing is at present not at all useful. It may be that protein markers in the juice such as lactoferrin or the stone protein will have a role in the future. Function testing alone may be insufficient to define chronic pancreatitis and should be combined with an imaging procedure. Duodenal intubation tests remain inappropriate in diagnosing acute disease, and here the serum amylase (isoamylase) or lipase levels remain the usual markers; however, elevated levels can occur without acute inflammation (cysts), and normal or subnormal levels may be found if measured later in the progress of an acute attack or if there is a severely damaged gland. So once again, function tests need to be combined with some imaging procedure to define the type of disease that is present.

The Cambridge group produced a working classification for the grading of the pancreatic damage by means of imaging techniques [endoscopic retrograde pancreatography (ERP), ultrasound, or computed tomography (CT) scanning] (Table 1). The value of this clearly depends on the availability and quality of these procedures in any individual unit, and again two points should be stressed. First, correlation between structure and function is uncertain (ductograms or scans may be normal in patients with proven disease, or abnormal images may be found but the function of the gland may be unimpaired), but this need not obscure diagnosis, since at present the definitions do not require correlation. Thus a patient may have pain, abnormal function, and a normal image but have chronic pancreatitis; alternatively, a patient may have pain with normal function but an abnormal image and still have chronic pancreatitis. The problem lies with the sensitivity of the tests; disruption of acinar function need not be reflected in a ductogram, and the sensitivity of ultrasound or CT to parenchymal damage is still poor. Nevertheless, this grading of change attempts to introduce a degree of precision into pancreatic classification that is most welcome. The second point rests with the role of ERP in the acute situation; this relates more to management than diagnosis, but the defining of an obstructed duct and its potential relief by endoscopic means are clearly of importance, although to what degree is yet to be defined.

Diagnosis should rest on histopathology, but tissue is generally not available. Features of both types of pancreatitis may be found in the same pancreas, and histopathology is often nonspecific, pathologists being unable to say that acute or chronic pancreatitis is due to one or other cause with any certainty. Perhaps ultrasound-guided biopsy will change this, and when histopathologists are given tissue much more frequently, precision in diagnosis and thus classification may improve. At present we have little information about early change in mild disease, and such as we do have is experimental. A histopathological distinction between disease that might be due to an obstructed duct on the one hand, or some

<table>
<thead>
<tr>
<th>TABLE 1. Grading of chronic pancreatitis by imaging methods*</th>
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</thead>
<tbody>
<tr>
<td><strong>Endoscopic retrograde pancreatography</strong></td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Good-quality study visualizing the whole gland without abnormal signs</td>
</tr>
<tr>
<td>Equivocal</td>
</tr>
<tr>
<td>&lt;3 Abnormal branches</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>&gt;3 Abnormal branches</td>
</tr>
<tr>
<td>Moderate Marker</td>
</tr>
<tr>
<td>All of above plus 1 or more of:</td>
</tr>
<tr>
<td>Cavity &gt; 10 mm</td>
</tr>
<tr>
<td>Intraduct filling defects</td>
</tr>
<tr>
<td>Calculi/pancreatic calcification</td>
</tr>
<tr>
<td>Duct obstruction (stricture)</td>
</tr>
<tr>
<td>Severe duct dilatation or irregularity</td>
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<tr>
<td>Contiguous organ invasion on US or CT</td>
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<tr>
<td>Ultrasound (US) or computed tomography (CT)</td>
</tr>
<tr>
<td>Good-quality study visualizing the whole gland without abnormal signs</td>
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<tr>
<td>1 Abnormal sign: main pancreatic duct 2–4 mm</td>
</tr>
<tr>
<td>2+ Abnormal signs:</td>
</tr>
<tr>
<td>Cavities &lt;10 mm</td>
</tr>
<tr>
<td>Duct irregularity</td>
</tr>
<tr>
<td>Focal acute pancreatitis</td>
</tr>
<tr>
<td>Parenchymal heterogeneity</td>
</tr>
<tr>
<td>Increased echogenicity of duct wall</td>
</tr>
<tr>
<td>Contour irregularity of head/body</td>
</tr>
<tr>
<td>As above</td>
</tr>
<tr>
<td>All of above plus 1 or more of:</td>
</tr>
<tr>
<td>Cavity &gt; 10 mm</td>
</tr>
<tr>
<td>Intraduct filling defects</td>
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* From ref. 3, with permission.
interference with acinar cell function on the other, is difficult to find. Presumably the latter group may show the effects of two problems—an initial intracellular change, of whatever cause, producing a viscous or otherwise altered juice, which in its turn eventually causes obstruction (? stone protein) with upstream intraduct enzyme activation and inflammatory damage of the acinar cells. The earliest changes reported include both ductal cell (separations of the epithelial cells) and acinar cell (swelling and disruption of cytoplasmic organelles) pathology, but we are still uncertain as to the progression of these changes—what is or is not reversible—and it is to be hoped that fine needle biopsy may supply the needed information here.

The established changes of chronic pancreatitis are well known, agreed on, and stated above, but it must be stressed that the changes

1. May be focal rather than diffuse, making sampling error a pitfall in diagnosis; and
2. Identical changes may be seen in the elderly, who have no defined pancreatic disease (but it may be that these patients do have pancreatic insufficiency).

Both the Cambridge and the Marseilles groups retained the term “chronic pancreatitis,” implying continuing inflammation when in fact it may be used to describe a gland that is simply a nugget of fibrous tissue entirely free of evidence of inflammatory change of any sort. However, the fibrosis is presumably the marker of earlier inflammation, and since the term is well established, it cannot now be discarded.

Perhaps reflecting who does what in medicine, surgeons in Cambridge were concerned with defining severity of acute pancreatitis and building in prognostic indicators to their classifications. Thus the terms “mild” (no multisystem failure and an uncomplicated recovery), or “severe” (multisystem failure with early or late local or systemic complications) were suggested as a qualification for any type of pancreatitis. Complications were also defined as follows:

1. A phlegmon is an inflammatory mass in or around the pancreas.
2. A pseudocyst is a localized collection of fluid containing high concentrations of pancreatic enzymes within, adjacent to, or remote from the pancreas.
3. An abscess is pus in or around the pancreas.

At this stage, with agreed criteria for inclusion in one or other group reasonably obvious, it is valuable to categorize the problems.

The first and most basic is that until we have a good understanding of the ways in which (acute) inflammatory change is initiated, an etiological classification, which in some ways would be ideal, will elude us. There are few data suggesting a distinct pathology for any individual etiology, although obstructive pancreatopathy may point the way. The improvement in imaging techniques and percutaneous ultrasound-guided biopsy in all varieties and stages of the disease will contribute substantially to this understanding. The role of alcohol in producing acute and chronic effects may become easier to understand then; one can but echo the cry of the 1984 group in Marseilles for more information about the association between acute pancreatitis and alcoholism. With regard to chronic pancreatitis, we still need to know which types may regress (improve) and how the obstructed but otherwise normal pancreas fits into this group. If the removal of the obstruction allows the gland to revert to normal in all respects, as in a patient with chronic pancreatic pain and a morphological abnormality that is reversible, does this patient have acute or chronic pancreatitis?

In seeking to categorize pancreatitis, there remain major problems in relation to the available investigations. We still need universally adopted criteria for loss of function and for morphological change. The table of changes on imaging is a major step in this direction if widely accepted. We need an equivalent for function testing. It would be of great value to be able to grade tests showing either normality or mild, moderate, or severe changes. Then the various modalities might be combined to provide a more precise diagnosis. One of the problems here is that the sensitivity of indirect tests such as pancreatic polypeptide release, radioactive trypsin inhibitor, or the tubeless pancreatic function tests such as the pancreateal test, is unsatisfactory. Ultrasound and CT scanning are still at a relatively early stage of refinement and cannot pick up minor changes with confidence. There is a need to know more about the meaning of proteins in the pancreatic juice, such as the stone protein or lactoferrin. These may be predictors of chronic disease or disease progress, but this is as yet unclear.

At present the clinician may be left with the patient whose presentation eludes precise categorization. Either there is acute pancreatitis, but information regarding potential reversion to normality is unavailable; or the patient has pancreatic pain but no definite abnormality of function or morphology. How is this patient categorized? Many clinicians will add the words “possible or probable” to whichever variety of pancreatitis seems most appropriate and then await events, but our inability to label this important group of patients merely reflects the quality of our investigative tests today.

An ideal classification system would be simple, unequivocal, and contain as much information as is needed to imply treatment and prognosis. We cannot reach this at present for pancreatitis, but a basic system might divide pancreatitis into acute and chronic and give for each category a definition, diagnostic criteria, and an internal clinical classification.
ACUTE PANCREATITIS

Definition

Acute pancreatitis is defined as an acute condition typically presenting with abdominal pain and is usually associated with raised pancreatic enzymes in blood or urine, owing to inflammatory disease of the pancreas.

Diagnostic Criteria

1. An elevation of plasma levels of pancreatic enzymes greater than ten standard deviations above the laboratory normal
2. Evidence of acute pancreatitis from imaging, laparotomy, and/or autopsy

Clinical Classification

1. Etiology where known (if unknown this should be stated)
2. Degree of severity: (a) mild (no multisystem failure and uncomplicated recovery); (b) severe (multisystem failure and/or development of a complication that should be stated, e.g., pseudocyst)

Examples

1. Severe acute gallstone pancreatitis with abscess and fistula formation
2. Mild acute pancreatitis of unknown etiology

CHRONIC PANCREATITIS

Definition

Chronic pancreatitis is defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphological change and typically causing pain and/or permanent impairment of function.

Diagnostic Criteria

1. Permanently impaired exocrine pancreatic function tests (greater than two standard deviations below the normal for the test)
2. Permanent morphological change in the gland (Table 1)

Clinical Classification

1. Etiology where known (if unknown this should be stated)
2. Pain present or absent
3. Degree of severity (mild, moderate, or severe changes in morphology and/or function data)
4. Complications: cysts, portal hypertension, diabetes mellitus, etc.

Examples

1. Severe chronic alcohol-induced pancreatitis with marked morphological and functional change
2. Mild chronic pancreatitis due to pancreas divisum

This relatively simple system of classification will not necessarily admit every patient with pancreatic disease and suffers, like all systems, from being either too rigid or too diffuse. The need, as always, is to collect data so that each case can be categorized to include cause, number of attacks, severity, complications, and graded data from endocrine and exocrine function testing, as well as morphology from ultrasound, CT, and ERP. Best of all, we need a histopathological classification based on “acute” and perhaps sequential histopathology.

If criteria can be universally agreed on and if wherever possible all data are obtained on each case of pancreatic inflammatory disease, we will be able to answer some of the questions relating to the natural history of pancreatitis and manage our patients with greater precision.

REFERENCES