

# Experimental Models of Pancreatitis

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## Abstract

*Experimental animal models are helpful tools that have been employed to study pancreatitis for more than a century. Although not closely related to all aspects of the human disease, they have contributed greatly to our current understanding of the pathophysiology and cell biology of this disease. They have also become a standard means of testing innovative treatments against pancreatitis. This article reviews the experimental models of acute pancreatitis in common use, their severity, the criteria for the selection of an appropriate model, standards in monitoring and relevance to clinical disease. Despite their undoubted value in elucidating the mechanisms involved in the early cellular events and pathophysiology of acute pancreatitis, these models have not lent themselves to the development of effective new therapies.*

*Models of chronic pancreatitis are also reviewed. The development of a reproducible model relevant to human chronic pancreatitis remains challenging. Experimental models of chronic pancreatitis have not yet added greatly to the understanding of the pathogenesis of this disease in man.*

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**Key words:** Acute pancreatitis, Animal models, Caerulein pancreatitis, Chronic pancreatitis, Experimental pancreatitis

## Introduction

From a historical perspective, the first experimental pancreatitis was induced by Claude Bernard in 1856<sup>1,2</sup> by the injection of bile and olive oil into the canine pancreatic duct, thus producing an acute necrotising pancreatitis. Since that time, acute experimental pancreatitis has attracted thousands of researchers, who employ animal models of pancreatitis for two principal reasons: to answer questions regarding the pathophysiology and cellular biology of the disease and to test novel treatment modalities. Ideally, such questions should be answered in studies of human acute pancreatitis, but this is often impossible since studies addressing the aetiology, pathogenesis and treatment of acute pancreatitis in man are necessarily restricted. A number of experimental animal models have therefore been developed to explore these issues.<sup>3,4</sup>

In this article an overview is given of the different models of experimental acute pancreatitis, both mild and severe, including choice of model, assessment of its pathophysiological effects and clinical relevance. We will review existing models of chronic pancreatitis, none of which are fully satisfactory at the present time.<sup>5</sup>

## Models of Acute Pancreatitis

An ideal model of acute pancreatitis should be reproducible, it should resemble the morphology and time

course of human pancreatitis, and it should be of a degree of severity such that a significant effect of treatment is easily demonstrable.\* Among several well-established and standardised models that have survived the test of time, there are noninvasive and invasive models. Noninvasive models, such as hormone-induced and diet-induced pancreatitis, are technically simple and highly reproducible. Their disadvantage is the fact that the pathophysiological mechanisms involved in the induction of pancreatitis are generally unrelated to the human disease. However, their morphological and biochemical characteristics resemble closely those found in clinical pancreatitis, and they offer an opportunity to study pathophysiological and cell biological alterations during the early course of the disease.<sup>3,4</sup>

### *Hormone-induced Pancreatitis*

Acute oedematous pancreatitis is induced by hyperstimulation of the exocrine function of the pancreas with the cholecystokinin analogue caerulein. This well characterised and highly reproducible model was originally described by Lampel and Kern.<sup>6</sup> It produces a nonlethal variety of pancreatitis following intravenous infusion of supramaximal doses of caerulein (5 and 10 µg/kg/h) or repeated intraperitoneal injections (4 hourly injections of 20 to 40 µg/kg body weight) in rats, mice, dogs and hamsters but not pigs.<sup>3,4</sup> This stimulus leads to

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morphological changes in the pancreas that resemble those found in human acute interstitial oedematous pancreatitis.<sup>4,6</sup> Although unrelated to the most frequent clinical aetiologies, gallstones and ethanol, this model appears to mimic the pathophysiology of acute pancreatitis induced by scorpion toxin<sup>7,8</sup> or anti-cholinesterase insecticide<sup>9</sup> in man. Its mild and highly reproducible course has made this model a favourite for investigations of the cell biology and pathophysiology of pancreatitis.<sup>2</sup>

#### *Diet-induced Pancreatitis*

A haemorrhagic and lethal form of pancreatitis can be induced in mice by feeding a choline-deficient, ethionine-supplemented (CDE) diet. This model, reported by Lombardi and coworkers in 1975,<sup>10</sup> is species-specific and sex-specific. It involves administering a 0.5% level of ethionine to young female mice, 4 to 6 weeks old and weighing 10 to 14 g.<sup>11</sup> Although the relevance to the human disease is tenuous, the morphological alterations bear striking similarities.<sup>2</sup>

This model is well defined and appears to be a good approximation of severe necrotising human pancreatitis. It is suitable for studying the pathophysiological aspects of the disease and the potential benefit of an experimental therapy by measuring survival. By limiting the period of feeding the diet, one can control the mortality rate at any desired level between 0% and 100%, which allows a better application of the diet model for therapeutic trials or cell biological studies.<sup>12</sup> The small size of the animals used limits the ability to monitor the condition or evaluate any surgical procedures. To obtain valuable data, several pitfalls have to be considered. The extent of injury depends critically on the sex, age and weight of the mice. Special care has to be taken to guarantee that the intake of the CDE diet is identical between different experimental groups.<sup>11,12</sup>

#### *Pancreatitis Induced by Pancreatic Duct Injection*

The retrograde injection of bile salts into the pancreatic duct of animals is a simple and effective technique to produce a severe, rapid, and lethal variety of experimental haemorrhagic pancreatitis.<sup>3,4</sup> Virtually any detergent injected into the pancreatic duct under pressure will produce pancreatitis in laboratory animals (dogs,<sup>13</sup> rats<sup>14-16</sup>). Either slow infusion or injection through a cannula placed in the pancreatic duct at the ampulla is used. The severity of the induced lesion can be altered by varying either the pressure or the concentration of bile salts. The resulting pancreatitis, which evolves rapidly over 2 to 24 h, is characterised by oedema, necrosis and haemorrhage. This model may be used to study both the local and distant manifestations of pancreatitis and to test various treatment modalities.<sup>14-17</sup>

The concentration of the infused bile salt greatly influences the homogeneity of the inflammatory lesions.

Moreover, as the various bile acids have different toxicities in pancreatic tissue, it is essential to use only standardised bile acid solutions.<sup>17</sup> One of the compounds best standardised for this type of pancreatitis is sodium taurocholate; injection of 0.2 ml of a 3%, 4.5% or 5% solution induces haemorrhagic pancreatitis with 72-hour mortality rates of 24%, 71% and 100% respectively.<sup>14-16</sup> In parallel with the rising mortality rates, the different concentrations of sodium taurocholate are associated with different morphological severity. Aho et al<sup>14</sup> suggested that the detergent effect of taurocholate at high concentrations immediately breaks down the integrity of the proximal biliopancreatic duct. Bile salts leak into the local interstitium and fail to reach acinar cells at the periphery of the duct system. High concentrations of bile acids, therefore, cause rapid severe necrosis with a marked regional disparity in the degree of acinar destruction (massive in the head, absent in the tail).<sup>17</sup>

#### *Combined Secretory Hyperstimulation with Minimal Intraductal Bile Acid Exposure*

The above models have the disadvantage of being either too mild or too catastrophic to be altered. Invasive reflux models, using high concentrations of bile acids, cause early and severe necrosis with heterogeneous injury.<sup>17</sup> The noninvasive models produce homogeneous inflammatory lesions, that range between minimal necrosis in the rat<sup>6</sup> and severe necrotising injury developing over a variable time range in young female mice.<sup>11</sup>

In an attempt to overcome these shortcomings, Schmidt et al<sup>18</sup> described a method of producing acute pancreatitis in the rat by combining minimal intraductal bile acid exposure [glycodeoxycholic acid (GDOC) at very low (5 or 10 mmol/L) concentrations] with intravenous caerulein. This model produces homogeneous pancreatitis of intermediate severity and acinar necrosis that can be modulated at will. Pancreatic injury can be further increased and death potentiated by increasing the volume and duration of the low-dose intraductal GDOC infusion. The model produces pancreatic injury that is substantial enough to require therapy but not so severe that initiated treatment is too little too late. It therefore provides an opportunity to study innovative therapy aimed at preventing or limiting the necrotising phase of pancreatitis.<sup>18</sup>

#### *Pancreatitis Induced by Pancreatic Duct Perfusion*

The low-pressure duct perfusion model reliably produces acute pancreatitis in cats.<sup>19-21</sup> The main pancreatic duct is made permeable in one of several ways: the perfusion of GDOC along the main pancreatic duct, the administration of intragastric ethanol, the stimulation of pancreatic secretion into an obstructed duct, or the creation of acute hypercalcaemia. Activated pancreatic enzymes are then perfused through the main pancreatic

duct via a catheter inserted into the duct in the tail of the gland, and acute oedematous pancreatitis results. Perfusion pressure never exceeds 20 cm H<sub>2</sub>O, which is below the maximal secretory pressure in the feline pancreas.<sup>19-21</sup> Simultaneous infusion of 16,16-dimethyl-prostaglandin E<sub>2</sub> converts acute oedematous into acute haemorrhagic pancreatitis.”

This animal model is reliable, reproducible and relevant to the human condition, since either oedematous or haemorrhagic pancreatitis can be created. The aetiological factors—duct obstruction, bile reflux, ethanol ingestion, hypercalcaemia—have clinical relevance. It can be used to study the pathophysiology of the disease as well as potential treatments. There are, however, important limitations. The model is invasive and moderately complex. The low mortality rate means that death cannot be used as an endpoint. Cats are expensive to purchase and maintain.<sup>21</sup>

#### *Pancreatitis Induced by Vascular Mechanisms*

Vascular mechanisms include any impairment of pancreatic inflow and outflow or any disturbances of the pancreatic microcirculation. They are not standard tools to induce acute pancreatitis,<sup>22</sup> but are used for special purposes to investigate the pathophysiological relevance of circulatory changes in the disease. Pancreatic arteries can be occluded in different animal species (dogs, rats).<sup>22</sup> Because of the rich collateral network, the reproducibility is small. Pancreatic artery occlusion is not generally recommended as a standard model for studying acute pancreatitis. Temporary arterial occlusion is accompanied by a transient rise in circulating pancreatic enzymes, but there is no histological evidence of acute pancreatitis. Permanent ligation of pancreatic vessels induces pancreatic tissue necrosis and elevated pancreatic enzymes, depending on the integrity of the collateral network.<sup>22</sup> Complete occlusion of the venous outflow induces haemorrhagic necrosis of the pancreas.<sup>23</sup> Experimental disturbance of the pancreatic microcirculation, using the microembolic technique, has been carried out in different animal species (dogs, pigs and rats).<sup>22,24</sup> Retrograde injection of 20 µm polystyrene microspheres through a distal branch of the splenic artery induces necrotising pancreatitis in rats.<sup>24</sup> Systemic changes associated with acute pancreatitis such as circulatory, respiratory or renal changes can be studied in the venous and microembolic models.<sup>23,24</sup>

#### *Immunologically-mediated Pancreatitis*

The first authors to report an immunologically induced pancreatitis were Thal and Brackney,<sup>25</sup> by first infusing meningococcal or *Escherichia coli* toxin into the pancreatic duct of rabbits and goats and by intravenous injection of a 1:40 toxin solution 24 h later. This insult resulted in a haemorrhagic and necrotising pancreati-

tis.<sup>25</sup> An interesting model of autoimmune pancreatitis develops spontaneously in MRL/Mp mice.<sup>26</sup> On the whole, immunological models of pancreatitis have not been widely used. They tend to be more difficult to establish in the laboratory, have limited reproducibility and are expensive and of uncertain clinical relevance.<sup>22</sup>

#### *Pancreatitis Induced by Surgical Duct Ligation*

Surgical ligation of the pancreatic duct in most laboratory animals does not cause pancreatitis. Rodents, for example, develop pancreatic atrophy and apoptosis of acinar and ductal tissue but do not develop much inflammation or necrosis.<sup>27</sup> Thus ligation of the pancreatic duct in rodents has become an established model of chronic pancreatic atrophy and is frequently employed for studies investigating regeneration of the exocrine pancreas.<sup>3,4</sup> An exception to the rule is found in the American opossum. This laboratory animal has a long common channel between the biliary and pancreatic duct with a firm smooth muscle layer. When the common pancreatic bile duct is ligated, acute necrotising pancreatitis evolves.<sup>28</sup>

#### *Pancreatitis Induced by a Closed Duodenal Loop*

The closed duodenal loop (CDL) technique was first described in dogs by Pfeffer et al in 1957.<sup>29</sup> The duodenum is surgically closed above and below the duodenal papilla, and bile is diverted into the jejunum through an implanted cannula. Pancreatic oedema, haemorrhage and parenchymal necrosis develop within 9 to 11 h. The model is reproducible and, since it was first described, it has undergone several modifications and has been employed in various animal species (dogs, monkeys, rats).<sup>30-34</sup> The mechanism of acute pancreatitis is triggered by the reflux of duodenal contents into the pancreatic duct. Disadvantages of this model are the need for operative intervention, the unphysiological pressure levels created in the closed duodenal segment and the pancreatic duct, and the uncertain role of bacterial infection. The role of duodenal reflux in the pathogenesis of acute pancreatitis in man is a matter of controversy, so the clinical relevance of this model seems limited. These drawbacks, along with the availability of other models, have lessened the popularity of the CDL model.<sup>34</sup>

#### *Alternative Approaches*

To transform mild oedematous pancreatitis into a more severe form, several alternative approaches have been described. Mild caerulein-induced pancreatitis in mice can develop into a necrotising form by repeated injections of supramaximal doses of peptide, but this form of pancreatitis causes no deaths.<sup>35</sup> Intensive stress over several hours (by water immersion at 23°C) can also transform caerulein pancreatitis into haemorrhagic disease.<sup>36</sup> However, the degree of acinar necrosis was no

greater in the caerulein/stress group, and again no deaths occurred. It is also possible that the development of pancreatic haemorrhage in this model was caused by hypothermia.

### **Clinical Relevance of Experimental Acute Pancreatitis**

Human acute pancreatitis encompasses a wide spectrum of severity, ranging from mild self-limiting inflammation to haemorrhagic necrosis which leads to multiple organ failure syndrome and death. Many aetiological factors have been associated with pancreatitis, but once the process has been initiated, the ultimate outcome is relatively independent of the causative agent. Gallstones and alcohol abuse cause 80% of cases of human acute pancreatitis, yet there are no strictly comparable animal models.<sup>37</sup>

Conversely, agents commonly employed to create experimental pancreatitis, such as caerulein and CDE diet, are not known to cause human pancreatitis. Existing models can reproduce the morphology and physiological derangements of certain phases of the illness. Since it is poorly understood how pancreatitis is caused by the passage of gallstones or alcohol consumption, and since there are no models that recreate the human situation, experimental models should be viewed simply as research tools to help understand specific phenomena occurring during the evolution and progression of acute pancreatitis. As such, their relevance to the human disease is limited to the phase of the illness that they most closely mimic. Depending on the agent or action that was used to induce pancreatitis, various models are suited only for specific pathophysiological or therapeutic questions.\*

Most existing models of acute pancreatitis are of limited use in studying novel therapies. Whereas some produce mild non-lethal pancreatitis, others result in sudden necrotising injury. Despite the plethora of experimental models, it is hard to identify a new treatment that has originated from laboratory investigation. Most animal studies of treatment strategies demonstrate a positive response. Conversely, very few human trials demonstrate the efficacy of a pharmacological intervention. Although the human pancreas can show a similar histological injury to that of experimental models, the method of induction and the course of illness are quite different. Another reason for the differences in experimental and clinical trials is the timing of therapy. Most experimental studies have demonstrated an agent's efficacy when an animal has either been pre-treated or receives the agent shortly after the induction of pancreatitis. This type of early intervention is difficult to achieve in human disease.<sup>2,3</sup>

### **Criteria for Selecting a Model of Acute Pancreatitis**

The choice of model depends on the objective of the

particular study. The onset, development, severity, extent of the acute inflammatory process and associated mortality rate vary considerably between models, and these facts must be taken into account when planning the experiment. Selecting the appropriate pancreatitis model determines the validity and interpretation of the results, especially with regard to the effects of therapeutic agents. The requirements to monitor the pancreatitis will also influence the size of laboratory animal chosen and the type of noxious agent.<sup>38</sup>

The models for inducing all degrees of acute pancreatitis in the rat and mouse are highly standardised and are therefore appropriate for over 90% of investigations. The caerulein model is recommended for the induction of oedematous pancreatitis. It is easy and reliable in most species other than the pig.<sup>3,39</sup> If a model of necrotising pancreatitis is required, the bile reflux model with or without caerulein should be used. The rat is an ideal animal for these experiments. Alternatively, necrotising pancreatitis can be induced by administering a choline-deficient ethionine-supplemented diet, but only in young female mice.<sup>38</sup>

Once the model of experimental pancreatitis has been determined, the most suitable animal must be selected. Small animals such as mice or rats usually suffice for studies on the aetiology, cellular and molecular biology, and pathophysiology of pancreatitis. Mice and rats are good subjects for simple serum monitoring and the registration of survival. For extensive monitoring with regular measurement of several serum parameters, or if the effects of surgical procedures (e.g. drainage systems) are to be tested, then larger animals are advisable (e.g. dog, pig).<sup>38</sup>

### **Standards in Monitoring Acute Experimental Pancreatitis**

After the suitable experimental model of pancreatitis has been selected, the next step is to set up a monitoring schedule. To standardize the test results and make them comparable, the experimental plan should include basic monitoring. Even when well-recognized models of pancreatitis are used, such as caerulein infusion, retrograde taurocholate injection or choline-deficient diet, the diagnosis of acute pancreatitis should still be checked. If the model used is new or is a modification of an established model, conclusive proof that acute pancreatitis has in fact been induced must be provided on the basis of enzyme measurements and histology. In this connection the reproducibility of the results is mandatory.<sup>38,40</sup>

Objective parameters must be used to confirm that the experimental model can induce pancreatitis and to determine the severity and extent of the pancreatic inflammation. These parameters include: (1) measurements of pancreatic serum enzymes (amylase and / or lipase); (2) histological examination of the pancreas; (3) mortality

rate and (4) morbidity rate.<sup>38,40</sup>

### 1. Serum enzymes

The progression of acute pancreatitis can be simply monitored by measuring serum levels of pancreatic enzymes. Serum amylase is the pancreatic enzyme most commonly analysed, but lipase is an alternative.<sup>38</sup>

### 2. Histology

Histological examination is a simple and reliable method for determining the severity of the pancreatic inflammation and the extent of oedematous and necrotic lesions. Acute pancreatitis is characterised morphologically by oedema, haemorrhage, parenchymal necrosis and fat necrosis. The inflammation is accompanied by infiltration of polymorphonuclear leukocytes. According to the absence or presence of necrosis, the disease can be divided into interstitial (or oedematous) pancreatitis and haemorrhagic-necrotising pancreatitis. The severity of the disease can be graded in histological sections either by giving scores to the different types of morphological alterations or by determining the proportion of necrotic tissue of the total parenchyma. Grading the extent of tissue damage is essential when the effects of different therapies are evaluated, and several histological scoring systems have been described for this purpose.<sup>40-42</sup>

### 3. Mortality rate

The mortality rate following induction of pancreatitis is a key parameter, especially for the evaluation of new approaches to treatment. The total number of deaths must always be determined as well as the time interval between induction of pancreatitis and death.<sup>38</sup>

### 4. Morbidity rate

Severe human acute pancreatitis, as defined by the Atlanta International Symposium on Acute Pancreatitis (1992),<sup>43</sup> is associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst. Organ failure is defined as shock (systolic blood pressure less than 90 mmHg), pulmonary insufficiency ( $\text{PaO}_2$  60 mmHg or less) and/or renal failure (creatinine level greater than 177 mmol/L [2 mg/dl]). Similar objective measures of severity could be applied to the experimental models and would help to grade the degree of morbidity, which is essential in investigating the effects of new therapeutic measures. Parameters that could be assessed in experimental models include systemic blood pressure,  $\text{PaO}_2$  or pulmonary wet/dry weight ratio, and serum creatinine level.

Further analyses such as electron microscopy, immunohistochemistry, cardiovascular monitoring, monitoring of other organ systems and determination of other pancreatic enzymes are not standard procedures. They are reserved for more comprehensive investigations or

for specific purposes as dictated by the experimental design and objectives of the study.<sup>38</sup>

## Models of Chronic Pancreatitis and Their Relevance to Human Disease

Experimental models of chronic pancreatitis have been introduced by many investigators, but it is very difficult to produce morphological and functional alterations that resemble human chronic pancreatitis. Moreover, the relevance of these models to the human disease remains in question.<sup>5</sup> Chronic pancreatitis is characterised by the progressive destruction of exocrine parenchyma and its replacement by fibrous tissue. It is associated with various degrees of inflammatory cell infiltration and, in the later stages, destruction of endocrine tissue is also frequently seen.<sup>44,45</sup> Attempts reliably to induce chronic pancreatitis by feeding alcohol to rats or dogs have largely failed.<sup>5</sup> Although some investigators have reported parenchymal degeneration with fibrosis and protein plug formation after alcohol feeding in rats and dogs, others have been unable to confirm these results. The only consistent effect of alcohol ingestion was accumulation of lipid droplets in the basal cytoplasm of the acinar cell.<sup>46</sup>

In 1971 Sarles and colleagues<sup>47</sup> described pancreatic lesions in alcoholic male Wistar rats that resembled those in human alcoholic chronic pancreatitis. These lesions consisted of focal areas of acinar depletion, duct multiplication, protein plugs (sometimes calcified in the ducts) and sclerosis, and they developed in more than half the animals given 20% ethanol freely for 20 to 30 months. Other investigators using similar ethanol-feeding protocols were unable to produce alcoholic pancreatitis consistently in rats.<sup>48,49</sup> In female Wistar rats, Reber and co-workers<sup>48</sup> failed to substantiate the findings of functional or morphologic abnormalities of the pancreas after chronic alcohol ingestion for 2 years. The results of secretory studies obtained in Wistar and Sprague-Dawley rats are also contradictory. Both hyposecretion and hypersecretion of protein have been reported.<sup>47,50,51</sup>

The reasons for these conflicting data are unclear. Variation in caloric intake secondary to prolonged ethanol administration has been cited as a factor.<sup>50</sup> In an attempt to develop a reliable model of chronic alcoholic pancreatitis, Sprague-Dawley rats were fed a nutritionally adequate diet (Lieber-DeCarli diet) with 40% of carbohydrate calories replaced by ethanol.<sup>52</sup> All the ethanol-fed animals developed morphological changes akin to human chronic pancreatitis with focal areas of parenchymal degeneration, fibrosis, protein plug formation and tubular complexes. Others used a similar liquid diet with a composition equivalent to that of an average American diet but containing a 5% (wt/vol) concentration of ethanol.<sup>46</sup> Protein plugs and pancreatitis were not encountered, but lipid droplets accumu-

lated in the acinar and ductal cells. In another experiment, ethanol-induced pancreatic injury was potentiated by dietary unsaturated fat but only in 20% to 30% of rats.<sup>53</sup>

The combined effects of duct obstruction and alcohol administration have been explored to try and produce a more consistent model of chronic pancreatitis in the rat.<sup>54</sup> Histological and biochemical alterations that resemble chronic obstructive pancreatitis were provoked in male Wistar rats with temporary occlusion of the biliopancreatic ducts with Ethibloc, and the changes were maintained by daily alcohol (12 g/kg, 20% vol/vol) administration by gavage for 2 months. Another model of obstructive chronic pancreatitis in cats has involved narrowing the proximal main pancreatic duct to approximately 25% of its original diameter,<sup>55,56</sup> but the histological picture is dominated by atrophy and mild fibrosis rather than chronic inflammation.<sup>57</sup> The full changes of chronic obstructive pancreatitis may only ensue when the ductal epithelium is injured by intraductal injection of ethanol.<sup>57</sup>

The combination of persistent (ischaemic) injury and partial obstruction of the pancreatic duct has been used to induce chronic pancreatitis in adult mongrel dogs.<sup>58,59</sup> Ischaemia was produced by ligation and separation of the splenic artery branches to the left pancreatic lobe,<sup>58,59</sup> while incomplete ductal obstruction involved ligation and separation of the minor pancreatic duct and placement of a polyethylene tube in the major pancreatic duct. After six months the pancreas exhibited morphological, histological, and functional features that were similar to those of human chronic pancreatitis.

Several other models have been described, but they all have limitations in reliability, reproducibility and relevance to human disease.<sup>5</sup> In one such model in the rat, chronic pancreatitis was induced by repeated caerulein injections (20 µg/kg ip once a week) plus water immersion stress (at 22°C to the depth of the xiphoid for 5 h) for 16 weeks.<sup>60,61</sup> In another, chronic pancreatic damage was induced in the rat by repeated injections of L-arginine (5 g/kg ip followed by three injections of 2.5 g/kg over 10 days).<sup>62</sup> Pancreatic lesions akin to those of chronic pancreatitis have been reported in rats three weeks after a single injection of trinitrobenzene sulphonic acid (0.4 ml of 2% TNBS) into the pancreatic duct,<sup>63</sup> and oleic acid infusion has been used in dogs<sup>64</sup> and rats.<sup>65</sup> Occlusion of the rat pancreatic duct with acrylate or prolamine (Ethibloc) merely causes acinar atrophy and exocrine insufficiency,<sup>66,67</sup> and the same effect follows duct ligation.<sup>68,69</sup>

All these experimental models are characterised by varying degrees of acinar cell damage, with replacement by fibrotic tissue, patchy acute and chronic inflammatory cell infiltrates, and evidence of glandular atrophy. There is no clear relation between inflammatory cell

infiltration and the degree of fibrosis in any of them, which suggests that the changes reflect parenchymal destruction and scarring rather than true chronic infiltration.<sup>5</sup>

Recently, a new model of chronic pancreatitis in rats has been described involving a single injection of dibutyltin dichloride (8 mg/kg iv).<sup>70</sup> After 2 months extensive interstitial fibrosis is accompanied by an active inflammatory process. The model may be suitable for studying cellular interactions and mediators involved in the development of pancreatic fibrosis; T lymphocytes predominate among the inflammatory cells. One advantage of this model is that the pancreas is not manipulated directly. There is even a model of spontaneous chronic pancreatitis in a particular strain of rat (male Wistar Bonn/Kobori) in which all the animals develop typical changes by the age of three months.<sup>71</sup>

## Conclusions

Since the recognition of acute pancreatitis as a disease entity over a century ago, there have been many attempts to determine its pathogenesis and develop effective treatments. Because access to the pancreas is difficult and direct investigation in humans is fraught with risk, much of our current knowledge has been derived from experiments in animals. Experimental models have been particularly useful in highlighting the role of inflammatory mediators in severe acute pancreatitis.<sup>72</sup> Despite providing invaluable information concerning the mechanisms involved in early cellular events, pathogenesis and pathophysiology of acute pancreatitis, however, these models have not lent themselves to the development of effective new therapies.

No satisfactory model for chronic pancreatitis exists at present. Those that are available have not yet added appreciably to our understanding of the pathogenesis of this disease.

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