Symposium on diagnosis of pancreatic disease

Pancreatic function tests: The physiological background

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It would seem self-evident that a good knowledge of the physiology of pancreatic secretion should be a preliminary quest of the physician in order that deviation from normal function can be recognized and understood and that pancreatic function tests may be formulated and based on sound principles. To this end a number of questions must be posed. What is the function of the pancreas? How is the gland controlled? What measurements must be made to assess function? What are the normal ranges of the parameter measured?

Briefly the function of the pancreas is to provide the appropriate enzymes for the hydrolysis of food-stuffs so that absorption and further digestion can occur, and to provide electrolyte to carry the enzymes into the duodenum and there, with the secretions of the liver and Brunner's gland, provide the appropriate milieu for enzymatic action.

The Control of Pancreatic Secretion

The control of pancreatic secretion may be conveniently classified for descriptive purposes into three phases, according to the site at which the stimuli act to excite secretion.

1 CEPHALIC PHASE

Pancreatic secretion is initiated by unconditioned and conditioned reflexes which are evoked on eating a meal. The taste of food, its sight, the accompanying noises and smell all combine reflexly to excite efferent fibres lying in the vagus nerves (Preshaw, Cooke, and Grossman, 1966a and b; Sarles, Dani, Prezelin, Souville, and Figarella, 1968; Novis, Banks, and Marks, 1971). In the dog the amount of pancreatic juice is very small and it has a high enzyme content and is very viscid. Its physical appearance has been likened to glycerine. The main purpose of this phase of secretion is to mobilize the pancreatic enzymes, that is, to extrude them from the acinar cells into the acinar and ductule lumen.

2 GASTRIC PHASE

As food enters the stomach the gastric phase begins and here food acts as a stimulus to pancreatic secretion in two ways: (a) By distending the stomach to elicit long reflexes, the afferent and efferent fibres of which lie in the vagus nerves. The receptors are stretch receptors which have been described in the stomach wall. (b) By releasing gastrin, through short reflexes situated in the pyloric mucosa. The most important stimuli for this action are protein digestion products and distension of the pyloric antrum (Blair, Brown, Harper, and Scratcherd, 1966).

These vago-vagal reflexes and gastrin reinforce the effect of the cephalic phase reflexes in further mobilizing the pancreatic enzymes.

There is probably only a relatively small amount of electrolyte secreted by vagal action in these two phases. The action of vagus on fluid secretion varies considerably from species to species. In man the vagus appears to have little effect on electrolyte secretion.

3 INTESTINAL PHASE

The major secretion of electrolyte does not occur until the acid in the chyme produced in the stomach by gastrin and vagal action enters the duodenum where at least two hormones play a predominant role. These are secretin and cholecystokinin-pancreozymin (CCK-PZ).

Secretin released from the duodenal mucosa by the acid chyme is usually regarded as the major stimulus for water and electrolyte secretion by the pancreas. The most potent physiological secretin-releasing agent is hydrochloric acid, which is effective at pH 5.0 and less. Using the pancreatic secretion of electrolyte as the index of secretin activity it has been observed that more bicarbonate is secreted by the pancreas as the pH in the lumen of the gut falls from pH 5.0 to pH 3.0. Below this pH level, the secretion of pancreatic juice increases,

being related to the load of acid reaching the duodenum and jejunum and not the concentration of hydrogen ion (Preshaw *et al*, 1966b; Meyer, Way, and Grossman, 1970a and b; Meyer and Grossman, 1972).

Secretin in the blood is difficult to assay by ordinary bioassay techniques but its radioimmunoassay is now being carried out. From published studies the concentration of secretin in plasma of the fasting individual has been variously estimated to be less than 100 pg (Bloom and Ogawa, 1973) and 486 ± 150 (SD) pg/ml (Boden and Chey, 1973). Instillation of acid into the duodenum raises the concentration from below 100 to 110 pg/ml according to Bloom and Ogawa (1973) and in three subjects from 200 to 1150 pg/ml, 250 to 800 pg/ml, and 500 to 800 pg/ml according to Boden and Chey (1973).

It is difficult to be critical concerning these estimations as little has been published. If Bloom and Ogawa (1973) are correct then it would seem that secretin may not be the sole factor required to stimulate water and bicarbonate secretion. It may, however, be potentiated by concurrently released CCK-PZ or vagal activity (Grossman, 1971; Brown, Harper, and Scratcherd, 1967), or perhaps a second humoral agent known to stimulate pancreatic electrolyte secretion is also released. This humoral agent is vasoactive intestinal polypeptide but it has not yet been demonstrated to play a normal functional role in the response of the pancreas to a meal (Said and Mutt, 1970).

Cholecystokinin-pancreozymin

This hormone is released from duodenal and jejunal mucosa by the chemical action of foodstuffs in the lumen of the bowel and its main function is to stimulate the secretion of enzymes from the acinar cells (Harper and MacKay, 1948) together with a small amount of electrolyte (Case, Harper, and Scratcherd, 1969). It is also responsible for causing gallbladder contraction. The most potent agents which release CCK-PZ are neutral amino acids and fatty acids. In both man and dog the most effective are L-phenylalanine (Go, Hofmann, and Summer-skill, 1970; Ertan, Brooks, Ostrow, Arran, Williams, and Cenda, 1971a; Meyer and Grossman, 1972) and the long-chain fatty acids such as palmitic, stearic, and oleic acids (Meyer and Grossman, 1971). Hydrogen ion is also effective but weak when compared with amino and fatty acids (Meyer and Grossman, 1972).

In addition there is some evidence that CCK-PZ may be under the control of local reflex arcs (Berry and Flower, 1971; Ertan *et al*, 1971) and that long vago-vagal reflexes with receptors in the small

intestine may also contribute to enzyme secretion (Thomas, 1950).

The Chemical Nature of the Secretory Product

For the purposes of description the pancreatic juice can be divided into two components, one electrolyte and the other enzyme.

ELECTROLYTE COMPOSITION OF THE PANCREATIC JUICE

The pancreas secretes a clear, colourless fluid which has an osmolality identical to that of plasma (Case *et al*, 1968). It is alkaline with a pH of about 8 due to its high bicarbonate concentration. The cations are largely sodium and potassium whose concentrations are similar to but not identical with plasma; in the case of sodium the concentrations in the juice is 10-12 mM higher than in plasma (Case *et al*, 1968). The cation concentrations are independent of flow rate which contrasts with those of the anions, bicarbonate and chloride. As the flow rate increases so does the concentration of bicarbonate, to reach a plateau which may be as high as 150 mM. The chloride is reciprocally related so that the sum of the concentrations of bicarbonate and chloride is constant and independent of flow rate (Case, Harper, and Scratcherd, 1969).

Of the other ions present in pancreatic juice only calcium and magnesium have any practical significance. The divalent ions probably have two origins, one associated with enzyme secretion from the acinar cell and the other independent of enzyme from the centro-acinar and ductular cells.

THE ENZYME COMPOSITION OF PANCREATIC JUICE

Enzymes are secreted in parallel into the pancreatic juice and can be divided into a number of groups according to the substances on which they act, as proteolytic, amylolytic, lipolytic, and a miscellaneous group (Beck, 1973).

Proteolytic enzymes

These are subclassified into endopeptidases and exopeptidases. Endopeptidases such as trypsin, chymotrypsin, and elastase, hydrolyse peptide bonds along the length of the molecule, at specific sites according to the amino acid makeup of the substrate molecule. The exopeptidases, carboxypeptidases A and B and aminopeptidase, remove the terminal amino acids from the carboxyl and amino terminus of the molecule respectively.

Amylolytic enzymes

Pancreatic amylase attacks the 1-4 α bonds between

C and the oxygen, of the interior of the polysaccharide molecules, the products being maltose, maltotriose, and α -dextrose (five to eight glucose molecules linked by one to four α bonds).

Lipolytic enzymes

These enzymes are concerned with the hydrolysis of triglycerides, phospholipids and cholesterol esters.

Miscellaneous group

This consists of many enzymes, including ribonuclease, desoxyribonuclease, and collagenase.

The Measurement of Pancreatic Function

The fundamental premise of a test of pancreatic function is that the maximal secretory response of the gland bears a relationship to the mass of functioning tissue. In other words, if the pancreatic secretory cells have been destroyed or are in any way impaired in their function, the deficiency should be revealed by submitting the gland to a stimulus capable of eliciting a maximal response and comparing this response with the norm. It is one of the major problems in human pancreatic physiology to define the normal range of pancreatic function. The first problem is to decide which is the best parameter or parameters to use in order to measure pancreatic function. It would seem logical that either the concentration or output of an ionic species which is subject to an active transport mechanism should be used. There are only two ions which might satisfy this criterion, sodium and bicarbonate (Case, Scratcherd, and Wynne, 1970; Case and Scratcherd, 1974). The concentration of sodium in pancreatic secretion is close to that of plasma and it would therefore be impossible from the clinical point of view to distinguish between an active or passive secretion. As sodium constitutes more than 95% of the cations in pancreatic juice and the osmolality of the latter is identical with that of plasma and independent of flow rate, there would seem to be little extra knowledge to be gained from a study of sodium secretion which could not be obtained by measuring the volume of secretion.

Bicarbonate is the ion of choice, as it is subject to an active transport mechanism (Case *et al.*, 1970) and exhibits a large concentration gradient between plasma and pancreatic juice. The range of concentration in pancreatic juice observed in the duodenal aspirate from the normal subject varies from 80 to 150 mM/l.

It might be expected that the normal gland would be more capable than one damaged by disease of transporting bicarbonate up a higher concentration gradient as indicated by the concentration ratio of

bicarbonate between plasma and pancreatic juice. Take the two extremes of the so-called normal range quoted above 80 and 150 mM/l, then the plasma-pancreatic juice bicarbonate ratio would be of the order of 3.2 and 6.0 respectively. Could these concentration ratios be used as an index of function? In other words, does a low ratio indicate that the gland is failing?

The concentration of bicarbonate in pancreatic juice depends upon (1) the osmolality of the plasma, (2) the bicarbonate concentration in the plasma, (3) the rate of secretion of pancreatic juice, (4) the state of the secretory cell, (5) the sampling interval when the rate of secretion is varying. The concentration in the duodenal aspirate is determined in addition to these by (a) dilution of pancreatic secretion by bile and Brunner's gland secretion; (b) any gastric juice which may have entered the duodenum causing the bicarbonate concentration to be lowered by loss of CO₂ and dilution.

The pancreas may be stimulated either indirectly or directly. Indirect stimulation can be evoked in a number of ways: by sham feeding, by the intravenous injection of insulin to lower the blood sugar, by gastric distension, or by taking a meal or instilling foodstuffs directly into the stomach or duodenum. In the case of the first three methods the stimulus acts through the vagus nerves with also some vagal release of gastrin to mobilize the pancreatic enzymes.

The stimulus is usually weak and is not amenable to standardization and is therefore of little practical use. Stimulants placed in the stomach or small intestine are more easily standardized and evoke a mixed response of electrolyte and enzyme and are of greater practical value, particularly when assessing enzyme secretion. These methods depend upon the integrity of the nervous pathways, the degree of apprehension of the subject, and the integrity of the intestinal mucosa and the hormone-releasing mechanisms.

Direct stimulation of the gland is a more reliable technique and the availability of pure secretin and CCK-PZ makes their use the method of choice in most instances. Physiological studies indicate that indirect stimulation of pancreatic secretion by a meal causes the gland to secrete well short of its maximal secretory capacity. In dogs the mean secretion rate of fluid and bicarbonate attained about one-third and the peak rate of secretion only about two-thirds of the maximal capacity. In the case of protein secretion the mean secretory rate was about one-fifth of the maximal capacity and the peak rate about one half (Henrikson and Worning, 1969). In man the maximum bicarbonate output from endogenous release of secretin by acid in the duodenum was 26 m-equiv/hr which was significantly

lower than the maximal bicarbonate output stimulated by exogenous secretion of 41 m-equiv/hr (Rune and Worning, 1970).

The amounts of secretin and CCK-PZ released by a meal are quite small and it is their rather remarkable property of interaction with one another and with the transmitter substances released by vagal action to augment their primary action which counts for their effectiveness as pancreatic stimuli in the course of normal digestion (Grossman, 1971; Brown *et al*, 1967). Two methods of direct stimulation are used to evoke electrolyte secretion, single intravenous injections and continuous infusion of secretin.

After the intravenous injection of a pulse dose of secretin the secretion rate of pancreatic juice rises to a peak rapidly, whereas the bicarbonate concentration does not; it lags behind to reach a maximum value at some interval later. The bicarbonate concentrations then remain at a steady level, the duration of which is a function of the dose of secretin, so that the larger the dose the longer the plateau (Case *et al*, 1969). The concentration of bicarbonate then gradually declines. Thus the shorter the sampling interval and the larger the dose of secretin (within limits) the more likely is the concentration of bicarbonate in the aspirated sample to reach a true maximal value.

Once a steady rate of secretion has been established by the continuous infusion of secretin then the time interval of sampling is of less consequence. However, the concentration of bicarbonate does depend upon the rate of secretion; at low rates the bicarbonate concentration increases as the rate of secretion increases but when the duodenal aspirate exceeds 50 ml/min the bicarbonate concentration begins to fall (Wormsley, 1968).

There are several reasons why the measurement of bicarbonate concentration may not be an ideal parameter to distinguish between the normal gland and one in which function is failing: (1) the bicarbonate concentration may not depend upon the mass of functioning tissue; (2) concentration is a function of secretion rate, and, as the method of collection of the duodenal aspirate varies from clinic to clinic, with sampling varying from 10 to 80 minutes, standardization of methodology is important before comparison between different laboratories is possible.

Maximal bicarbonate output is likely to be a better index of functional capacity than is concentration alone. A relationship exists between the maximal secretory capacity of both bicarbonate and fluid and body weight (Banwell, Northam, and Cooke, 1967) and therefore presumably also of the pancreas. Supporting evidence from work on the dog has demonstrated that the maximal bicarbonate

response to secretin is directly related to pancreatic weight (Hansky, Tiscornia, Dreiling, and Janowitz, 1963).

Unlike the determination of concentration, reliable figures for output depend upon a complete recovery of all the secreted fluid, and, to be certain that this is achieved, some inert non-absorbable marker should be instilled into the duodenum.

The definition of the normal maximal secretory capacity has still not yet been satisfactorily established. Thirteen series of reports have been retrieved from the literature and the maximal secretory capacity was found to vary from 24.1 to 55.8 mM per hour. One of the largest series of normals has been reported by Wormsley (1971) who illustrates 23 individual results. When the rate of secretin (GIH) infusion was 4.0 CU/kg hr then the lowest maximal bicarbonate output was 24.9 mM/hr, and the maximum 55.8 mM/hr (mean 39.0 ± 8.5 (SD) mM/hr). It should be stressed that these results have been expressed in mM/hour although the collection periods have varied from 10 to 30 minutes and include responses to steady-rate infusion of secretin to produce maximal secretory rates and some are maximal rates achieved during the response to single intravenous injections. It should also be added that many of the normal subjects are patients 'unlikely to be suffering from pancreatic disease'. Finally in many of the series Vitrum secretin was used, a product known to have a variable potency and sensitive to rapid inactivation in solution.

The results so far reported in the literature confirm the cautious view of Wormsley (1972) that a bicarbonate output in response to stimulation at 2 CU/kg hr is normal if it is greater than 15 mM in 30 minutes and abnormal is less than 10 mM in 30 minutes. Intermediate values should be regarded as equivocal.

The Secretion of Enzymes

The acinar cells are the source of the enzyme of the pancreatic juice (Harper and MacKay, 1948), and as these cells form by far the greatest part of the pancreatic tissue, it might be expected on *a-priori* grounds that the enzyme output into the duodenum should be a better index than electrolyte outputs of the functional tissue mass. However, as in the case of electrolyte output, the normal range of enzyme secretory capacity is uncertain and therefore a dogmatic definition of the normal limits of function cannot be made. Direct stimulation has been carried out using CCK-PZ alone and in combination with secretin in various dose regimes (Wormsley, 1969; Wormsley, 1972). When acting alone the electrolyte-stimulating effect of CCK-PZ is quite small and

therefore not all the mobilized enzymes are swept out into the duodenum. When used in combination with secretin, there are two possible types of electrolyte response in addition to enzyme secretion. In combination with submaximal secretin stimulation, a marked potentiation of the action of secretin occurs so that not only is there an increase in the volume output but also an increase in bicarbonate concentration (Brown *et al*, 1967). When CCK-PZ stimulation is carried out during maximal secretin stimulation the increase in volume is only modest, and this is accompanied by a rise in chloride and a fall in bicarbonate concentration (Case *et al*, 1969). It should always be remembered that CCK-PZ has a dual action so that simultaneously with enzyme secretion the gallbladder contracts and the duodenal aspirate will be contaminated to varying degrees by gallbladder bile.

Indirect stimulation of the pancreas by administering a liquid meal containing protein, carbohydrate, and fat (Lundh, 1962) mimics the physiological intestinal phase of digestion and has been successfully used to test pancreatic function (Lundh, 1962).

The Secretion of Calcium and Magnesium

The study of calcium and magnesium in pancreatic juice has been pursued with less vigour than the other electrolytes.

When the isolated pancreas is perfused with a protein-free bicarbonate Ringer solution and secretion stimulated by secretin the concentration of calcium in pancreatic juice is about 25% of the ionized calcium in the perfusate (Argent, Case, and Scratcherd, 1973). This concentration is independent of secretory rate, except at very slow flow rates when the concentration of calcium parallels the amylase concentration which also increases. Following enzyme stimulation the output of calcium in pancreatic juice is increased in proportion to the total amylase secreted (Scratcherd and Case, 1973). Magnesium behaves in a similar fashion to calcium (Scratcherd, 1975).

The pancreatic ductular epithelium is sensitive to damage which is revealed by an increase in permeability (Case and Scratcherd, 1970). Damage to the pancreas brought about by submitting the gland to low-sodium or calcium-free environments increases the permeability of the gland, allowing molecules which do not normally appear in the juice to be secreted (Case, Harper, and Scratcherd, 1968) and the ionized calcium to equilibrate between perfusate and pancreatic juice (Argent *et al*, 1973).

Now that cannulation of the human pancreatic duct is possible, the functional integrity of the pancreatic epithelium could be tested by examining

the permeability of the gland to various probing test molecules. It remains to be seen, however, if such an approach would enable pancreatic dysfunction to be diagnosed at an earlier stage.

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Pancreatic secretory testing in 1974

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Numerous modifications have been suggested to improve the technique of analysis of pancreatic secretion following the introduction of secretin testing in the 1940s (Dreiling and Hollander, 1948; Dreiling, 1970) (table I). Few have offered any diagnostic advantage over the standard classical test (Lagerlöf) which would justify modification of the original protocol, namely, (1) gastroduodenal intubation and separate collection of gastric and duodenal secretions under constant suction; (2) sequential aspirations for 60 to 80 minutes following a submaximal hormonal stimulant, secretin (1 cl U/kg); (3) scrutiny of the aspirates for blood, enzymes, fluid and electrolytes, and cytology. Of these parameters, flow, bicarbonate concentration, and rate of enzyme secretion were observed to

characterize pancreatic secretion and define pancreatic function.

Lest there be any misunderstanding, I consider the combined secretin-pancreozymin test of Howat and Harper the absolute equivalent of the standard secretin test. I shall, however, base my remarks on my experience with the latter test of which almost 10 000 examinations have been done in my laboratory. The combined test was discontinued after 1000 tests because of the additional expense, more frequent reaction, the equivalence of information, and the lack of availability of CCK-PZ for clinical use in the USA.

Study of the normal population with a standard dosage of secretin, ie, 1 cl U/kg, enabled the establishment of normal ranges which were usually expressed as a 2 sigma minimum value (Dreiling, 1955), ie, (1) for volume 2.0 ml/kg; (2) for bicarbonate concentration 90 m-equiv/l; and (3) for enzyme amylase 6.0 U/kg.

For many years the emphasis was placed upon the minimal value of the normal range since for purposes of diagnosis attention was directed towards secretory deficiency states. Indeed, the patterns of secretion in the abnormal population were observed to be (1) total deficiency, ie, depression of all three parameters characterizing extensive destruction; (2) quantitative deficiency, ie, depression of flow but not bicarbonate concentration characterizing pancreatic ductal obstruction as seen in cancer; (3) qualitative deficiency, ie, depression

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1	<i>Changes in Technique</i>
	a Various hormonal combinations
	b Test meals
	c Synthetic hormones
2	<i>Changes in Technique of Stimulant Administration</i>
	a Subcutaneous
	b Continuous infusion
	c Intraduodenal
3	<i>Changes in Strength of Stimulus</i>
	a Fixed dosage
	b Augmented dosage
4	<i>Changes in Parameters Determined</i>
	a Intraduodenal lipase and trypsin
	b Faecal lipase and trypsin
	c Duodenal pH
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Table I *Recent modifications of the secretin test*