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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.

1	*Changes in Technique*	
	a	Various hormonal combinations
	b	Test meals
	c	Synthetic hormones
2	*Changes in Technique of Stimulant Administration*	
	a	Subcutaneous
	b	Continuous infusion
	c	Intraduodenal
3	*Changes in Strength of Stimulus*	
	a	Fixed dosage
	b	Augmented dosage
4	*Changes in Parameters Determined*	
	a	Intraduodenal lipase and trypsin
	b	Faecal lipase and trypsin
	c	Duodenal pH

Table I *Recent modifications of the secretin test*

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

of bicarbonate concentration but not flow characteristic of chronic pancreatic inflammation; (4) isolated enzyme deficiency, ie, depressed enzyme with normal flow and normal bicarbonate concentration as seen in nutritional pancreatic fibrosis; and (5) discordant secretion (hypersecretion), ie, increased flows. This was originally poorly understood but is now known to be characteristic of disease entities associated with hypertrophy and hyperplasia of the hepatic and pancreatic ductal systems as seen in cirrhosis, the Zollinger-Ellison syndrome and alcoholism.

These patterns of secretion for diagnosis, originally proposed by me (Dreiling and Janowitz, 1962; Dreiling, Janowitz, and Perrier, 1964), have stood the test of time, though they did pose a number of questions which had to be answered:

1 How complete and accurate was the recovery of duodenal drainage? It is clear that with very low or very high flow rates collection errors can occur but these can be corrected by a marker infusion technique. In clinical usage, however, these errors do not influence diagnostic accuracy (Dreiling and Janowitz, 1962), rather do they influence attempts at estimating or quantitating secretory capacity.

2 Is there justification for deemphasis of enzyme secretion in the diagnosis of pancreatic inflammation and pancreatic cancer? Despite an extensive trial and a considerable literature concerning the addition of enzyme stimulants such as prostigmine, urecholine CCK-PZ and caerulein to the secretin test, as well as the trial of a meal-stimulated-enzyme response test (Lundh test), there is no evidence that the enzyme data significantly increase the overall diagnostic accuracy (Dreiling, 1971). Let me emphasize, however, that I continue to determine enzyme secretion because there are instances of isolated enzyme defect. The pancreas comprises three separate parenchymal systems: (*a*) the endocrine cells; (*b*) the exocrine enzyme-secreting cells (acini); and (*c*) the exocrine electrolyte-secreting cells (ductular system). In diverse inflammatory and neoplastic pathologies these systems may be involved to differing degrees, a fact which is becoming more apparent from correlations of histological section, peroral visualization of the duct systems, and pancreatic exocrine function. I am opposed to the use of the Lundh test as a sole examination because the abnormal response, diminished enzyme concentration and secretion, does not permit the differentiation of inflammation from cancer. On the other hand, I strongly support the use of the Lundh test as a complementary procedure to the secretin test because it does offer information, ie, the digestive functional capacity, that the hormonal tests do not. Thus, following gastrectomy, whereas hormonal tests may indicate that the pancreas is capable of responding normally to exogenous stimuli, the Lundh procedure would correctly indicate that the gland does not respond normally under conditions of digestion. Neither result is erroneous; both furnish important clinical data.

3 Should the rate of bicarbonate secretion following secretin be used in addition to or instead of bicarbonate concentration as a diagnostic parameter? This is a question concerning which needless confusion exists. The answer is an unequivocal 'No'. It should be obvious that a low rate of bicarbonate secretion may arise either from a low flow rate combined with a normal bicarbonate concentration, ie, quantitative deficiency or pancreatic cancer, or a normal flow rate combined with a low bicarbonate concentration, ie, qualitative deficiency or pancreatic inflammation. In short, the use of the rate of bicarbonate secretion as a diagnostic parameter obliterates the difference between pancreatic cancer and pancreatitis (Dreiling, 1970) (table II).

Chronic Pancreatitis	{Low[1] [HCO_3]}	×	{Normal Volume}	=	{Low[2] HCO_3 Secretion}
Cancer Pancreatitis	{Normal [HCO_3]}	×	{Low[1] Volume}	=	{Low[2] HCO_3 Secretion}

Table II *Rate of bicarbonate secretion as diagnostic parameter*

[1]Characteristic defect parameter
[2]Indeterminate parameter

4 What are the pitfalls and what is the diagnostic accuracy of the standard secretion test for pancreatic cancer? In our hands, with experience of 5 000 cases, the accuracy range is around 90% (table III).

	Total No.	*No. of Errors*	*Percentage of Errors*
No pancreatic disease	2725	139	5·1
Proved pancreatic disease	1818	93	5·2
Indeterminate cases	500	(250)[1]	(50·0)[1]
Total series	5043	482	9·6

Table III *Diagnostic accuracy of 'standard' secretin test*

[1]Accepting a 50% error.

For pancreatic cancer, admittedly recognition is excellent for head lesions, good for body lesions, and poor or non-existent for tail lesions, since the abnormal pattern necessary for diagnosis depends upon the amount of pancreatic parenchyma obstructed by the tumour and thus excluded from the flow response (Dreiling *et al*, 1964; Dreiling, 1970, 1971). Are there alterations in the technique of secretion analysis which might result in a pattern of

secretion enabling the recognition of more tumours of the body, tail, and uncinate process of the so-called 'blind' areas in secretin testing? The answer, I think, may be 'Yes', and would employ precise estimation of secretory capacity or pancreatic ductular cell mass by an augmented secretory test. Furthermore, in the equivocal case, crucial information may be made available from secretory studies upon juice obtained directly from the pancreatic duct following peroral intubation.

The idea of an augmented test of pancreatic secretion, similar in concept to the augmented histamine test of gastric secretion, is not new. It was first proposed by me at a Ciba symposium in London

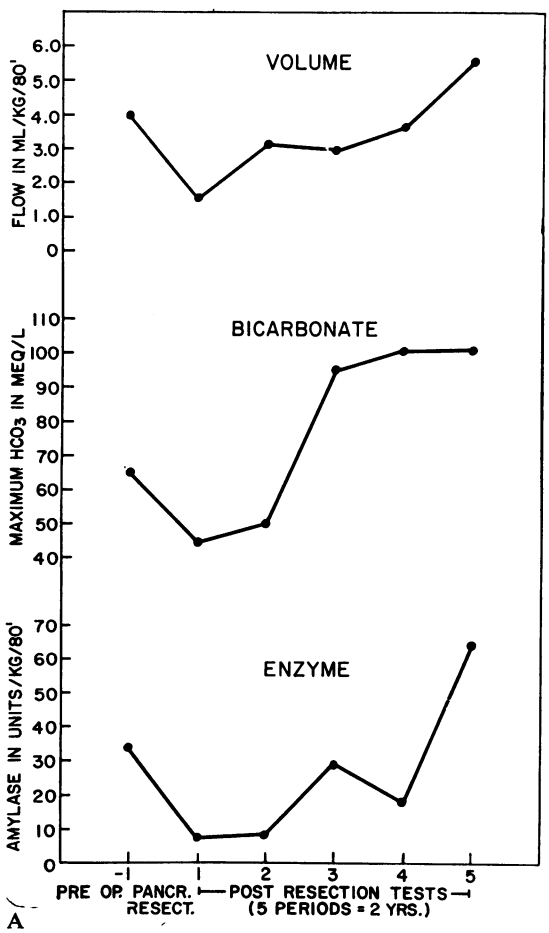
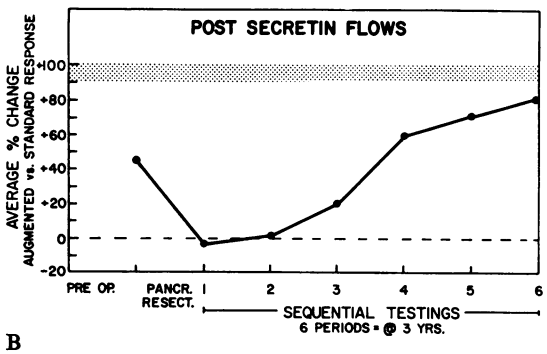
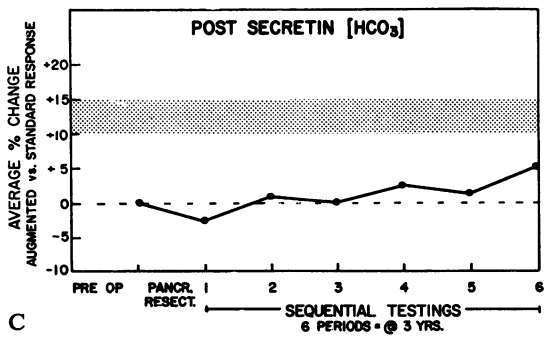


Fig *Evidence of pancreatic regeneration and functional recovery following major pancreatic resections in man. A Sequential secretin tests before and after resection, showing major loss of secretory capacity following resection and then gradual recovery of function with recovery after a two-year period beyond control levels*





B and C *Test secretin flows and bicarbonate concentrations expressed as a ratio between augmented and standard responses in operations before and after major pancreatic resection. The stippled area corresponds to the normal range of responses.*

in 1962 (Dreiling and Janowitz, 1962), to define the maximum secretory capacity of the pancreas. It required, however, the introduction of a purified secretin and the necessity to elucidate the pancreatic hypersecretory states to prompt a systematic investigation of standard and augmented secretory responses in the same patient with the expectation of defining the patterns of secretion for the augmented stimulus in individuals with and without pancreatic disease (Dreiling, Greenstein, and Bordalo, 1975).

That the pancreatic ductular mass can undergo dynamic change ranging from atrophy to regeneration by hypertrophy and/or hyperplasia can no longer be questioned. The affirmative evidence includes: (1) data from patients with hypersecretory states, ie, cirrhosis, haemochromatosis, Zollinger-Ellison syndrome, alcoholism (Dreiling, 1972; Dreiling, Greenstein, and Bordalo, 1973a); (2) observed augmentation of the pancreatic parenchyma in the experimental animal in response to administration of hormones trophic to the pancreas, ie, growth hormone, gastrin, CCK-PZ; (3) observed histological regeneration and functional recovery in animals and man after injury to the pancreatic

parenchyma followed by withdrawal of the noxious agent (Tiscornia and Dreiling, 1966a and b); (4) sequential studies of secretory capacity in man, specifically in alcoholics and following major pancreatic resection, indicating recovery and regeneration of pancreatic parenchyma (Dreiling and Bordalo 1973; Dreiling *et al*, 1973b) (see fig).

The protocol for the augmented test of pancreatic secretion (Dreiling *et al*, 1975) as used clinically in the Pancreatic Laboratory at Mount Sinai is as follows: (1) a standard secretion test using 1·0 cl U/kg of secretin and collecting sequentially for 80 minutes is routinely performed; (2) if the standard test shows an abnormal pattern of secretion or if pancreatic disease is strongly suspected, this standard test upon completion is followed seriatim by the augmented test employing 4·0 cl U/kg secretin; (3) the data of the augmented response are interpreted not only in accordance with classical patterns of secretion derived for the standard test, but more importantly the response parameters of the standard test are compared with the corresponding parameters for the augmented test. The ranges of normalcy for the augmented test have been derived from the data of patients without pancreatic disease (table IV).

	Standard	*Augmented*
Volume (ml/kg)	2·0-4·4	4·5-8·1
HCO_3 (m-equiv/l)	90-130	93-141
HCO_3 (m-equiv)	12·2-31·0	22·5-58·9
Amylase (μ/kg)	6·6-35·2	8·3-65·1

Table IV *Normal ranges established for augmented and standard testing ± 2SD*

Our growing experience with augmented stimulation has permitted the following observations, hypotheses, and conclusions.

Augmentation of stimulation appears to enhance the specific secretory defect in pancreatic inflammation and pancreatic cancer and may, therefore, be expected to increase the diagnostic accuracy of secretion analysis. Whether this procedure will enable the recognition of a majority of tumours in the body and tail remains to be proved by greater experience.

Under certain circumstances, the augmented response is identical to the standard response, indicating the definition of a maximum secretory capacity for flow and electrolyte. This delineation of the pancreatic ductular cell mass is of enormous interest from the physiological and clinical point of view, and permits direct quantitation of pancreatic regeneration following major pancreatic resections.

Comparison of standard and augmented secretin responses in the same patient permits the description of a secretory pattern for the normal patient which is distinct from that observed in the patient with pancreatic inflammation and pancreatic cancer. Three patterns of secretion have been deduced from analysis of standard/augmented secretion data in over 500 patients:

Normal

The application of an augmented secretion stimulus in the normal patient affects the discriminative parameters of the standard response in the following manner: flow is increased 100%; bicarbonate concentration is increased 15%; and the amylase secretion rate is increased 30%.

Chronic pancreatitis

The application of an augmented secretin stimulus in patients with chronic pancreatitis alters the standard response as follows: flow is increased 40%; bicarbonate concentration is fixed or decreased; the amylase secretion rate is increased 30%.

Pancreatic cancer

The augmented responses in the patient with pancreatic cancer upon comparison with the standard response yield the following patterns: flow is increased 15% or is fixed; bicarbonate concentration is increased 10%; and amylase secretion is increased 30%.

We have used the standard/augmented test to evaluate the response of patients with chronic pancreatitis to various resectional and ductal decompression procedures. The data allow of a very accurate assessment of the secretory parenchyma following major resections and also observation as to whether or not the surgery resulted in improvement of function. In the majority of patients, the initial post-resection studies show a marked loss of secretory response. The standard and augmented tests do not differ. Sequential testing in these patients has demonstrated the ability of the gland to recover secretory capacity.

As to the future, other avenues of secretion analysis will be provided by the application of peroral pancreatic duct cannulation. With the availability of pure uncontaminated pancreatic juice, albeit in very small quantities, it will be possible to obtain (1) direct analysis for blood; (2) more consistent and rewarding cytological diagnosis; (3) characterizations of protein secretion profiles specifically searching for serum constituents such as lactoferrin and specific cancer antigens such as CEA; (4) more precise pancreatic cellular metabolic investigations employing radio isotope-based techniques.

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The Lundh test in the diagnosis of pancreatic disease: A comment from the Moderator

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Dr Dreiling's excellent account of the value of the secretin test for the diagnosis of abnormal pancreatic function is based on a large experience gained over many years. Many workers, however, find the secretin test impracticable and the results difficult to interpret. The busy clinician needs a simple test of pancreatic function with a reasonable diagnostic success rate. Our experience, based on data from nearly 1000 patients, suggests that the Lundh test of pancreatic exocrine function (Lundh, 1962) fulfils these criteria. Moreover it is physiological and inexpensive in terms of resources (Cook, Lennard-Jones, Sherif, and Wiggins, 1967; Mottaleb, Kapp, Noguera, Kellock, Wiggins, and Waller, 1973). Other workers have reported similarly (Levin, Youngs, and Bouchier, 1972; Zeitlin and Sircus, 1974).

Estimation of exocrine function by any method has a limited diagnostic value because the range of normal is wide and very extensive pancreatic damage or duct obstruction must be present before pancreatic function is markedly diminished. Severe focal pancreatic destruction may be present without alteration of exocrine secretion; patients with non-gastrointestinal disorders may have abnormally low pancreatic function. The Lundh test is frequently criticized on the grounds that it is not a function test in physiological terms because the pancreas is stimulated indirectly. It is therefore important to determine whether under clinical conditions this procedure is as useful as the secretin test in the diagnosis of pancreatic disease. Preliminary comparisons have suggested that it is (Waller, Kapp, Noguera, Kellock, and Wiggins, 1972; Lurie, Brom, Bank, Novis, and Marks, 1973). We have now extended our comparison of the two tests. Twenty patients with non-gastrointestinal disorders acted as controls. These patients and 21 patients with pancreatic disease proven by means other than a function test had both a Lundh and a secretin test. The Lundh test was performed as described previously (Cook *et al*, 1967; Mottaleb *et al*, 1973). For the secretin test, Jorpes secretin was given by intravenous infusion for two 40-minute periods at doses of 1 and 2 clinical units/kg/hour. Ten-minute collections of duodenal juice were made throughout the test. Limits of normal were calculated for the following variables from the data on controls: the maximum bicarbonate concentration/10-minute period, the maximum bicarbonate output/kg/30 minutes, and the maximum volume secreted/kg/half hour. The latter two variables were calculated from the three consecutive 10-minute collections during the 80

	Chronic Pancreatitis	*Pancreatic Carcinoma*
No. of patients	13	8
Lundh successful	13	8
Secretin successful	13	6
Lundh abnormal	9	7
Secretin abnormal	8	5

Table I *Comparison of Lundh and secretin tests*

	Chronic Pancreatitis	*Pancreatic Carcinoma*
Lundh abnormal, Secretin normal	1	1
Lundh normal, Secretin abnormal	0	1
Lundh suggests carcinoma, Secretin no lead	0	2
Lundh no lead, Secretin suggests carcinoma	1	2

Table II *Lundh and secretin tests in the differential diagnosis of chronic pancreatitis and pancreatic carcinoma*