A REVIEW OF TESTS OF GASTRIC ACID SECRETION AND THEIR APPLICATION IN CLINICAL PRACTICE*

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It is nearly 150 years since Prout[1] first demonstrated that the acid present in the human stomach is hydrochloric acid. Soon aferwards, when Alexis St Martin had regained his strength after being accidentally shot in the upper abdomen on 6 June 1822, Beaumont[2] began his historic series of experiments. Bassow and Blondlot[3] established gastric fistulae in dogs; but it was not until 1869, when Kussmaul[4] reported that aspirating the stomachs of patients with pyloric obstruction afforded them symptomatic relief and prolonged the lives of many, that intubation of the stomach became an acceptable clinical procedure.

Thereafter interest in the stomach and its contents increased rapidly. A method for titrating gastric juice with sodium hydroxide was introduced by Szabó,[5] 'degrees of acidity of the gastric juice' were postulated by Jaworski and Gluzinski,[6] and Ewald and Boas[7] suggested their test breakfast, which consisted of 35 G white bread and either 400 ml. water or 2 glasses of tea.

At the turn of the century fractional test meals were probably performed on most patients with gastro-intestinal complaints. The tips of the stomach tubes used were continually being modified so as to permit easier extraction of the gastric contents, and in 1917 Crohn and Reiss[8] suggested that gruel was a more satisfactory stimulant than the test breakfast. In 1921 Bennett and Ryle[9] published a chart indicating the limits of 'hyperchlorhydria', 'hypochlorhydria' and 'achlorhydria', and soon the gruel fractional test meal was accepted as the standard test for estimating the ability of the human stomach to secrete hydrochloric acid.

But the fact that gruel buffered some of the secreted acid and the technical difficulties of titrating a mixture of gastric juice and undigested gruel encouraged the search for alternative stimuli of gastric acid secretion. Popielski[10] noted that the intravenous or subcutaneous administration of histamine to dogs provoked a secretion of an acid gastric juice. Several gastro-enterologists[11-13] saw the opportunity of using histamine in place of gruel in the fractional test meal and in the 1930s and 1940s the histamine 'fractional test meal' was extensively employed in clinical practice. The dose of histamine used was usually 0·01 mg./kg. body-weight. It was demonstrated that about half the patients suspected of having achlorhydria after gruel fractional test meals were capable of secreting significant quantities of acid in response to histamine,[14] and it was confirmed that patients with duodenal ulceration secrete more acid than normal individuals[15] and that patients with pernicious anaemia have achlorhydria which persists after the anaemia has been successfully treated.[16]

However, before long there were suggestions[17,18] that histamine, in a dose of 1·0 mg. or less, was in some instances an inadequate stimulus for gastric acid secretion; but the known side-effects of histamine precluded the use of bigger doses.

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Kay[19] was impressed by the observation of Halpern[20] that the antihistamine compounds antagonized all the effects of histamine other than those on gastric secretion. Kay studied the effect of increasingly large doses of histamine on the acid secretion by the human stomach, the untoward effects of the drug having been prevented by the injection of an antihistamine, and found that 0·04 mg. histamine/kg. body-weight produced the maximum response and that no further increase in the secretion of acid occurred when as much as 12 times the previous standard dose of histamine was administered. The augmented histamine test (AHT) has been extensively used in recent years and has proved of much value in clinical gastro-enterology.

In 1961 Gregory and Tracy[21] succeeded in isolating gastrin, and recently a synthetic gastrin-like pentapeptide underwent clinical trial.[22] This drug will probably soon become available for routine use.

It seems an appropriate moment, therefore, to review the present position of tests designed to indicate qualitatively and quantitatively the presence of acid in the stomach and to discuss the clinical application of such tests.

TECHNIQUES

Qualitative Techniques

A suitable tube is passed into the stomach and the contents are aspirated. The reaction is tested against litmus or a multi-range pH-indicator paper. If there is no acid in the aspirated juice, histamine acid phosphate 0·5 mg. can be given subcutaneously and the stomach contents aspirated half-an-hour later. If there is still no detectable acid in the gastric juice it is advisable to perform a test of maximal stimulation.

In an attempt to overcome the necessity for intubation, Segal *et al.*[23] devised the method of 'tubeless gastric analysis'. The principle of this technique is that a suitable cation exchange resin is dissociated by the hydrochloric acid in the stomach. The cation is absorbed into the bloodstream and excreted in the urine, where the quantity of cation can be estimated. A suitable cation is the dye azure A. This is used in 'Diagnex blue' (azuresin). Segal *et al.*[23] originally used caffeine benzoate as parietal-cell stimulant, but the histamine isomer betazole hydrochloride (Histalog) can also be used.[24]

Test procedure. After an overnight fast the bladder is emptied and the urine discarded. The patient is given either 500 mg. caffeine benzoate or 50 mg. betazole hydrochloride in a glass of water. One hour later the bladder is emptied again and the 'control' urine specimen collected. The patient is then given 2 G of the granules containing the dye azure A in a glass of water and instructed not to drink anything during the next 2 hours, at the end of which time the 'test' specimen is obtained. The colour of the 2 urine samples is then compared in a simple comparator block with standards supplied by the manufacturers.

A review of the literature in 1961[25] indicated that 146 false-negative results (7·1%) and only 27 false-positive results (1·3%) were detected in 2,054 tubeless analyses which were checked by gastric intubation; more recent experiences give similar results.[26] False-negative results are not a source of worry, because negative results will usually be confirmed by intubation of the stomach. False-positive results appear to be extremely infrequent when the test is properly performed. It is advisable to stop administration of iron tablets a few days before the test, and caution should be exercised in the interpretation of the test in patients where absorption or excretion of the dye may be impaired.

Quantitative Techniques

The augmented histamine test (AHT).[19] After an overnight fast a radio-opaque tube is slipped through the nostril and positioned under radiological control to lie in the most dependent part of the stomach, immediately to the left of the vertebral column. It is important that the tube is not coiled in the fundus of the stomach, because this extra length of tube may allow it to enter the duodenum during the course of the test. In a patient who has had a partial gastrectomy the tube is advanced until the tip is about 4 inches beyond the gastro-oesophageal junction. When the tube is in position it is strapped to the side of the face.

The fasting contents are aspirated. To achieve this the patient may have to be turned from side to side and sat forward. The patient is then turned slightly onto the left side. Either by continuous suction of about 13 mm.Hg, which is interspersed by regular syringe suction and the blowing of air down the tube to ensure that the tube remains patent, or by continuous syringe suction, the spontaneous secretion (basal acid output—BAO) is collected. This is continued for an hour. Midway through the hour the antihistamine (50 mg. mepyramine maleate is a suitable drug) is given intramuscularly. At the end of the hour histamine acid phosphate in a dose of 0·04 mg./kg. body-weight is given intramuscularly. The juice is collected for another hour (the maximal acid output—MAO).

It is customary to pool the first and second ½-hour collections of the BAO separately and to pool the post-histamine secretion at 15-minute intervals. If, during the course of the test, bile-stained gastric juice is aspirated, it may mean that the tube has entered the pylorus, although in a proportion of patients bile does appear in the aspirate at some stage during the progress of the test. Ideally the position of the tube should be checked again, but in practice shortening the tube by ½ - 1 inch often stops the bile reflux.

Wherever possible, only trained personnel should perform the tests. In this way collection errors are minimized. Some patients swallow air and recovery of the secreted juice is easy, but in other patients the juice is only aspirated after air has been blown down the tube. It does need some practice before reliable and reproducible augmented histamine tests are obtained.

Undoubtedly, swallowed saliva will buffer some of the secreted acid, and if the patient is secreting a lot of saliva he should be asked to spit it out. But the majority of patients will become sleepy after the injection of the antihistamine, and salivary secretion will be at a minimum.

Augmented histamine tests can be performed on persons of any age. Hypertension, bronchial asthma or a history of allergy is not a contraindication to the performance of the test. Unpleasant reactions are rare, but the odd patient may have a headache at the end of the test. The warm flush that reaches its maximum between 10 and 20 minutes after the injection of the histamine may be unpleasant on a hot summer's day, but lasts no more than 10 - 15 minutes.

Kay[19] demonstrated that the augmented histamine test gives consistent results when the test is repeated in the same individual, and Card and Marks[27] found that there was a close correlation between the MAO and the number of parietal cells in the stomach—the parietal cell mass.

The mean BAO for men has been found to be 2·4 mEq./hour (range 0 - 17·1 mEq./hour) and that for women 1·3 mEq./hour (range 0 - 15·0 mEq./hour).[28]

Card and Sircus[29] reported that the mean MAO of 29 males was 22·7 mEq./hour (range 10·1 - 41·5 mEq./hour) and that of 28 females 17·2 mEq./hour (range 6·2 - 34·6 mEq./hour); and Marks[30] commented upon the fact that augmented histamine tests performed in different centres in the western world yielded remarkably similar results. A study in India[31] revealed a considerably lower mean MAO for men (10·2 mEq./hour) and women (7·0 mEq./hour) than that reported from the western countries. Other Indian workers[32] have suggested that this might be because histamine acid phosphate, in a dose of 0·04 mg./kg. body-weight, may not always be a maximal stimulant for individuals weighing less than 60 kg.

Ever since the introduction of the augmented histamine test, clinicians who have used the test extensively have wondered to what extent maximal histamine stimulation mirrors physiological events in the stomach, such as that occurring after the ingestion of food. Rune,[33] in an elegant manner, has shown that it probably does. He estimated acid secretion by measuring the increase in base concentration of arterial blood—the 'alkaline tide'—after the ingestion of solid food and compared these results with the amount of acid secreted during augmented histamine tests performed on other days. Twenty-two patients were studied. The mean acid secretion after a meal was 31 mEq./hour (range 0 - 56 mEq./hour), whereas that during the augmented histamine test was 32 mEq./hour (range 0 - 59 mEq./hour).

The histamine-infusion test (Lawrie, Smith and Forrest).[34] A steady state of gastric secretory activity can be induced by a continuous infusion of histamine, and the above workers found that a maximal plateau can be obtained with a dose of histamine acid phosphate of 0·04 mg./kg. body-weight/hour. They advised that a small dose of antihistamine should be given at the start of the infusion, but this is probably not necessary. Although the amount of acid secreted during the infusion test is higher than that secreted during the AHT, it is unlikely that the infusion test will replace the AHT because it is a lot more cumbersome to perform. A constant infusion apparatus is needed and the histamine has to be given intravenously. It has not been demonstrated that the test reduces the considerable overlap in the acid secretion which exists between normal individuals and patients with duodenal ulceration, nor has it been reported that a patient with AHT-fast achlor-

hydria was able to secrete acid after the intravenous infusion of the same dose of histamine.

Maximal Histalog test (Kirsner and Ford,[35] Wormsley and Grossman[36]). Betazole hydrochloride (3-(beta-aminoethyl) pyrazole) (Histalog) has in recent years become increasingly popular in the USA as a stimulant for gastric secretion because it has been found that the drug is a potent stimulant and has few side-effects.

The amount of acid secreted in response to various doses of Histalog has been compared with the amount of acid secreted after maximal doses of histamine. It was found that, whereas less acid was secreted after 50 mg. Histalog, more acid was secreted after 100 mg. and 200 mg. Histalog.[37] However, with the higher doses of Histalog, side-effects such as nausea, dizziness, headache and sudden collapse occurred, and 'because of these experiments, we are reluctant to recommend a "standard" dose of 2·0 mg./kg. of Histalog in the "maximal Histalog test".'[38] Histalog, in a dose of 1·5 mg./kg. body-weight given subcutaneously, appears to elicit a response comparable to that of maximal histamine stimulation but with fewer side-effects.

The maximal Histalog test is performed in a manner similar to the AHT, except that the calculated dose of Histalog replaces the histamine and there is no need to give an antihistamine. The drug is relatively expensive.

Pentagastrin test (multicentre pilot study).[22] The results of a multicentre pilot study, in which the secretion in response to a synthetic gastrin-like pentapeptide ICI 50,123 was compared with that following augmented doses of histamine, have recently been published.[22] The maximal response to pentagastrin is achieved at doses of 6 μg./kg. body-weight subcutaneously or 6 μg./kg. body-weight/hour by intravenous infusion. The mean response to the subcutaneous administration of the synthetic pentapeptide was virtually the same as that to augmented histamine stimulation, although others[39,40] have found a greater response when using the naturally occurring hormone gastrin II. Furthermore, the response to a single subcutaneous injection of pentagastrin was found to be reproducible to a degree acceptable for clinical use.

Side-effects were mainly those of a slight headache and nausea; in no instance had the test to be abandoned because of the severity of the side-effects.

The pentagastrin test is performed in the same manner as that described for the AHT, but the dose of pentapeptide is injected intramuscularly after the spontaneous acid secretion has been collected.

Insulin test (Hollander).[41] The vagus nerve is stimulated by hypoglycaemia and in the normal individual this stimulation causes an increase in the volume and acidity of the secreted gastric juice. After division of the vagus nerve fibres this response does not occur. It is therefore possible to determine the intactness of the oesophagogastric portion of the vagus nerve by producing hypoglycaemia, which can conveniently be done by injecting soluble insulin intravenously.

After an overnight fast the nasogastric tube is passed and positioned as in the case of the AHT. The fasting contents are aspirated. A 1-hour basal secretion is obtained, pooling the collected juice at 30 minutes and again at 60 minutes, when 20 units soluble insulin are injected intravenously. The juice is collected for a further 2 hours and pooled at ½-hourly intervals. An hour after the injection of insulin a capillary blood sample is taken for blood-sugar determination.

The blood-sugar level should fall below 50 mg./100 ml.

Hollander[41] recommended that aliquots of the aspirated juices should be titrated against bromphenol blue (pH 3·5) to determine the concentration of 'free acid' and against phenol red (pH 7·0) to determine the concentration of 'total acid'. A positive response is indicated by a rise in the 'free acid' concentration of more than 20 mEq./litre (or more than 10 mEq./litre if the basal juice contains no acid) in any of the periods after the injection of insulin.

The majority of patients tolerate the test well, but some are upset by the sweating, tachycardia and the anxious sensation which they experience. The patients should, therefore, be under continuous supervision, and it may occasionally be advisable to end the hypoglycaemia abruptly with an intravenous infusion of dextrose.

Patients who have had cerebrovascular accidents, or those who have severe hypertensive heart disease, should preferably not be subjected to the insulin test, unless supervision is very close and adequate reason exists for doing the test.

Insulin tests can only be performed on patients in whom other tests have indicated that their stomachs are still capable of secreting acid.

Some of the problems in the interpretation of the insulin test are discussed in the section on duodenal ulceration.

Nocturnal secretion (Dragstedt).[42] After the tube has been passed and positioned in the most dependent part of the stomach, the contents are aspirated. The gastric juice secreted between 8 p.m. and 8 a.m. is collected by means of continuous suction.

Dragstedt postulated 'that the fasting nocturnal hypersecretion of gastric juice commonly displayed by duodenal ulcer patients was of nervous origin', and this led, in 1943, to his introduction of supradiaphragmatic division of the vagus nerve as a method of treatment of duodenal ulceration.[43] Discussing what he would do if he had a duodenal ulcer, Dragstedt[42] wrote, 'If I discovered that my stomach secreted in excess of 75 mEq. of free hydrochloric acid in a 12-hour period, as compared with the normal of 15 to 20, I would conclude that my problem was a serious one and that medical treatment might well prove inadequate'. He recently reiterated this viewpoint.[44]

Analysis of the Collected Specimens

Of each specimen of gastric juice collected, the following should be ascertained:

(*i*) the volume;
(*ii*) the concentration of titratable acid—expressed as mEq./litre;
(*iii*) the amount of titratable acid contained in each specimen—expressed as mEq. and obtained by multiplying the volume and mEq./litre and dividing by 1,000.

The correct method for determining the concentration of titratable acid (mEq./litre) has been, and is still to some extent, a matter for debate.

Prout[1] originally introduced the terms 'free acid', 'combined acid' and 'total acid'; he probably borrowed them from chemists of the time. After the description of a method for titrating gastric juice with sodium hydroxide[5,6] the concepts of the 'free acid' and the 'total acid' of the gastric juice gained general acceptance and were apparently firmly established by the experiments of Michaelis.[45] Töpfer's reagent (diaminoazobenzene), which changes from a red to a salmon-pink colour at pH 2·8 - 3·5, was accepted as the preferred indicator for 'free acid', and either phenolphthalein or neutral red was used to determine the concentration of 'total acid' in the specimen being titrated.

In 1961 attention was drawn to the fact that the shapes of the titration curves of gastric juice collected during histamine stimulation were similar to that of 0·1 N HCl (Fig. 1).[46] In none of the specimens titrated was there a flattening-off in the shape of the titration curve between pH 2·5 and 4·0 as had been the experience of Michaelis. It seemed likely, therefore, that Michaelis neglected to allow for the buffering capacity of the test meals which he used. It was suggested that the terms 'free acid', 'total acid' and 'combined acid' should be abandoned and that gastric juice should be titrated to pH 7.

Lubran[47] has recently advanced theoretical and experimental reasons why gastric juice should be titrated to pH 3·5. His thesis is that because gastric juice contains a strong acid, titration to pH 7 will always overestimate the true value, whereas titration to pH 3·5 (Töpfer's reagent) 'would provide an acceptable compromise (between the buffering capacities of the strong and weak acids contained in gastric juice) for the end-point of a titration method for gastric hydrochloric acid'.[47]

From a practical point of view, however, it should be noted that the shape of the titration curve of uncontaminated gastric juice is nearly vertical between pH 4 and 7, so that only a small amount of alkali is needed to advance the pH from 4 to 7. If the clinician is interested in mEq., the overestimation should in no way jeopardize the interpretation of his test: for example, it is not likely that the clinician will decide that because one of his patients secreted 6·0 mEq. of acid in an hour after maximal gastric acid stimulation this patient is less likely to have a carcinoma of the stomach than another patient who secreted an estimated 5·5 mEq. under the same conditions. On the other hand, if the clinician is to be guided by variations in the mEq./litre—as he would be when interpreting the insulin test—then it may be more correct to titrate to pH 3·5, when, as Lubran pointed out, the overestimation is small.

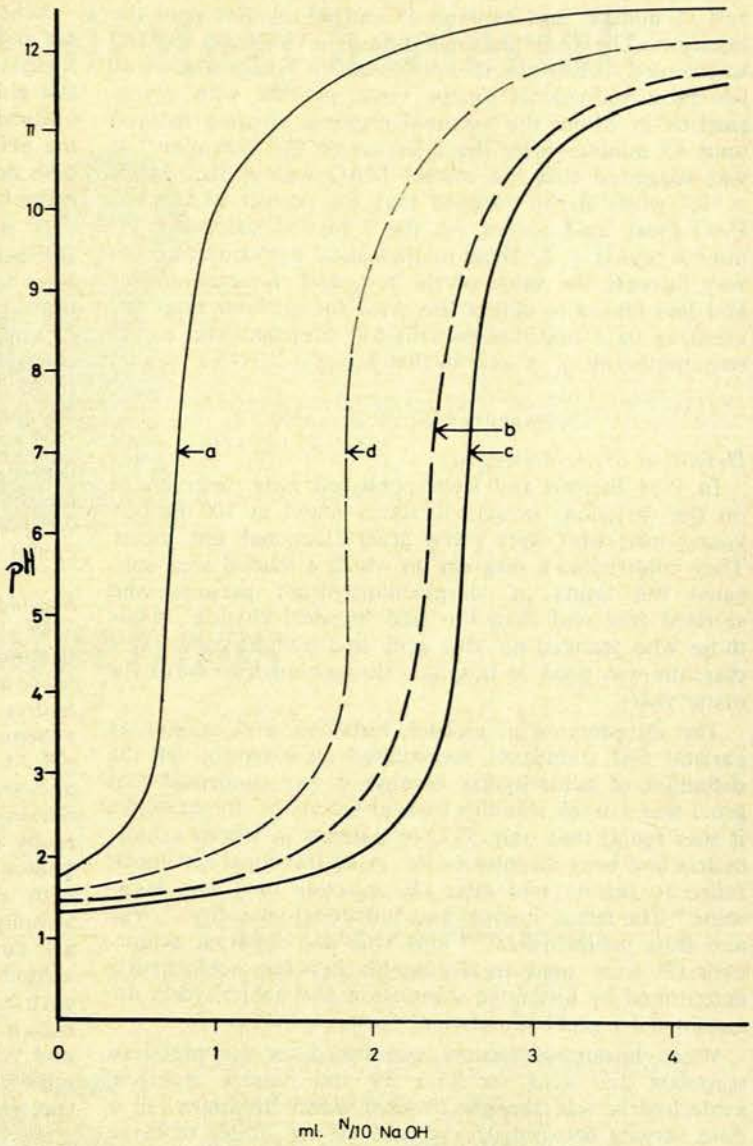

Fig. 1. The titration of 2-ml. aliquots of 3 samples of gastric juice (*a*, *b* and *c*) compared with the titration curve of 2 ml. 0·1 N HCl (*d*). Sample *a* was collected before histamine administration, whereas samples *b* and *c* were post-histamine collections.

Basal Acid Output (BAO), Maximal Acid Output (MAO) and Maximal Histamine Response (MHR)

The basal acid output (BAO), expressed as mEq./hour, is the product of the volume of the juice secreted during the basal hour and the concentration of titratable acid (mEq./litre) of that juice, divided by 1,000.

The maximal acid output (MAO), also expressed as mEq./hour, indicates the amount of acid secreted by the stomach after the injection of the parietal cell stimulant and is obtained by multiplying volume by mEq./litre and dividing by 1,000.

Unfortunately there has been a tendency to complicate the method used for calculating the maximally stimulated acid output. It was noted that the volume and the concentration of titratable acid of the gastric juice secreted between 15 and 30 minutes and between 30 and 45 minutes after the injection of maximal doses of histamine were greater than those of the gastric juice secreted between 0

and 15 minutes and between 45 and 60 minutes after the injection. The term maximal histamine response (MHR) was coined to describe this phenomenon, which holds true for most individuals except some patients with severe gastritis in whom the maximal response is often delayed until 45 minutes after the injection of the histamine.[48] It was suggested that the correct MAO was in fact MHR × 2,[19] while Baron[49] argued that the correct MAO was PAO (peak acid output, i.e. the 2 highest successive 15-minute peaks) × 2. These mathematical manoeuvres in no way increase the value of the test, and it seems simpler and less biased to collect the juice for an hour after the injection of a maximal parietal cell stimulant and to determine the mEq. of acid in that juice.

INTERPRETATION OF RESULTS

Definition of Achlorhydria

In 1921 Bennett and Ryle[9] published their observations on the variations in acid secretion noted in 100 healthy young men who were given gruel fractional test meals. They constructed a diagram on which a shaded area indicated the limits of 'normochlorhydria'; persons who secreted less acid than this had 'hypochlorhydria', while those who secreted no 'free acid' had 'achlorhydria'. This diagram was used in hospitals throughout the world for many years.

The introduction of alcohol, histamine and caffeine as parietal cell stimulants necessitated an extension of the definition of achlorhydria because it was confirmed that gruel was a weak stimulus of acid secretion: for example, it was found that only 53% of patients in whom achlorhydria had been diagnosed after gruel fractional test meals failed to secrete acid after the injection of 1 mg. histamine.[34] The terms 'organic and functional anacidity',[50] 'true and false achlorhydria'[34,51] and 'true and apparent achlorhydria'[52] were used to distinguish between achlorhydria determined by histamine stimulation and achlorhydria determined by gruel stimulation.

When histamine became established as the preferred stimulant for acid secretion by the human stomach, achlorhydria was thought to exist when histamine, in a dose varying between 0·5 mg. and 1·0 mg., failed to cause the secretion of gastric juice more acid than pH 3·5.[53]

In 1940 Palmer and Nutter[17] drew attention to the fact that acid could sometimes be detected at the fourth attempt when three previous histamine gastric analyses had indicated achlorhydria, and in 1951 Watkinson and James[18] showed that a series of histamine injections, given at 20-minute intervals, could produce a significant acid secretion in a patient who was thought to have histamine-fast achlorhydria. Ihre[15] had noted that 'free acid' could on occasions be detected after the intravenous injection of insulin in persons with histamine-fast achlorhydria.

These doubts about the validity of the newer definitions of achlorhydria were confirmed when the augmented histamine test was introduced. Card and Sircus,[54] for example, re-examined 58 patients thought to have achlorhydria after the ordinary histamine test, and detected titratable acid in half of them. In 500 hospital patients examined with the augmented histamine test, achlorhydria was detected in 29, of whom 23 had pernicious anaemia.

Achlorhydria is now redefined in terms of hydrogen ion concentration. According to Card and Sircus,[54] achlorhydria is present if the pH of the secreted juice does not fall below pH 6 after augmented histamine stimulation. Callender *et al.*[55] consider achlorhydria to be present when the pH of the gastric juice is never less than pH 3·5 and does not change more than one unit to the acid side after maximal histamine stimulation.

If it is accepted that acid secretion by the human stomach should be expressed as mEq./hour, then it would seem logical to define achlorhydria as that situation when 0 mEq. acid is secreted in an hour following the injection of a maximal parietal cell stimulant, the juice having been titrated to pH 7. With a pH meter it is possible to titrate small differences in hydrogen ion concentration with confidence.

It has to be remembered, however, that titration of gastric juice, as practised by clinical laboratories, cannot detect those instances in which the non-parietal cell secretion completely buffers the small amount of acid which is secreted by the remaining parietal cells.

Megaloblastic Anaemias

In 1886 Cahn and Von Mehring[56] reported that a patient with pernicious anaemia had achlorhydria, and it is now accepted that augmented histamine-fast achlorhydria is a prerequisite for the diagnosis of pernicious anaemia.[55] In many patients with pernicious anaemia the pH of the gastric juice actually becomes more alkaline, and the volume of the juice secreted smaller, after the administration of histamine; and in others there is virtually no juice secreted at all during the test, a situation known as achylia gastrica. It has been shown that patients with pernicious anaemia have either gastric mucosal atrophy[57] or severe atrophic gastritis,[58] conditions which are commonly associated with augmented histamine-fast achlorhydria.[59] Thus, the detection of titratable acid in the gastric juice precludes the diagnosis of pernicious anaemia except in an exceptional patient. In a study with Richards and Witts,[59] 2 of the 14 patients who had gastric mucosal atrophy had an MAO of 0·25 mEq. and 0·02 mEq., respectively; the latter patient's anaemia fulfilled all the other criteria for the diagnosis of pernicious anaemia, and in particular her absorption of radioactive vitamin B_{12} was much enhanced by intrinsic factor. The other exception to the rule occurs in the condition known as juvenile pernicious anaemia. In these young people the histological appearance of the gastric mucosa and the ability to secrete acid are normal. Some of them seem to have an inherited defect in not being able to secrete intrinsic factor (and it is therefore easy to explain why they became deficient in vitamin B_{12}), but others do secrete intrinsic factor and the explanation for their vitamin-B_{12} malabsorption is not known.[60]

On the other hand, the fact that a patient with a megaloblastic anaemia is found to have achlorhydria after maximal parietal cell stimulation does not mean that the patient has pernicious anaemia. There is now evidence which indicates that gastric mucosal lesions may frequently be associated with small bowel disease. Brody *et al.*,[61] for example, reported 4 patients who had pernicious anaemia but in whom there were in addition small bowel

absorptive defects; in one patient the defects were attributed to sprue, in a second to jejunal diverticulosis and in a third to an old side-to-side entero-entero anastomosis, and in the fourth patient the malabsorption of vitamin A, d-xylose and vitamin B_{12} was no longer present after 10 months' treatment with parenteral vitamin B_{12}. In 2 studies of patients with idiopathic steatorrhoea, 4 of 19 patients[62] and 4 of 10 patients[63] had augmented histamine-fast achlorhydria.

It is therefore necessary to demonstrate in the case of a patient who is suspected of having pernicious anaemia, that the anaemia is due to lack of vitamin B_{12} and that there is no small bowel disease.

Gastric Ulceration and Carcinoma of the Stomach

Patients with benign gastric ulcers situated in the body of the stomach on the average secrete less acid after maximal stimulation than control individuals;[28] whereas patients with carcinoma of the stomach as a group secrete less acid than the patients with benign ulcers (Fig. 2). It is evident from Fig. 2 that an MAO of less than 5 mEq. is more commonly found in carcinoma and that it is most unusual for a benign ulcer to be associated with achlorhydria. It is wise, therefore, to regard the combination of gastric ulcer and achlorhydria as indicating malignancy unless other evidence suggests the opposite. Contrariwise, the fact that the MAO is 20 mEq. or higher is no assurance that the ulcer is benign, although it is unusual for the ulcer to be malignant (Fig. 2). Others,[65] however, have concluded, 'we have not been able to distinguish clearly between ulcer and cancer of the stomach by means of the augmented histamine test'.

As far as prepyloric ulcers are concerned, the published results agree that patients with ulcers in this site secrete more acid than normal individuals[28,30,65] and the experience is that tests of acid secretion are of less help in differentiating benign from malignant ulceration than is the case in patients with ulceration of the body of the stomach.

Duodenal Ulceration

Aid to diagnosis of duodenal ulceration. Patients with duodenal ulceration tend to secrete more acid after maximal histamine stimulation than control persons do,[30] but there is a considerable overlap in the observed results (Fig. 3).[64] Nevertheless, tests of maximal acid secretion can be of value in the diagnosis of duodenal ulceration. It has not yet been reported that duodenal ulceration occurs in individuals with augmented histamine-fast achlorhydria. Although the occasional patient with a proved duodenal ulcer has an MAO of less than 5 mEq., it is wise to reconsider the diagnosis in such patients and to search for alternative explanations for the patient's symptoms and the radiological deformity. Farman *et al.*,[66] for example, have reported radiological deformities of the duodenal bulb, which simulated duodenal ulceration, in patients with pancreatitis.

On the other hand, if the patient's symptoms are suggestive of duodenal ulceration, but the radiologist is unable to demonstrate a duodenal ulcer, an MAO of 50 mEq. or more and a satisfactory response to treatment may be enough reason to diagnose a duodenal ulcer. Equally, if the patient's symptoms are in keeping with peptic ulceration and the radiologist finds no ulcer in either the stomach or duodenum, an MAO of less than 10 mEq. should suggest the possibility of a gastric ulcer and in such individuals a gastroscopic examination may reveal a small ulcer on the lesser curve at or near the angulus.

The basal acid secretion of patients with duodenal ulceration also tends to be higher than that of normal individuals, and Dragstedt[44] has recently restated his contention that a 12-hour overnight basal secretion of 75 mEq. or greater is very suggestive of active duodenal ulceration.

Surgical management of chronic duodenal ulceration. In recent years several groups of clinicians have taken into consideration the amount of acid secreted during the augmented histamine test when planning the surgical treatment for their patients suffering from chronic duodenal ulceration.

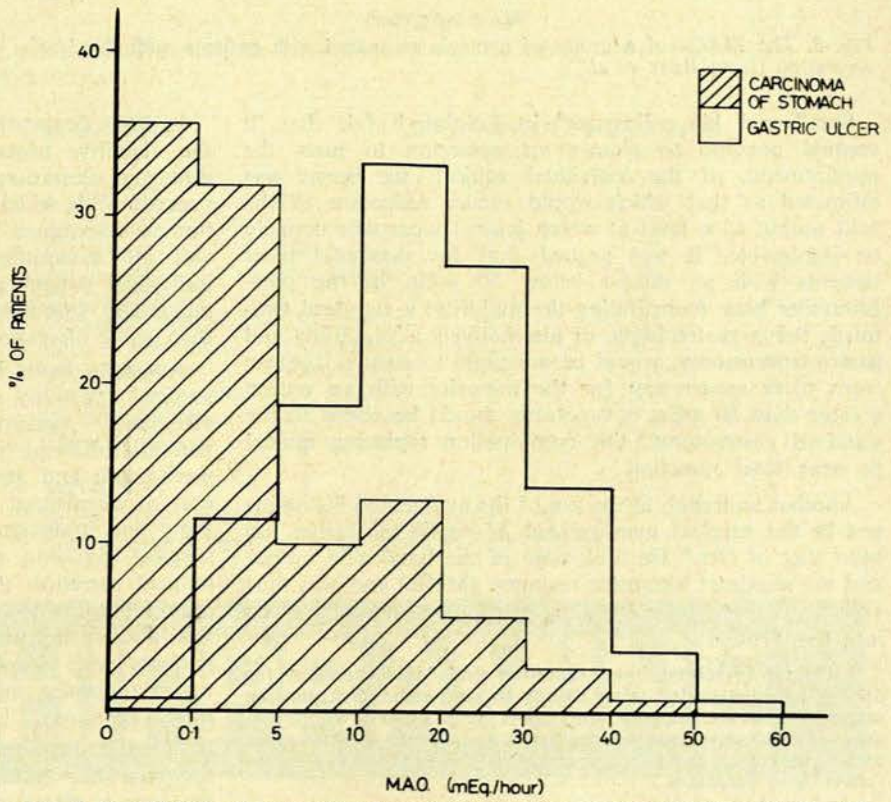

Fig. 2. The MAOs of patients with gastric ulceration compared with patients with carcinoma of the stomach (from Bank *et al.*[64]).

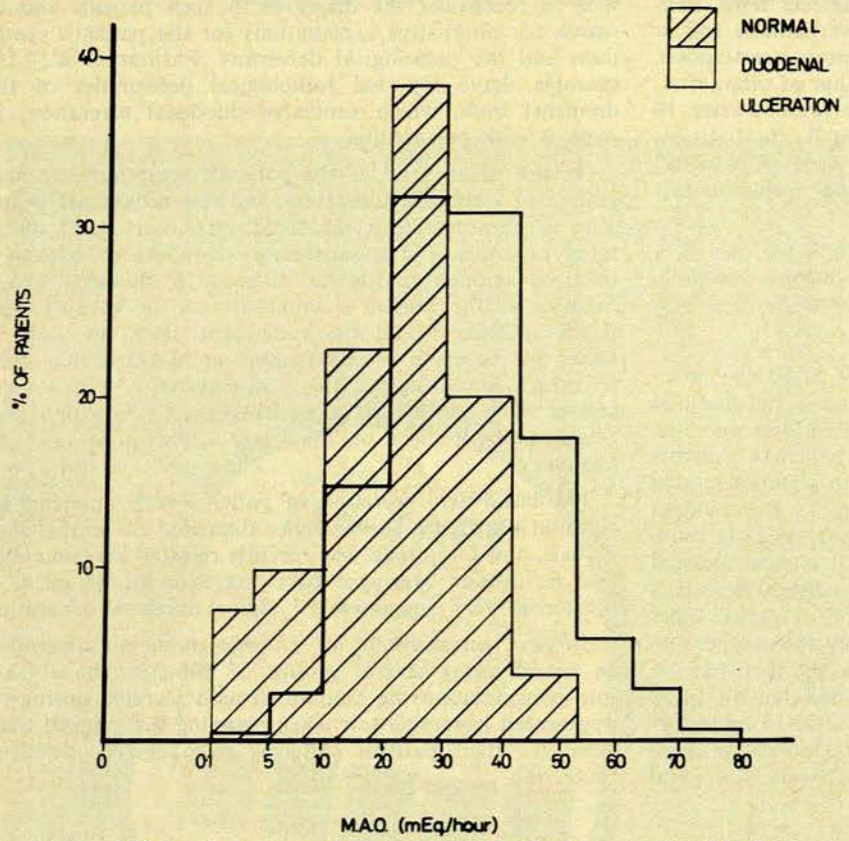

Fig. 3. The MAOs of a group of controls compared with patients with duodenal ulceration (from Bank *et al.*[64]).

Small and his colleagues[67] in Edinburgh felt that 'it seemed possible to choose an operation to meet the requirements of the individual subject; its extent was estimated as that which would ensure reduction of the acid output to a level at which jejunal ulcer was unlikely or impossible. It was argued that for duodenal ulcer patients with an output below 50 mEq. in the post-histamine hour (constituting the majority) a standard two-thirds Polya gastrectomy, or alternatively a vagotomy and gastro-enterostomy, would be adequate to ensure freedom from ulcer recurrence; for the minority with an output greater than 50 mEq. a vagotomy should be added to the standard gastrectomy, this combination replacing radical or near total resection.'

Another approach to the use of the augmented histamine test in the surgical management of peptic ulceration has been that of Orr.[68] He took note of the basal acid output and the maximal histamine response (MHR) and was thus able 'to make a selective division of peptic ulcer patients into five groups:

'1. Those in whom basal secretion and MHR are low (as applies to most gastric ulcer cases). In such patients it may be assumed that the ulcer is the result of a breakdown in the defence mechanism and an operation designed to by-pass or to excise the ulcer need not include any radical procedure to reduce acid secretion.

'2. Those in whom the basal secretion is normal or low, but in whom the MHR is increased. In such patients it may be assumed that the parietal cell mass is greater than normal and that hormone stimulation is responsible for the hypersecretion. In such patients the pyloric antrum must be removed along with some of the parietal cell mass. This can be effected by a hemigastrectomy leaving an adequate gastric reservoir.

'3. Those patients (the majority of male duodenal ulcer patients) in whom basal secretion is raised and the MHR is also raised. In such patients it may be assumed that the parietal cell mass is in excess and that vagal as well as hormone activity plays a part in stimulation. In such patients a vagotomy combined with a hemigastrectomy is adequate.

'4. Those in whom basal secretion is very high (10 to 20 mEq.) but the MHR is not proportionally excessive. These may be assumed to have a normal parietal cell mass, but the stimulation is continuous and predominantly vagal, and a vagotomy and a drainage procedure might be expected to bring about healing of the ulcer and protection against recurrence. In women a vagotomy and gastro-enterostomy, and in young males in whom the ulcer is very small and there is no oedema or distortion of the duodenum, a vagotomy and pyloroplasty would be the operations chosen.

'5. Those in whom basal secretion is very high and the MHR is also excessive. One must assume a greatly increased parietal cell mass stimulated by vagal and hormone stimuli, and a vagotomy combined with a two-thirds or even in exceptional cases a three-quarters gastrectomy is essential to reduce the parietal cell mass to safe proportions and protect against recurrence.'

In 1943 Dragstedt and Owens[69] introduced vagotomy as the definitive procedure in the surgical management of duodenal ulceration, and today vagotomy with a drainage procedure[89] is widely practised. The success of this operation is determined by the completeness of the vagotomy and the assumption that total vagotomy will, in the individual patient under consideration, reduce basal and maximally stimulated gastric acid output to such levels that peptic ulceration is unlikely to recur.

Attempts have been made to predict the effect of surgical vagotomy on gastric acid secretion. Kay and his associates[70,71] performed augmented histamine tests on 40 patients following 'medical vagotomy', induced with hexamethonium and atropine, and compared this result with that of augmented histamine tests performed after vagotomy and drainage. The comparison was good, although surgical vagotomy in general effected a greater reduction in acid secretion than medical vagotomy. On the other hand, Johnston *et al.*[72] concluded that 'medical vagotomy' was not worth using in the pre-operative assessment of patients with duodenal ulcer: they produced evidence which suggested that 'medical vagotomy' was an incomplete vagotomy.

There is, however, a growing body of evidence which suggests that recurrent ulceration after vagotomy and drainage is determined not by the maximal acid secretory response after surgery, but by the completeness or other-

wise of the vagotomy.[72,73] It is therefore wise to perform insulin tests on patients in whom the definitive surgical manoeuvre was vagotomy. In the average patient the performance of the insulin test presents no problem, but the titration of the samples of gastric juice is not always easy and the interpretation of the test is often difficult. Hollander[71] thought that a rise of more than 20 mEq./litre of 'free acid' (using Töpfer's reagent) in any of the ½-hour periods following the injection of insulin indicated incompleteness of the vagotomy. In clinical practice this is not always so clear-cut. In most instances, where the vagotomy is subsequently shown to be incomplete, the volume and concentration of the secreted juice fall in the first period after the injection of insulin and then start to rise quite markedly in the second period, a level of secretion which is usually maintained for the duration of the test. On the other hand, in patients whose postoperative course is in keeping with the completeness of the vagotomy, the spontaneous secretion contains little or no titratable acid and the injection of insulin does not influence this. The problem is how to report on those tests in which the concentration rises only a little more than 20 mEq./litre after insulin, especially when a rise occurs in the 3rd or 4th periods. Kay[73] has suggested that, provided the postoperative maximal acid secretion has shown a reduction of at least 50%—the observed reduction after complete vagotomy approaches 70%[74]—these tests can be interpreted as indicating an 'adequate vagotomy'. There is some evidence to support this contention. Bell *et al.*,[75] for example, found that whereas 10 of the 28 patients in whom the positive insulin test response occurred in the first hour after the injection of insulin developed recurrent ulceration, only 1 of the 14 patients in whom the positive response occurred during the second hour subsequently had a recurrent ulcer.

It seems, therefore, that wherever possible tests of maximal acid secretion should be performed on all patients both before and after surgery for chronic duodenal ulceration. Insulin tests ought probably to be carried out in all individuals in whom the definitive procedure was vagotomy, but it would be reasonable not to do insulin tests when the postoperative maximal acid secretion is less than 40% of the pre-operative value. In the patients in whom tests reveal a significant reduction in acid secretion and in whom vagotomy is judged to be complete, the clinician may rest on his laurels, whereas he may ponder the advisability of continuing medical treatment in those individuals in whom the acid secretion is still high and in whom the insulin test provides unequivocal evidence of an intact vagus.

(From a technical point of view, these tests are preferably not performed within 4 weeks after surgery so that artefacts due to gastric retention do not complicate the interpretation of the tests.)

Recurrent Peptic Ulceration

Recurrent ulceration after surgery for peptic ulceration remains a worrying clinical problem. Radiological diagnosis of the new ulcer is often difficult, especially where pyloroplasty was the drainage procedure performed. Fortunately the augmented histamine and insulin tests have proved to be of value in elucidating postgastrectomy and postvagotomy and drainage dyspepsia.

The gastric secretory findings of a group of 49 patients with proved recurrent ulceration are depicted in Fig. 4.[64]

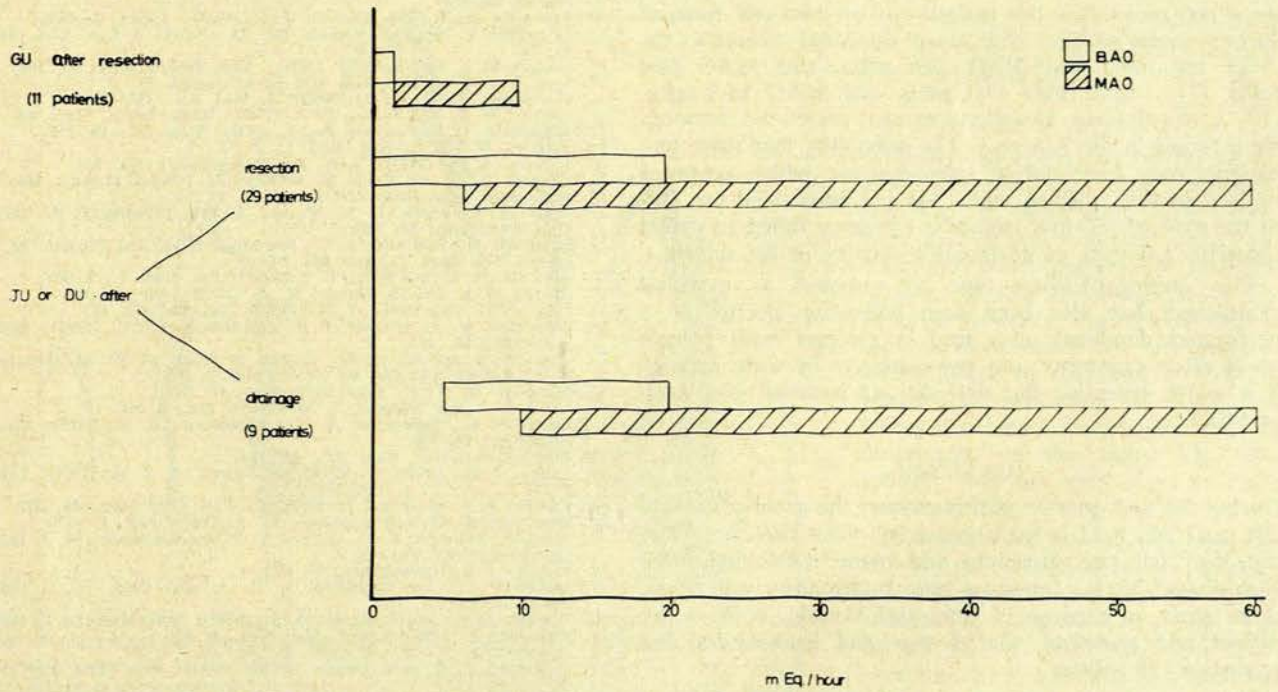

Fig. 4. The BAOs and MAOs of 49 patients with recurrent ulceration after surgery for chronic duodenal ulceration (from Bank *et al.*[64]).

None of the patients had achlorhydria, and it is reasonable, therefore, to regard achlorhydria after maximal stimulation as good evidence against recurrent ulceration. On the other hand, a BAO of 10 mEq. or more and an MAO of 20 mEq. or more was a frequent finding among these patients.

Thus, in a patient who had undergone surgery for a chronic duodenal ulcer a year or two previously and who presented with typical ulcer symptoms, an MAO of more than 20 mEq. would be suggestive evidence of recurrent ulceration. If the definitive procedure had been vagotomy, a positive insulin test would clinch the diagnosis.

Augmented Histamine Test and the Zollinger-Ellison Syndrome

One of the characteristic features of the Zollinger-Ellison syndrome is tremendous basal acid hypersecretion.[76]

In 1964 Ellison and Wilson[77] reviewed the 285 known cases of this syndrome. Augmented histamine tests had been performed on 21 of these patients. It was striking that in 16 of them the BAO was 75% of the MAO.

Although Winship and Ellison[78] have recently stressed that the BAO of some patients with the Zollinger-Ellison syndrome may fluctuate widely from day to day, with the result that the characteristic secretory findings may not be present on the particular day on which the AHT is performed, it is the possibility of alerting the clinician to this diagnosis which justifies performing a test of maximal acid stimulation on patients with duodenal ulceration. This should be done irrespective of the patient's age because the non-beta-cell adenoma has been associated with duodenal ulceration in 15-year-olds as well as in octogenarians.[77]

But finding a BAO/MAO ratio of greater than 60% does not mean that the patient has an islet-cell tumour. In two recent patients with active duodenal ulceration the AHT responses were BAO 34·0 mEq. and MAO 41·0 mEq. (77%) and BAO 19·0 mEq. and MAO 26·5 mEq. (72%), respectively. Despite a careful search no tumours were found in the pancreas. The possibility that these two patients may have diffuse adenomatosis, which occurred in 19% of the collected series, has not been ruled out, but in the case of the first patient a rat assay failed to detect excessive amounts of gastrin-like activity in his serum.

The Zollinger-Ellison type of response to maximal stimulation has also been seen following closure of a perforated duodenal ulcer and in patients with pyloric stasis after vagotomy and pyloroplasty. In such patients it is worth repeating the test after an interval of a week or two.

CONCLUSION

During the first quarter of this century the gruel fractional test meal was held in high regard by many clinicians. The test then fell into disrepute and many concluded, with Moynihan,[79] 'that I found so little information was given, at so great an expense of time and trouble, both to the patient and ourselves, that I was glad to abandon the procedure altogether'.

However, the more recent experiences with tests of maximal acid secretion, which are relatively simple to perform and which cause patients comparatively little discomfort, suggest that these tests are worthy of more widespread clinical application.

SUMMARY

The stages in the development of tests of gastric acid secretion are briefly mentioned. The technique of 'tubeless gastric analysis' is a useful screening test to determine whether the gastric juice contains acid.

The various tests of maximal acid secretion are discussed. The pentagastrin test will probably succeed the augmented histamine test as the most commonly used test of maximal acid secretion. The insulin test, although easy to perform, still presents problems in the interpretation of the results. It is possible that more note should be taken of the nocturnal acid secretion.

Achlorhydria should be considered to be present when 0 mEq. acid/hr is secreted after the administration of a maximal stimulant. Although achlorhydria is usual in patients with pernicious anaemia, the presence of achlorhydria in a patient with a megaloblastic anaemia does not mean that the patient has pernicious anaemia. The detection of achlorhydria in a patient with a gastric ulcer suggests that the ulcer is most probably malignant. Normal or high acid secretion after maximal stimulation, however, does not exclude malignancy.

The roles of the various tests of gastric acid secretion in the diagnosis and management of chronic duodenal ulceration and recurrent ulceration are reviewed in detail.

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