THE HISTAMINE-INFUSION TEST OF GASTRIC ACID SECRETION IN MAN

A thesis submitted in part fulfilment
of the requirements for the degree
of Doctor of Medicine of the
University of Glasgow

by

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September, 1968.

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Dedicated to the Surgical Unit

of the Welsh National School

of Medicine, 1963 - 1967.

We still seek a theory of order in its most interesting and important form, that which is represented by the complex functional and structural integration of living organisms.

P. B. Medawar (1967)

In seeking absolute truth we aim at the unattainable and must be content with broken portions.

W. Osler (1849 - 1919)

The path of histamine is strewn with dead scientific ideas.

C. F. Code (1966)

CONTENTS

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INTRODUCTION

The measurement of gastric acid in man has proved deceptively simple, and has resulted in a vast and inconclusive literature accumulated over three hundred years. In spite of this, fundamental questions remain unanswered. Normal values have eluded definition, and the significance of abnormality of gastric secretion in relation to diseases of the upper digestive tract is still, to a large extent, speculative.

Tests of gastric secretion are apparently only of marginal value in the management of the major disorders related to the stomach. Yet such disorders as peptic ulcer and gastric cancer so obviously relate to the secretory status of the stomach, that it has seemed proper to most investigators to measure gastric acid by the most accurate means currently available. With each new technique has come renewed hope of more useful meaning from the results.

The use of histamine by intravenous infusion to produce a steady state of maximal gastric acid secretion was known to be of value as a research method in man and in the laboratory animal, but had not been widely applied in clinical practice.

A technique was evolved whereby this method of gastric acid stimulation could be used to study large numbers of patients and control subjects.

CHAPTER 1

THE EVOLUTION OF GASTRIC ACID TESTS

The history of the development of tests for gastric acid has been both erratic and repetitive. Periods of apparent progress have alternated with periods during which new concepts have been abandoned temporarily in favour of a return to older methods. General hypotheses were introduced early, such as 'hyperchlorhydria' and 'free' and 'combined' acid, which have exercised succeeding authors until recent times, tending thereby to preserve the historical unity of the subject. Progress has been tentative and on a broad front, rather than in positive stages.

Nevertheless, four phases of activity can be defined.

1. Recognition of gastric acidity 1692 - 1906
2. Stimulation of gastric acidity 1910 - 1932
3. Applications of gastric acidity 1932 - 1948
4. Analysis of gastric acidity 1948 -

(i) Recognition of gastric acidity - 1692-1906

The word 'acid' simply meant sour. Early writings such as those of Viridet in 1692 are concerned with the origin of the sour or sharp tasting liquid which was capable of dissolving food. The established view was that this was saliva, but he argued that food could still be

dissolved in the complete absence of saliva, and that the acid liquid probably derived from the stomach. The precise nature of this acid, and attempts at quantitative measurement, were a matter of speculation for more than a hundred years. It was identified as muriatic or hydrochloric acid by Prout in 1824, who introduced an immediate complication to the subject by defining 'fixed', 'free' and 'total' acid by different methods of saturation with potash and titration with silver nitrate. He quoted values for the acidity of gastric juice in three men with dyspepsia, obtaining the stomach contents by vomiting, ranging from 4.28 to 5.15 grains per pint. This corresponded approximately to 18 mEq/litre, but no comment is made either on the nature of the indicator used in these titrations, or on the possible significance of the results.

During the remainder of the nineteenth century the 'test meal' became established. The gastric tube, long used crudely as a therapeutic weapon, became more elegant and practical after the process of vulcanising rubber was introduced in 1844.

Endless eponymous meals were devised in the rather illogical hope that one would be found to stimulate gastric secretion to maximal and reproducible levels, without

inevitably contaminating, and therefore partly neutralising, the secretions produced.

Many of these investigations were directed towards objects other than acid secretion. Although primarily interested in the emptying rate of a standard meal of soup, beef, puree, vegetables and bread, Leube in 1876, found the acidity of the aspirate at 7 hours to be low, and suggested that a better estimate of acid activity would be obtained by aspirating stomach contents 'fractionally' at different times after the meal.

Food-free gastric juice was obtained by Ewald and Boas in 1885, during an investigation of hysterical vomiting in a mental patient, by giving 50 - 100 ml of distilled water, but this was found to be normally neutral, and a test meal of cooked egg-white was required to produce a weak acid juice. Evidence of this sort accumulated to suggest that different constituents in the test meal would result in differing acidity responses. Measurements of gastric acidity appeared to be related more to the stimulus used, than to the actual secretory status of the stomach.

This fundamental doubt concerning the validity of test meals must have prompted Kast in 1906, in summary after an investigation of alcohol as a test meal, to note that

'hyperchlorhydria is the result of investigation; hypersecretion is its physiological explanation'.

Although a new phase of study was soon to develop with the introduction of parenteral methods of stimulation, test meals lingered on.

(ii) Stimulation of gastric acidity - 1910-1932

Histamine dominated this period, from the demonstration by Sir Henry Dale and his colleagues in 1910 of its general action as a secretogogue, to the studies of Teorell in 1932 showing a precise relationship between the dose of histamine administered and the amount of acid produced by the stomach.

In the initial reports on histamine by Dale and Laidlaw (1910) the stomach was not specifically mentioned but β-iminazolylethylamine (histamine) was found to induce vomiting and diarrhoea, to increase tone and rhythym in viscera, and to stimulate tears, saliva, bronchial and pancreatic secretion. These other effects, along with the marked vasodilation and death described in animals by Barger and Dale (1910) prejudiced for many years the use of histamine in man, especially in relation to its toxic effects and the upper limits of dosage.

In retrospect, however, the doses used in those studies were very large, being up to sixty times that

later shown to produce a maximum response from the gastric mucosa. Although histamine was administered by various routes in those studies, no significance was attached to the difference in response resulting from different routes of administration.

The first planned experiments to study this aspect of the action of histamine were in Popielski's dog 'Bialy' (1920). By the subcutaneous route, larger doses of histamine gave greater secretion of acid. Given intravenously, histamine produced only a little mucus, and the dog was violently sick. However, the dose used was approximately 4 mg/kg/hour, an enormous dose, perhaps one hundred times that actually required to produce a response from the gastric mucosa.

These complications were attributed by Popielski (1920a) variously to anaphylaxis, dehydration and an adrenaline-like effect, and after recording severe side effects in his assistant after a subcutaneous injection, concluded that histamine should not be given intravenously 'for fear of collapse'.

Detailed studies of the acid response to subcutaneous histamine in man were first described by Carnot, Koskowski and Libert in 1922, aspirating gastric juice through a small Einhorn tube. They showed that volume and acidity

both reached a peak about ninety minutes after the injection of histamine.

The analysis of this peak response was carried out with considerable elegance by Matheson and Ammon in Scotland in 1923. Taking as subjects twelve convalescent patients without stomach trouble, they followed the acid response to a subcutaneous injection of 1.5 mg histamine acid phosphate, taking 10-minute specimens by syringe aspiration. Maximum volume was reached in 30 minutes, maximum acidity usually at 20 minutes. There is no mention of untoward side effects following these tests, and in view of this it is remarkable that thirty years passed before a similar procedure became accepted as standard practice, particularly since the data from these tests represent acceptable 'normal' values. This was a clear and important contribution to many aspects of the subject, insufficiently acknowledged. Two aspects of the subject, however, still lay in the future. The dose of histamine used, selected apparently arbitrarily, was about half the maximum secretory dose. In addition, the idea of output was not explored.

Continued interest in the route and rate of administration of histamine was continued by Gutowski in 1924 working with canine gastric fistulae. Subcutaneous,

intramuscular and slow intravenous histamine all gave similar acid responses, but a rapid intravenous injection resulted in only a very small volume of acid. He suggested that this apparently poor response was due to the rapid destruction of histamine in the blood stream, so that an effective threshold level was not sustained.

Although not primarily concerned with the relationship between histamine dose and acid response, the extensive studies of Teorell in 1932 marked the beginning of a true appreciation of this problem. He used continuous intravenous infusions of histamine in decerebrate cats, and showed that both volume and free hydrochloric acid increased with the rate of injection.

During this period of steadily developing efficiency in the stimulation and collection of uncontaminated gastric juice, the problems of definition of acidity became increasingly prominent. In particular, the comparison between the acidity of gastric juice and of pure hydrochloric acid led Michaelis in 1927 to enunciate the theory of 'free' and 'combined' acid. He demonstrated the similarity of gastric juice to a solution of hydrochloric acid 'combined' with peptone, and considered that the factors which made the titration curve of gastric juice depart from that of pure

hydrochloric acid were either food contaminants or weak acids such as lactic or acetic acid. Most of his evidence for these assumptions is derived from artificial model solutions rather than specimens of gastric juice. He considered then that normal acidity lay between 35 and 45 mEq/litre.

Not all of the investigators of this period were concerned with progress towards parenteral stimulation of strongly acid gastric juice. Fully as great a stimulation was found to result from water drinking by Bergeim and others in 1914, as from the traditional Ewald test meal. The gastric juice so obtained was uncontaminated and the test could be repeated frequently.

As quantitation evolved, it became important to know whether the individual stomach had, in fact, a constant acidity. One healthy subject was studied on 20 consecutive days (except Sundays) by Bell and Macadam in 1924 and was found to have fairly reproducible acidity of 74 mEq/litre by any of the known methods of stimulation.

In spite of this Rehfuss in 1927 was still able to produce evidence that the acidity might be related to the stimulating agent. He considered that an acidity of 120 mEq/litre in response to a meat meal might be normal, whereas 100 mEq/litre in response to gruel might represent

hyperacidity. The relationship of buffer solutions to gastric acidity lay in the future.

A 'physiological' approach to the problem was attempted by Chalfen in 1928, who studied 200 subjects by intermittent aspiration of the unstimulated stomach. He demonstrated considerable variations in acidity throughout the day, a majority of his patients producing gastric juice of 30-70 mEq per litre of hydrochloric acid, values comparable with those resulting from test meals. This interest in basal secretion as an index of gastric status persists until the present day.

From all these widely differing approaches to the study of gastric acid, sufficient agreement appeared to have been reached to move on to the next period, that of assaying the population, normal and diseased, to discern patterns in human gastric acid secretion.

(iii) Applications of gastric acidity - 1932-1948

Prodigious effort and unjustified optimism persist throughout this period, the effort exemplified by a detailed analysis of 3746 tests carried out at the Mayo Clinic by Vanzant and her colleagues (1932), and the optimism by the conclusions of Polland (1933) to a similar study that 'the question of normal standards is now settled for all time'.

In fact, most of the surveys of the period failed to define the normal.

Polland and Bloomfield (1931) rather begged the question when they excluded subjects (all hospital patients) who were found to have a low acidity, below 10 mEq/litre. In spite of this there was an enormous range of both volume and acidity in response to a submaximal dose of histamine. Curiously, both men and women were grouped together in this study. Later, however (Polland, 1933), acidity was shown to be lower in women than men, and to fall slightly with age.

Laxity in definition of normal had to be accepted by Vanzant and others (1933), when they included patients suffering variously from 'fatigue, neurosis, constipation, negative dyspepsia, irritable bowel and mucous colitis'. Ewald test meals were used throughout this survey, and the results showed a high incidence of achlorhydria, increasing with age in both sexes. Acidity varied from 0 - 108 mEq/litre, and it was admitted that the limits of normality could not be usefully defined.

This group later investigated the possibility of a double histamine test (Rivers and others, 1936). Though primarily interested in the pattern of pepsin secretion, they showed that occasionally a plateau of acid secretion resulted, instead of two peaks, in response

to two submaximal doses of subcutaneous histamine. Calculation of acidity was simplified by this means, but no wider use was made of this technique.

Parallel to the search for absolute standards in patients, interest was increasing in absolute values for gastric acid. The theoretical maximum acidity was calculated by Hollander in 1938 as 167 mEq/litre, while observed values lay between 115 and 119 mEq/litre.

Higher acidity was demonstrated by Ihre in 1938, using more sophisticated techniques of collection and titration, though still using as the stimulus 0.01 mg histamine/kg subcutaneously - a sub-maximal dose. Normal concentration of acid ranged from 130 - 150 mEq/litre, but similar acidity was demonstrated in his patients with duodenal ulcer, leading him to conclude that 'the concept of hyperacidity thus lacks actual foundation'. Also with this work began the long controversy about the source of the non-parietal secretion. At that time Ihre could demonstrate no definite evidence for the existence of another alkaline secretion, and postulated some diffusion process through the gastric mucosa.

The apparent failure of methods of stimulation to discriminate between normal and abnormal, led Bloomfield

and others in 1940 to question whether possible differences were being in fact obliterated by the stimulation, and to postulate that perhaps a study of basal secretion might give truer indices of gastric activity.

He demonstrated a rough correlation between basal secretion and that following histamine, and similar patterns of secretion. There was a very broad overlap in acidity between normal and duodenal ulcer, but levels of 120 mEq/litre were indicative of duodenal ulcer. Normal basal output was about 0.4 mEq/hour, compared with 1 mEq/hour for patients with duodenal ulcer.

The obvious inaccuracy of 'basal' studies over a short period of an hour, encouraged Levin and others in 1948 to investigate the possibilities afforded by 12-hour nocturnal secretion. There was a wide variation in volume, from 148 to 1188 ml within the group, and a 25% variation in the same subjects on different nights. No new information appeared to accrue from this approach, and a similar study by Sandweiss and others in 1946 on normal subjects and patients with duodenal ulcer, gave similar inconclusive results. They showed that both groups secreted acid at night of about the same

concentration, 60 - 80 mEq/litre. Night volume estimations provided a slight degree of discrimination, but only to the extent that 25% of duodenal ulcer patients secreted more than 300 ml in 7 hours (Sandweiss and others, 1946a), while no normal subjects exceeded this volume.

In spite of the vast surveys and the application of all the acknowledged principles and techniques, little emerged which appears now to be of great value. A silent comment can perhaps be read into the work of Ryle at the end of this period. In 'The natural history of disease' (1948) writing on duodenal ulcer, he makes no mention at all of gastric secretion, nor of gastric tests, nor of acidity in any context!

(iv) Analysis of gastric acidity - 1948-

The present phase, like the others, shows multiple random facets of interest, rather than much organised progress, but, in general, two main lines of investigation can be appreciated, one towards increasing precision in the measurement of gastric acidity and the other towards greater accuracy in the diagnostic labels attached to the patients being studied.

The safe use of large doses of histamine was justified after Halpern in 1947 had shown that guinea

pigs could be protected against the shock-like effects of massive doses of histamine by the antihistamine drug thiodiphenylamine (Antergan). Although gastric acid was not actually measured, he inferred that the antihistamine had not blocked the action of histamine in the gastric mucosa, since the animals died in 48 hours from perforated gastric ulcers. He did not, however, make the more useful observation on whether or not antihistamine had any measurable influence on the minor side effects of the much smaller doses of histamine required for stimulation of gastric acid. It was widely assumed from his work that antihistamines were effective and necessary. Most investigators were agreed that the antihistamine by itself had no effect one way or the other on the secretion of acid, in spite of the observation of Wood in 1948 that histamine with Antergan gives a greater mean output of acid than histamine alone, in different groups of cats. This was, however, an incidental and insignificant observation during his main work, which was to induce a steady state of secretion by continuous infusion of histamine, against which background he could assay the effect of other drugs.

Previous tentative observations on the dose/response or, as he preferred to describe it, the concentration/action

curve, were consolidated by the work of Öbrink in 1948. Studying dog pouches he showed that there was no threshold for histamine stimulation, the lowest dose producing an acid response being not significantly different from 0. More widespread attention to this observation would have simplified many later discussions on dose/response curves. He further proved that during an infusion of histamine, the blood level and the tissue concentration both reached 'steady state values', and that the acid output rose with the tissue concentration of histamine to reach a maximal value. What this indicated in terms of parietal cell activity was not at that time known.

Different doses of histamine were used by Conard and others in 1949, and gave different acid responses, but these authors were more concerned with a definition of achlorhydria, and did not equate output with dose.

It is interesting to observe that at this time Dragstedt and others in 1950, anxious to quantitate gastric acid secretion as accurately as possible, chose the 12-hour night secretion to discriminate between normal and peptic ulcer.

The essence of most of the previous experimental work on histamine was distilled into the crucial paper of

Kay in 1953, in which he used increasing doses of histamine to study normal subjects and patients with peptic ulcer, within the context of a clinical department of surgery. Dose/response relationships were demonstrated and from these the maximal secretory dose of 0.04 mg subcutaneously per kilogram body weight used as the basis for a reproducible test with an acceptable coefficient of variation. Volume and concentration of acid were similarly stimulated, the major period of response being normally between 15 and 45 minutes following the injection of histamine. Outputs of acid had to be calculated rather arbitrarily in terms of a 30-minute response, and it was appreciated at that time, that such a response was difficult to quantitate, consisting as it did of the products of two curves, of volume and acidity. Normal values for output ranged from 4 - 20 mEq/45 minutes, and those for duodenal ulcer patients from 14 - 63 mEq/45 minutes, a considerable overlap but giving better diagnostic discrimination than had previously been possible.

This procedure soon became adopted as the most acceptable test of gastric acid secretion, making possible for the first time valid comparison between results from different centres.

The other major contribution at this time was the detailed analysis of dose response relationships by Adam and his colleagues in Edinburgh in 1954.

They studied 'normal' subjects, three of themselves, by means of infusions of histamine at different dose rates. Fairly steady states resulted which permitted outputs to be calculated directly from the products of volume and total acid over a period of one hour. The observed dose response curves fitted well with the estimated values for parietal cell secretion, whether calculated as the probability integral curve or the logistic. They succeeded in demonstrating this relationship where others before and since have failed, by choosing many of their doses at a low level, just above the threshold value. The technique, using large volumes of fluid as a gravity intravenous drip, was cumbersome for routine use, but the precision of the answers given and the lack of major side effects, justified the claim of Code in 1956, that continuous intravenous infusion is the preferred mode of administration for many types of physiological tests - in man as well as in the experimental animal.

Test meals still flourished in many centres, 'a tribute to the medical profession's steadfast devotion to

tradition' (Illingworth, 1953). From Guy's Hospital one thousand test meals were analysed by Enticknap and Merivale in 1954. The upper limit of acidity for normal subjects was 67 mEq/litre and they therefore defined 'hyperacidity' as any value in excess of this. By this standard hyperacidity was 'suggestive but not diagnostic' of duodenal ulcer. In a more critical study of acid secretion before and after adrenalectomy for Cushing's syndrome by Kyle and others in 1956, gruel fractional test meals were used. These authors recognised the 'serious limitations' of the test, but it was the only method readily available.

The first large scale use of histamine by intravenous infusion was by Hirschowitz and his colleagues in 1957. Sub-maximal doses were used in one study to show that pepsin as well as acid was secreted as a sustained plateau, rather than as a 'wash-out' process. The technique was applied further (1957a) to discriminate 'with a high degree of certainty' between benign gastric ulcer and gastric cancer. This was partly on the basis of no cancer patient having acidity greater than 90 mEq/litre, a result which could be explained better on the basis of selection in their small numbers of patients rather than by any technique of acid stimulation.

The dose was regulated subjectively by keeping the patients flushed, which from their data was evidently approximately half the maximal secretory dose for histamine.

Investigating the relationship between maximal acid output and parietal cell mass, in dogs, Marks and his colleagues (1958), used infusions of histamine at the upper range of dosage. Again, in 1960, a similar study compared the responses following subcutaneous histamine with those during intravenous histamine. Similar maximal responses were obtained by the two methods, but the authors were more concerned with absolute values obtained over a short period of 15 minutes, rather than with the sustained steady state of secretion.

Further applications of intravenous histamine were described in 1960 by Køster and Thorsøe from Copenhagen. They complicated the results to some extent by carrying out a three-hour test, with an increased dose each hour. A plateau was reached only after three hours, although concentration of acid rose to a sustained maximum level at one hour.

Such tests were considered to be unjustifiably elaborate for clinical practice and further efforts were

directed towards a more critical interpreation of simpler tests. An 'index' of night gastric secretion was devised by Johnson (1962) as a guide to surgical management of peptic ulcer. Being a function of unstimulated volume and acidity ($\frac{3 \times \log \text{volume}}{\text{pH}}$), this was no better than an estimate of output.

Even more elaborate meaning was read into the results of subcutaneous histamine tests in the detailed statistical analysis (Baron, 1963 & 1963a) of all possible aspects of gastric acidity related to age, sex, body weight and diagnosis. Valuable though these studies are, it is doubtful if the small numbers of subjects and the data from the individual tests warranted such treatment, the author admitting that it was 'impossible to obtain a true range' of normal, partly because of the 'unavoidable collection errors in so short a period of time'.

The increasing use of the glass electrode has made colorimetric titration obsolete (Rovelstad, 1963) and, more significantly, has induced a more critical attitude towards the definition of acidity. The obvious rational interpretation in terms of milliequivalents of HCl (or H^+) per litre (Bock, 1962) does not exclude the possibility of titrating to various end points. Most

recent studies have considered pH 7 as a practical end point, and have avoided the use of the terms 'free' and 'total' acid.

This assumes little contribution to the gastric secretion of any alkaline or non-parietal components, probably justified when 'the mucosa is driven at high rates of secretion by histamine' (Hunt, 1965).

Thus, though many aspects of histamine, the 'universal gastric secretory stimulant' (Code, 1965), are settled and proven, its place in clinical investigation is uncertain. The measurement of gastric acid in man remains largely empirical.

CHAPTER 2

THE HISTAMINE-INFUSION TEST

A side-room procedure

The tests which form the basis of this thesis were carried out over four years and the description which follows refers to the method which was evolved for the great majority of the tests in the last three of these years. During the first year the tests were carried out personally by the author as different techniques were explored. Many tests carried out during this early period were discarded as unsatisfactory or incomplete.

The obligation to carry out these tests in a detailed personal fashion arose from the unsatisfactory conditions under which gastric secretory studies were performed at that time. It may have appeared as a truism for Hunt in 1965 to have to state that 'if a test is worth doing it is worth doing skilfully' yet standard practice in most centres accepted that such tests be performed in a general ward, in the early morning, with perhaps the passage of nasogastric tubes, the administration of stimulants and the collection of specimens all being more or less the function of the nursing staff. Reference to old case notes of our own patients, and discussions with workers in other centres, reinforced

our doubts about the validity of any tests, however computed, which were carried out under these conditions.

All the tests were therefore carried out in a side room arranged for the purpose, so that nasogastric tubes could be passed, infusions set up, gastric juice collected and titrated, all under standard conditions.

During the early stages of the study, all these aspects of the test were carried out personally by the author, enabling an intimate knowledge of the difficulties and complications to be accumulated, and the tests had to be carried out in the early hours of the morning.

Later, as the numbers of patients grew and what had started as a research project developed into a hospital laboratory service, technical help became necessary, and tests were then carried out in part or in whole by a series of part-time technicians. These were personally trained to carry out the tests by the author, using the method then established so that there was complete continuity of method. In addition, the author was consulted by the technicians in all cases of doubt, difficulty or complications. All patients in this study were, at some stage in their referral, investigation, management or follow-up, known to the author.

Technique of nasogastric intubation

Introduction

The passage of a nasogastric tube is an unpleasant experience, and if carried out without anaesthetic, causes a burning pain in the posterior nasal cavity and retching at the pharynx. Since most of our patients were ambulant and generally fit, and many required repeated tests, it was obligatory to carry out this part of the procedure with as little disturbance to the patient as possible.

Local anaesthetic

Both nostrils and throat were sprayed with about 100 mg lignocaine solution (an aerosol of 'Zylocaine' supplied by Astra-Hewlett Ltd., Watford, England), the patient being encouraged to inhale the nasal instillation well back into the posterior naso-pharynx. This was allowed to act for 3-4 minutes until the patient was assured that his nose and throat were quite numb.

In addition, the nasogastric tube was lubricated with about 1 ml (20 mg) of zylocaine gel (Astra-Hewlett Ltd., Watford).

Nasogastric tube

'Portex' Ryles tubes (Portland Plastics, Hythe,

Kent, England) were used, size 14 FG. Very occasionally in a small subject with narrow nostrils a size 12 FG had to be used. Very exceptionally a patient would volunteer to swallow his own tube, by mouth, unaided. These tubes are 107 cm long with markings at 37.5, 50 and 62.5 cm from the tip. Four steel ball bearings are embedded in the tip as markers, and aspirating apertures are provided at 2, 4, 6 and 8 cm from the tip.

Method of intubation

The patient sat upright in a chair, leaning a little forward, with his head and neck flexed so that the chin was almost on his chest. The operator sat beside him, encouraged him to relax and breathe normally, and very slowly and gently passed the tube horizontally along the floor of one nostril. If any resistance was encountered, the other nostril was attempted.

At the level of the epiglottis there was a momentary pause, the patient was asked to swallow, and the tube could be felt being drawn down to the upper oesophagus. From this level down the tube was simply allowed to pass down unimpeded, largely by means of the patient's own swallowing actions. No force was used to pass the tube at any stage.

At the level of the cardia there was commonly a

considerable pause of up to half a minute before the tube could be felt passing into the stomach.

Tube distance

The tube was passed until the third mark was about the level of the nostril, i.e. to a total distance of 55 - 60 cms from nose to tip of tube. Thus, in the average build of patient, the aim was to have 15 - 20 cm of tube lying within the stomach.

Tube position

At an early stage in this investigation it became apparent that effective aspiration from a stomach tube was not related solely to its position within the stomach as demonstrated radiologically. An apparently well-placed tube could, on occasion, give erratic unsatisfactory collections, while another, curiously curled in the upper part of the body of the stomach, might provide an uninterrupted flow of gastric juice. The objective evidence for a 'well-placed' tube could thus be anomalous. An attempt was made to resolve this conflict by taking special radiographs with the tube passed as described above, with the patient lying on his left side, and with both the tube and the pool of resting gastric juice outlined by means of radio-opaque medium.

A series of 42 patients was studied in this way.

They were unselected in so far as the convenience of the Department of Radiology dictated. The positions of the tubes could be allocated to three main groups (Fig. 1) depending on whether the tube

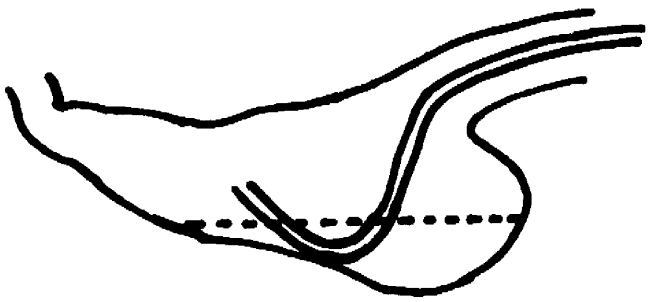
(a) lay along the greater curvature with the tip towards the antrum (25/42 = 59%) (Fig. 2)

(b) dipped down into the greater curve (10/42 = 24%) (Fig. 3).

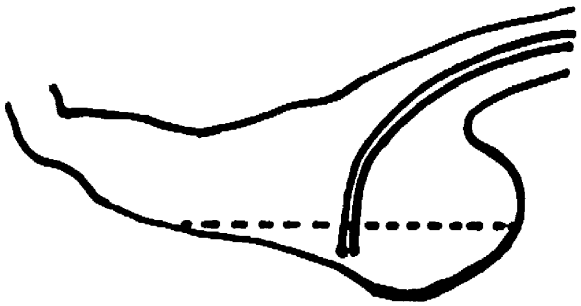
(c) curled round in the body of the stomach (7/42 = 17%) (Fig. 4).

Diluted barium solution (15 ml) was injected slowly down the gastric tube and allowed to mix in the resting pool of gastric juice. All 42 tubes were demonstrated lying at least partly in the resting pool. All the tests on these patients with the tubes in these positions proved satisfactory in terms of regular volumes of collected gastric juice.

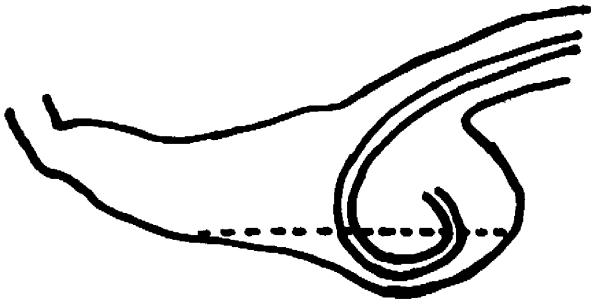
From this, it was concluded that a tube was satisfactorily placed when it was in a position to aspirate the resting gastric juice. Therefore, as soon as a tube had been passed in the manner described above, the patient was placed in the aspirating position on a couch, aspiration started, and the final position of the



25 (59%)



10 (24%)



7 (17%)

Figure 1: The three positions assumed by naso-gastric tubes in 42 subjects, passed without fluoroscopic control. The diagrams show the outline of the stomach with the subject lying on his left side. The resting pool of gastric juice is indicated.

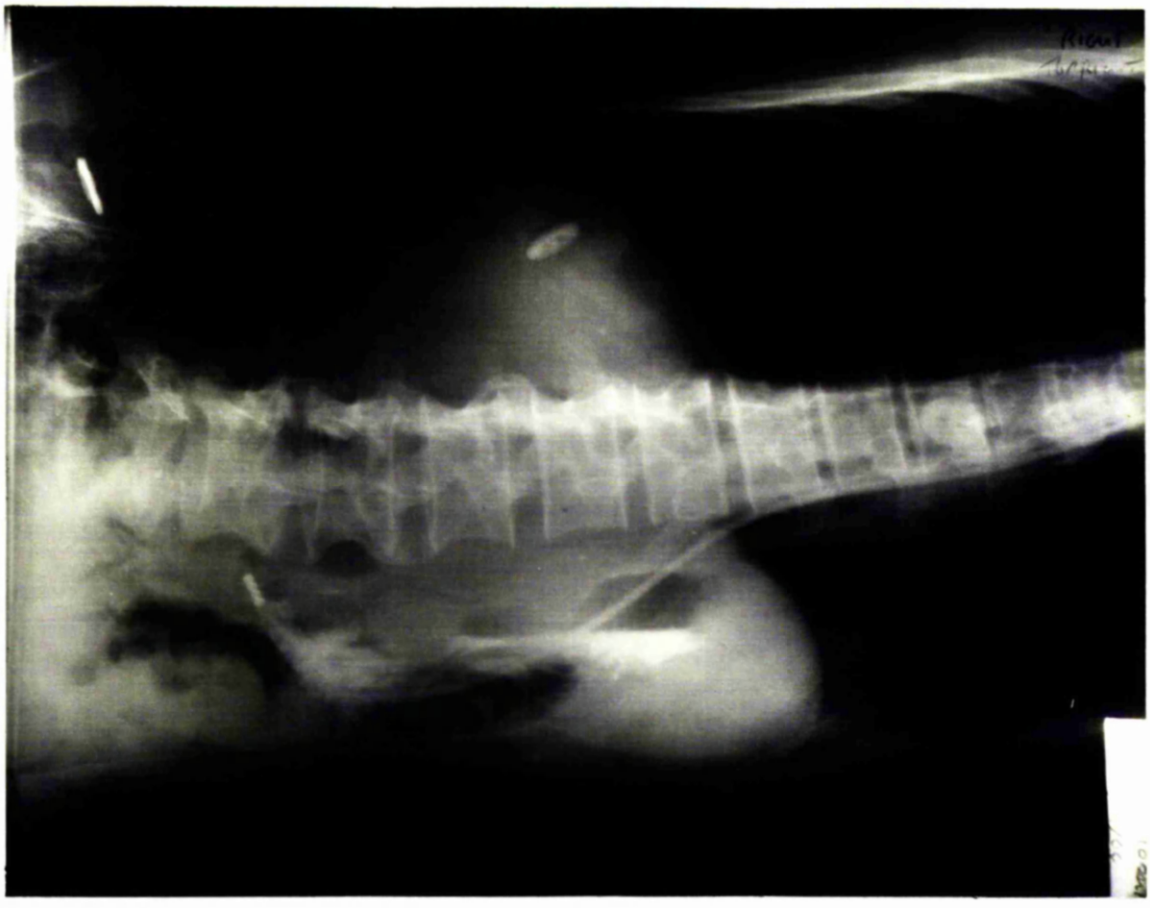


Figure 2: A radiograph of the stomach with the patient lying on his left side, showing the naso-gastric tube lying along the greater curve, passing through the resting pool of gastric juice. The tube was in this position in 25 of the 42 subjects studied (59%).

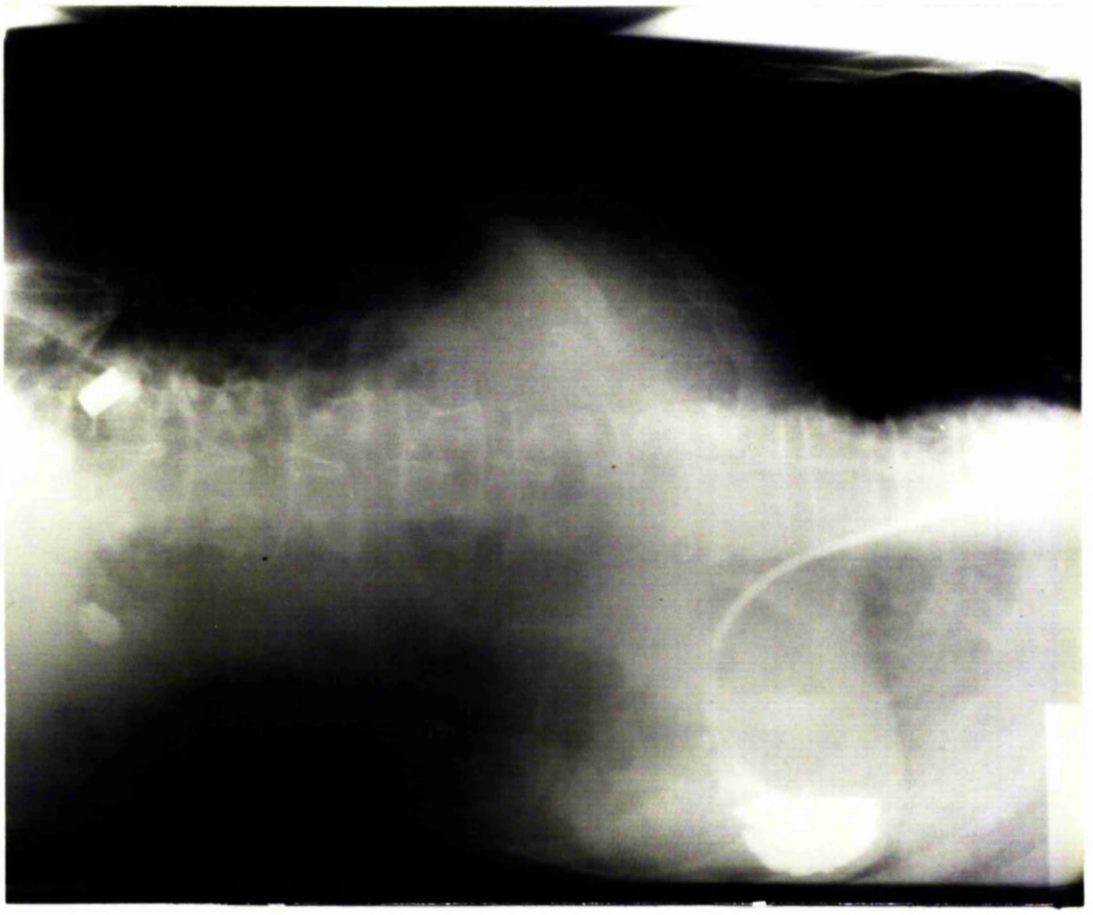


Figure 3: A radiograph of the stomach with the patient lying on his left side. The nasogastric tube dips down into the resting pool of gastric juice in the most dependent part of the stomach. The tube was in this position in 10 of the 42 subjects studied (24%).

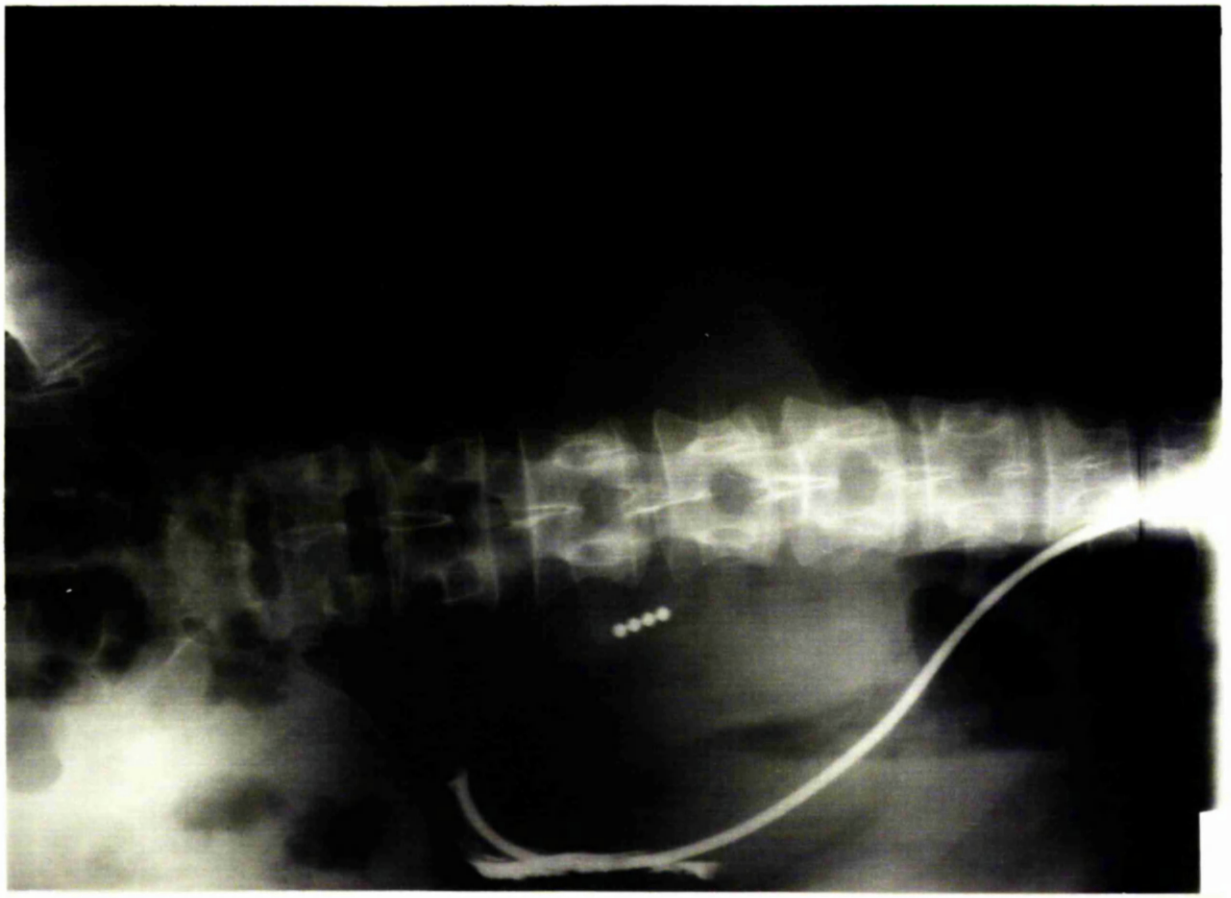


Figure 4: A radiograph of the stomach with the patient lying on his left side. The nasogastric tube passes through the resting pool of gastric juice before turning upwards into the body of the stomach. The tube was in this position in 7 of the 42 patients studied (17%).

tube determined by the flow of resting juice.

The aspirating position of the patient

The patients were asked to lie comfortably, almost fully over on the left side (Fig. 5). In this position, the resting pool of gastric juice collects in quite a well-localised area of the greater curvature (Figs. 2, 3 & 4). Its outline is often broken by the indentation of the spleen, but the main pool is normally at the mid-part of the greater curvature.

Salivation

No particular instructions or precautions were taken to prevent patients from swallowing saliva. In practice it was found that swallowing becomes increasingly uncomfortable after a tube has been lying in the pharynx for more than half an hour, and most patients used a series of paper handkerchiefs to absorb their saliva and so avoid the necessity of swallowing.

Aspirating technique

Continuous suction was applied to the nasogastric tube by means of an electric pump creating a low vacuum of 5 - 10 cm of water. This amount of comparatively gentle suction will, however, draw the mucosa of the

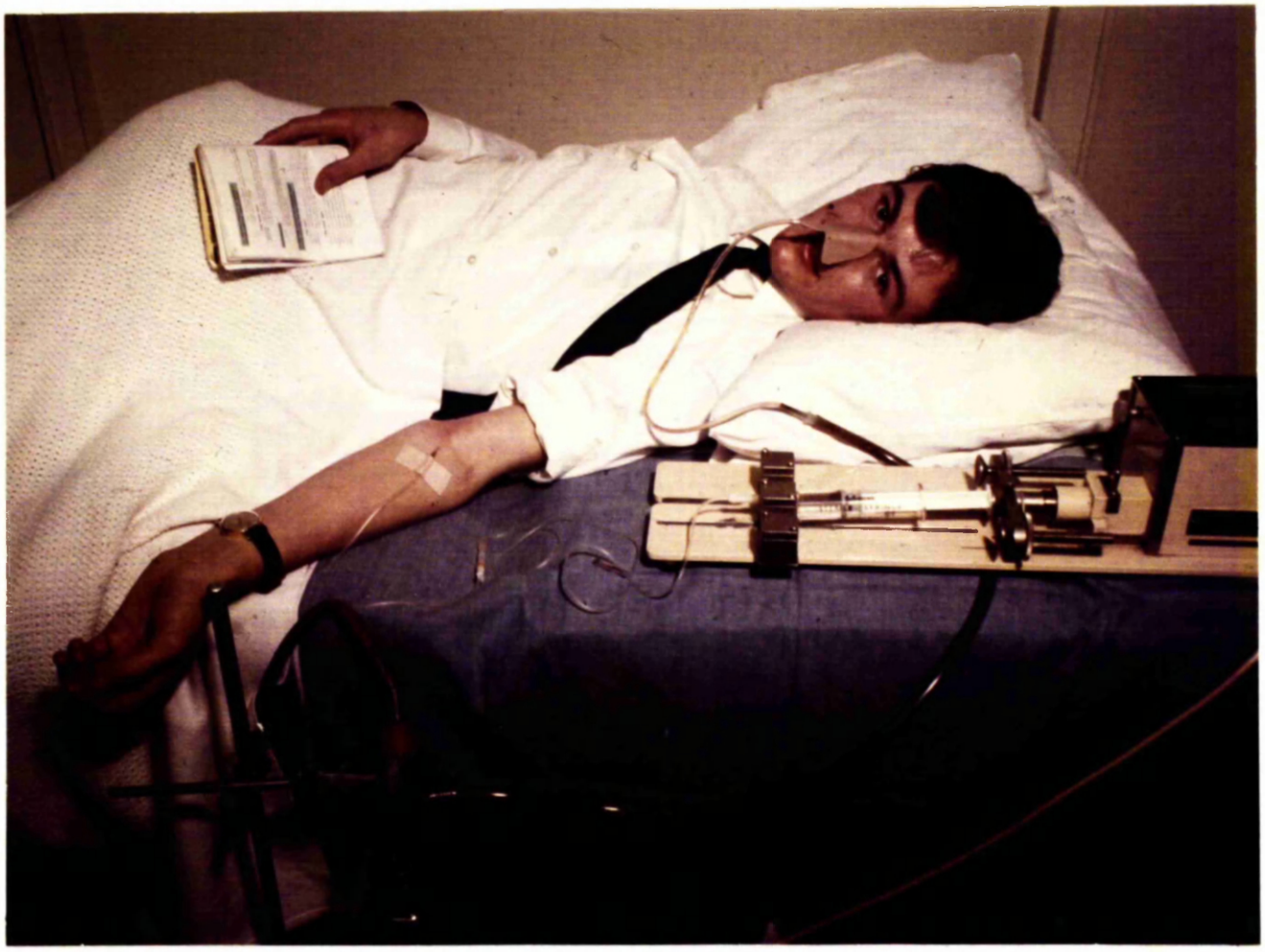


Figure 5: A subject during a histamine-infusion test, lying flat on a couch, almost fully over on his left side. The histamine solution is being delivered by the Palmer pump from the 20 ml plastic syringe through fine plastic tubing to a paediatric needle in an antecubital vein. Gastric juice is being collected by gentle suction in the conical flask.

empty stomach into the aspirating holes and so prevent the aspiration of gastric juice as it is secreted. Accordingly, the suction was interrupted every 2 - 3 minutes, to allow the injection of 2 - 3 ml of air down the tube to clear the aspirating holes. Confirmatory evidence for the proper positioning of the tube was provided by listening with the ear close to the patient's epigastrium, when the injected air could be heard clearly gurgling within the stomach.

Method of infusion

A constant rate of infusion was used for all patients, the dose of histamine being determined for each patient by varying the concentration of the infused solution in relation to the individual body weight.

The Palmer pump was used, at a setting which advanced the ram 1 inch in 80 minutes. Combined with a 20 ml plastic Johnson disposable syringe, this system would deliver 5.37 ml per hour and thus run continuously for about 4 hours without change of syringe. To minimise dead space in the system the solution was infused via a fine-bore Baxter anaesthetic connecting tube and a paediatric scalp-vein needle set.

Given the exact volume of fluid delivered by this

system per hour, and since it is required to deliver 0.04 mg histamine acid phosphate per kilogram body weight per hour, it is a matter of simple proportion to prepare a 20 ml solution in 0.9% saline in a 'universal' container.

Dose of histamine

The maximum secretory dose of histamine was known to lie between 10 and 20 µg/kg/hour of histamine base (0.03 and 0.06 mg/kg/hour histamine acid phosphate; Nordgren, 1963). Hanson and others (1948) had demonstrated a maximal response in one patient with 0.02 mg/kg/hour histamine dihydrochloride. Most other studies had been more concerned with a steady state of acid secretion (Adam and others, 1954; Hirschowitz and others, 1957) rather than with maximal responses.

Accordingly, dose-response or concentration-action curves were constructed to relate various doses of histamine by infusion to the acid output per hour during a steady state of secretion. For convenience in comparison with other studies, histamine acid phosphate was used in doses of 0.005, 0.01, 0.02, 0.04 and 0.08 mg/kg body weight/hour.

Dose-response curves

Seven patients each submitted to five histamine infusion tests, having the order of the different doses

selected at random. The five different responses for one of these patients is shown in Figure 6. Table 1 shows that in all seven patients the acid output increased with increase in dose of histamine, up to the dose of 0.04 mg/kg/hour. At the highest dose rate of 0.08 mg/kg/hour 3 patients had a decrease, one an increase and 3 more or less the same output as that resulting from the 0.04 mg dose. The 7 individual dose response curves are shown in Figure 7. The mean acid output for each dose rate is shown in Table 1 and Figure 8.

The highest mean acid output occurs in response to the 0.04 mg/kg/hour infusion, although this value of 40.4 mEq/hour is not significantly greater than that for 0.02 mg/kg/hour (28.8 mEq/hour) and for 0.08 mg/kg/hour (36.3 mEq/hour). This is probably due to the wide range of acid levels in the 7 patients, who did not constitute a homogeneous group, resulting in a large standard deviation.

These dose-response curves were studied as percentages, by probit transformation and by computer analysis, in order to discover from them the precise maximal secretory dose of histamine. The conversion of the outputs to percentages of the maximum for each

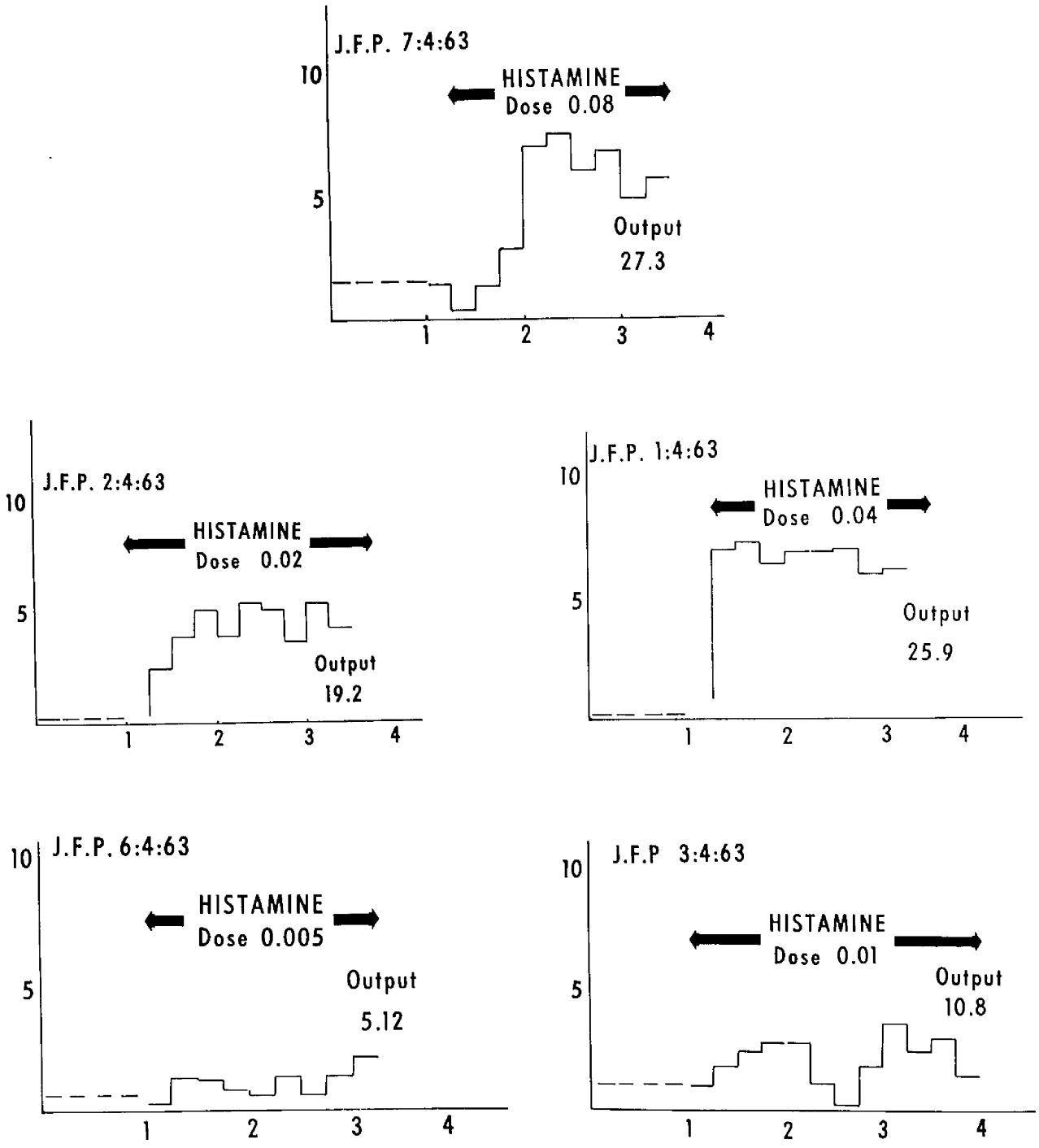


Figure 6: The five graphs of acid output in one patient after five separate histamine infusions at different doses of histamine. The abscissa is time in hours, the ordinate output in mEq/HCl/15 minute period, the dose of histamine is mEq/kg body weight/hour, and the output for each dose rate is shown in mEq/HCl/hour.

Table 1. The acid output in 7 patients, each having 5 different histamine-infusion tests, with the mean output for each of the 5 doses.

Dose (H.A.P.) mg/kg/hour	0.005	0.01	0.02	0.04	0.08
J.O'S.	3.3	2.6	8.0	25.5	21.3
W.L.	0.6	1.9	6.3	8.3	11.0
A.H.	20.8	30.4	36.0	41.7	41.6
W.H.	20.8	23.0	47.3	72.5	54.9
D.C.	11.6	22.4	39.8	60.0	49.2
J.P.	5.1	10.8	19.2	25.9	27.3
H.D.	26.9	29.9	45.1	49.1	48.5
Mean	12.7	17.3	28.8	40.4	36.3
S.D.	10.2	12.1	17.4	22.2	16.5
Mean difference			11.6	4.2	
Significance of difference			P > 0.2	P > 0.7	

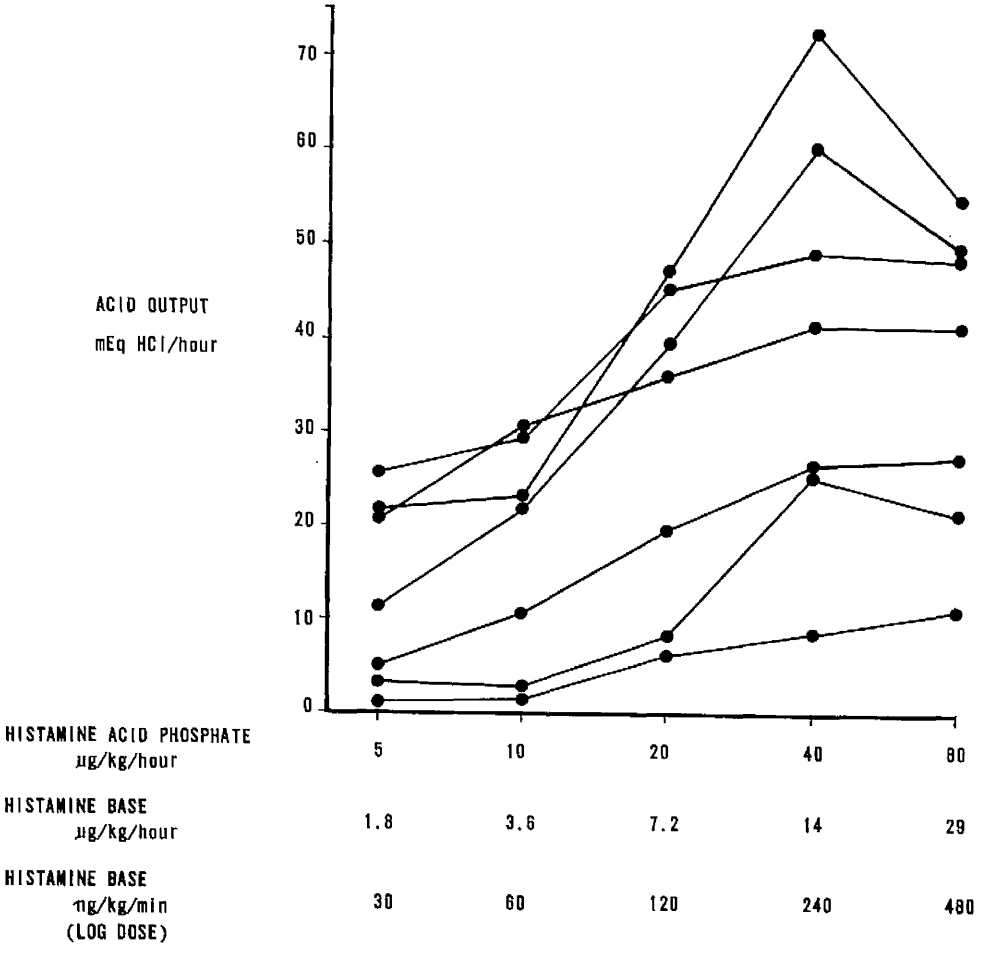


Figure 7: The dose-response curves obtained from 7 patients, each point on each curve being the acid output in response to a histamine-infusion test using increasing doses of histamine acid phosphate from 5 to 80 µg/kg/hour. The equivalent doses of histamine base are shown.

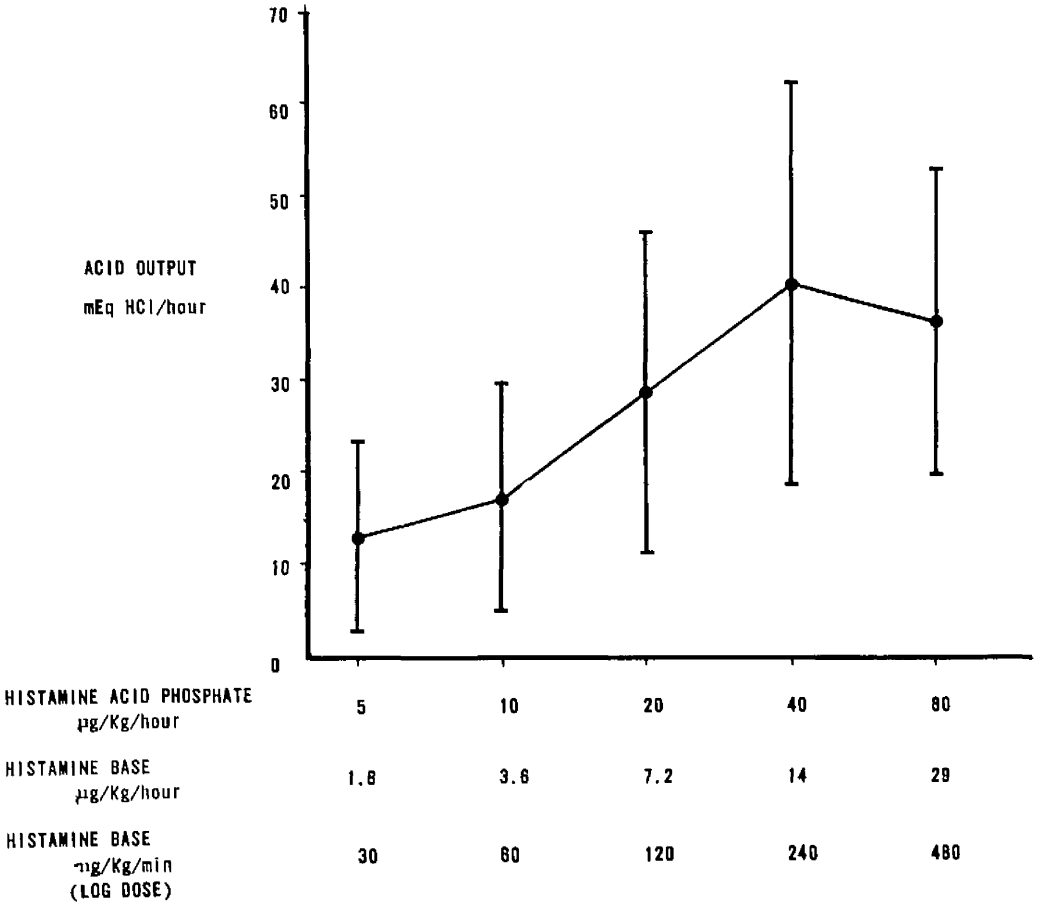


Figure 8: The mean acid output (± 1 S.D.) from the 7 patients at each dose rate of histamine acid phosphate from 5 - 80 µg/kg/hour with the equivalent doses of histamine base shown below.

patient (Fig. 9) proved no more meaningful than the numerical values. Probit transformation did not result in a stright line for any of the patients, suggesting that these doses represented only the upper part of a dose-response curve. Attempts at analysis of the curves to determine the precise dose of histamine which would produce a theoretical maximal response were inconclusive and would have required many more points on the curves, or many more tests on each patient.

Accordingly, after discussion with the Department of Medical Statistics, Welsh National School of Medicine, it was agreed that 0.04 mg/kg/hour could be taken as a maximal secretory dose for this method of administering histamine acid phosphate, since doubling this dose did not produce any further significant increase in acid response.

Preparation of solution for infusion

For example:

a 70 kg patient requires (0.04 mg x 70) H.A.P. in 5.37 ml solution, i.e. $\frac{0.04 \times 70}{5.37}$ x 20 in 20 ml solution.

i.e. 10.42 mg in 20 ml solution.

Histamine acid phosphate was made available in ampoules of 5 ml containing 5 mg and 5 ml ampoules of 0.9% NaCl were used for dilution.

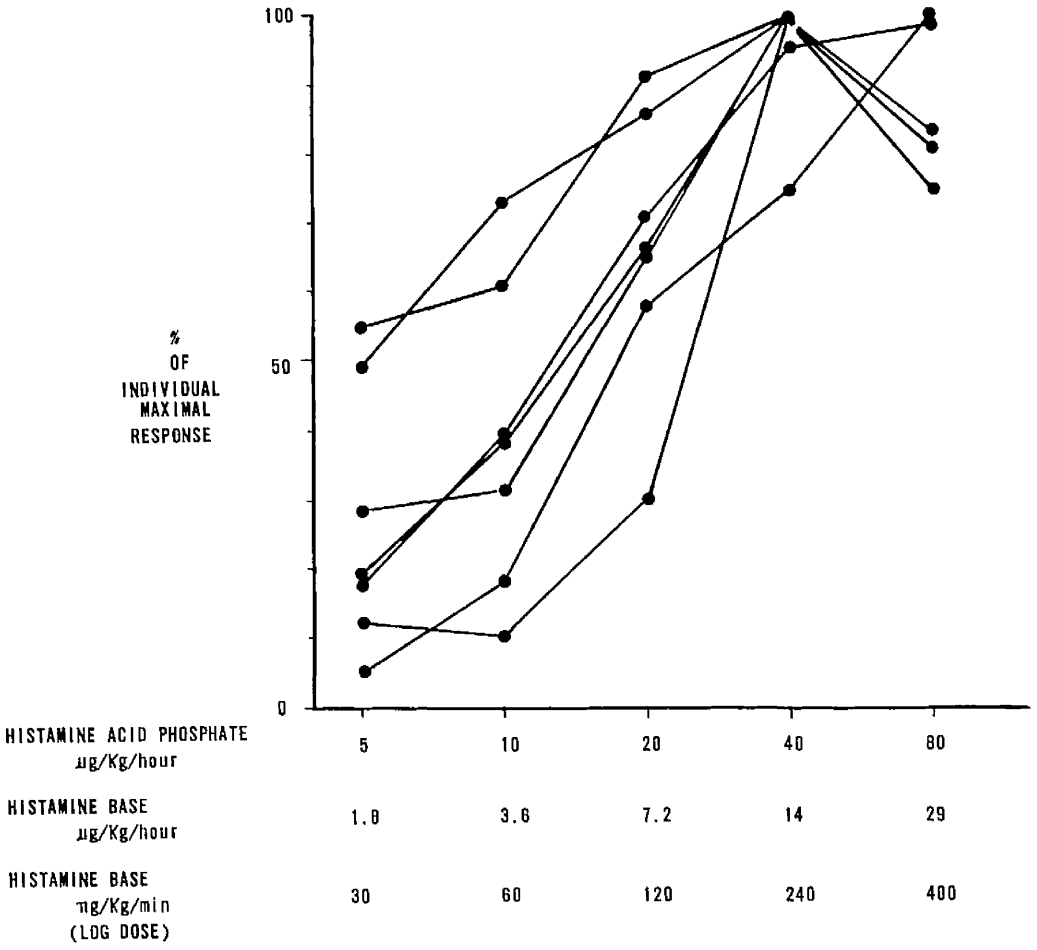


Figure 9: The graphs of acid output from the 7 patients shown in Table 1, showing the results as percentages of the maximum acid output attained by each patient.

Therefore, the required solution for this patient consisted of:

10.42 ml H.A.P. + 9.58 ml 0.9% NaCl = 20 ml solution. A table and graph were made for the whole range of patients' weights, so that this simple proportion of H.A.P. to saline could be read off at a glance. The basic equipment used is shown in Figure 10.

Anti-histamine

During early tests using different doses of histamine, on the author, other members of the staff and certain co-operative patients, it became apparent that there were more or less constant sensations of headache and flushing associated with a histamine infusion. These were not obviously related to dose, nor were they abolished by the accepted standard use of 'Anthisan', mepyramine maleate, 50 mg. Many tests were carried out without anti-histamine with no increase in side-effects. It proved difficult to assess objectively the difference in side-effects from an infusion of histamine, compared with those from a subcutaneous injection, but the opinion was formed that infusion side-effects were less severe. Logically, this might be expected, since the dose of 0.04 mg/kg is infused over a period of one hour, while the subcutaneous test requires the same dose to be given as a single injection.

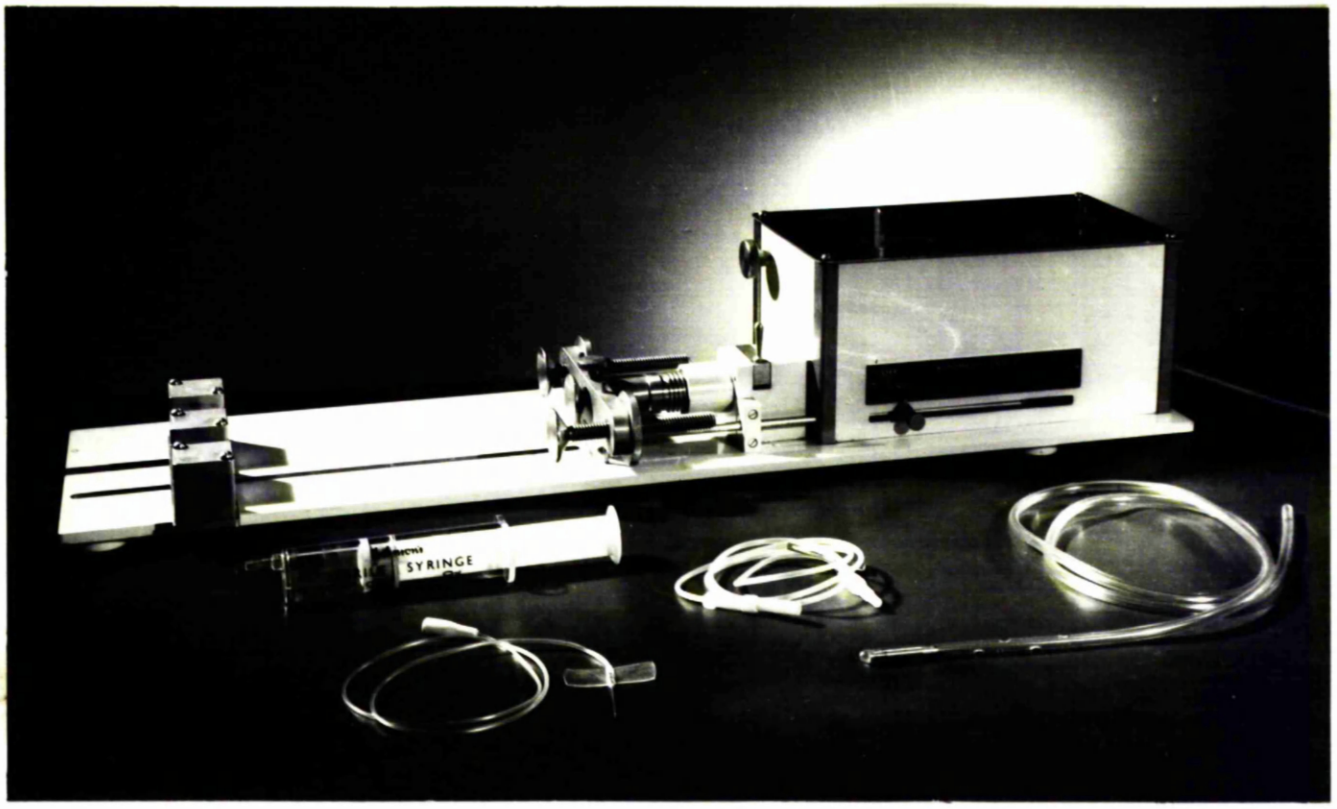


Figure 10: The Palmer pump used for the infusions. The 20 ml plastic syringe, paediatric scalp vein needle, fine anaesthetic connecting tubing and plastic naso-gastric tube, are all pre-sterilised and disposable.

On two aspects of this problem there was no doubt, namely that the side-effects passed off within a few minutes of the infusion being discontinued, whereas the effects of a single injection subcutaneously were less predictable and more prolonged, and that the drowsiness associated with subcutaneous tests was mainly due to the anti-histamine.

Two patients submitted to three tests each, all at standard rate of histamine 0.04 mg/kg/hour, with and without anti-histamine (Table 2). There was no particular trend either way, with or without the anti-histamine. The variation in acid output about the mean was 1.8 mEq/hour in one patient, and 2.2 mEq/hour in the other. This is comparable with a mean difference of 3 mEq/hour in duplicate tests for reproducibility.

Accordingly, a small dose of anti-histamine, 25 mg mepyramine maleate, was given into the paediatric scalp vein needle set as a starting solution to ensure that the needle was well placed in the vein. The effect of this small dose given intravenously had worn off by the end of the test, and since the effects of histamine also diminished rapidly when the infusion was discontinued, the histamine-infusion test carried out in this way proved suitable for out-patient practice, the patients being able

Table 2. The acid outputs in two patients each having three histamine-infusion tests, with and without anti-histamine (50 mg mepyramine maleate).

(+) with anti-histamine (-) without "		Acid Output mEq/hour	Mean	Difference
H.R. (male D.U.)	(+)	41.8		+ 1.1
	(-)	42.3	40.7	+ 1.6
	(-)	37.9		- 2.8
I.F. (female Ca.)	(+)	23.2		- 0.4
	(-)	20.7	23.6	- 2.9
	(+)	26.8		+ 3.2

to leave soon after the test and go about their normal business.

Titration

Specimens of gastric juice were collected every 15 minutes, with the patient still lying half over on his left side, and the pump suction interrupted every few minutes by the injection of a few millilitres of air into the naso-gastric tube. This kept the tube patent and provided a useful monitor of the position of the tube in the pool of gastric juice.

The volume of gastric juice increased during the first two or three periods and from the fourth period onwards was more or less constant. Variations in volume indicated faulty aspiration or tube position, both of which could be easily rectified and the infusion continued until four comparable specimens constituting a one-hour plateau had been obtained.

The gastric juice became darker in colour, and contained less mucus. After measuring the volume of the specimens, a 10 ml aliquot was pipetted into a small beaker and titrated to pH 7, using constant magnetic stirring, with 0.2 N NaOH.

The titrator used was the automatic titration assembly (Fig. 11) Radiometer, Copenhagen, TTT 1C. This

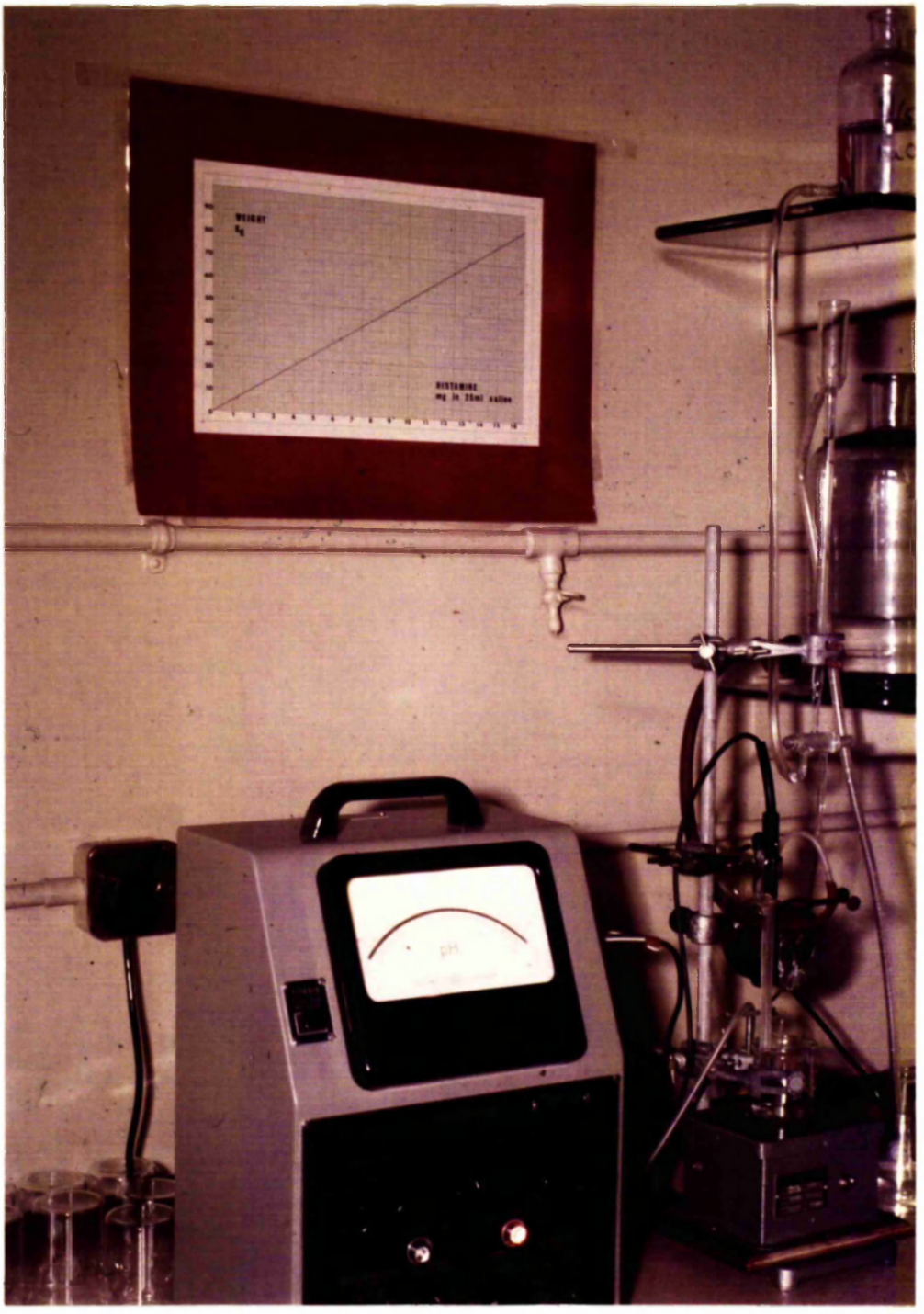


Figure 11: The pH meter, Radiometer TTT 1C, and the automatic burette assembly.

indicated the pH of the specimen, and from the volume of NaOH used, the concentration or acidity in milliequivalents per litre could be read directly.

Calculation of output

The output of H^+ or HCl per 15-minute period, was taken as the product of volume (in litres) and the concentration (in milliequivalents per litre) and was recorded as milliequivalents per 15 minutes. Four such consecutive periods gave the acid output in milliequivalents per hour (Fig. 12).

Validity of plateau

By observation it was apparent that plateaux of both volume and concentration of acid were reached and sustained for several hours in response to this maximal dose of histamine by infusion. The validity of the assumption that four consecutive 15-minute collections represented a 'steady state' and could therefore be taken as a constant, maximal one-hour output, was assessed by a statistical comparison between them. To standardise the 15-minute outputs of individual patients, each was expressed as a percentage of the mean of their four 15-minute periods. Since percentages are not normally distributed, their logarithms were used for analysis. The means and the standard error of the means of each of

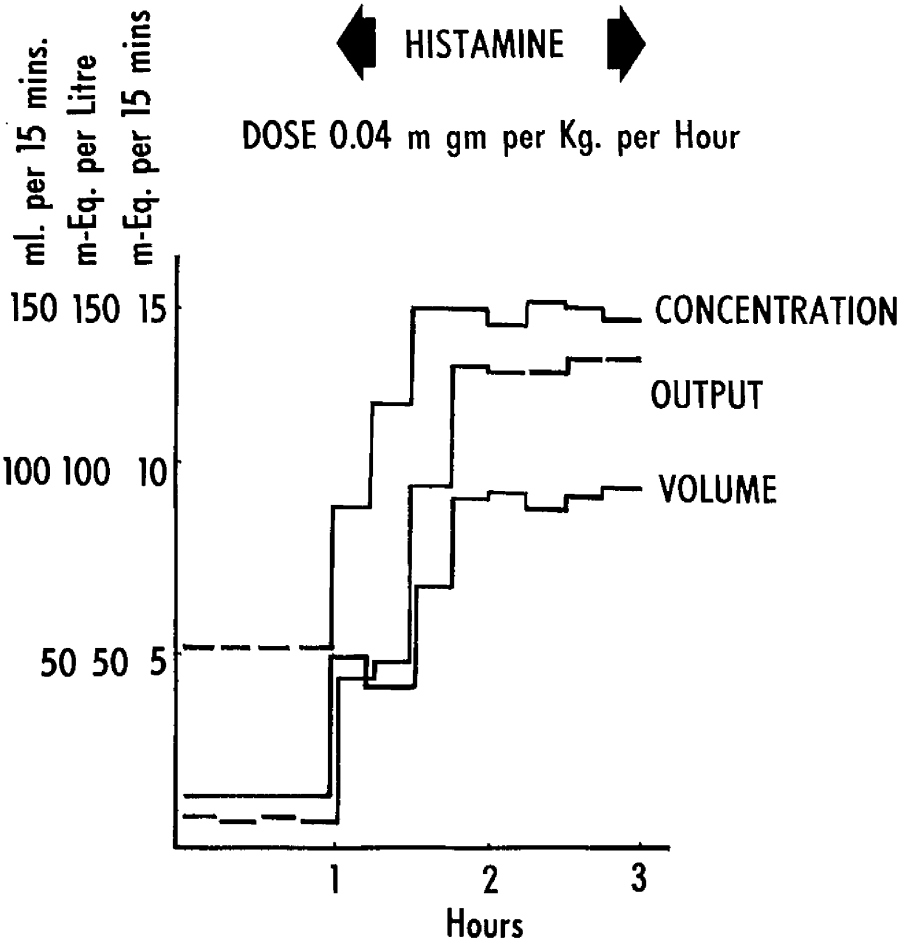


Figure 12: A histamine-infusion test. Concentration of acid has reached a maximum by the third 15-minute period, volume by the fourth. Output for each 15-minute period is calculated as the product of volume (litres) and concentration (mEq/litre) and the maximum acid output per hour as the sum of the last four 15-minute outputs of the plateau.

the four successive periods were then calculated for 140 tests. The significances of the difference between the means were estimated by the t test. No significant difference was found (Table 3).

Reproducibility

Thirteen patients submitted to two identical histamine-infusion tests within 2-3 days, in order to assess the reproducibility of this procedure. The same dose of histamine (0.04 mg/kg/hour) was used in each test (Table 4; Fig. 13).

The outputs ranged from 20.9 - 61.3 mEq/hour and the differences between the two tests ranged from 0.5 - 8.7 mEq. It is accepted that the coefficient of variation may not be a proper method of assessing a laboratory method for tests over a wide range, but within these limits the coefficient of variation was 9% (Snedecor, 1962).

An analysis of variance showed that there was no significant difference between these duplicates (F between duplicates 0.5314, not significant; F between patients 39.25, $P < 0.001$).

Comparison between histamine-infusion test and 'augmented' histamine test

In the present study a comparison was attempted

Table 3. Analysis of differences between four 15-minute outputs of acid obtained during 'steady state' plateaux used to calculate the secretory response (mEq/hour) in 140 histamine-infusion tests.

15-minute period	Mean output HCl (expressed as log % of each patient's mean)	Mean difference ± S.E.
1	1.992	
		0.006 ± 0.024 (P = 0.8)
2	1.986	
		0.015 ± 0.023 (P > 0.5)
3	2.001	
		0.002 ± 0.021 (P > 0.9)
4	2.003	

Table 4. Duplicate histamine-infusion tests in 13 patients.

Patient	Acid output mEq/hour 1st test	2nd test	Difference	Mean	Variance
R.J.	54.0	52.4	1.6	53.20	1.28
A.P.	23.3	18.1	5.2	20.70	13.52
W.W.	26.8	30.7	3.9	28.75	7.61
T.K.	60.5	61.3	0.8	60.90	0.32
M.D.	22.4	24.6	2.2	23.50	2.42
H.D.	40.0	41.0	1.0	40.50	0.50
F.W.	38.8	44.0	5.2	41.40	13.52
J.J.	47.1	38.4	8.7	42.75	28.85
P.D.	27.8	22.8	5.0	25.30	12.50
A.M.	26.7	22.5	4.2	24.60	8.82
H.R.	42.3	41.8	0.5	42.05	0.13
I.F.	23.2	26.8	3.6	25.00	6.48
K.C.	23.3	20.9	2.4	22.10	2.88

Mean of 26 tests	35 mEq/hour
Mean difference	3 mEq
Coefficient of variation	9%
F between duplicates	0.5314 (not significant)
F between patients	39.25 ($P < 0.001$)

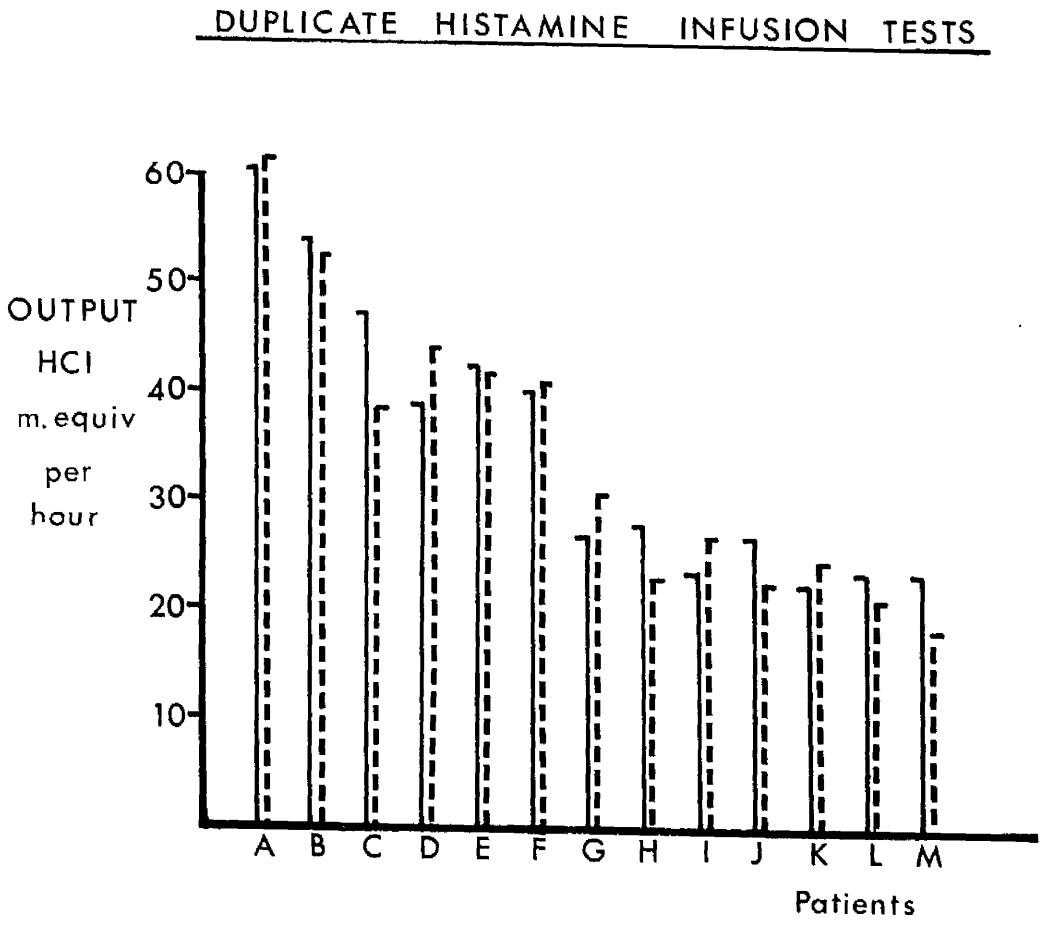


Figure 13: The acid output from duplicate infusion tests carried out on 13 subjects, using the same dose of histamine, 0.04 mg/kg/hour. There is no significant difference between duplicates (see Table 4).

between the histamine-infusion test and the augmented-histamine response (Kay, 1953). Both tests were carried out on 45 patients, within a period of two days (Fig. 14). Each test was carried out by the same operator and under the same conditions of gastric intubation, aspiration and titration.

The mean acid output by the infusion tests (in milliequivalents per hour) for these 45 patients was compared with the mean acid output by the augmented-histamine tests (Fig. 15) calculated by four different methods: (1) four times the peak 15-minute response (2) twice the sum of the two highest successive 15-minute periods (3) twice the sum of the second and third 15-minute periods, and (4) the simple sum of the four successive 15-minute periods.

The continuous histamine infusion gave a consistently greater (and significantly different) output than the augmented-histamine response as calculated in these four different ways (Fig. 15).

Of the four methods of assessing the augmented-histamine response, that derived from four times the peak period gave the highest value and was the nearest approximation to the histamine-infusion output. The significance of the difference between these various outputs is shown in Table 5.

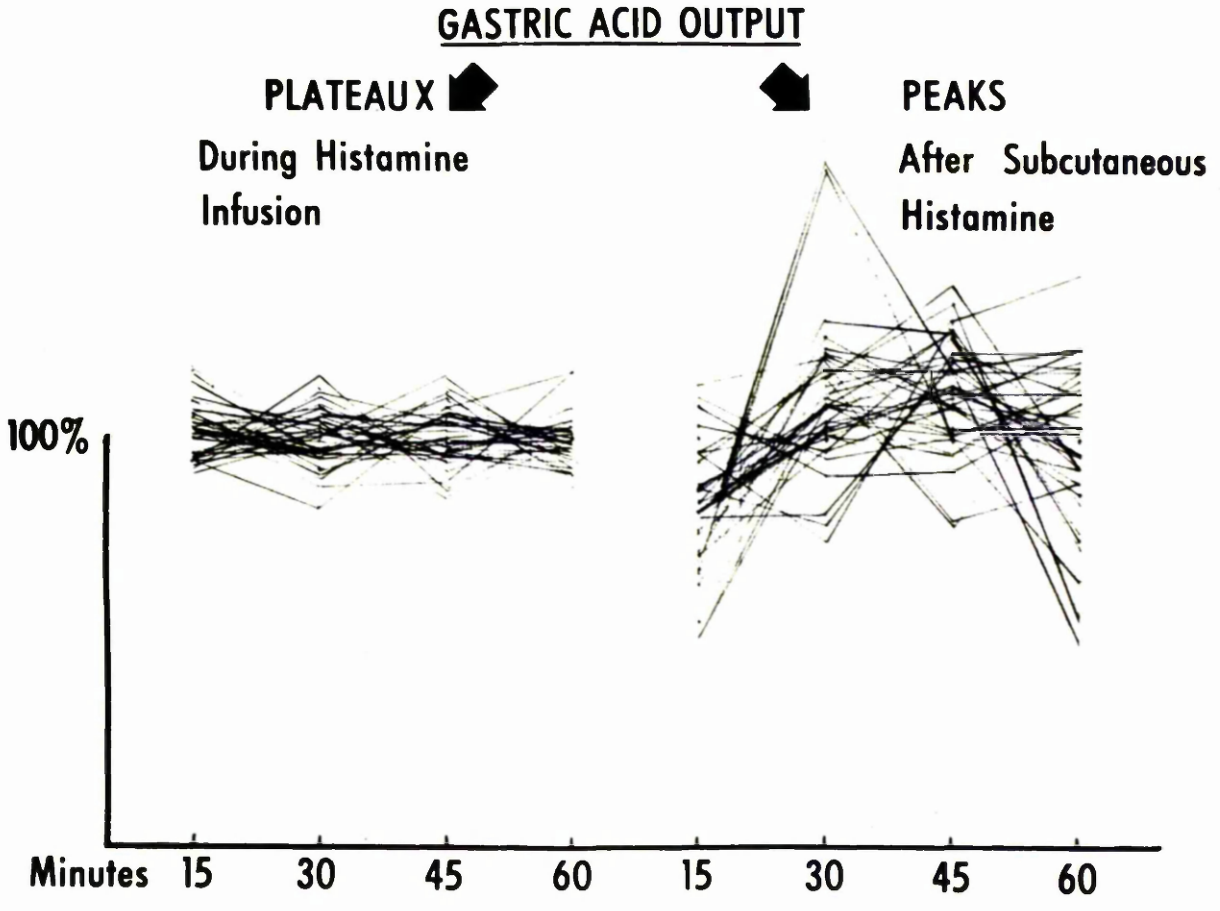


Figure 14: A comparison between the acid output during a histamine-infusion test and after an augmented histamine test (subcutaneous) in 45 subjects having both tests. The acid output for the four 15-minute periods forming the plateau during the infusion, and the four forming the peak response to the subcutaneous injection are illustrated as percentages of their means.

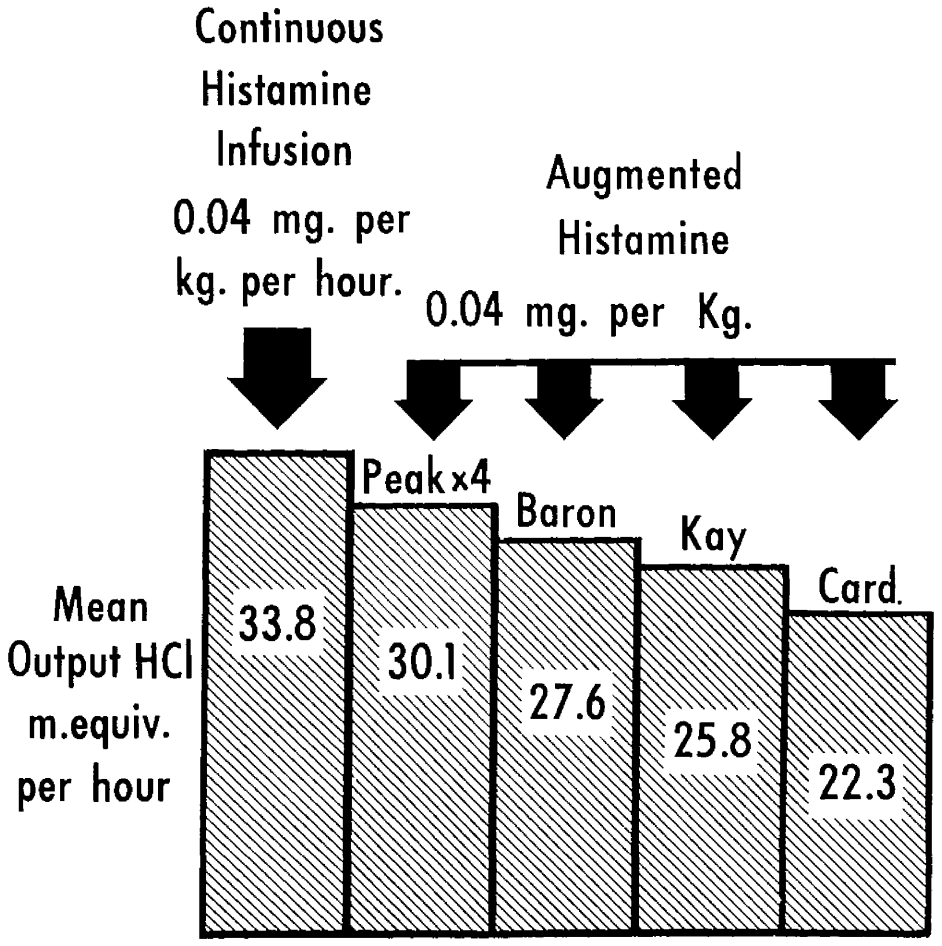


Figure 15: The mean acid output from 45 infusion tests, compared with that from 45 subcutaneous histamine tests carried out on the same subjects, calculated by four methods:

'Peak x 4' = (best 15-minute output) x 4
'Baron' = (best two 15-minute output) x 2
'Kay' = (second and third 15-minute output) x 2
'Card' = sum of the four 15-minute outputs after histamine.

Table 5. Significance of differences in acid output between histamine-infusion tests (H.I.T.) and augmented-histamine response.

	Mean difference ± S.E.	P
H.I.T./Peak x 4	3.70 ± 1.05	< 0.01
H.I.T./Best 30 min. x 2 (Baron)	6.14 ± 1.14	< 0.001
H.I.T./15-45 min. x 2 (Kay)	8.00 ± 1.49	< 0.001
H.I.T./0-60 min. (Card)	11.50 ± 1.56	< 0.001

The correlation between the outputs of acid by the histamine-infusion test and by the augmented-histamine test calculated by the method of Kay is shown in Figure 16. The regression equation calculated from the 90 tests is:

A.H.T. = -0.4 + 0.774 (infusion output)

The correlation between the outputs from the two tests is highly significant ($P < 0.001$).

Similar regression lines and coefficients of correlation were calculated relating the outputs of hydrochloric acid by the histamine-infusion test, with the outputs by the augmented-histamine test calculated by the four methods (Fig. 17). The outputs of acid in the histamine-infusion test are significantly correlated with those obtained by all four methods of calculating the augmented-histamine, although evidently higher than those latter values.

Side effects and complications

Side effects

Within minutes of the administration of histamine by any parenteral route, all patients look flushed, particularly about the face, and often show demarcated patchy erythema around the arm being infused. These feelings are tolerable within the context of the general

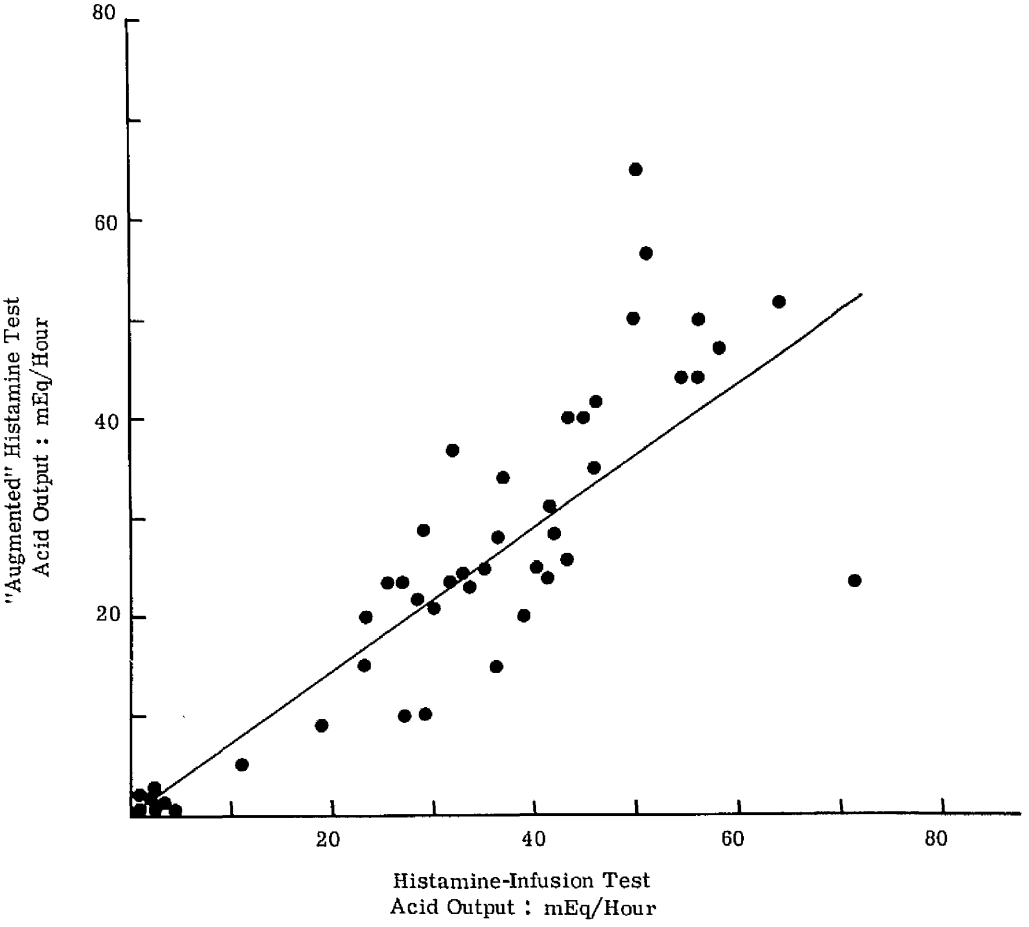


Figure 16: The correlation between acid output obtained by the histamine-infusion test and by the 'augmented' histamine test in 45 subjects, each of whom had the two tests carried out on separate days. (Regression equation A.H.T. = -0.4 + 0.774 H.I.T. $P < 0.001$).

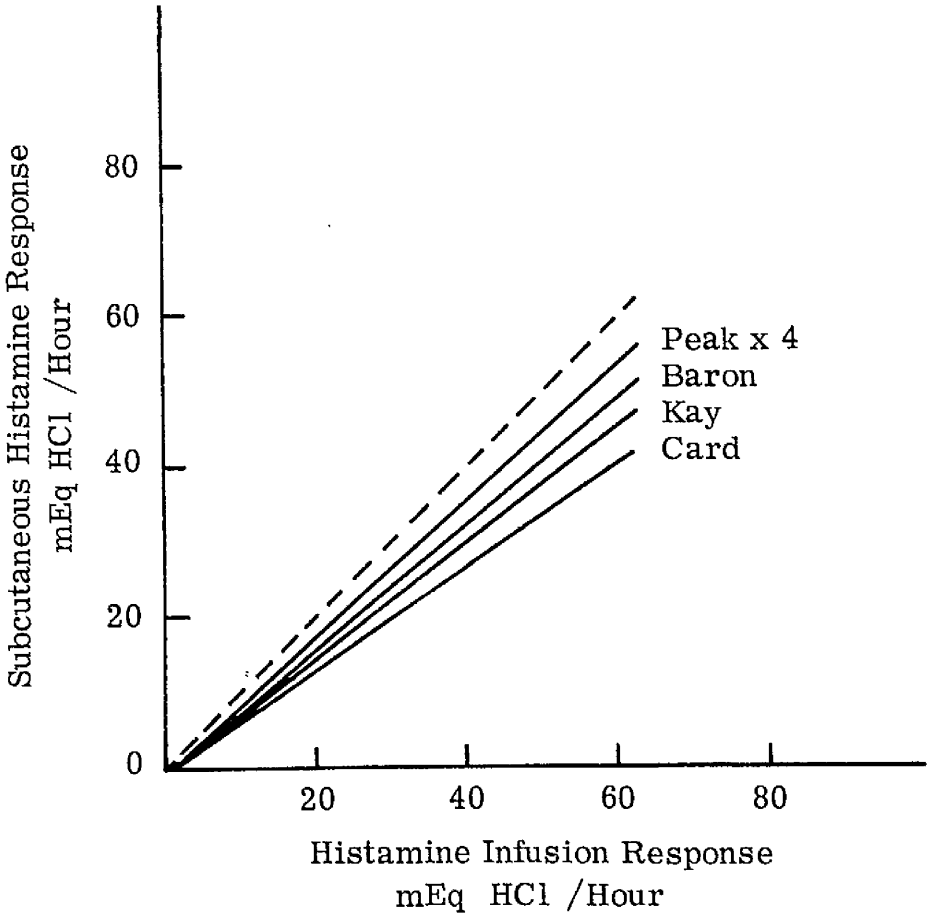


Figure 17: Regression lines relating response to infusion tests (H.I.T.) with response to subcutaneous tests calculated in various ways. Regression equations:

(Peak x 4) = -0.3 + 0.898 (H.I.T.) $P < 0.001$
(Baron) = -0.6 + 0.834 (H.I.T.) $P < 0.001$
(Kay) = -0.4 + 0.774 (H.I.T.) $P < 0.001$
(Card) = -0.7 + 0.679 (H.I.T.) $P < 0.001$

unpleasantness of lying in one position for about 2 hours with a tube in the nasopharynx. In spite of this, it was a source of surprise and encouragement to the author during this study to observe how many patients suffered little discomfort at all while undergoing this apparently quite complicated procedure.

This variation in severity of symptoms, with minimal symptoms in many patients, became even more noteworthy during the later study comparing histamine with pentagastrin side-effects, when several patients having had both stimulants, preferred in retrospect the histamine (see Pentagastrin, Side-effects).

At the conclusion of the test the flushing passed off in a few minutes, and the predominant feeling of hunger was relieved by offering the patient tea or cold milk. Patients were thus able to return to their wards, or, if out-patients, to leave the hospital, unaided.

Complications

During this period of four years and over an experience of 1100 tests, 7 patients were recorded as having abandoned the procedure due to severe side-effects. Five were men, two women. Most were in middle age, one was 78 and the conditions being investigated were varied. None was obviously ill before the test.

All suffered apparently syncopal attacks, four at the start of the test, while the infusion was being set up, and these might incriminate the anti-histamine rather than the histamine. Two suffered a similar syncopal attack when the histamine infusion had been running for 45 minutes, one producing acid, one achlorhydric. The last patient had tolerated the infusion for 1¾ hours when he, a heavy plethoric man of 48, also fainted.

Since the patients were already lying flat, no special manoeuvres were required to revive them and they all made an uncomplicated recovery within a few minutes.

DISCUSSION

Tube position

Two quite separate difficulties have prevented agreement on a satisfactory method of placing a gastric tube for optimum collection of gastric secretion. The first is the traditional acceptance of this procedure as being within the province of routine nursing care. Thus, nasogastric tubes are commonly passed by a relatively inexperienced nurse in the course of busy early morning ward duties, with the patient supine, his head and neck extended, and with much discomfort, coughing and gagging. Under such conditions it was not unexpected that Retief (1959)

found more than a quarter of tubes to be unsatisfactorily placed. The technique evolved in the present study was discovered to be the reverse of the above, namely with the patient sitting up, co-operating and well anaesthetised so that the operator was in complete control of the tube and its movements.

The second difficulty has arisen from a logical belief in the value of the radiographic demonstration of tube position. Usually the most dependent part of the stomach has been considered satisfactory (Johnston & McCraw, 1958; Marks & Shay, 1960; Baron, 1963) although the left side of the vertebral column (Adam and others, 1954) and along the greater curvature (Køster & Thorsøe, 1960) are frequently quoted.

Examining in detail the position of 161 tubes Baron (1963) found only 21 (15%) in a 'correct' radiological position, the others being in all possible variations of inappropriateness, including 2 in the right bronchus. The majority of his tubes, however, rejected as incorrect, may, in fact, have been satisfactorily related to resting gastric juice.

Kay (1953) adjusted the position of patient and tube until the residual pool of gastric juice had been tapped by syringe aspiration.

The present study attempts to combine both these concepts, by taking radiographs of the patient in the left lateral position with opaque medium in the gastric tube. A simple radiological assessment of tube position would probably have rejected a quarter of these tube positions as unsatisfactory yet they were shown to lie in the pool of gastric juice and to result in satisfactory collections during infusion tests.

A partial explanation of this apparent anomaly may be that most radiological screening for tube position takes place in a separate department, and in a different position, either erect or supine, from that finally adopted for aspiration. When the radiographs were taken with the patient in the left lateral position, it was instructive to see how 'high' along the greater curvature the resting pool extended (Fig. 3), and that in this position the 'most dependent' part of the stomach is, in fact, near the fundus. More important, however, than these strictly anatomical considerations, is the actual technique of aspiration.

Technique of aspiration

There being valid grounds (Öbrink, 1948; Adam and others, 1954) for assuming a steady state of gastric acid secretion in response to an infusion of histamine, it

became more than normally obligatory to ensure complete collections. At the same time, it was reasonable to assume that irregularities in volumes of aspiration would be a reflection of inadequate collections due to inefficient aspiration.

Syringe aspiration produced impeccable 10-minute collections in the peak responses to histamine as early as 1923 (Matheson & Ammon) and as recently as 1958 was shown to be the most efficient of several methods by Johnston and McCraw, using radioiodine labelled albumin as a marker. Their study was, to some extent, a contrived experiment designed simply to collect marker solution, the stomach being unstimulated. Continuous suction and intermittent aspiration gave comparable volumes when Sandweiss and others (1946) were studying nocturnal secretion.

Most investigators use continuous suction (Kay, 1953) though with qualifications in the form of 'constant attention' (Køster & Thorsøe, 1960). These authors admit that intermittent suction may be easier. The patency of the tube was maintained by interrupting the suction frequently and injecting warm water (Hanson and others, 1948; Adam and others, 1954) or by injecting air (Baron, 1963).

Variations in technique accounted for observed differences in duplicate tests using subcutaneous histamine (Clark and others, 1964). They found a difference of about 5 mEq/hour which was not related to the secretory rate, compared with a mean difference of 3 mEq in the present study.

Therefore, there appears to be no proper method of assessing the actual efficiency of aspiration in an individual undergoing a test. It is difficult to present objective evidence for the efficiency of the methods used in this study, nevertheless two contributory observations encouraged the belief that a series of equal volumes of collection over many 15-minute periods did represent more or less complete collections of maximal gastric secretion.

The first concerned the possibility of duodenal reflux invalidating the collection of maximal gastric acid. If this had been a factor of any consequence, it would have been reflected in a fall in acid concentration during the test, without concurrent fall in volume. This was never seen, concentrations rising to maximum levels before volume had reached maximum values, and being maintained there in spite of possible fluctuations in collected volumes.

The second was more speculative, and again difficult

to prove objectively, but it is rational to assume that, provided the aspirating tube lies constantly in the resting pool throughout the period of steady secretion, a series of equal 15-minute collected specimens represent the true secretion rate, regardless of whether or not the stomach is completely emptied, rather on the analogy of measuring what is added to a shallow bath by means of the overflow only.

Minor mechanical variations in the method of aspiration were tried from time to time, such as providing a small air-leak on the suction line, and installing a subsidiary air-vent tube alongside the aspirating tube as a form of sump drainage (Williams & Benn, 1965), but no contrivance was found comparable with simple personal attention to keeping the tube clear and maintaining a constant collection in response to the constant stimulation. Equally efficient methods might be applicable to tests using a single injection of stimulant, but should errors arise or be suspected, the response is passed and lost before any adjustments or corrections can be made. On the other hand, during the steady state of stimulation by histamine infusion, errors in collection become immediately apparent (Fig. 18) and the test can therefore be continued for a further four 15-minute

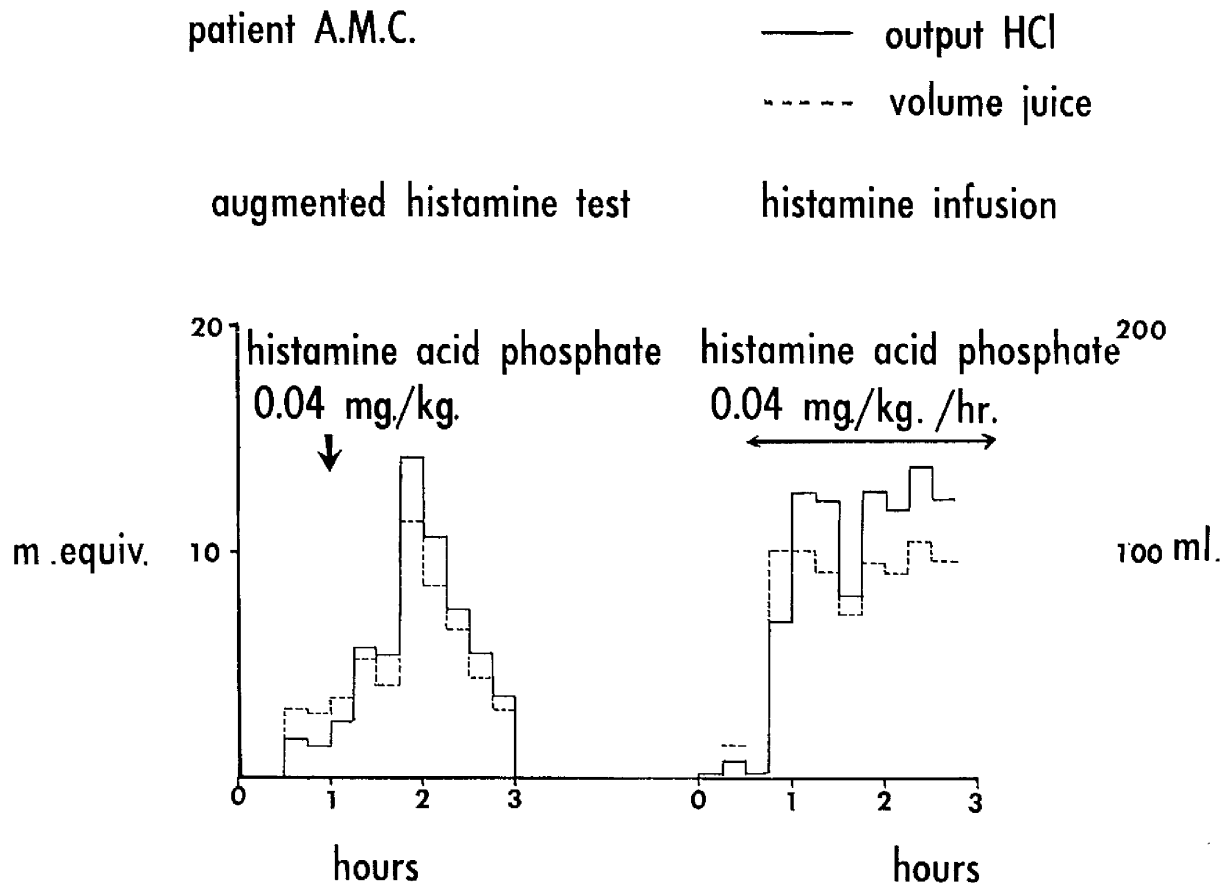


Figure 18: The results of an 'augmented' histamine test and a histamine-infusion test on the same patient. The fall in volume and output during the fifth 15-minute period of the infusion test was apparent. The test was continued for a further four 15-minute periods to give a maximal output for 1 hour.

periods to give a maximal output for 1 hour. Potentially, therefore, a histamine-infusion test offered possibilities for refinement in several aspects of the measurement of gastric acid.

Titration methods

Colorimetric methods of titration have been most widely used to estimate the concentration of hydrochloric acid in gastric juice, in early studies and up to the present day. In the classical investigations of Ewald and Boas on test meals in 1885, neutral red and methyl violet were used as indicators. Topfer's reagent was used to indicate free acid by Ostrow and others (1960) Marks and Shay (1960) and Bell and others (1965). Total acid was estimated with phenol red by Marks and Shay (1960), Gelb and others (1961) and Baron (1963).

As early as 1938 Ihre pointed out that protein, salt, mucus, physical opacity and bile would all affect colorimetric pH determination. An observer error of 30 clinical units with Topfer's reagent (approximately pH 3.5) and 12 clinical units with phenolphthalein (approximately pH 7.4) was found in the test meal titrations of Berk and others in 1942.

The concept of free and total acid though 'originally hardly justified' (Rovelstad, 1963) has

persisted until recent times, partly on account of these two apparently distinct end points at pH 3.5 and pH 7, and partly due to a failure to appreciate fully the implications of the pH notation as a logarithmic scale of acidity. Hollander in 1938 showed that the actual difference was small, gastric juice of pH 3.5 being equal to 77 mM and pH 7 equivalent to 80 mM.

The terms 'free' and 'total' were introduced by Prout in 1824, but without real justification. Michaelis in 1927 used the idea to explain the very shallow slope of the titration curves of gastric juice from test meals, compared with the almost vertical end point of pure HCl. He guessed that some HCl must be 'combined' with peptone, and any HCl in excess of this was therefore 'free'. In retrospect his gastric juices were probably diluted, and buffered by the stimulants. The position was simplified in 1962 when Bock showed that acidity was related solely to hydrogen ions which were present up to pH 7 and that this should therefore be the end point. This is probably an over-simplification (Lubran, 1966) but is sufficiently accurate in clinical practice (Lawrie, 1966).

During the preliminary work in this present study, using electrometric titration with NaOH, it became apparent that the end-point of gastric juice, even of

specimens of quite low acidity, was distinct, being indicated by a sharp swing through pH 3 to 7 on addition of minute volumes of NaOH. Figure 19 shows the titration curves for 9 different specimens of gastric juice of widely varying acidity, from 43 mEq/litre to 143 mEq/litre. Also shown is a titration curve produced by titrating under identical conditions a specimen of pure HCl, and it can be seen that the shape of the curves, in particular the vertical components or end-points, are similar and pass through pH 7. From this it was decided to use pH 7 as the end-point throughout this study, as a measure of hydrogen ion concentration or total acidity.

Interpretation of responses to histamine stimulation

Although the augmented histamine test (Kay, 1953) gave a precise and reproducible response, it proved difficult to calculate output from this, being a product of a varying volume of gastric juice of varying acidity. In his results Kay quoted some in terms of the 45 minutes after histamine, and others in terms of the best half hour.

The total response to a subcutaneous injection normally extends over 1½ hours, the concentration being at a maximum when the volume has begun to fall (Carnot & others, 1922), though the peak response may occur during the first 20-minute period (Ihre, 1938), or the 2nd and

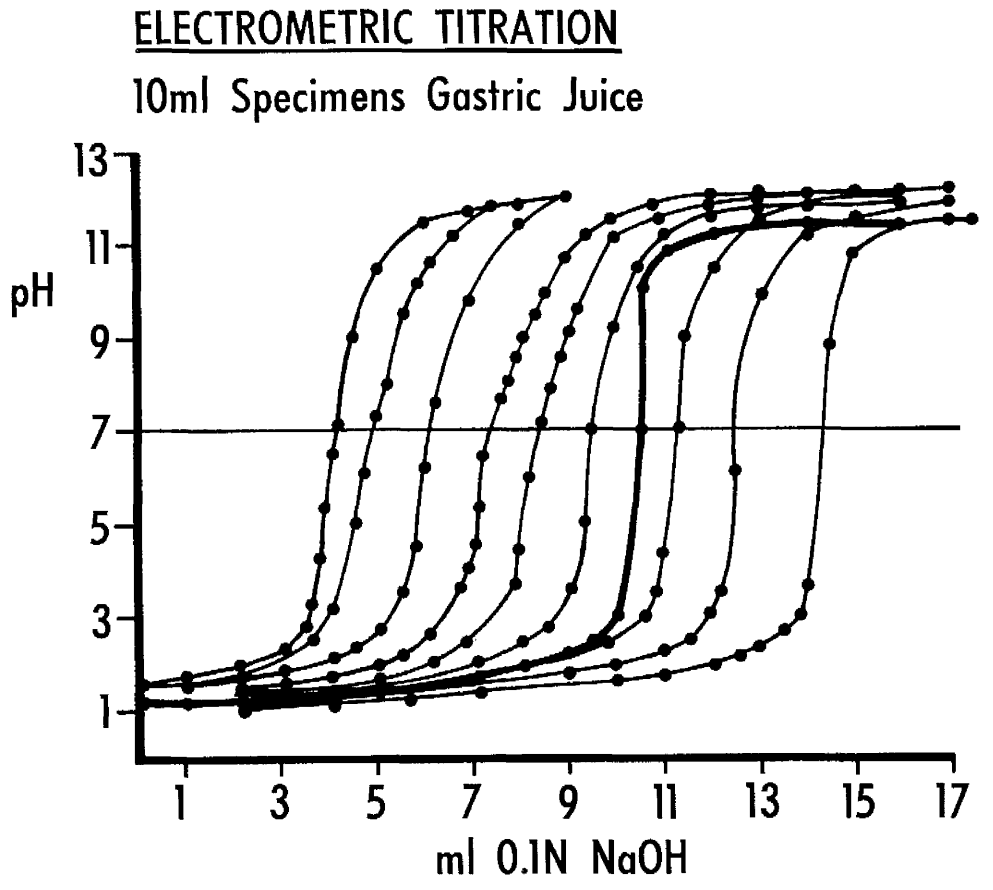


Figure 19: Titration curves of 9 different specimens of gastric juice obtained during infusion tests, of varying acidity from 43 to 143 mEq/litre, along with the titration curve of pure 0.1 N HCl (the heavy line).

3rd 15-minute periods (Gelb and others, 1961). The peak may occur during any 15-minute period of the hour after histamine (Baron, 1963) and he found the most reproducible period to be the best half hour. Marks, Komarov and Shay (1960) narrowed this down to the best 15 minutes to obtain a true maximum output. The peaks of volume and acidity may not coincide (Matheson & Ammon, 1923) making the notion of 'output' difficult to quantitate.

Various periods after histamine have been compared (Carneiro de Moura & Correia, 1964) but all were found to have an unwieldy coefficient of variation. The simplest and probably adequate period for evaluation of a subcutaneous histamine response is the one-hour period immediately following injection (Bruce and others, 1959; Card & Marks, 1960).

These are all elaborate practical demonstrations of a result which is apparent in theory. Following a subcutaneous injection of a maximal secretory dose of histamine, the response in terms of acid output may indeed be maximal in the sense that no further increase in acid output can be expected from a larger dose of stimulant. Yet this apparently maximal response consists of gastric juice of constantly varying secretory rate and concentration, being at basal rates as the stimulus begins and increasing to

transiently maximal levels of volume and concentration, before returning to basal levels. Variables abound and thwart the best technical efforts at precision.

The infusion test, though still beset with many basic problems of collection, offers the investigator the opportunity of collecting gastric juice at maximum concentration of hydrogen ions, at maximum rates of secretion, persisting for several hours. An example of such a response is shown in Figure 12 in which concentration rises rapidly during the initial three 15-minute periods, volume similarly increases, and both are sustained at maximal levels for several hours. From the product of volume in litres and concentration in milliequivalents per litre can be obtained the true output referred to a definite period, usually one hour.

Variations may occur. A fall in concentration of acid would indicate regurgitation of duodenal content of the stomach. A fall in volume would indicate faulty collections and can be corrected by attention to the position of the tube or the technique of aspiration. To this extent the test is 'self-checking'. Whatever the cause, minor difficulties are immediately apparent, and can be corrected without jeopardising the test. The infusion is continued until four comparable 15-minute

collections have been obtained, demonstrating a steady state of maximal secretion from which the maximal acid output can be calculated.

CHAPTER 3

NORMAL STANDARDS

It has evidently proved difficult to define a normal control population against which to compare acid secretion from patients with known pathology. Even truly normal subjects contain the variables of age, sex and body weight, while control groups of patients selected because they had no demonstrable pathology (Vanzant and others, 1932) may not be normal. Highly selected groups such as Air Force recruits (Leonard, 1954) or medical students (Lander & MacLagan, 1934) provide controls only for similarly limited groups of patients. Attempts to relate acid secretion to normal gastric histology (Bock and others, 1963) are of even more limited application.

Selection of normal subjects

In the present investigation a composite group of normal subjects was accumulated over the four years of the study. They consisted of students, laboratory staff, medical staff and patient volunteers. They were chosen to cover as wide a range of ages as possible. They were followed for periods of one to three years to discover as far as possible any occult pathology. This precaution proved in the event to be justified, when several subjects had to be removed from the normal

group on account of the development of dyspepsia, the recognition of an abnormal duodenal mucosal pattern, or the discovery of anaemia.

The final control groups are thus still to some extent selected, but at the final analysis remain free of such abnormalities as are known to affect or be related to an abnormal state of gastric acid secretion.

Definition of normal values

The results of previous work have been difficult to quantitate, since both volume and concentration of acid were themselves altered by the constituents of the test meals of early studies, while in more recent work using single injections of stimulant, these factors are varying continuously about a transient maximum secretory rate. The steady state of maximum secretion produced in the tests in the present study allowed both volume and acidity to be analysed and used for comparison, and from the product of these two factors, the output in one hour could be precisely calculated as a measure of the maximum secretory rate for each subject. These three factors, volume in millilitres per hour, concentration of hydrogen ions in milliequivalents per litre, and output of hydrogen ions in milliequivalents per hour, all as maximal values, have been used throughout for analysis and comparison.

No particular study has been made of basal secretory rates, since these have been adequately reported by many other authors.

Acid secretion in normal subjects

Normal men

Fifty-four normal men were studied and the details of their ages, body weight, volume, concentration of acid and maximal acid output are listed in Appendix Table 1.

The mean values for these various factors are given in Table 6 with their ranges and standard deviations.

Figure 20 shows the relationship between acid output and age in normal men. There is a significant decrease in acid output with age ($r = -0.36$; $P < 0.01$).

Figure 21 shows that there is a slight increase in acid outputs in relation to increased body weight ($r = 0.256$) but that this is not statistically significant.

No relationship exists between volume and concentration of gastric acid in these men (Fig. 22), large and small volumes being apparently randomly associated with high or low acidity.

Normal women

There were 50 women in the normal group and their ages, weight, volume, concentration and output of gastric

Table 6. The age and body weight, with the volume, concentration and output of acid estimated during histamine-infusion tests in 54 normal men.

	Range	Mean	S.D.±
Age (years)	14 - 75	33.9	13.3
Body weight (kg)	42 - 85	68.3	10.1
Volume (ml/hour)	131 - 440	251.2	63.2
Concentration (mEq/litre)	73 - 135	108.4	17.5
Output (mEq/hour)	9.5 - 42	25.3	7.6

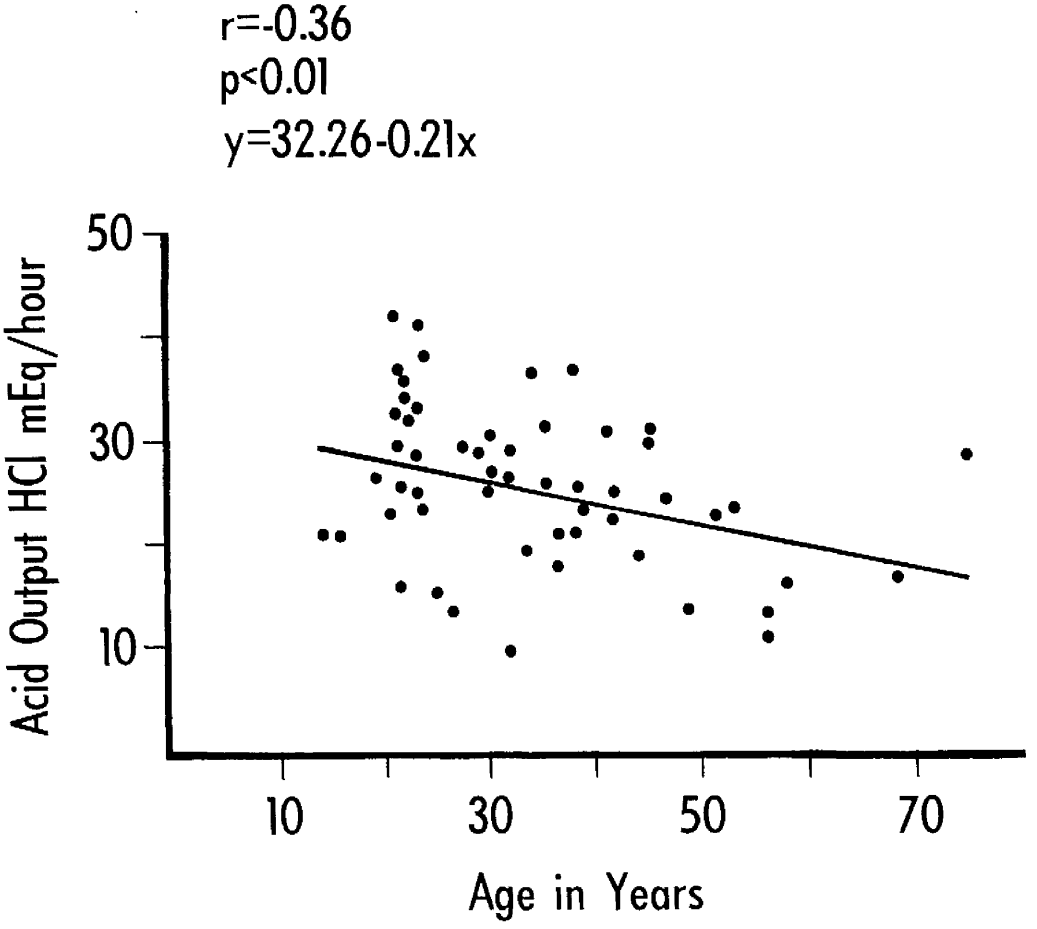


Figure 20: The correlation between acid output and age in 54 normal men. There is a significant negative correlation ($r = -0.36$; $P < 0.01$).

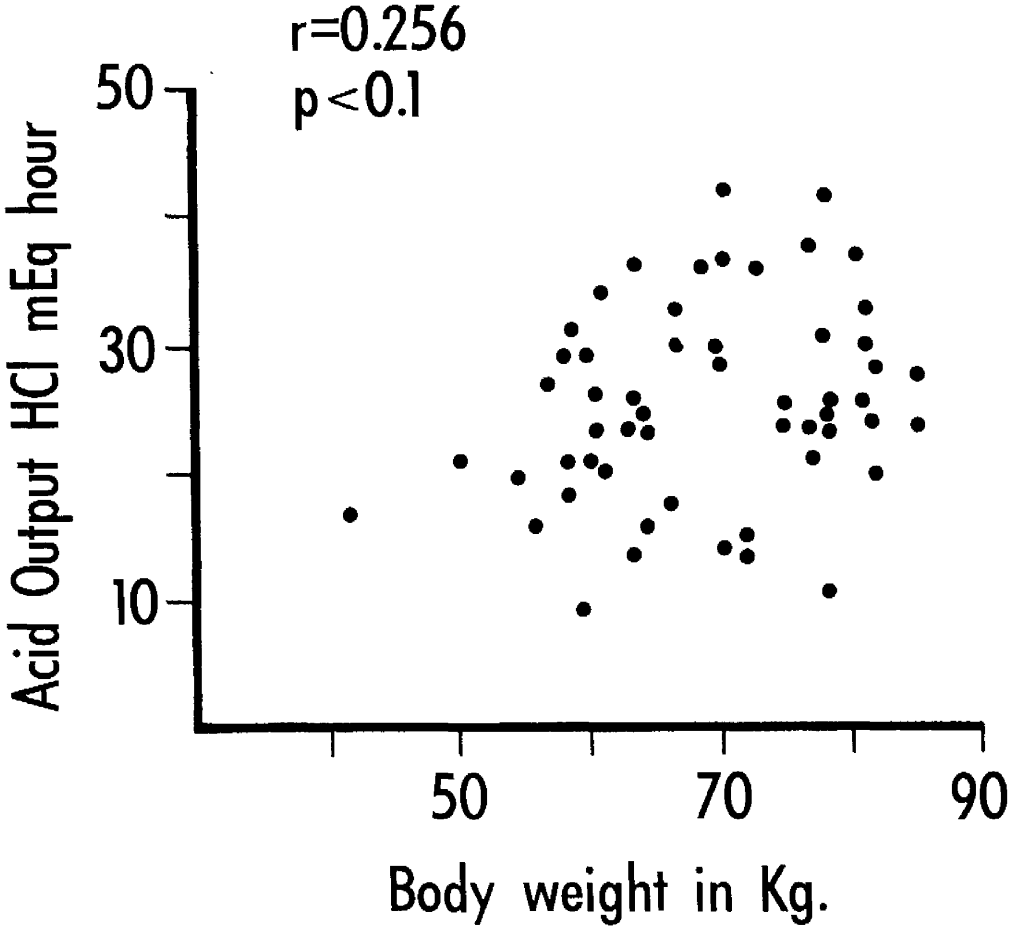


Figure 21: The relationship between acid output and body weight in 54 normal men. The correlation coefficient (r = 0.256) is not significant (P < 0.1).

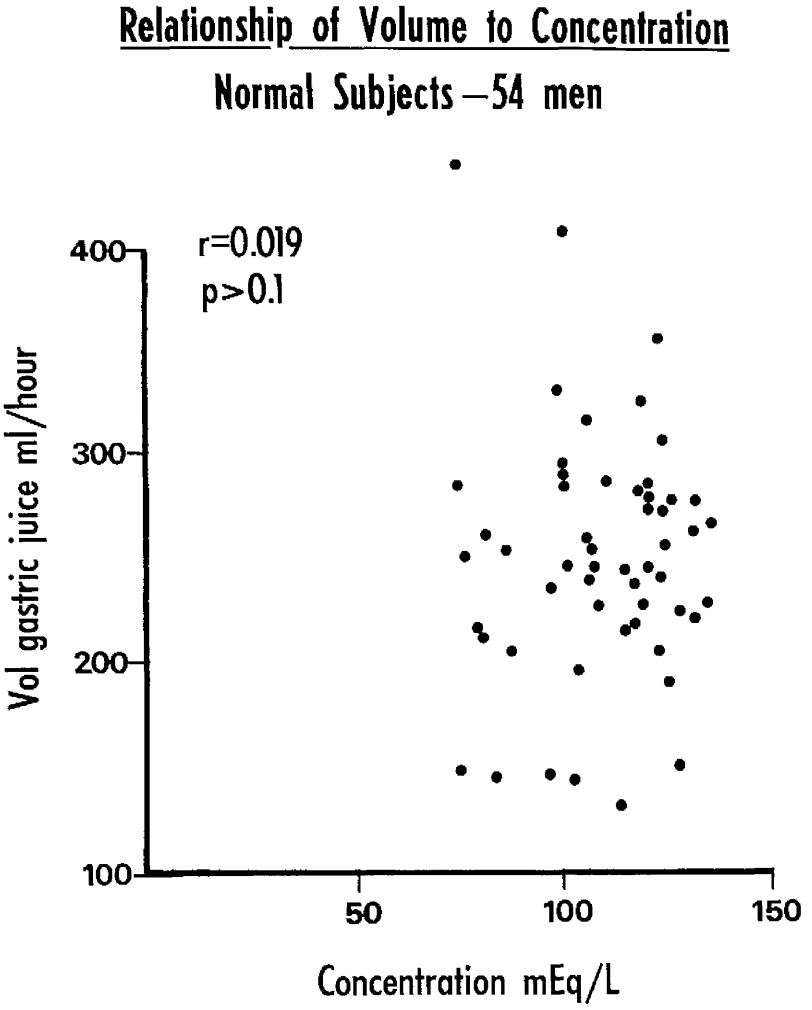


Figure 22: The distribution and relation between the volumes of acid secreted per hour and the maximum concentrations of acid in 54 normal men. There is no significant correlation between these two factors. ($r = 0.019$; $P > 0.1$).

acid are listed in Appendix Table 2.

The mean values, with the ranges and standard deviations for these various factors are given in Table 7.

Figure 23 shows that, though there is an apparent slight decline in acid output with advancing age, this relationship is not statistically significant ($r = -0.196$; $P < 0.1$).

Figure 24 shows that in women there is no significant relationship between acid output and body weight.

Figure 25 demonstrates a significant negative correlation between volume and concentration of acid ($r = -0.282$; $P < 0.05$), lower volumes of gastric juice being associated with a higher concentration of acid.

Comparison of acid output in normal men and women

The distribution of values for acid output in 54 men and 50 women is shown in Figure 26. The ranges are similar for both men and women. The mean output for men, 25.3 mEq/hour, is significantly higher than that for women, 21.7 mEq/hour ($P < 0.02$).

The comparison of age, weight, volume, concentration and output is shown in Table 8. The ages are comparable. The body weights, as might be expected,

Table 7. The age, body weight, with the volume, concentration and output of acid estimated during histamine-infusion tests in 50 normal women.

	Range	Mean	S.D.±
Age (years)	17 - 69	37.5	15.1
Body weight (kg)	42 - 85	59.1	9.8
Volume (ml/hour)	107 - 399	215.0	55.8
Concentration (mEq/litre)	38 - 136	110.4	23.4
Output (mEq/hour)	9.7 - 47.1	21.7	6.9

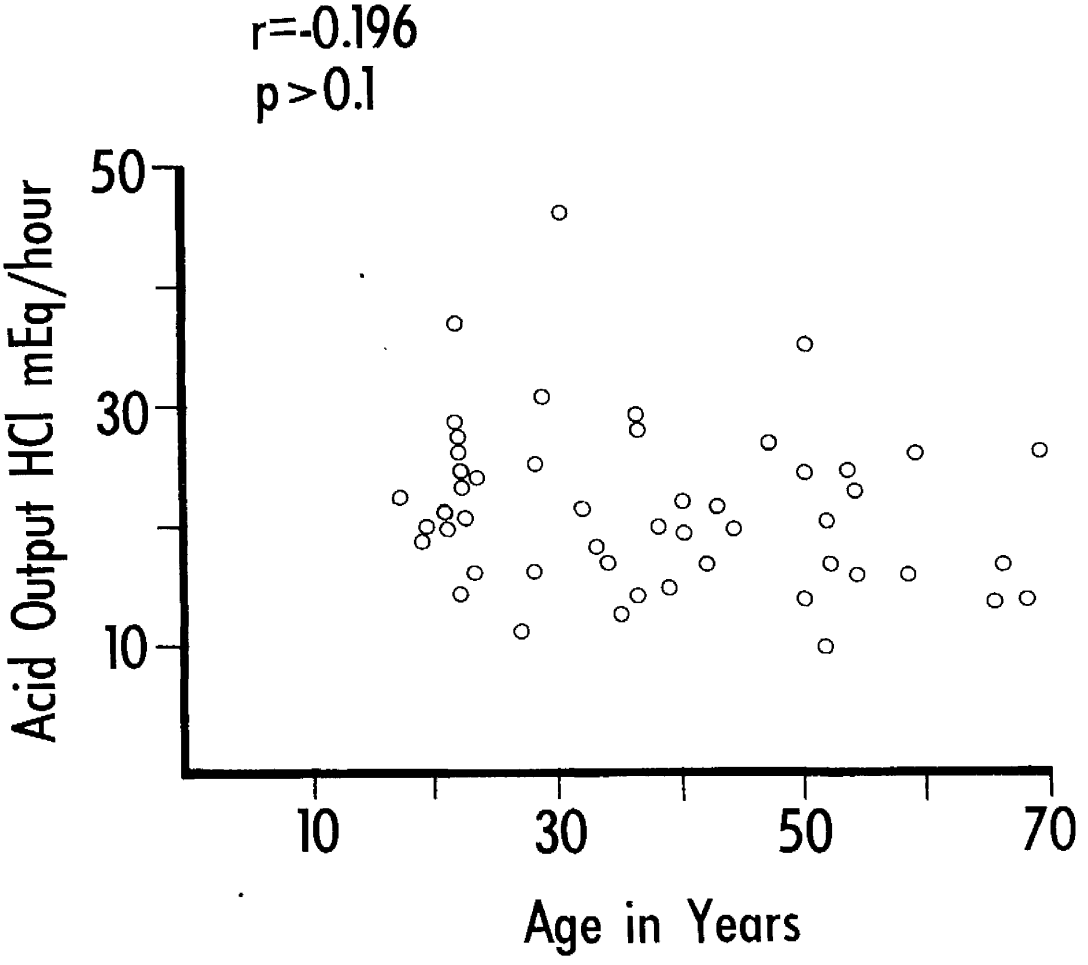


Figure 23: The relationship between acid output and age in 50 normal women. There is no significant correlation between these two factors. ($r = -0.196$; $P > 0.1$).

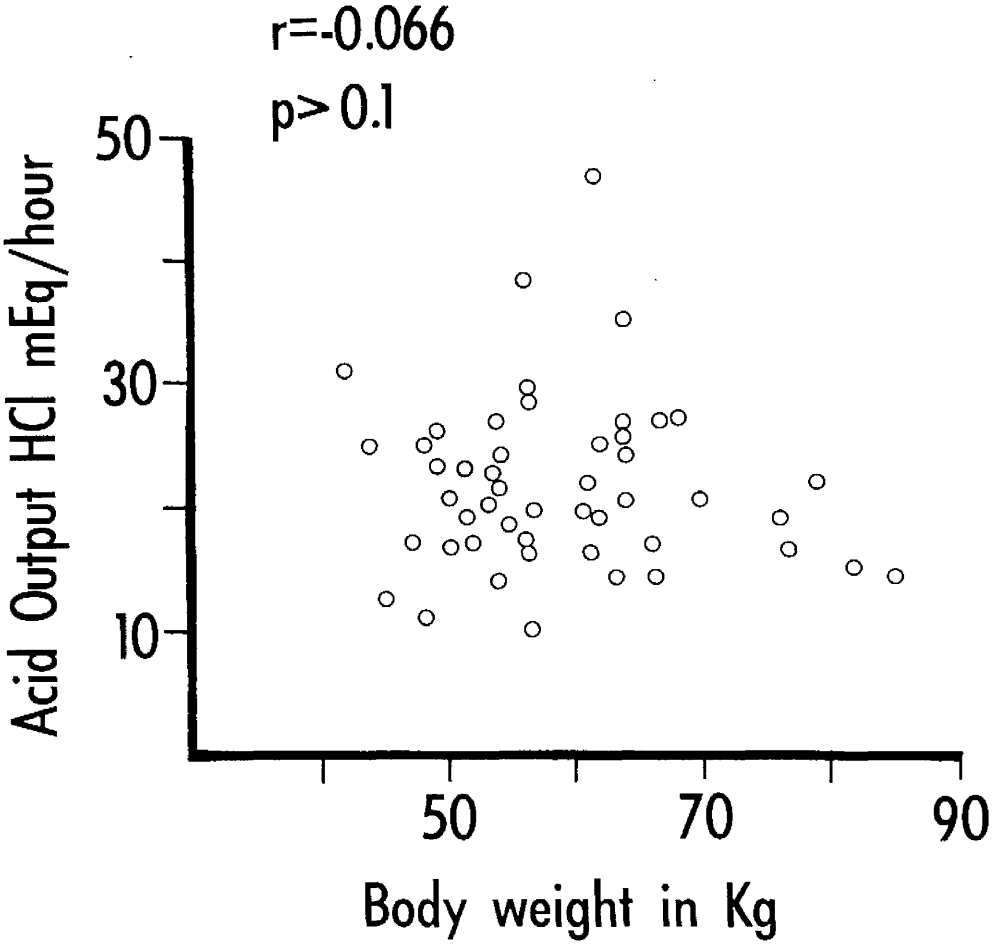


Figure 24: The relationship between acid output and body weight in 50 normal women. There is no significant correlation between these two factors. ($r = -0.066$; $P > 0.1$).

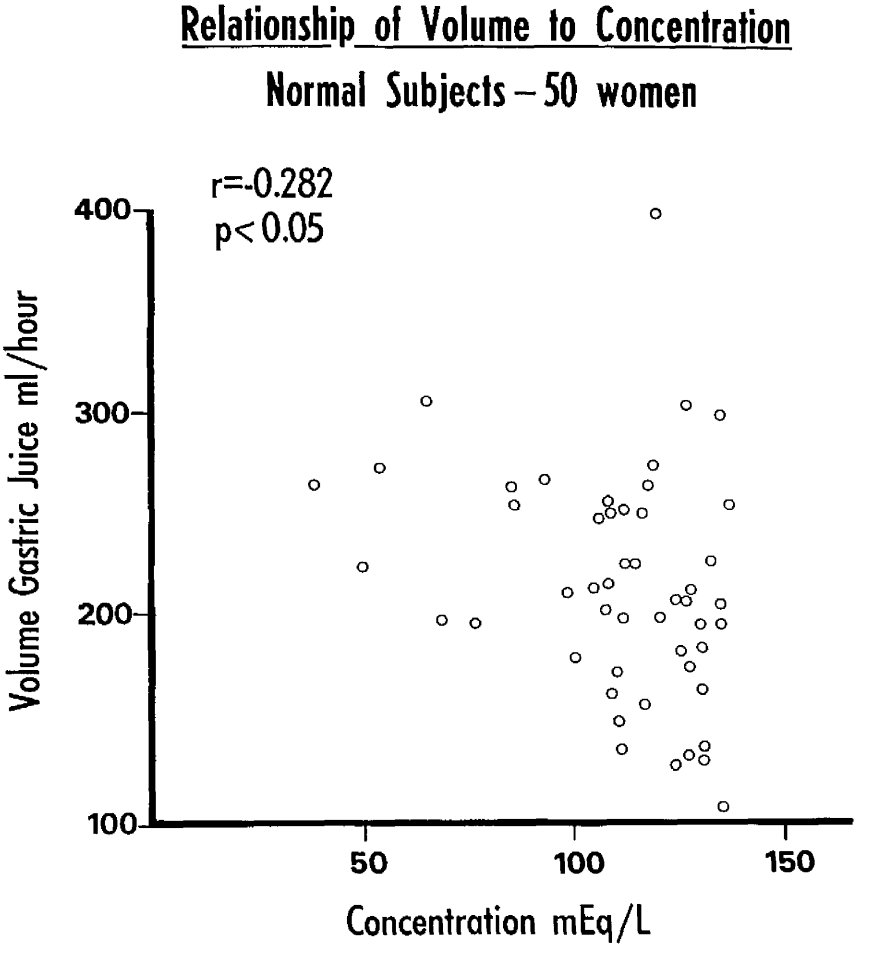


Figure 25: The correlation between volumes of acid and concentrations of acid in 50 normal women. There is a significant negative correlation ($r = -0.282$; $P < 0.05$) between these two factors.

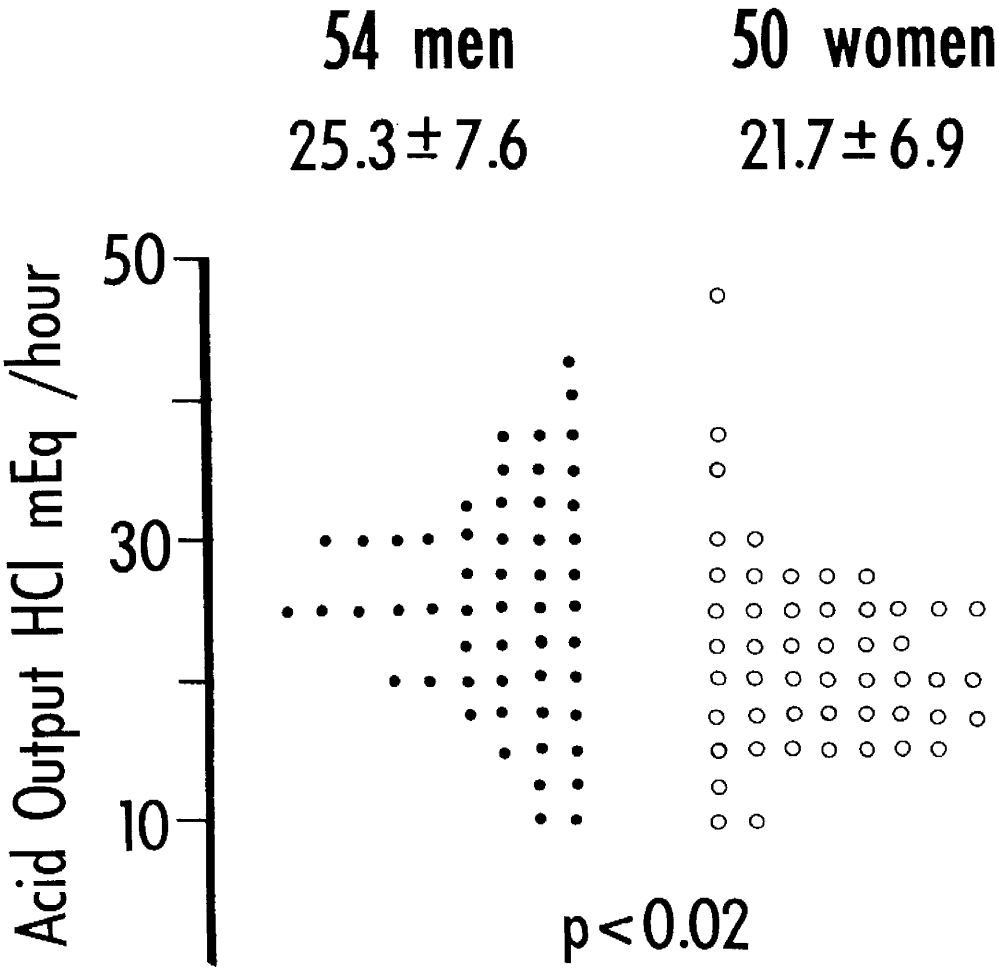


Figure 26: The distribution of acid output in the two groups of normal subjects, 54 men and 50 women, showing the means and standard deviations. There is a significant difference between these mean values ($P < 0.02$).

Table 8. The comparison in ages, weights, volumes, concentration and output of acid in the two normal groups of 54 men and 50 women.

	Normal Subjects		Mean diff.	S.E.	P
	Men 54	Women 50			
Age (years)	33.9	37.5	3.6	2.8	> 0.2
Body weight (kg)	68.3	59.1	9.3	1.9	< 0.001
Volume (ml/hour)	251.2	215.0	36.3	11.7	< 0.01
Concentration (mEq/litre)	108.4	110.4	1.9	4.0	> 0.6
Output (mEq/hour)	25.3	21.7	3.6	1.4	< 0.02

are greater for the men than the women.

Volume of gastric juice is significantly greater in men, 251.2 ml., than in women, 215.0 ml ($P < 0.01$) while the concentration of acid is similar in the two groups, 108.4 and 110.4 mEq/litre respectively ($P > 0.6$).

Normal acid secretion

Discussion

The validity of attempts to define normal states of gastric acid secretion depend as much on the criteria adopted in the selection of normal subjects, as on any particular method of gastric analysis. At one point in the present study (Lawrie & Forrest, 1965) a group of 49 patients, apparently normal, was analysed and no significant difference in output was found between men and women. The acid outputs in the 26 men at that time were 24 mEq/hour and for the 23 women 21 mEq/hour. As the groups were expanded over the following year and subjects excluded who were discovered to have some previously occult pathology, the higher output in men, 25.3 mEq/hour, became significantly greater from that in women, 21.7 mEq/hour.

Clearly this process of selection is arbitrary. Inspection of the outputs in Figure 26 shows that,

although the men form a compact group within the range 9.5 - 42 mEq/hour, the women, ranging similarly from 9.7 - 47.1 mEq/hour have only three subjects in the upper ranges and the majority lie between 10 and 30 mEq/hour. It may be that this particular group of women is still not wholly representative of the normal.

The lower limit for normal in both men and women appears to be around 9 mEq/hour, a finding similar to that of Shearman and others (1967) in a smaller number of subjects. Larger groups in the past have commonly included subjects with very low acidity or achlorhydria, as Badenoch and others reported when studying hospital visitors (1957). An apparently normal population analysed by Carneiro de Moura and Correia (1964) gave the low mean of 16.1, on account of the inclusion of several subjects with achlorhydria. Recent surveys by Bruce and others (1959) and Køster and Thorsøe (1960) have given a comparable lower limit of 10 mEq/hour for men, although the mean values were lower than the present author's, being 22.4 mEq/hour from the Edinburgh group and 19.3 mEq/hour from the Copenhagen group. A similar mean for men of 21.6 mEq/hour was calculated by Baron (1963) while his mean of 12.3 for women, like Bruce's 14.6, is much lower than the present findings, apparently due to the inclusion of subjects who were almost achlorhydric.

The question was, to some extent, begged by Polland and Bloomfield (1931) when they arbitrarily excluded from their control group those subjects with acid output below 10 mEq/hour, assuming that such low levels must be abnormal. A similar, though much later, pre-judgment was made by Ihre (1938) when he stated that the normal should be assessed in men and women in their twenties when 'acidity reducing factors' have least effect. This stricture he never fully substantiated.

The upper ranges found in this work are higher than in most other similar studies, 42 mEq/hour and 47 mEq/hour for men and women respectively, and the significance of acid levels higher than these will be discussed in the section on duodenal ulcer and coarse duodenal mucosal folds.

Acid output declines with age, in normal men significantly, in normal women not so. Early studies showed similar trends, although Bloomfield and Keefer (1928) did so simply by demonstrating an increased incidence of achlorhydria with advancing years. Both volume and acidity decreased with age in the studies of Polland (1933), although he found 'such a wide range that no normal standards can be set up'. In observations on smaller numbers, Køster and Thorsøe (1960) and Baron (1963) found a decline in output with age in both men

and women, although again both these series contained subjects with acid output well below 10 mEq/hour.

It is likely that the higher values for acid output obtained in this work on the elderly group of women, is due to the exclusion of anaemic subjects, who might in other studies have been included in a normal group. Such women, without gastric symptoms and otherwise normal, have a high incidence of hypo-acidity and have been examined separately in the chapter on "Iron-deficiency anaemia".

An inspection of the relationship between acid output and body weight for normal men (Fig. 21) and normal women (Fig. 24) shows that while there is a trend towards increasing acid output with increased body weight in men, an opposite trend appears in the women, heavier women appearing to have lower acid output. Neither of these trends is, however, significant.

No correlation was found by Booth and others (1957) and by Baron (1964) in either men or women.

It might logically be expected that larger subjects might have larger stomachs and hence a greater parietal cell mass (Card & Marks, 1960) and acid output. Taking men and women together Hume and Melrose (1967) have demonstrated a good correlation between acid output and

lean body mass in a small number of subjects.

Since the histamine-infusion test provided a convenient means of estimating both volume and concentration of gastric acid at maximum rates of secretion, these values were analysed in normal subjects to discover any particular pattern or relationship. Ihre in 1938, while demonstrating greater volumes of secretion in men than women, also found a correlation between low rates of secretion and low acidity. There is in individual patients (Nordgren, 1963) an exponential relationship between rates of secretion and acidity during stimulation with intravenous histamine, but there is no information from large numbers of normal subjects relating secretory rate and acidity.

The scatter of values for volume and acidity in normal men is apparently random (Fig. 22) some subjects having high rates of secretion of acid of low concentration, while some have low rates of secretion of acid with concentration varying throughout the entire range of acidity. In general, the values are clustered around the means, 250 ml/hour for volume and 110 mEq/litre for concentration.

Among the normal women, although there is again a

wide scatter of both volume and acidity (Fig. 25) nevertheless there is a negative correlation between volume and concentration of acid ($r = -0.282$) which is significant at the 5% level, suggesting that at least throughout this group of women, there is a tendency to produce either larger volumes of low acidity or smaller volumes of high acidity.

Of greater interest, however, is the comparison which these figures provide between the acidity of gastric juice in men and women. Although the range of concentration is wider in women than men, due to a few women having gastric juice of low acidity, nevertheless the upper limits and the means are both identical in the women and the men. The mean value for the 50 women is, in fact, slightly higher (110.4 mEq/litre) than that for the 54 men (108.4 mEq/litre). These means are not significantly different ($P > 0.6$).

The normal men, however, secrete significantly larger volumes of gastric acid than the women, 251.2 ml/hour compared with 215.0 ml/hour respectively ($P < 0.01$).

Thus, the greater output of acid in normal men over normal women is due to the secretion of larger volumes of the same concentration of gastric acid.

The early studies of Vanzant and her colleagues (1932) and Polland (1933) gave higher values for acidity in men than women. Comparable values for acidity with a marked difference in volumes for men over women were later shown by Levin and others (1948). The normal men studied by Baron (1963) had higher acidity, 94.7 mEq/litre, than the women, 87.2 mEq/litre, though not significantly so.

Valid though the present observations may be, they derive from the mean values of the cumulative data of the groups, and do not yet explain the wide variation which may be found in volume and concentration of gastric acid secreted by individual, apparently completely normal, subjects.

Summary of gastric acid values in normal subjects

A control group of normal subjects was drawn from a mixed population of patient volunteers, staff and students who were followed for one to three years to exclude occult abnormalities.

In the group of 54 men acid output declined significantly with increasing age, but was not related to body weight. There was no relationship between the volume and the concentration of acid secreted.

In the group of 50 women acid output was not significantly related either to age or to body weight. The volumes and concentrations of acid secreted showed a significant negative correlation.

The range of acid output is similar in men and women, from approximately 10 - 40 mEq/hour, but the mean output for men, 25.3 mEq/hour, is significantly higher than that for women, 21.7 mEq/hour. This higher value for output is due to the larger mean volumes secreted by men, 251.2 ml/hour, compared with women, 215.0 ml/hour, the concentration of acid being similar for both men and women, 108.4 mEq and 110.4 mEq/litre respectively.

CHAPTER 4

ACID OUTPUT IN DUODENAL ULCER

A curious paradox exists between the failure to define the nature of acidity in the investigation of duodenal ulcer, and the universal acceptance of acid-reducing procedures in its treatment. Comparing acidity in normal men and in men with duodenal ulcer, Ihre (1938) decided that 'the concept of hyperacidity thus lacks actual foundation', while, more recently, Burge (1964) stated that 'gastric acid studies serve no useful purpose'.

The patients with duodenal ulcer

The present study includes 237 men and 35 women with radiologically proved duodenal ulcer. The majority were verified at operation but where any doubt existed about the final diagnosis, the patient was excluded from this series. This is a selected group to the extent that some clinicians referred all patients for acid studies, while others referred for investigation only those in whom the diagnosis was initially in doubt. In general, however, the large numbers, the varied sources and the four-year period of accumulation might be expected to produce a fairly homogeneous population. For the same reasons, the ratio of men to women (6 : 1) is probably a valid index of the relative incidence in South Wales.

The data relating to these patients with duodenal ulcer are listed in the Appendix Table 3.

The mean values for age, body weight, volume, concentration and output of acid for the 237 men are given in Table 9, and for the 35 women in Table 10.

The comparison between men and women for all these factors is shown in Table 11. The ages are similar. The men are significantly heavier than the women. Acid output is significantly greater in men, 41.5 mEq/hour, than in women, 31.2 mEq/hour, but of the components constituting this, only volume is greater in men than women, while the concentration of acid is similar for both sexes.

The distribution of values for acid output in all the duodenal ulcer patients is shown in Figure 27.

A comparison has been made between these 237 men with duodenal ulcer and the 54 normal men, Table 12, and in both volume and concentration and therefore in output there is a highly significant increase in the ulcer patients.

A similar comparison between the 35 women with duodenal ulcer and the 50 normal women, Table 13, gives similar results, volume, concentration and output all

Table 9. The age and body weight, with the volume concentration and output of acid in 237 men with duodenal ulcer.

	Range	Mean	± S.D.
Age (years)	16 - 86	45.3	12.9
Body weight (kg)	39 - 103	69.5	11.5
Volume (ml/hour)	175 - 750	356.8	98.9
Concentration (mEq/litre)	72 - 158	121.9	14.8
Output (mEq/hour)	19.3 - 103	41.5	12.8

Table 10. The age and body weight, with the volume, concentration and output of acid in 35 women with duodenal ulcer.

	Range	Mean	± S.D.
Age (years)	12 - 73	47.0	13.9
Body weight (Kg)	43 - 83	60.5	12.1
Volume (ml/hour)	153 - 532	275.5	75.8
Concentration (mEq/litre)	81 - 147	120.3	15.3
Output (mEq/hour)	17.6 - 73.3	31.2	10.1

Table 11. Comparison in age, body weight, volume, concentration and output of acid, in the 237 men and 35 women with duodenal ulcer.

Number of patients	DUODENAL ULCER MEN 237	WOMEN 35	Mean diff.	S.E.	P
	Mean				
Age	45.3	47.0	1.7	2.4	$> .4 < .5$
Body weight (Kg)	69.5	60.5	9.0	2.1	< 0.001
Volume (ml/hour)	356.8	275.5	81.3	5.5	< 0.001
Concentration (mEq/litre)	121.9	120.3	1.6	2.7	$> .5 < .6$
Output (mEq/hour)	41.5	31.2	10.3	2.3	< 0.001

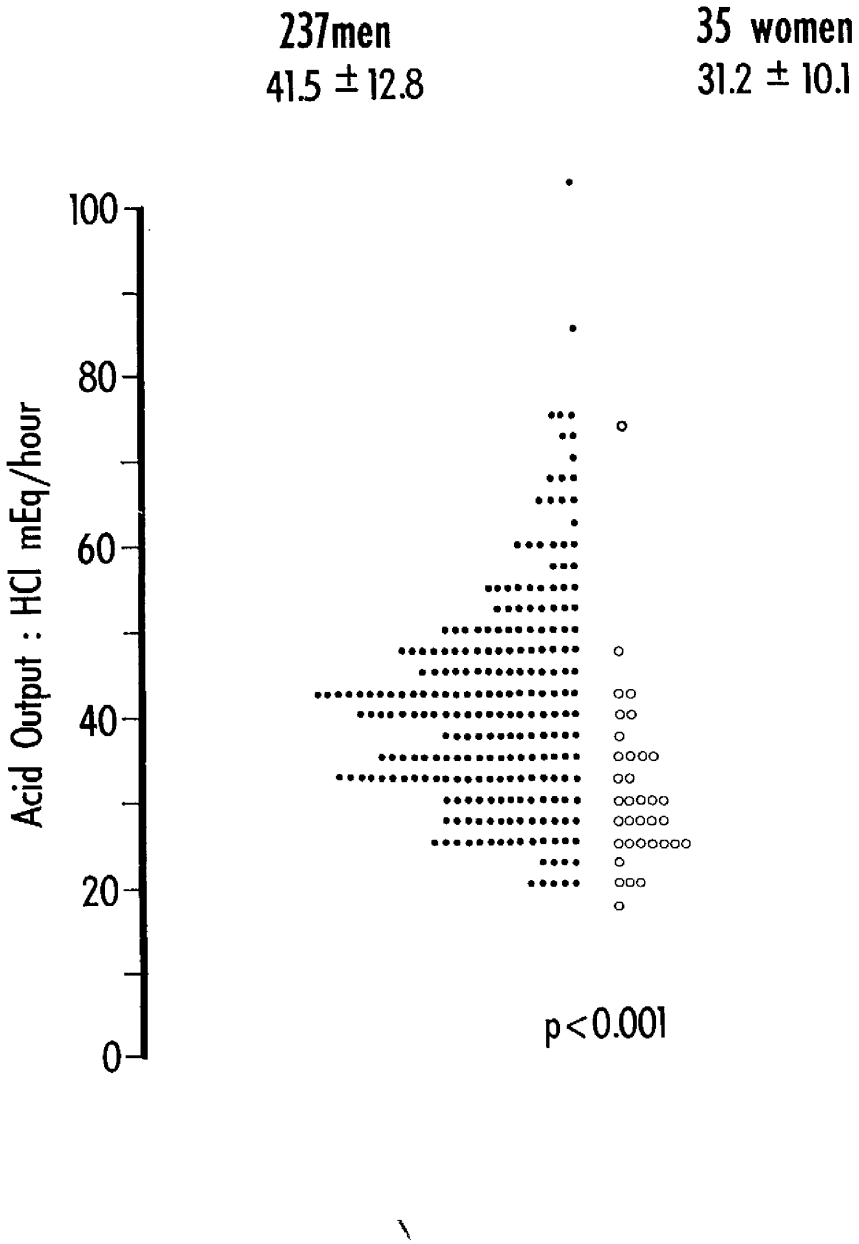


Figure 27: The distribution of values for acid output in the 237 men and the 35 women with duodenal ulcer. The mean and standard deviation in mEq/hour is given for each group.

Table 12. Comparison in volume, concentration and output of acid between the 54 normal men and the 237 men with duodenal ulcer.

MEN

	Normal	Duodenal ulcer	Mean diff.	S.E.	P
Number of subjects	54	237			
Volume (ml/hour)	251.2	356.8	105.6	14.1	<0.001
Concentration (mEq/litre)	108.4	121.9	13.5	2.3	<0.001
Output (mEq/hour)	25.3	41.5	16.2	1.8	<0.001

Table 13. Comparison in volume, concentration and output of acid between the 50 normal women and the 35 women with duodenal ulcer.

WOMEN

	NORMAL	DUODENAL ULCER			
Number of subjects	50	35	Mean diff.	S.E.	P
Volume (ml/hour)	215.0	275.5	60.5	14.3	<0.001
Concentration (mEq/litre)	110.4	120.3	9.9	4.5	<0.05
Output (mEq/hour)	21.7	31.2	9.5	1.8	<0.001

being significantly greater in duodenal ulcer patients than in normal subjects.

Acid output in duodenal ulcer

Relationship to sex, age and weight

The distribution of acid output in all the patients with duodenal ulcer, in relation to their ages, is shown in Figures 28 and 29. There is a wide scatter of output values throughout the age groups and there is no significant correlation between output and age in either sex. The higher outputs occur in middle age in both men and women.

There is no relationship between acid output and body weight in men with duodenal ulcer (Fig. 30), but in the group of women a significant correlation does exist (Fig. 31), heavier women having an increased acid output.

Volume and concentration of gastric acid in duodenal ulcer

The distribution of maximum values for volume and concentration of acid are shown in Figure 32 for men, and in Figure 33 for women. There is no relationship between volume and concentration in either sex. There are wide ranges for volume, but both men and women show a similar narrow range of concentration of acid, 72-158 mEq/litre in men and 81-147 mEq/litre in women.

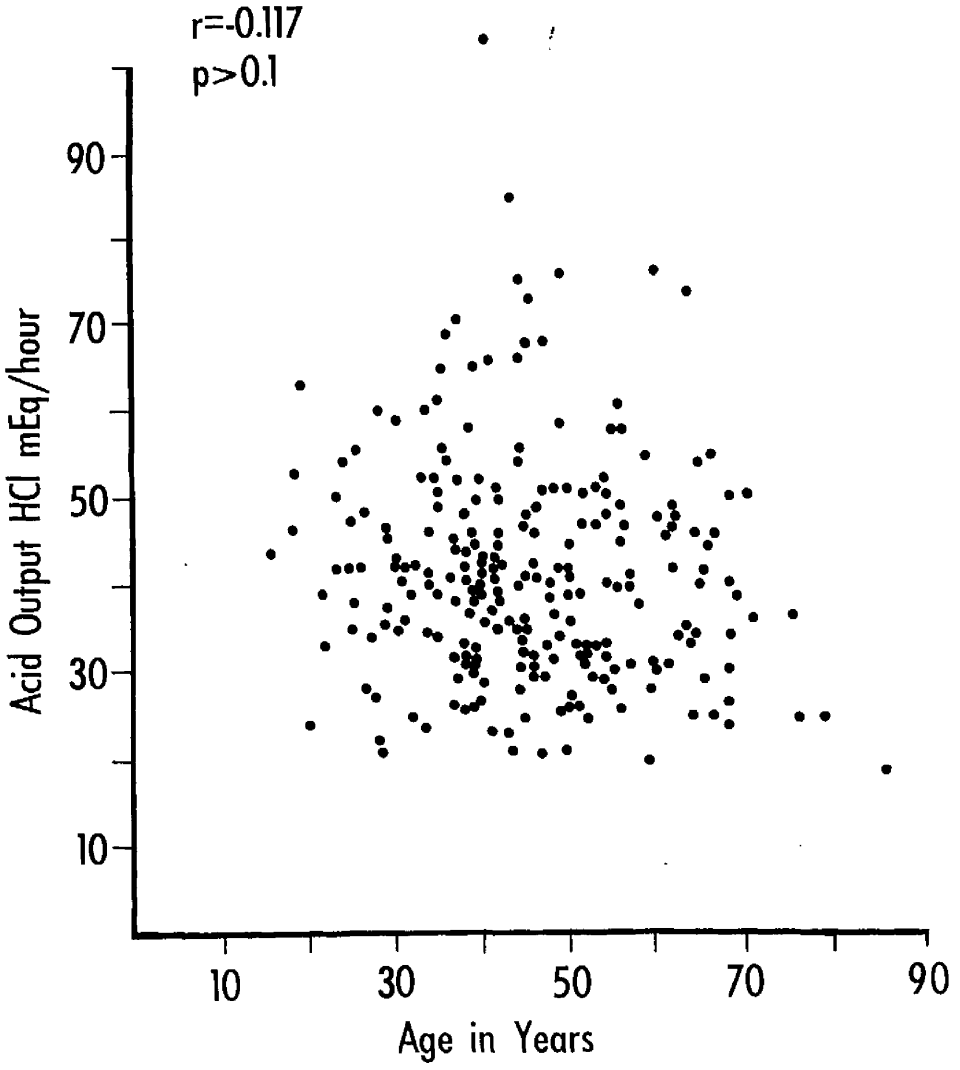


Figure 28: The relationship between acid output and age in 237 men with duodenal ulcer ($r = -0.117$; $P > 0.1$).

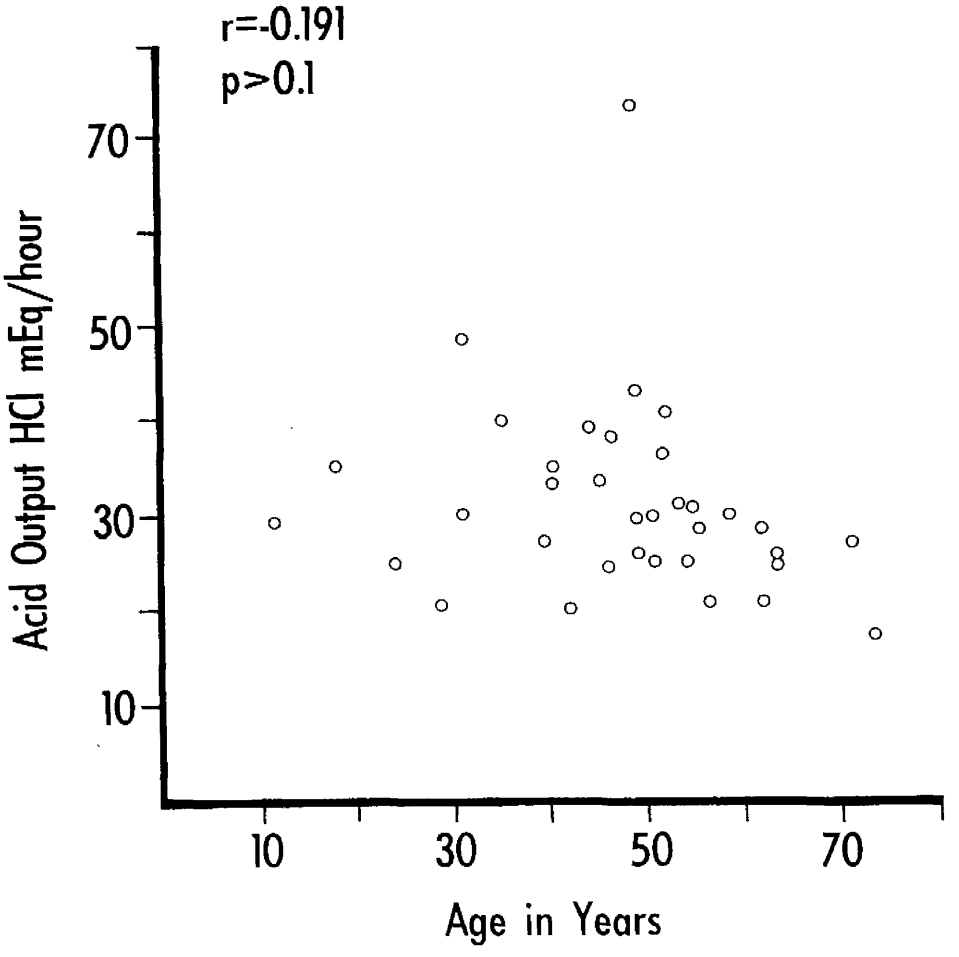


Figure 29: The relationship between acid output and age in 35 women with duodenal ulcer ($r = -0.191$; $P > 0.1$).

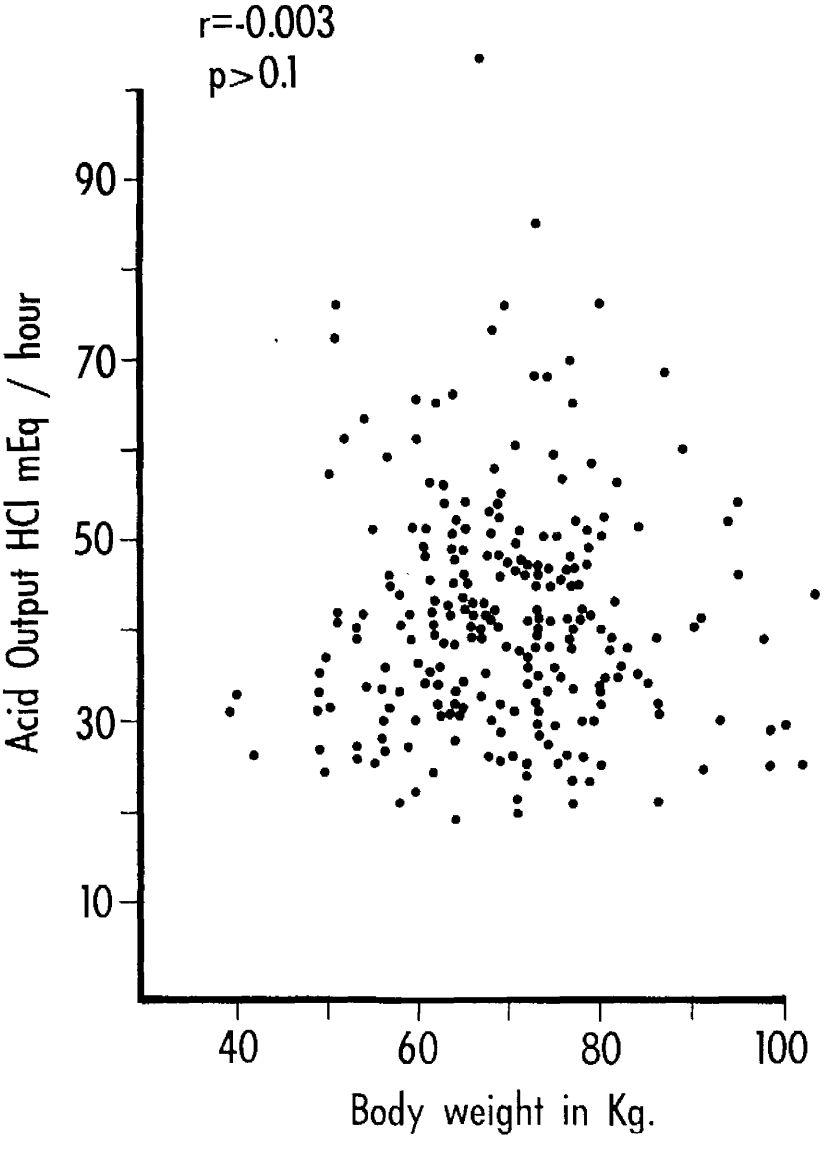


Figure 30: The relationship between acid output and body weight in 237 men with duodenal ulcer ($r = -0.003$; $P > 0.1$).

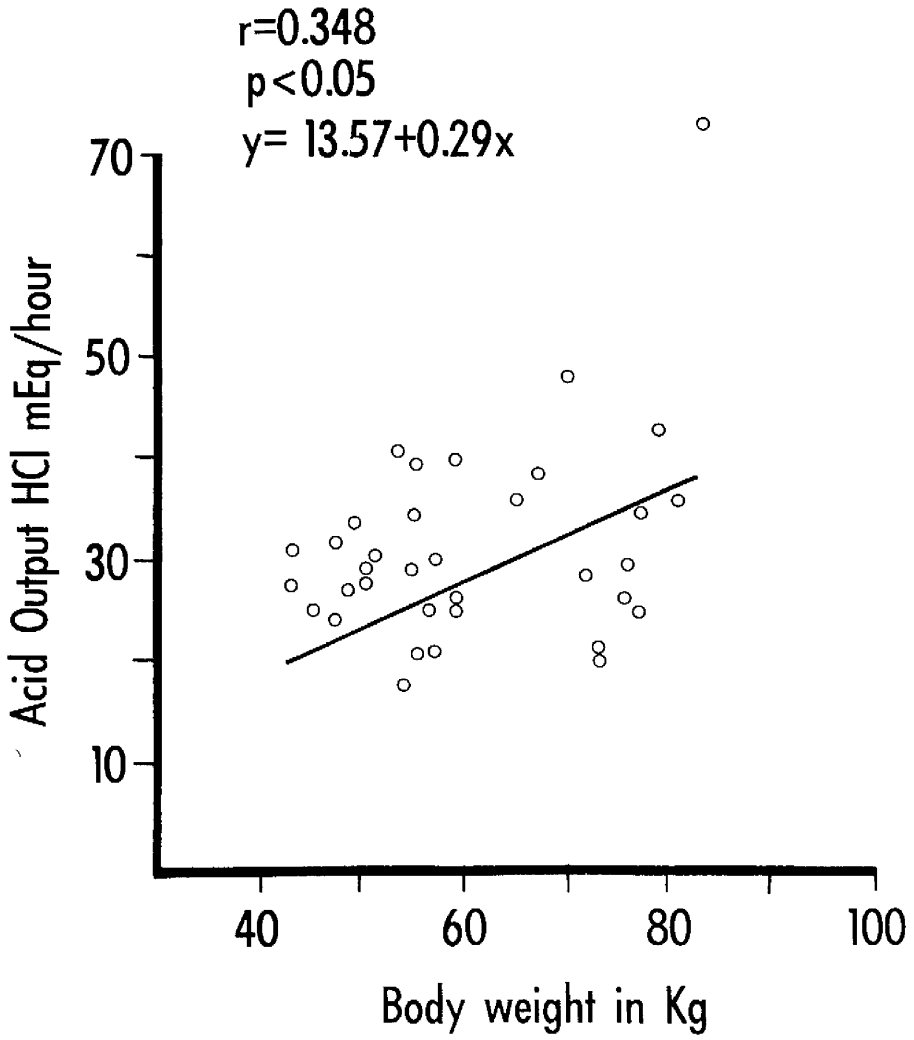


Figure 31: The relationship between acid output and body weight in 35 women with duodenal ulcer. There is a significant correlation between these two factors, $r = 0.348$, $P < 0.05$;
(acid) = 13.57 + 0.29 (weight).

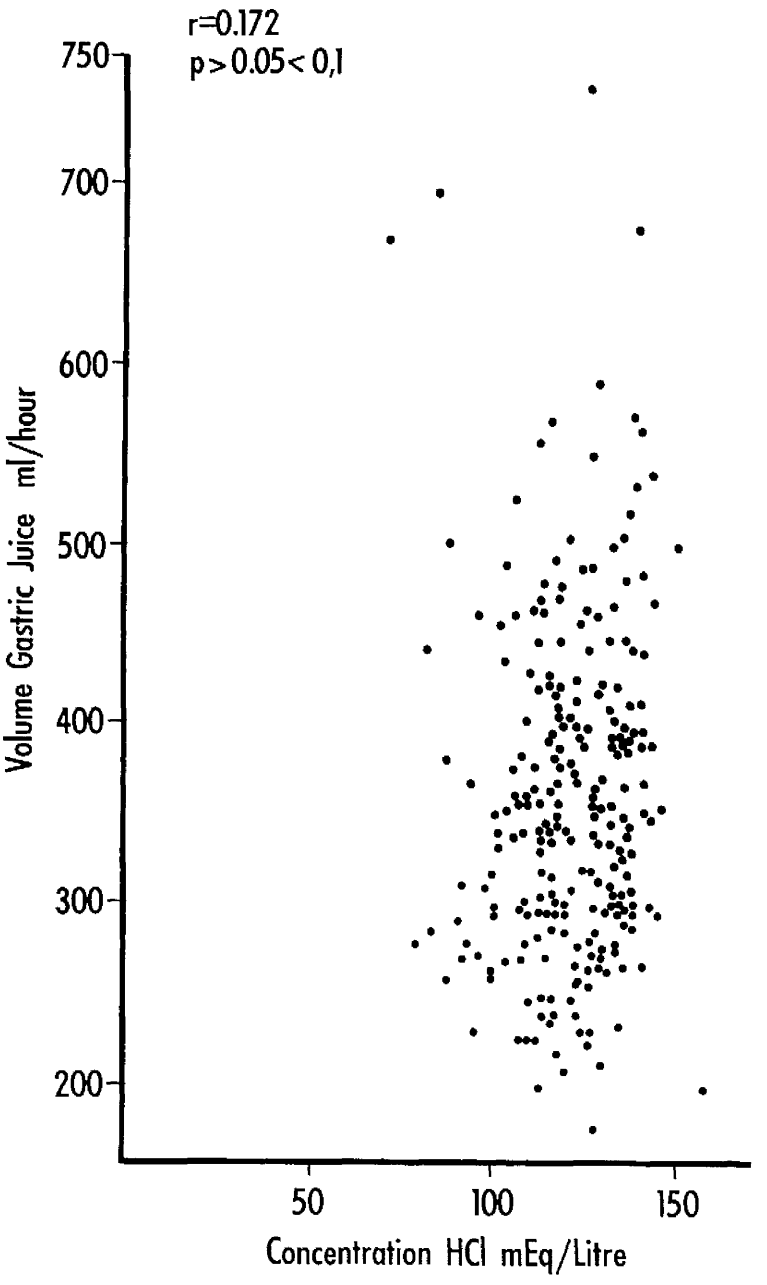


Figure 32: The relationship between volumes and concentrations of acid in 237 men with duodenal ulcer ($r = 0.172$; $P > 0.05 < 0.1$).

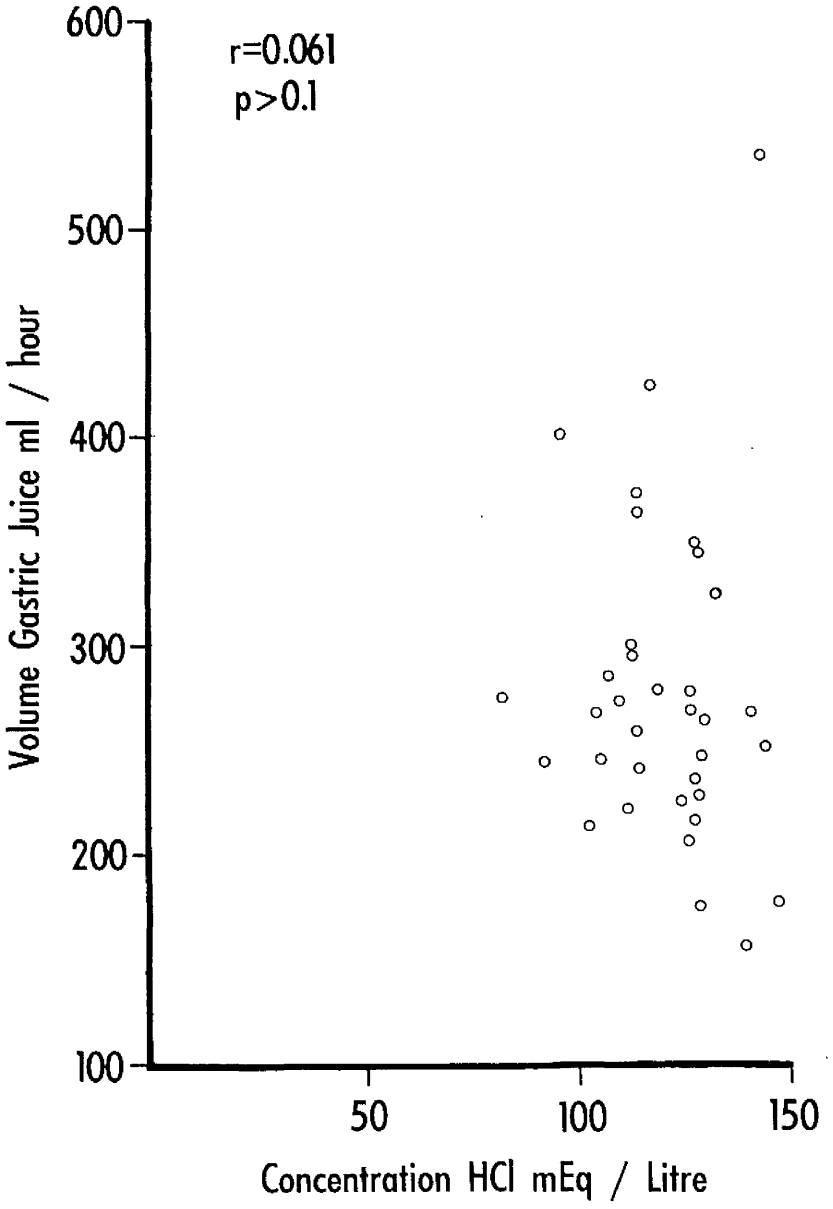


Figure 33: The relationship between volumes and concentrations of acid in 35 women with duodenal ulcer (r = 0.061; P > 0.1).

Diagnostic discrimination between normal and duodenal ulcer

If the upper limit of acid output in normal men is considered to be 40 mEq/hour, of the 237 men with duodenal ulcer 120 have an output greater than this 'normal' value, that is, 50% of men with duodenal ulcer have acid output above the normal range.

The range of output shown by the series of normal women can be taken as having an upper limit of 35 mEq/hour, and of the 35 women in the duodenal ulcer series, 10 had outputs greater than this. Thus, only 20% of women with duodenal ulcer appear to have acid outputs above the normal range.

Discussion: Acidity and duodenal ulcer

In recent years, estimates of the mean acid output in men with duodenal ulcer have varied considerably, from 20.6 mEq/hour (Gelb and others, 1961) to 46.2 mEq/hour (Marks & Shay, 1960). In general, these differences reflect the authors' particular method of interpretation of the augmented histamine test, the lower values resulting from estimates of the total hour after histamine. Using this method of calculation, maximal outputs of 37.5 mEq were reported by Bruce and others (1959), 28.4 mEq by Myren and Semb

(1961), 26.7 mEq by Ventzke and Grossman (1962), 36.2 mEq by Carneiro de Moura and Correia (1964), 28.9 mEq by Clark and others (1964), 28.6 mEq by Dotevall and others (1965), and 33.1 mEq by Shearman and others (1967). Taking the best peak of the augmented histamine response and extrapolating to estimate the output per hour, most authors quote values similar to those in the present study, 42 mEq (Baron, 1963a), 44 mEq (Køster, 1966), 45.4 mEq (Sircus, 1966) and 44.6 mEq (Grossman, 1966) although the low value of 20.6 mEq found by Gelb and others was calculated in this way.

This study provided further data related to the 'threshold' for duodenal ulcer, decided by Baron (1963a) as being 15 mEq in men and 18 mEq in women. This aspect of acid secretion in duodenal ulcer appears from the literature to be the most uncertain. Even those authors who have found high mean acid output, have included at the lower ranges of their series many patients with very low acid output. Such low values as 10.0 mEq (Køster & Thorsøe, 1960), 2 mEq (Myren & Semb, 1961), 4.7 mEq (Ventzke & Grossman, 1962), 8.5 mEq (Clark and others, 1964) and 10.8 mEq (Shearman and others, 1967) are difficult to reconcile logically

with a disease generally associated with hyperacidity, but could be explained through fallibility in the tests used which might be acceptable in a survey of a group, but would be insensitive in assessing an individual patient for purposes of diagnosis.

The lower limits of output in both the male and female group in this study, are similar - 19.3 mEq and 17.6 mEq respectively. Inspection of the scatter of output values in Figure 27 indicates the extreme rarity of outputs lower than 20 mEq/hour and it could be inferred from this that the finding of an acid output below this level might render the diagnosis of duodenal ulceration doubtful, or at least justify a careful review of the other diagnostic indices in that particular patient. Such studies as have been attempted on patients with 'non-ulcer' dyspepsia (Bruce and others, 1959; Baron, 1963a; Kirkpatrick, 1968) suggest that the acid output is normal.

Whether the very high values which have been found in this series are of diagnostic value in the individual patient remains in doubt. Certainly the finding of such a value might spare the patient the label of a 'functional' disorder until organic peptic abnormalities had been excluded.

Hyperacidity has always proved difficult to define, and its validity is still occasionally doubted. It has already been noted in the study of normal subjects that, although men have a higher acid output than women, the mean concentration of acid is similar for both sexes and, to this extent, normal men do not show 'hyperacidity' in comparison with normal women.

This study of duodenal ulcer shows, however, that compared with the normal, both volume and concentration are significantly increased in both men and women, and that the higher mean outputs of acid in duodenal ulcer are evidently due to a true state of hypersecretion or hyperacidity (Lawrie, 1967)(Tables 12 and 13). Ihre (1938) could find no difference in concentration of acid between normal subjects and patients with duodenal ulcer, and similar findings have been reported more recently by Rødbro and Christiansen (1967).

Of equal interest, although not of diagnostic importance, is the similarity in concentration of acid secreted by both men and women with duodenal ulcer, in spite of the enormous difference in both volume and output in men over women. This is the same pattern of secretion which was observed between normal men and women. Men with duodenal ulcer as a group, apparently

secrete larger volumes of gastric acid than women, but of the same concentration, 121.9 mEq and 120.3 mEq/litre respectively.

The lack of correlation between acid output and age in either sex, contrasts with the normal group, in which the men showed declining acid output with increasing age. Similar findings were reported by Baron (1963a), though the early studies of Polland (1933) had shown a fall with age and the recent extensive survey in Copenhagen by Køster (1966) also showed a significant fall with age in men, though not in women. The true relationship may be obscured by the possible increase in acid output with duration of symptoms (Sircus, 1966).

The correlation between output and body weight in women only is not explained by this study, although Hume and Melrose (1967) grouping men and women together, did find a significant relation between acid and lean body mass.

With each new development in the technique and interpretation of gastric acid tests, there has arisen the hope that a test for gastric acid might discriminate more clearly between normal and duodenal ulceration. At the beginning of this study when obviously higher individual acid outputs were being recorded, it was

hoped that the infusion test might contribute usefully to this problem. However, ranges have, in fact, been elevated for both normal and duodenal ulcer, so that the diagnostic discrimination afforded by this investigation is similar to that of some previous work (Baron, 1963a; Carneiro de Moura & Correia, 1964). One-half of all male patients with duodenal ulcer have acid output above the range of normals. It is possible, however, that attempts to compare directly acid output in these two groups are artificial, since normal subjects and duodenal ulcer patients probably form two different populations, in which acidity is merely one isolated factor in the mechanism of digestion, and in which a given acid output has a different 'meaning' for each population. Of the hundred normal students having histamine tests in 1934 (Lander & MacLagan) seven had developed a duodenal ulcer by 1961 (Baron, 1962) and their acid levels had been in the lowest quarter of the original group.

Summary: Acidity and duodenal ulcer

The patients with proved duodenal ulcer included 237 men and 35 women. The range of acid output in men was 19.3 - 103.0, mean 41.5 mEq/hour, and for women 17.6 - 73.3, mean 31.2 mEq/hour. In both men and women

the volume, concentration and output of acid are all significantly greater than normal. Within the duodenal ulcer group, however, men have a significantly greater output of acid than women, due to larger volumes of gastric juice of comparable concentration. Thus, the concentration of acid in duodenal ulcer (men 121.9, women 120.3 mEq/litre) is higher than normal (men 108.4, women 110.4 mEq/litre) regardless of sex.

There is a significant correlation between acid output and body weight in women with duodenal ulcer, but no other relationship with body weight or age is apparent. There is no relationship between volume and concentration of acid secreted. The diagnostic discrimination is 50% in men, and 20% in women.

CHAPTER 5

ACID OUTPUT IN GASTRIC ULCER

Little importance has been attached to quantitative determination of acid secretion in gastric ulcer, in part due to uncertainty in method and in part to the apparently multifactorial nature of gastric ulcer (Aagaard, 1963), wherein acid output may play only a minor role in the condition. Investigators are further discouraged since most results are normal or subnormal, with a wide variation, thus providing little guidance in diagnosis. Further, since gastric ulceration is notoriously a relapsing and remitting condition, and there is some evidence that the acid output may likewise fluctuate widely in the same subject (Marks & Shay, 1959), isolated estimations of acidity have been considered of incidental importance.

The patients with gastric ulcer

A group of 73 patients has been studied; 43 men and 30 women. After a preliminary retrospective study of barium meal reports and radiographs and the finding of frequent disagreement between radiological appearances and operative findings, it was decided to include in this series only patients who had the diagnosis and site confirmed by at least two of the three diagnostic

measures - barium meal, laparotomy or gastroscopy/ fibroscopy.

Acid output

There is a wide range of values for acid output in both men and women, 2.1 - 41.2 mEq/hour in men and 4.5 - 26.8 mEq/hour in women. The mean for men, 21.4 mEq, is significantly higher than that for women, 13.5 mEq. The distribution of output in the two groups is shown in Figure 34.

Site of gastric ulcer

A more detailed study of this group was undertaken including only those in whom the exact site of ulcer could be determined. The classification adopted was that proposed by Ball (1961) with the addition of a group of ulcers which were clearly high in the cardia and which it seemed rational to classify separately from the majority which arose in the body. There were 21 men and 20 women finally included in this study. The majority of the ulcers, 25 of 41, were in the middle of the body of the stomach, 10 were high in the cardia, 4 were at the angulus and only 2 lay in the antrum.

Acidity and site of ulcer

The volume and concentration of acid in the groups of patients with gastric ulcer of known site are

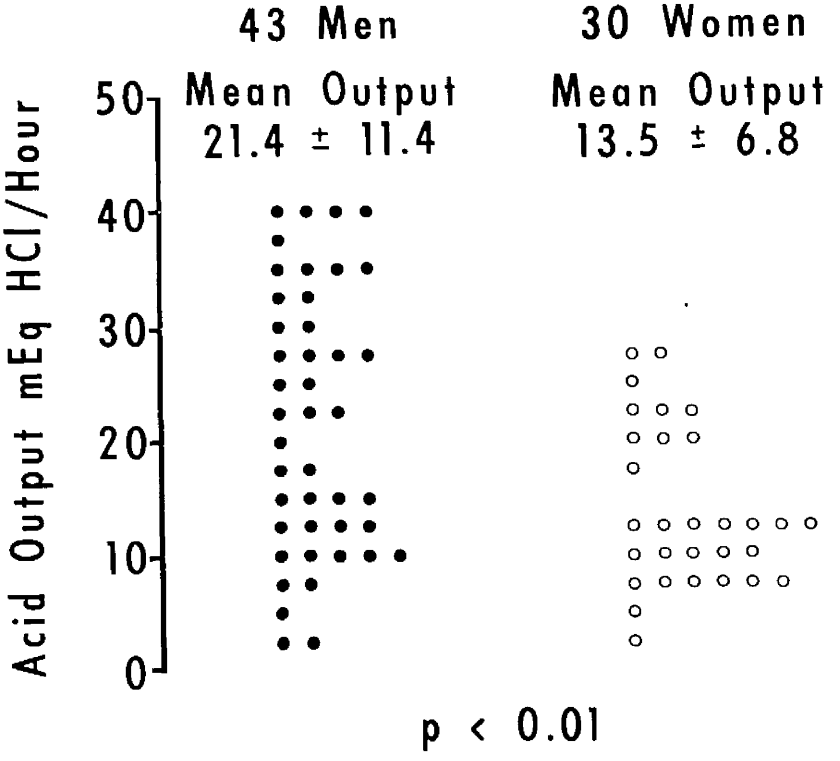


Figure 34: The acid output in 43 men and 30 women with benign gastric ulcer. The mean output for the men of 21.4 mEq/hour is significantly higher than that for women, 13.5 mEq ($P < 0.01$).

given in Tables 14 and 15 and, in addition, the output for each patient is tabulated according to the site of the ulcer.

The distribution of these acid output values is shown graphically in relation to the sites of the ulcers in Figure 35. The numbers do not warrant a proper statistical analysis, but inspection of the scatter indicates no particular trend of acid output in relation to site of ulcer. There appear to be fairly random high and low values at all sites in both sexes. Taking both men and women together, the four mean values for the four sites passing distally down the stomach are shown in the following table.

No. of patients	Site of ulcer	Mean acid output
10	High	17.9
25	Mid-body	14.8
4	'Angulus'	17.2
2	Antrum	29.8

Comparison of acidity in gastric ulcer and normal

In both men and women, volume, concentration and output of acid are significantly less than normal. Table 16 shows the analysis of results from the smaller detailed group of gastric ulcers with the original normal control group, described in Chapter 3.

Table 14. The age, body weight, volume, concentration and output of acid in 21 men with benign gastric ulcer. The outputs are tabulated according to the site of the ulcer and correspond to the points on Figure 35.

	AGE (years)	WEIGHT (Kg)	VOLUME ml/hour	CONC. mEq/litre	OUTPUT mEq/hour			
					HIGH	MID	ANGULUS	ANTRUM
I.J.	38	62	168	92	12.8			
W.J.	69	46	137	94		11.9		
J.McG.	35	61	424	115		36.4		
W.M.	50	64	150	82	10.1			
J.M.	46	63	177	103	17.7			
P.T.	50	76	227	82	16.6			
R.R.	21	86	278	102		27.5		
A.R.	50	67	300	118			34.8	
T.S.	63	43	148	36		4.2		
T.A.	64	55	355	124	39.3			
P.B.	47	59	188	81		13.2		
E.B.	50	85	289	71			19.2	
K.B.	19	53	279	114		31.1		
R.C.	41	61	96	44		3.2		
J.C.	49	63	213	77		15.1		
T.C.	40	85	269	131				33.8
H.G.	50	67	123	84	10.1			
A.G.	23	102	422	102	41.2			
R.S.	60	55	160	106			11.6	
W.W.	71	51	184	56		9.5		
W.G.	56	65	158	62		7.6		

Table 15. The age, weight, volume, concentration and output of acid in 20 women with benign gastric ulcer. The outputs are tabulated according to the site of the ulcer and correspond to the points on Figure 35.

	AGE (years)	WEIGHT (Kg)	VOLUME ml/hour	CONC. mEq/litre	OUTPUT mEq/hour HIGH	MID	ANGULUS	ANTRUM
M.H.	65	35	231	114		26.7		
F.H.	39	38	166	87		13.7		
L.J.	61	60	125	96		10.7		
E.M.	49	51	185	107		19.2		
E.M.M.	69	36	188	116		20.6		
A.O.	77	53	120	70		8.3		
E.P.	66	45	152	80		11.7		
E.R.	64	43	141	85		11.5		
L.R.	47	72	165	70		10.3		
V.S.	63	60	118	79	8.5			
I.B.	58	56	243	108		22.2		
D.B.	64	65	144	70	9.4			
S.B.	22	55	166	86	13.3			
L.C.	58	69	234	86		17.1		
A.D.	80	51	45	78			3.2	
E.G.	74	52	164	91		13.0		
F.H.	43	55	185	66		10.7		
I.H.	46	49	194	38		6.6		
J.H.	41	59	238	117				25.8
O.Y.	37	47	103	70		6.7		

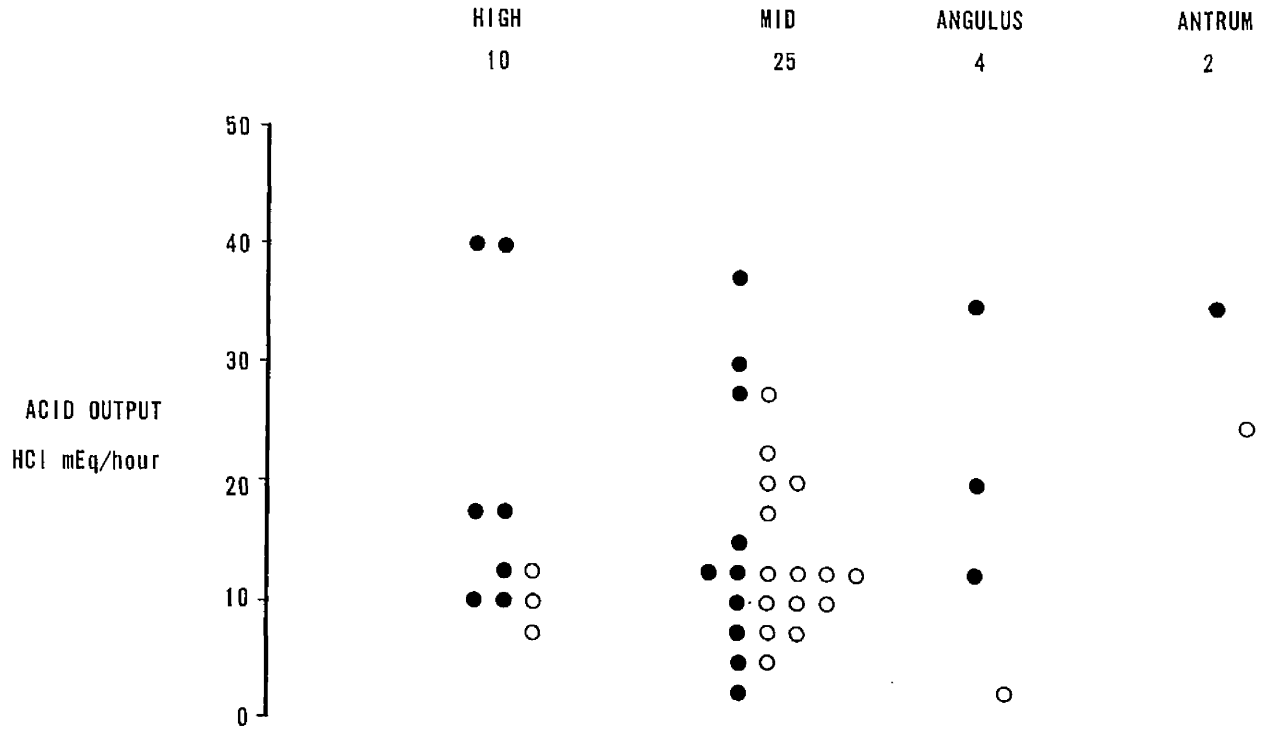


Figure 35: The distribution of acid output in 21 men (closed circles) and 20 women (open circles) with benign gastric ulcer, grouped according to the site of the ulcer. 'High' denotes an ulcer within 5 cm of the oesophagogastric junction, 'mid' the main part of the body of the stomach, 'angulus' within 2 cm of the angulus or incisura, and 'antrum' distal to this but excluding the pyloric canal and prepyloric region.

Table 16. The comparison in volume, concentration and output of acid between benign gastric ulcer and normal.

		GASTRIC ULCER 21	NORMAL 54	P
MEN	Volume: ml/hour	226.0	251.3	< 0.01
	Concentration: mEq/litre	89.3	108.4	< 0.001
	Output: mEq/hour	19.4	25.3	< 0.001
		20	50	
WOMEN	Volume: ml/hour	165.4	215.0	< 0.001
	Concentration: mEq/litre	85.7	110.4	< 0.001
	Output: mEq/hour	13.5	21.7	< 0.001

Discussion: Acidity and gastric ulcer

Since most of the gastric ulcers in this series occurred in the body of the stomach where it has been shown that, in addition to the ulcer, there are marked histological changes in the surrounding area (Ball & James, 1961), it would be expected that the group as a whole would show a diminution in gastric acid. Although all three factors, volume, concentration and output, are significantly reduced in comparison with the normal, an inspection of the individual results in Tables 14 and 15 indicates that a gross reduction in total output is usually the result of a marked decrease in volume, while the concentration of acid remains only slightly reduced. For example, five of those with the lowest outputs had a concentration of 70 mEq/litre or more. This differs from the 'virtual achlorhydria' noted in many patients by Marks and Shay (1959).

There were no patients with output above the normal range, the highest in men being 41.2 and in women 26.8 mEq/hour. Køster and Thorsøe (1960) found none over 20 mEq/hour, though there was a wide scatter of concentration. Dragstedt and others (1950) found a normal range, using nocturnal secretion. Comparable results in men were found by Baron (1963a) but his values

for women are considerably lower than the present results, concentration of 68.3 mEq/litre and output of 9.6 mEq/hour. Using an 'index' of gastric secretion relating volume and pH, Johnson (1962) found gastric ulcer falling within the normal group.

Summary: Acidity and gastric ulcer

The mean acid output in gastric ulcer is less than normal in both men and women, 21.4 and 13.5 mEq/hour. The lower ranges, 2.1 and 4.5 mEq/hour respectively, represent significant acid secretion. The upper ranges never exceed normal limits, 41.2 and 26.8 mEq/hour respectively. Acid output was not related to the site of the ulcer in this series.

CHAPTER 6

ACID OUTPUT AND GASTRIC CANCER

It is generally agreed that a substantial number of patients with gastric cancer are achlorhydric by any test for gastric acid, and that the demonstration of acid does not necessarily exclude cancer. Further, it is known that in the differentiation of cancer from benign ulcer, all the diagnostic features, including acid secretion studies, may be equivocal. Nevertheless, it seemed useful to assess a group of patients with gastric cancer, in order to compare the results with those from the benign ulcer group, and to discover, if possible, any pattern of secretion within the group.

The patients with gastric cancer

This is a highly selected group, in that many patients were ill on presentation, the diagnosis on clinical and radiological grounds was not in doubt, and it seemed unreasonable and unnecessary to carry out further investigations. Thus, to some extent, the patients studied have included an excess of those in whom the diagnosis was in doubt, and in whom the results of the test were thought to be of some value in the assessment of the patient. There were 22 men and 7 women in the series. The data relating to them are given in

Tables 17 and 18. The volume and concentration of acid are given, and, in addition, where there was no titratable acid, the pH of the gastric juice is shown. The sites of the tumours fell into three groups, the cardia, the body of the stomach and the antrum, and the patients were classified in relation to laparotomy findings.

Achlorhydria and gastric cancer

No titratable acidity was found in 11 patients (10 men and 1 woman) that is, one-third of this series were achlorhydric. The mean volume of gastric juice secreted by these patients was 50 ml/hour, with pH varying from 6.4 to 7.6.

Acidity and gastric cancer

The range of concentration among the remaining patients who did secrete acid is shown in Figure 36, and extends from 13 to 130 mEq/litre. Both sexes are represented throughout this range.

Metastases were present in 13 of the 29 patients. The distribution of acid output in these patients with gastric cancer is shown in Figure 37. Of the 4 patients with lesions of the cardia, all were achlorhydric or virtually so. Only 2 of the 13 patients with lesions of the body of the stomach produced normal acid, 7 being

Table 17. The age, weight, volume, concentration and output of acid in 22 men with gastric cancer. The pH of the gastric juice is indicated in those patients with no titratable acidity. The presence of metastases (+) at laparotomy is indicated.

	AGE (yrs)	WT. (kg.)	VOLUME ml/hour	ACIDITY conc. mEq/litre	pH	OUTPUT mEq/hour Cardia	Body	Antrum	METASTASES
W.M.	69	55	49	0	7.0		0		+
T.T.	50	57	375	112				41.2	-
C.L.	73	62	276	84				17.8	+
P.F.	66	85	90	0	6.4			0	+
A.S.	58	69	68	0	6.7		0		-
C.B.	35	75	194	13			1.0		-
J.P.	70	86	23	0	7.4	0			-
A.S.	68	55	105	93			9.3		+
C.G.	64	57	55	0	7.6		0		-
A.O'R.	71	49	114	86				6.4	-
E.C.	56	50	191	112				19.7	+
H.R.	59	46	211	88				18.1	+
P.H.	64	57	59	105				3.5	+
F.J.	50	67	77	0	6.8		0		-
W.C.	60	54	58	18		1.0			+
E.T.	70	40	65	0	6.6	0			+
H.E.	64	64	30	18		1			+
R.M.	74	62	21	0	7.2		0		-
L.M.	67	76	46	0	7.3		0		-
A.A.	62	77	51	0	7.0		0		+
D.O.	41	60	21	28				0.6	-
W.S.	59	59	208	48			9.4		-

Table 18. The age, weight, volume, concentration and output of acid in 7 women with gastric cancer. The pH of the gastric juice is indicated in those patients with no titratable acidity. The presence of metastases (+) at laparotomy is indicated.

	AGE (yrs)	WT. (kg.)	VOLUME ml/hour	ACIDITY conc. mEq/litre	pH	OUTPUT mEq/hour Cardia	Body	Antrum	METASTASES
M.C.	71	51	13	0	7.5			0	-
D.C.	67	46	19	20			0.4		+
V.S.	63	58	62	83			2.5		+
E.G.	52	42	214	130				22.9	-
M.L.	59	64	108	88				8.7	-
M.D.	62	77	226	70				13.1	-
R.L.	58	43	108	42			4.0		-

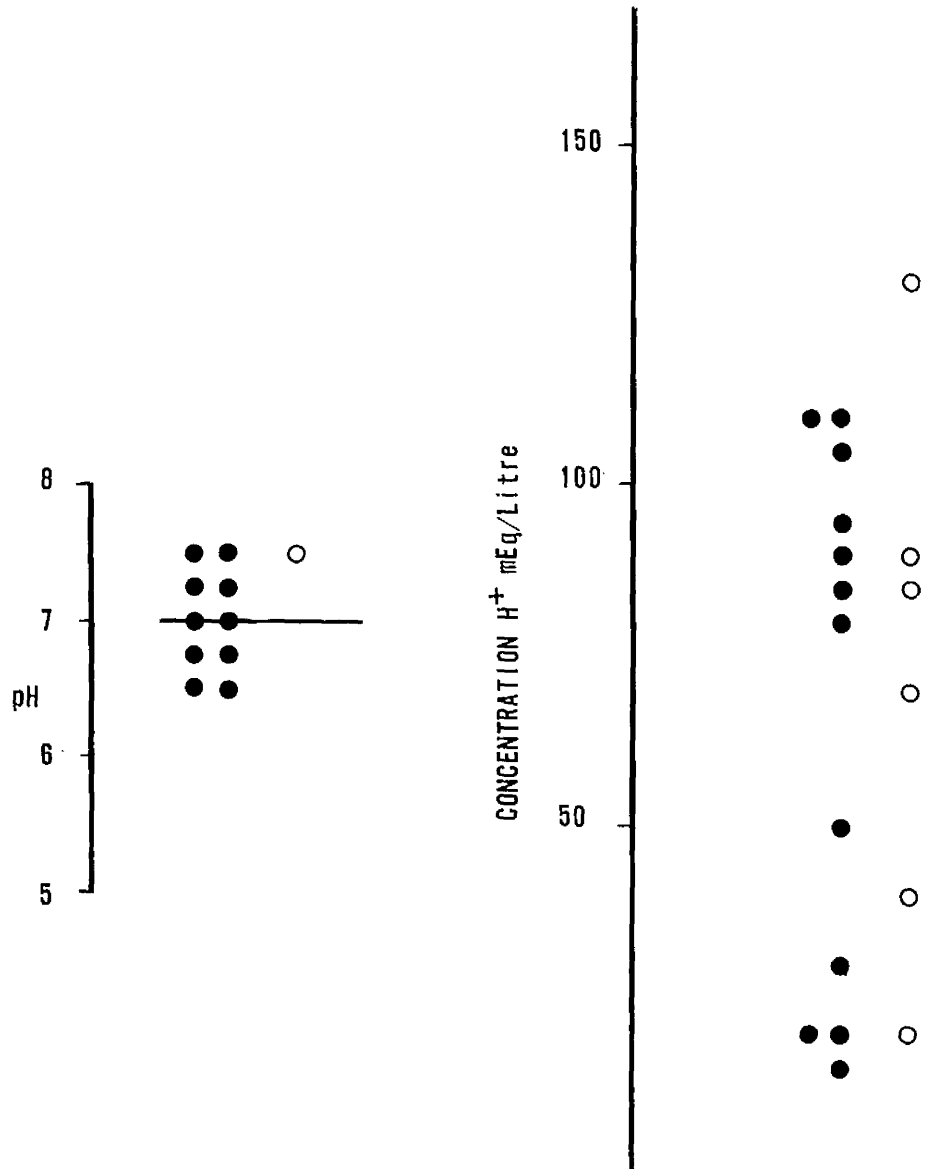


Figure 36: Concentration of acid secreted by 29 patients with gastric cancer (22 men, closed circles; 7 women, open circles). Eleven patients had no titratable acidity and the pH of the gastric juice is indicated on the left. On the right is shown the concentration of acid in the remaining 18 patients.

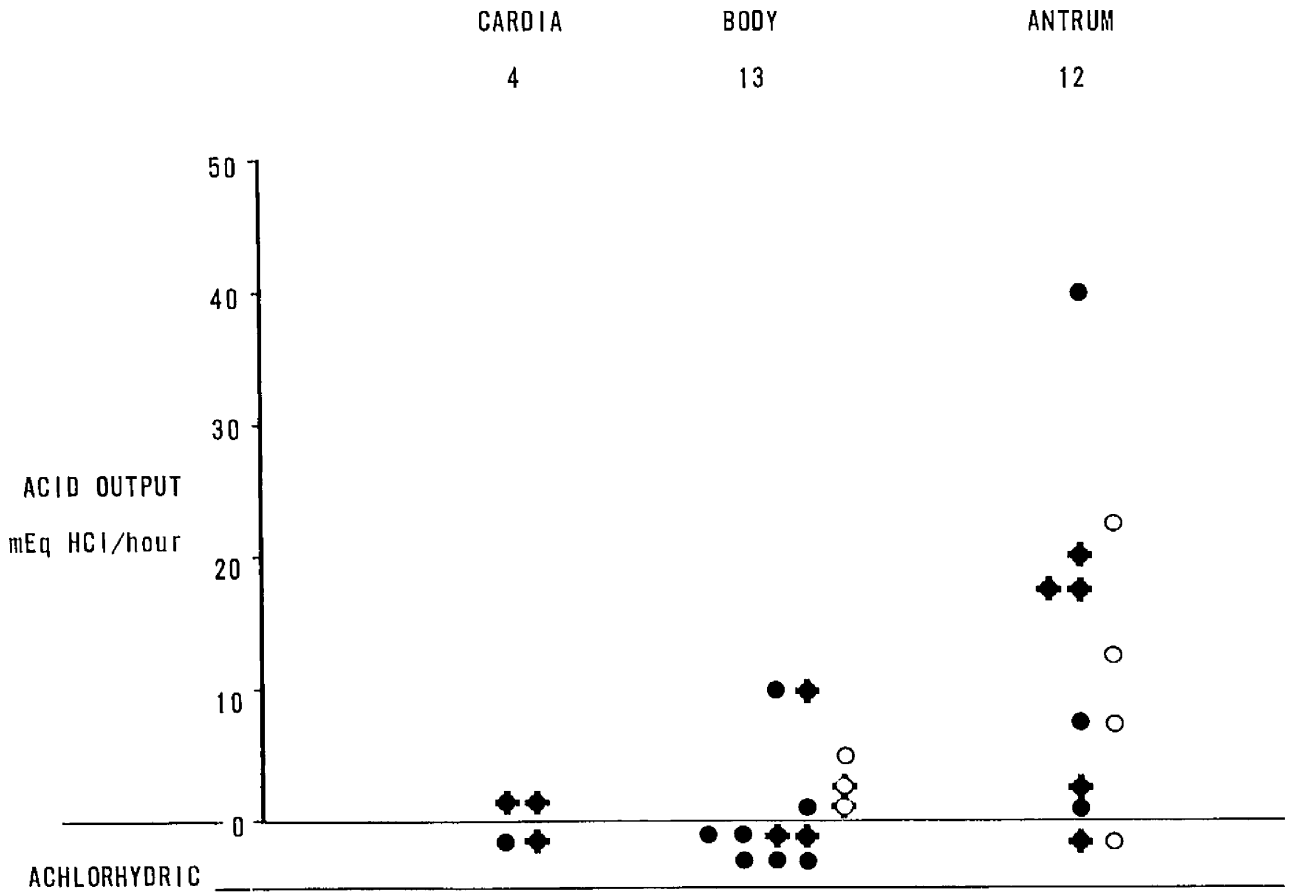


Figure 37: The distribution of acid output in 29 patients (22 men, closed circles; 7 women, open circles) according to the site of tumour. The 11 patients shown below the zero line were achlorhydric. Patients with metastases are shown crossed.

completely achlorhydric. The 12 patients with lesions of the antrum, however, included 8 with acid levels through the whole range of normal, and only 2 were achlorhydric.

As far as the numbers permitted proper estimate, sex did not seem to be related to either site of tumour or level of acidity.

Similarly, the presence of metastases did not appear to be related either to site, or to the secretory status of the stomach.

In so far as it is meaningful to assess the means of such irregular groups, the output for men with cancer is 5.9 and for women 7.4 mEq/hour (Table 19). The output according to site increases with more distally placed lesions, being 0.5 mEq for tumours of the cardia, 2.0 mEq for tumours of the body and 12.7 mEq for tumours of the antrum.

Discussion

A smaller incidence of achlorhydria, 30%, has been found in this series than in most others, Polland (1933) finding 70%, and more recently Pack (1953) 51%. Similar values for output have been reported by Shearman and others (1967) although these authors found no relation between extent of tumour and acidity. Attempts to

Table 19. The mean concentration and output in 22 men and 7 women with gastric cancer, together with the outputs of acid related to the site of the tumour.

	Mean concentration (± S.D.) mEq/litre	Mean output mEq/hour	(± S.D.)
22 men	36.6 (44.4)	5.9	(10.2)
7 women	61.9 (44.4)	7.4	(8.3)
4 cardia		0.5	(0.6)
13 body		2.0	(3.5)
12 antrum		12.7	(12.2)

distinguish benign ulcer from tumour on the basis of acid secretion have not proved on the whole rewarding, although Hirschowitz and others (1957) achieved useful discrimination plotting both H^+ ion concentration and Cl^- ion concentration. A concentration of 80 mEq/litre of H^+ ions excluded most of the cancers, but in the present study one-third of the patients had acid concentrations above this level.

The only tentative diagnostic conclusion which might be derived from the present study would be that proximal lesions of the body or cardia, with a normal acid output, are most unlikely to be cancer.

Summary: Acidity and gastric cancer

Acid values have been studied in 22 men and 7 women with gastric cancer. One-third were achlorhydric. The range of concentration of acid is very wide among those who did secrete acid, being 13 - 130 mEq/litre. The output in men was 5.9 mEq/hour (range 0 - 41.2) and in women 7.4 mEq/hour (range 0 - 22.9). Acid output increases markedly with more distally placed tumours, in the cardia 0.5, in the body 2.0 and in the antrum 12.7 mEq/hour.

CHAPTER 7

ACID OUTPUT IN PREPYLORIC ULCER

Acidity in association with prepyloric ulcer is commonly considered to be high, although the actual evidence for this is conflicting. It was not the purpose of this study to investigate pyloric channel disease (Burge and others, 1963) nor the syndrome of duodenal ulcer combined with gastric ulcer. The diagnostic difficulties involved in classifying ulcers as 'prepyloric' even at laparotomy are notorious, nevertheless from time to time there arose in the course of this investigation ulcers which were neither duodenal, nor gastric, but lay within 3 cm of the pyloroduodenal junction. Such ulcers form this present group. Ulcers further proximally, such as are included by Køster and Thorsøe (1960a) at 6 cm from the pylorus, seemed to be more 'gastric' than prepyloric and have been excluded.

The patients with prepyloric ulcer

There were 13 patients in this series; 9 men and 4 women. Their ages, weights and acid values are shown in Table 20. Apart from one man with output of 83.9 mEq/hour, they are entirely comparable both in mean and range with normal, being 21.7 for the men and 21.0 mEq/hour for the women.

Table 20. The age, weight, volume, concentration and output of acid in 11 men and 4 women with prepyloric ulcer.

	AGE (years)	WEIGHT (Kg)	VOLUME ml/hour	CONC. mEq/litre	OUTPUT mEq/hour
MEN					
D.J.	55	64	259	64	14.4
W.M.	59	59	109	123	11.8
J.C.	61	71	739	120	83.9
S.R.	60	82	190	98	18.5
L.J.	41	65	321	136	43.1
O.M.	73	48	121	76	7.7
W.R.	49	59	295	93	25.3
T.J.	43	89	375	113	39.6
G.N.	61	87	149	87	12.9
WOMEN					
E.M.	50	63	127	111	13.0
M.H.	50	58	286	135	31.0
E.G.	51	84	170	106	16.6
M.J.	50	62	341	76	23.4

Discussion

As far as it is valid to draw any conclusions from this very small but definite group of patients, it would appear that their acid secretory status is more akin to gastric than duodenal ulceration, in spite of the proximity of such ulcers to the common site of duodenal ulceration. The obvious exception to this observation, the man with output of 83.9 mEq/hour, was explored by the author and found to have an ulcer crater 0.5 cm in diameter, lying 1 cm proximal to the pyloro-duodenal mucosal junction. The meaning of this remains obscure.

'Slightly higher' acid output was found by Marks and Shay (1960) in prepyloric ulcer compared with gastric ulcer, while higher levels, about the same as duodenal ulcer, were found by Grossman (1966).

This syndrome is therefore, to some extent, a curiosity.

CHAPTER 8

ACID OUTPUT AND COARSE DUODENAL MUCOSAL FOLDS

Dyspepsia without ulcer has long been accepted as a clinical entity, but the radiological and secretory evidence necessary to establish the condition as a respectable syndrome has been less convincing. Duodenitis was first reported as a pathological entity by Judd from the Mayo Clinic in 1921, and soon after, from the same centre, Kirklin (1929) described the radiological changes associated with this condition. The duodenal bulb was irritable and emptied rapidly, there was spasm but no organic deformity and the duodenal mucosa appeared to have a coarse irregular pattern with wide folds.

Interest in the condition in this centre arose following the frequent recognition of the radiological changes by Dr. R. G. Pitman, Department of Diagnostic Radiology, The Royal Infirmary, Cardiff, the simultaneous observations on the effect of hyperacidity on the duodenal mucosa by James (1964) and the discovery of several patients with dyspepsia, without ulcer, and with high acid output. Various aspects of the group of patients who were thus defined as having 'coarse mucosal folds in the duodenum' are described by Fraser, Pitman, Lawrie,

Smith, Forrest and Rhodes (1964) and Rhodes, Evans, Lawrie and Forrest (1968).

Radiological features

The coarse, irregular, reticular or cobblestone pattern of the duodenal mucosa is illustrated in Figure 38. There are all grades of this abnormal appearance, both in extent and in severity, but only those patients showing significant abnormalities were included in this series.

Clinical features

Patients were aged between 20 and 65 years, the mean age for the group being 41 years. Thirty-nine patients were men and only one was a woman. Four of the patients were brothers but, apart from this, there was no family history of dyspepsia or peptic ulcer in the other patients. The symptoms were typical of duodenal ulceration, consisting of periodic epigastric pain, related to food and relieved by alkali and vomiting.

Association with duodenal ulcer

During the early part of this study patients with this appearance only, and no ulcer, were examined as a separate group and their acid output compared with normal and with duodenal ulcer. The significance of

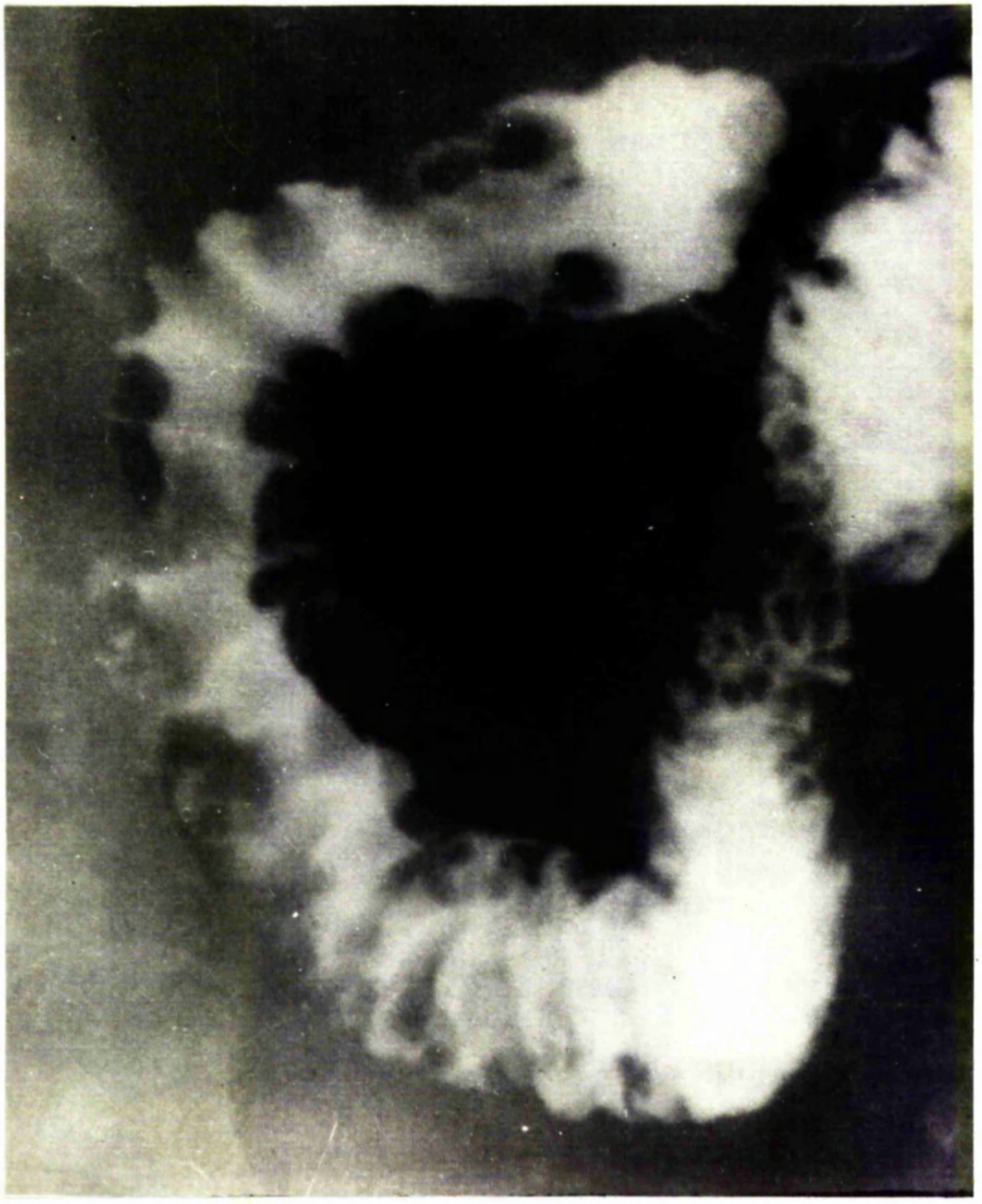


Figure 38: Film taken during barium meal examination of a patient with severe dyspepsia, and maximal acid output of 96 mEq/hour. A coarse, cobblestone appearance of the mucosa is shown in the first and second parts of the duodenum, with a more normal appearance in the fourth part. No constant niche was seen during the barium series and no ulcer was found at subsequent laparotomy.

the difference at that time was:

	No. of patients	Acid output mEq/hour ± S.E.		P
Normal controls	14	24.9	2.2	<0.001
Coarse duodenal folds	23	45.6	2.6	>0.5
Duodenal ulcer	80	42.9	1.6	

More recently, the numbers in all three groups have been expanded (Fig. 39) and, in addition, patients with coarse duodenal folds and an associated duodenal ulcer have been included.

The acid output is still high in patients with coarse folds, whether or not they have, or develop later, a duodenal ulcer (Fig. 40).

Even with the increase in size of all the groups and this alteration in criteria for inclusion in the coarse folds group, the acid output in this syndrome is still high, comparable with that in duodenal ulceration and significantly higher than normal:

Subjects	No.	Acid output mEq/hour Mean	S.D.	S.E.
Normal (men)	54	25.3	7.6	1.0
Duodenal ulcer (men)	237	41.5	12.8	0.8
Patients with coarse folds	39	44.3	17.5	2.8

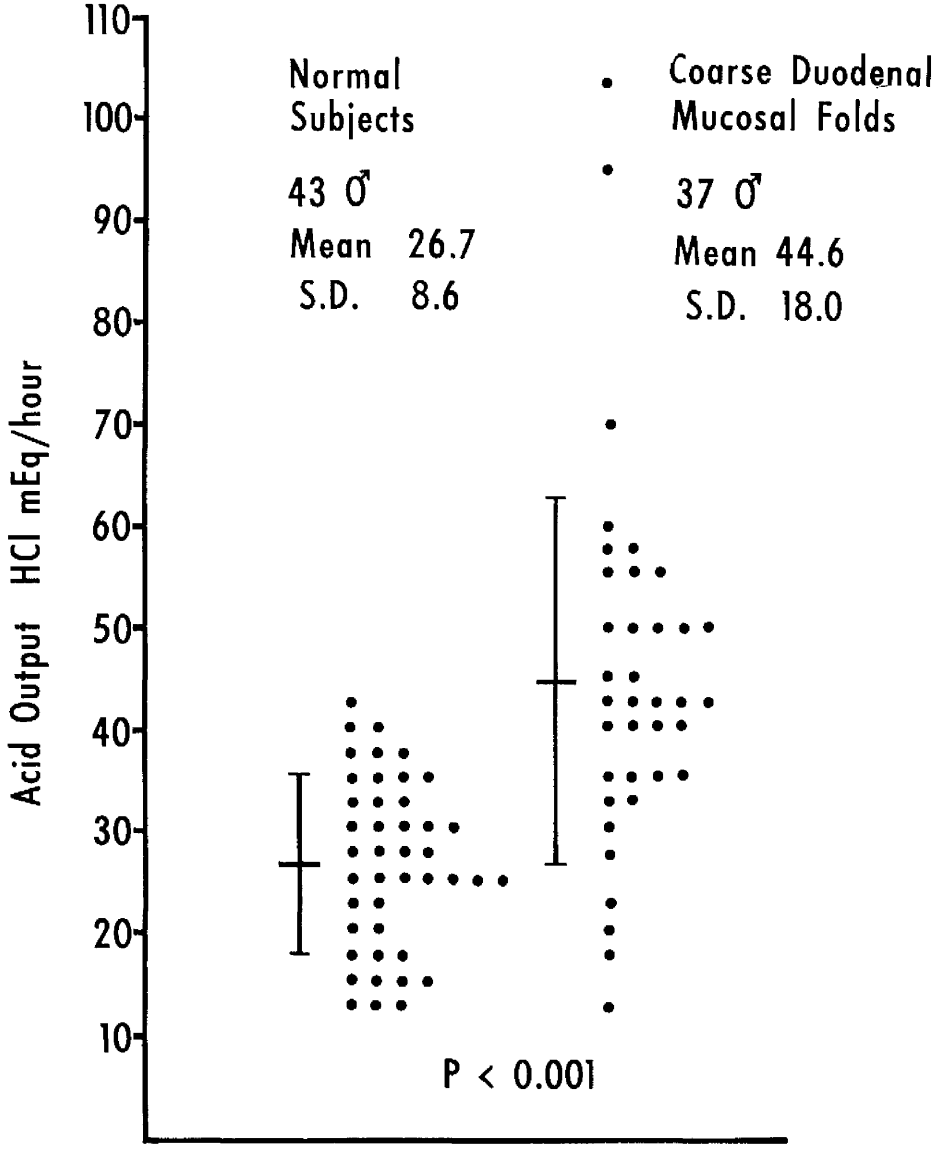


Figure 39: The distribution and comparison of acid output in 37 patients with 'coarse duodenal mucosal folds' and 43 normal men.

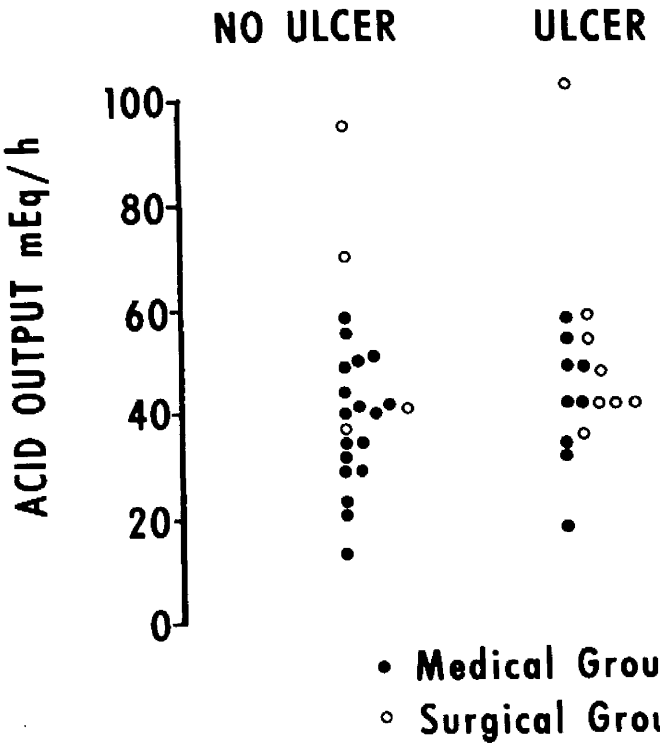


Figure 40: Acid output in patients with coarse duodenal mucosal folds, with and without a duodenal ulcer. Patients treated surgically are shown as open circles, those still treated medically as closed circles. Output in those with no ulcer = 42 ± 3.7 mEq/hour; in those with ulcer = 47 ± 4.2 mEq/hour. ($0.4 > P > 0.3$).

Further evidence that this abnormality might constitute one part of the peptic ulcer diathesis, was provided by a separate study of barium meal films on which a definite diagnosis of peptic ulcer had been made. The films were then studied, without knowledge of the diagnosis previously made, for evidence of coarse folds (Rhodes, Lawrie and Evans, 1967). Of the 88 patients with duodenal ulcer, 22 (25%) had coarse duodenal folds, and in 6 of these the abnormality was obviously 'severe'. The mean acid output in the group with duodenal ulcer alone was 40.3 mEq/hour, in those who also had coarse folds 45.8 mEq/hour, while those with 'severe' changes had the highest outputs of all. Of the 14 patients with gastric ulcer, having a low mean acid output of 19.4 mEq/hour, only 2 had coarse folds and these had relatively high acid outputs of 34.8 and 41.2 mEq/hour.

Acidity and severity of radiological change

Each patient's barium meal films were graded according to the severity of the abnormality in the bulb, and second and third parts of the duodenum, giving a maximum score of 6. Accepting the rather arbitrary and inaccurate nature of this assessment, there is a significant correlation between acid output and severity of coarseness of folds (Fig. 41).

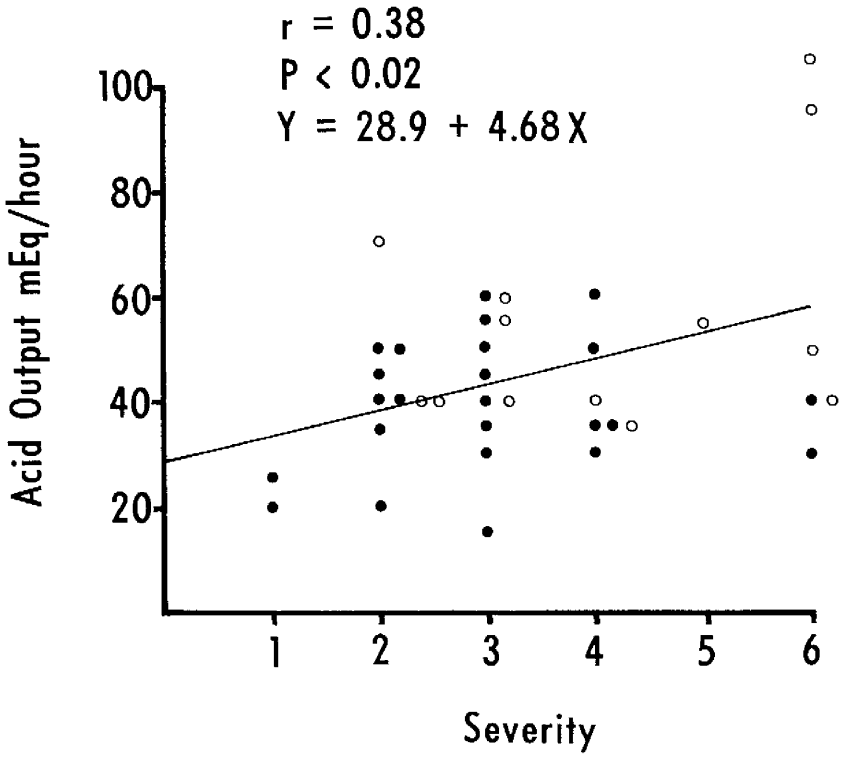


Figure 41: The correlation in 37 patients with coarse duodenal mucosal folds, between the acid output and the severity of the radiological changes in the bulb, and second and third parts of the duodenum.

Acidity and severity of histological change

The histological features in the duodenal mucosa associated with this syndrome consist of (1) flattening of villi (2) cellular infiltration of the lamina propria, and (3) the appearance of 'gastric-type' epithelium (James, 1964), and these features provided the basis for grading of such biopsy material as was available. Since the numbers were small (18) this aspect of the study was expanded to include biopsies of 15 patients with duodenal ulcer and 7 with various non-peptic disorders, in all of whom the acid output was known. There is a significant correlation between acid output and histological changes in this composite group (Fig. 42). There were minimal changes in those of the non-peptic group with a very low acid output, and the most severe changes were seen in those of the coarse folds group with the highest acid output (Patrick and others, 1967).

Discussion

Patients who are found on barium meal examination to have coarse duodenal mucosal folds have a high mean acid output, similar to that found in duodenal ulcer, whether they have an associated ulcer or not. This could be taken as further confirmatory evidence for the association of

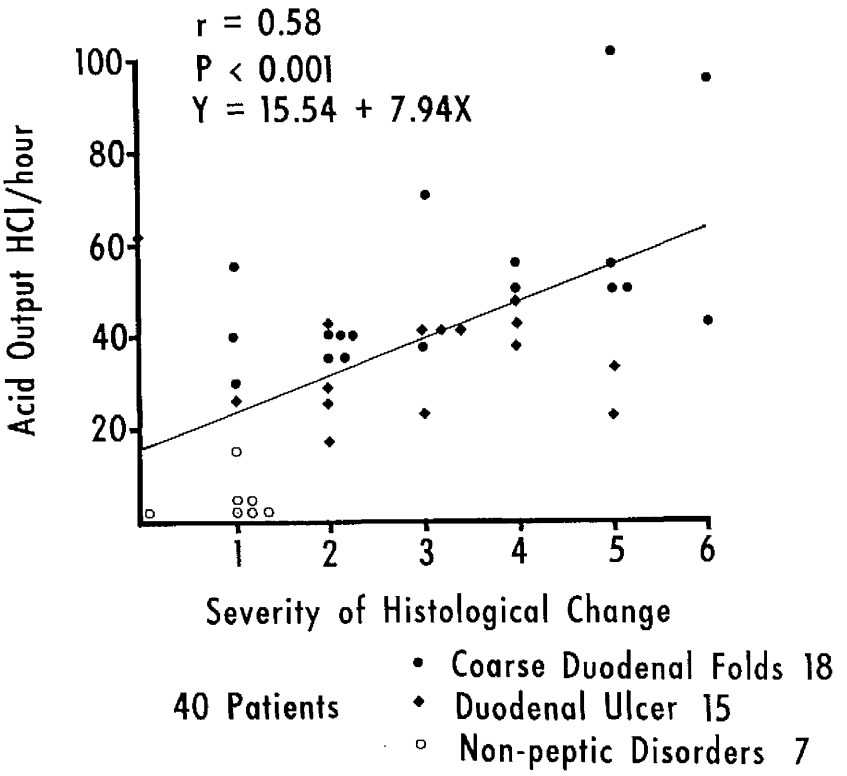


Figure 42: The correlation between acid output and severity of histological change in the duodenal mucosa in 40 patients [a composite group of coarse duodenal mucosal folds (18), duodenal ulcer (15) and non-peptic disorders (7)]. The histological changes were assessed in relation to stunting of villi, cellular infiltration and the appearance of 'gastric-type' epithelium.

hyperchlorhydria, duodenitis and duodenal ulcer (Ostrow & Resnick, 1959) and would justify in the individual patient a precise estimate of acid output. The finding of a high acid level and coarse folds should warrant the fullest investigation and follow up of the patient as being truly dyspeptic. Whether the actual changes within the duodenum are structural, as Stokes and others (1964) have suggested in relation to hypertrophy of Brunner's glands, or due only to spasm (Pitman, 1966), is not yet proved. It is of interest to speculate on the cause of the symptoms in duodenal ulcer, when precisely similar symptoms present with no ulcer, and whether, in fact, an overt ulcer is but one incident in a much more prolonged and more fundamental abnormality.

CHAPTER 9

ACID OUTPUT AND SYMPTOMATIC HIATUS HERNIA

The symptoms of hiatus hernia are probably due to the resulting reflux and oesophagitis. This was defined as a clinical entity, peptic oesophagitis, by Winkelstein in 1935. He described six patients with hiatus hernia, oesophagitis and dysphagia. Of these, three had duodenal ulcers, one a gastric ulcer, and five of the six had some degree of hyperchlorhydria. Since then there has been a recognised association between hiatus hernia and duodenal ulcer, from which it has been assumed that both conditions were due to hyperacidity. However, no studies have distinguished between hiatus hernia alone and combined with duodenal ulcer, and this section of the work was undertaken to demonstrate the acid secretory patterns in patients with symptomatic hiatus hernia with and without duodenal ulcer (Williams and others, 1967).

Historical

The reported association of duodenal ulcer with symptomatic hiatus hernia has varied widely from 32% of the 65 patients of Hoffman, Cruze and Byron (1959) to 80% of 20 patients reported by Winkelstein and others (1954). The various series most commonly quoted are shown

in Table 21. An inevitable degree of selection presumably influences these differing results, since the studies are of groups of patients who came arbitrarily to investigation or treatment. They were not designed to assess the incidence of hiatus hernia and duodenal ulcer in any particular population.

The emphasis in some of these reports is on the result of treatment, in particular treatment designed to reduce gastric acidity. Both Burge (1964) and Casten (1967) claim a high success rate for vagotomy in the treatment of symptomatic hiatus hernia, from which they infer that the condition is at least in part due to hyperacidity, though no data related to acid output are given. Various methods of estimating acid secretion have indicated some degree of hyperacidity. Winkelstein et al (1954) demonstrated hyperacidity in 17 of 20 patients, again using the fractional test meal and taking the upper limit of normal acidity arbitrarily as 40 clinical units.

Using 12 hour night secretion rates, Casten and others (1963) showed that patients with hiatus hernia with symptoms had higher acid output levels than patients without symptoms, and he therefore associates symptomatic hiatus hernia with 'hypersecretion'. However, his figures of

Table 21. The reported incidence of duodenal ulcer associated with symptomatic hiatus hernia.

Author	Symptomatic hiatus hernia No. of patients	Associated duodenal ulcer No. of patients	
Winkelstein (1935)	6	3	50%
Winkelstein et al (1954)	20	16	80%
Hoffman et al (1959)	65	21	32%
Casten et al (1963)	47	26	55%
Burge (1964)	20	7	35%
Casten (1967)	88	54	61%
Present series (1967)	43	9	21%

20 - 30 mEq HCl in 12 hours are not obviously in the duodenal ulcer range. Burge (1964) gives no figures of acid output in his patients. He recognises symptomatic hiatus hernia as being associated with hyperacidity, on account of the high association with peptic ulcer and pyloric channel disease, and on account of the symptomatic relief provided by vagotomy.

The three features, hiatus hernia, duodenal ulcer and high rates of gastric acid secretion, are to some extent related, but the precise relationship has not been defined.

Patients and Investigations

Forty-three patients have been studied over a period of three years. They have been selected only in so far as it was possible to carry out complete investigations. Their acid outputs are listed in Appendix Tables 5, 6 and 7. They all had symptoms due to hiatus hernia of the sliding type, namely epigastric or substernal pain, heartburn, occasional regurgitation or vomiting, and occasional dysphagia. No patient was severely ill or cachectic, and although in some there was a history of haematemasis, none was severely anaemic at the time of investigation. The diagnosis was established

by barium meal examinations carried out in the Department of Radiology, Cardiff Royal Infirmary. Twenty-four were men and 19 were women. Nine patients, all men, had in addition a duodenal ulcer. Histamine infusion tests were carried out on all patients. A control group was selected from the normal subjects, consisting of 15 men and 15 women of comparable age.

Results

The mean acid output for the 34 patients with hiatus hernia alone is 19.5 mEq/hour (S.E. $\pm$ 1.32). This is almost identical to the mean output in the control group of 19.9 mEq/hour (S.E. $\pm$ 1.13, $P > 0.7$). The 9 patients who had both hiatus hernia together with duodenal ulceration had a mean acid output of 39.0 mEq/hour (S.E. $\pm$ 2.92) being significantly greater than the normal mean, but not significantly different from the mean value in duodenal ulcer (Fig. 43). The comparison of these various acid values in hiatus hernia with those from the total groups of normal subjects and patients with duodenal ulcer, is given in Table 22.

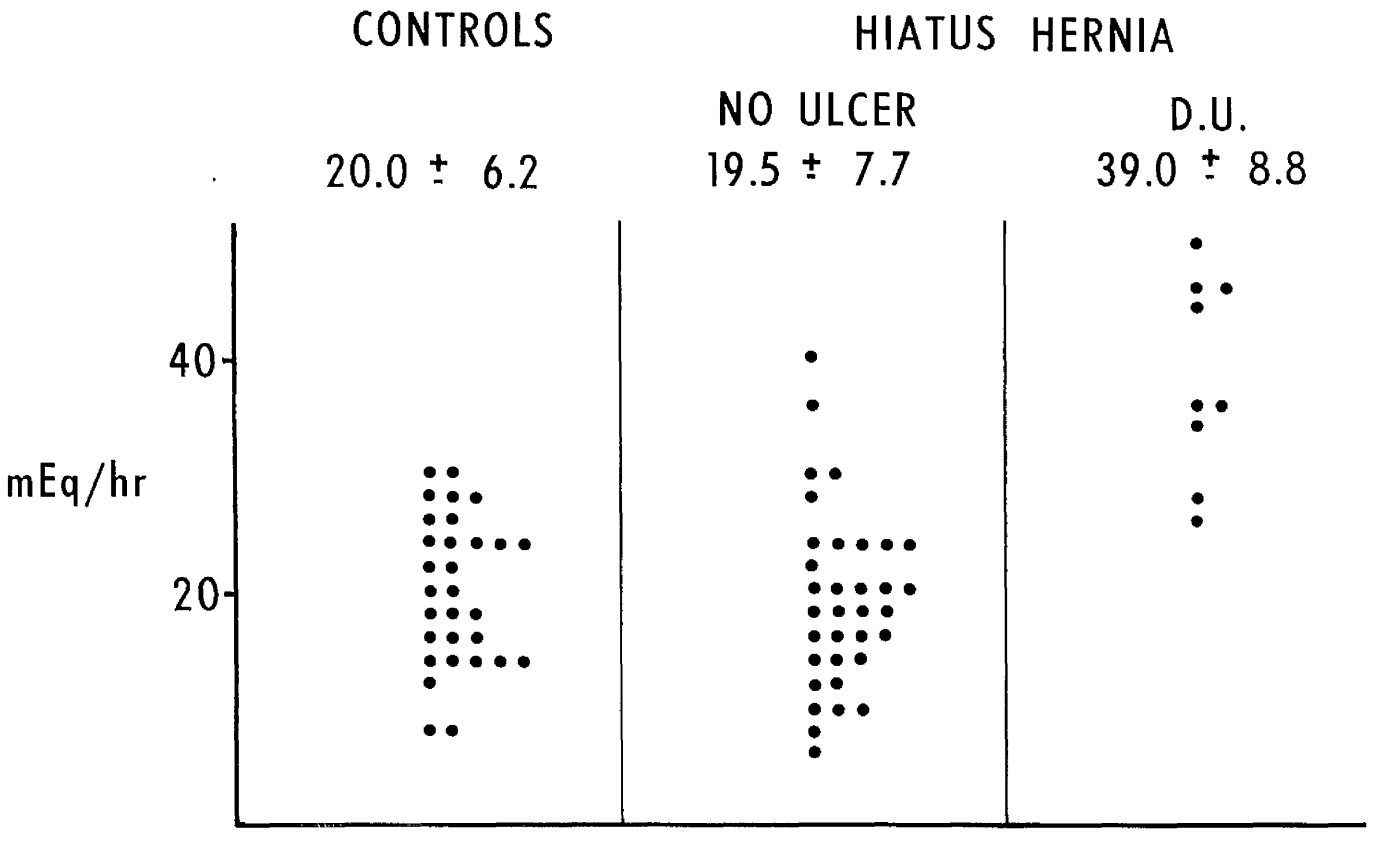
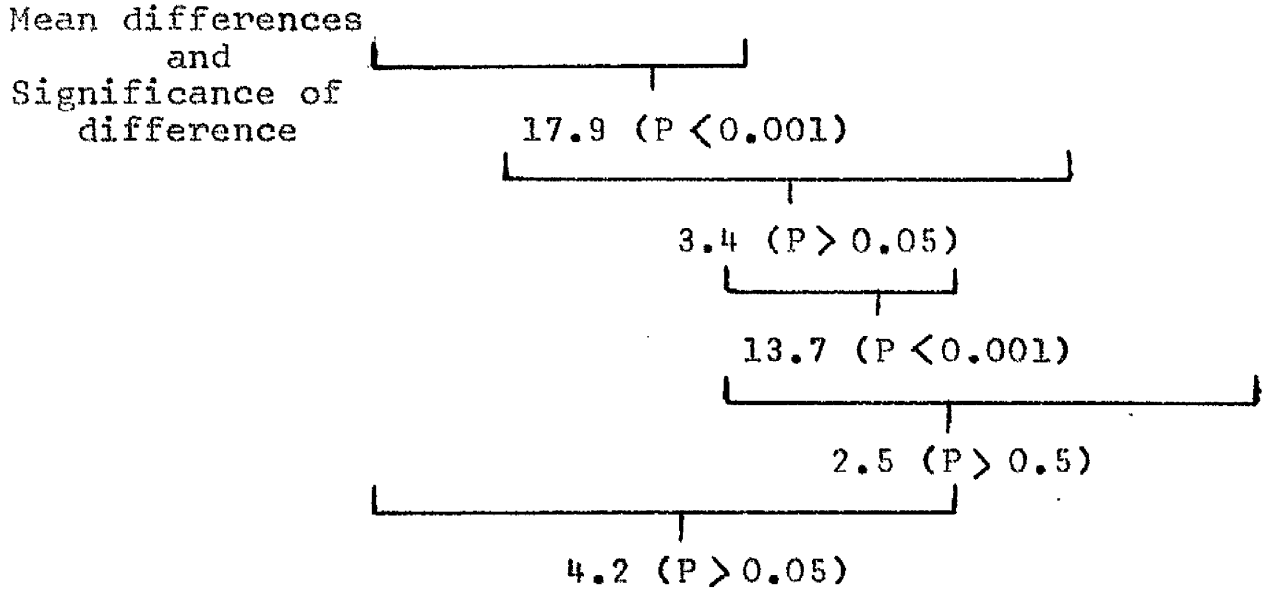


Figure 43: The mean acid output (± S.D.) in 34 patients with hiatus hernia alone, in 9 patients with hiatus hernia with duodenal ulcer, compared with a control group of 30 normal subjects.

Table 22. The means, standard deviations, mean differences and significance of the differences, in acid output in hiatus hernia with and without duodenal ulcer, compared with the output in normal subjects and patients with duodenal ulcer.

	Hiatus hernia alone		Hiatus hernia with duodenal ulcer	Normal		Duodenal ulcer
	Men	Women	Men	Men	Women	Men
Number of patients	15	19	9	54	50	237
Acid output	21.1	18.2	39.0	25.3	21.6	41.5
S.D. ±	8.2	7.2	8.8	7.6	6.9	12.8



Discussion

There is, to a certain extent, an association between symptomatic hiatus hernia, and duodenal ulcer, in that among such patients are many who could be called hypersecretors of gastric acid. However, the incidence of duodenal ulcer in this series is low, 9 of 43 (21%) compared with 32% reported by Hoffman and others (1959) and as high as 80% by Winkelstein and others (1954). This is best explained by accepting that many patients with both radiological lesions could have symptoms referable to either. A patient with a duodenal ulcer, with symptoms, who had an incidental hiatus hernia, might or might not be included in a series such as this, depending on the clinical evaluation of his symptoms.

The range of acid output in those patients with hiatus hernia alone was from 6.6 - 40.4 mEq/hour with a mean of 19.5 mEq/hour. These figures would be regarded as normal by most criteria, and are not significantly different from those of the control group chosen for this study. The acid output in the 9 patients with both hiatus hernia and duodenal ulcer ranged from 26.2 - 51.0 mEq/hour, the mean being 39.0 mEq/hour.

These figures are in the duodenal ulcer range and are indicative of 'hyperacidity'.

Of the individual patients, 9 had acid levels outside the control range, and could thus be described as hypersecretors. This is a much lower incidence than has been previously quoted, though exact figures are not available. Perhaps the best comparison would be with the 9 of 47 (19%) described by Casten and others (1963) who had 12 hour night secretion rates of more than 30 mEq. Hyperacidity and hyperchlorhydria as mentioned by Winkelstein and others (1954), Hoffman and others (1959) and Burge (1964) are in qualitative terms only and it is not possible to assess their figures. The present series all had similar symptoms clinically due to a sliding hiatus hernia, yet they clearly fall into two secretory groups, based on whether or not they have a coexisting duodenal ulcer. Those with a duodenal ulcer have a mean acid output in the duodenal range, while those without a duodenal ulcer have a mean acid output in the normal range. From this the validity of operations such as vagotomy and pyloroplasty (Burge, 1964) which are designed to lower gastric acidity, could be questioned. Good results are reported from such procedures (Casten, 1967) from which it is postulated that hypersecretory

states are being treated. In the present series this would apply only to a minority of the patients, the rest having a normal range of acid output. It may be that a lowering of gastric acidity from any level, even a normal level, may assist in the control of symptoms of hiatus hernia, but it would appear to be rational to recognise this by estimating as precisely as possible the acid output in all patients with hiatus hernia before any operative interference.

Summary: Acid and hiatus hernia

Symptomatic hiatus hernia alone, without duodenal ulceration, is associated with a normal acid output (19 mEq/hour). Patients who have both hiatus hernia and a duodenal ulcer have high acid secretion levels (39 mEq/hour) similar to those found in duodenal ulcer alone. The pattern of symptoms is identical in these two secretory groups.

CHAPTER 10

GASTRIC ACID AND IRON-DEFICIENCY ANAEMIA

Achlorhydria is associated with either pernicious anaemia or iron-deficiency anaemia, but whereas one is the predictable result of loss of the intrinsic factor from the gastric secretion, the other is related to loss of hydrochloric acid in only about half the patients affected (Beveridge and others, 1965). A good correlation has been shown by Badenoch and others (1957) between gastritis and achlorhydria, and evidence has been offered to support the alternative explanations that the achlorhydria may be either the result or the cause of the gastritis. Lack of gastric acid due to some degree of gastritis may lead to iron-deficiency anaemia either through occult blood loss (Bannerman and others, 1964) or through relative malabsorption of iron (Goldberg and others, 1963). Conversely, iron deficiency may interfere with the enzyme systems supporting the rapid cell turnover of the gastric mucosa, and the resulting disorganisation of cells may then induce the formation of auto-antibodies and aggravation of the gastritis (Adams and others, 1964).

Of the several methods available to assess the

integrity of the gastric mucosa, histology, radiology, endoscopy and secretory estimations, the ability of the stomach to secrete hydrochloric acid was considered by Tomenius (1957) to be the best single measure.

Critical investigation of this disorder, in which the incidence of achlorhydria is high and in which many subjects have low secretory rates, obviously requires an efficient and sustained gastric stimulant. The incidence of achlorhydria which is associated with this syndrome has varied with the stimulus used. Using fractional analysis or small doses of histamine, Witts (1966) originally reported an incidence of 40% but later, using the augmented histamine test, only 16% of his 70 patients had complete achlorhydria. It was thought reasonable to investigate a group of patients attending the haematology clinic with chronic iron-deficiency anaemia by means of the histamine-infusion test, to define precisely the nature of their acid secretion. In addition, as far as was practical, it was proposed that these patients should have their iron stores repleted by means of parenteral or oral iron and that after a stable period with restored haemoglobin levels, their acid output should be reassessed to discover any

possible change (Jacobs and others, 1966). Some improvement in acid secretion had been reported after treatment of the anaemia by Leonard (1954) and by Badenoch and others (1957) but Lees and Rosenthal (1958) could not confirm this in a group of patients studied one year after treatment of the anaemia.

Patients and clinical features

The total group initially investigated was 44 (42 women and 2 men). Their ages ranged from 14 - 78 years (mean 44.8). They had no evidence of pathological blood loss nor steatorrhoea. They all had chronic iron-deficiency anaemia, with haematological data as follows:

	Mean	Range
Haemoglobin (G/100 ml)	7.03	4.6 - 9.9
M.C.H.C. %	25.5	22 - 32
Serum-iron (µg/100 ml)	29	0 - 105
Total iron-binding capacity (µg/100 ml)	458	300 - 704
Saturation of iron-binding protein (%)	6.3	0 - 26

After estimation of acid output by the histamine-infusion test, they were treated with oral or parenteral iron. Three months to two years after they had become haematologically normal, the test was repeated.

Results

The distribution of acid output is shown (Fig. 44) in 31 of these patients, on whom the most reliable data are available and who had a repeat histamine-infusion test after treatment of anaemia.

Complete achlorhydria occurred in 5 (16%), normal acid levels were produced in 9 (30%) and abnormally low acid output was found in the remaining 17 (54%).

Within this last group of low acid secretors were 5 who had normal concentration of acid (53 - 109 mEq/litre) although their outputs were less than 5 mEq/hour.

The mean acid output for the group was 6.1 mEq/hour (0 - 26.9 mEq/hour) while the mean for those who produced measurable acid in any quantity was 7.9 mEq/hour (range 0.1 - 26.9 mEq/hour).

The results of the two tests on each patient before and after restoration of normal haemoglobin levels are shown in Figure 45. Seven had a significant increase in acid output (> 5 mEq/hour) while two had a further decrease. The majority, 22 (70%), showed no alteration in output.

All of the 13 patients who were achlorhydric or virtually so, remained at these low levels.

Six of the patients were under 30 years of age, and 4 of these increased their acid output, while only

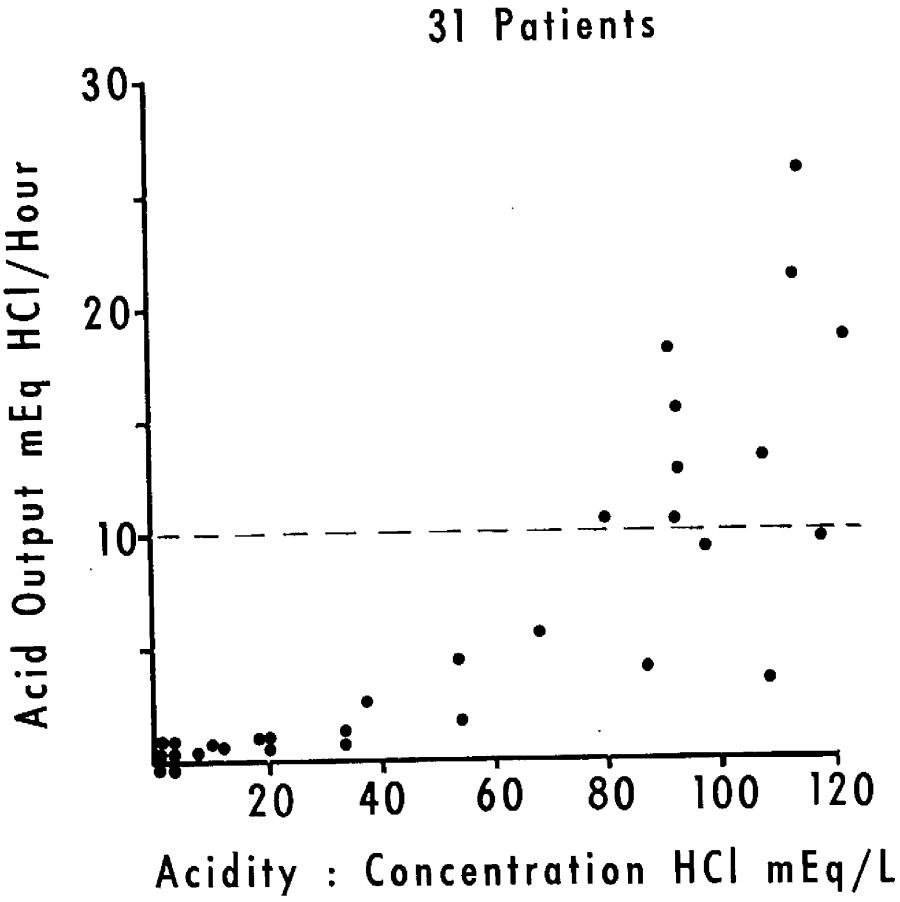


Figure 44: The distribution of acid values in 31 patients with chronic iron-deficiency anaemia, expressed in terms of output in mEq/hour and concentration in mEq/litre. The dotted line at 10 mEq/hour is an approximate indication of the lower limit of normal.

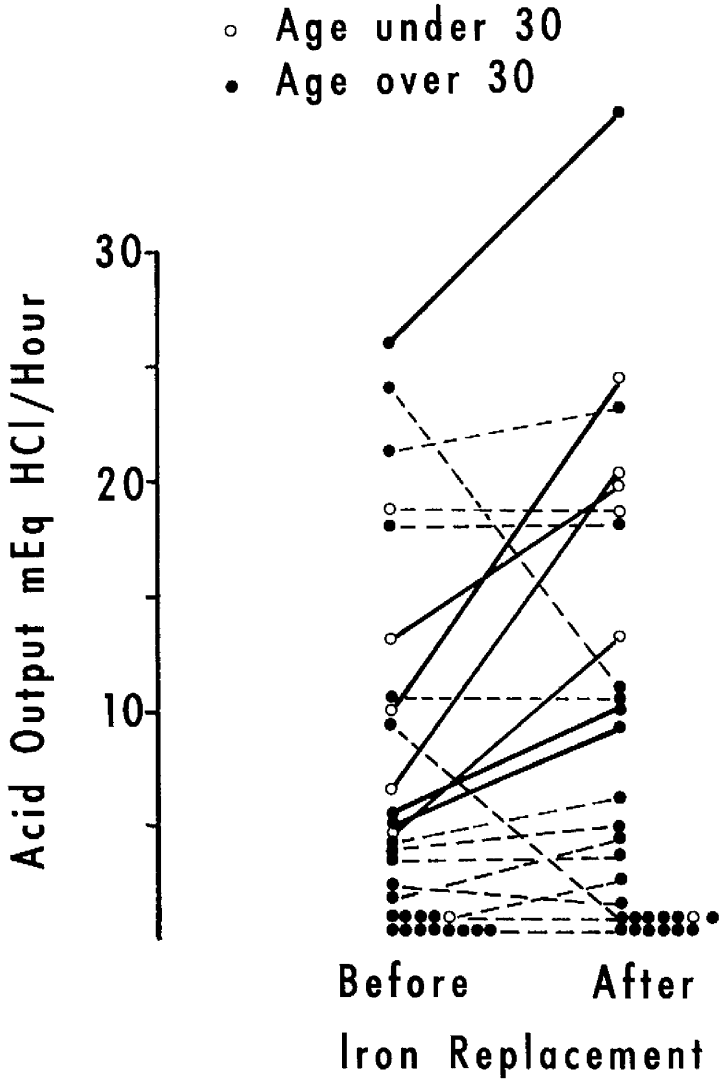


Figure 45: The acid output before and after treatment with iron in the 31 patients with iron deficiency anaemia. Solid lines indicate the 7 patients who had significant increase in acid output. Solid circles indicate the 25 patients over 30 years of age; open circles the 6 under 30 years of age.

3 of the 25 who were over 30 years of age did so.

Discussion

Although the patients in this group are highly selected and were almost all women, the chronic iron-deficiency which they exhibited corresponds with that of similar studies by Beveridge and others (1965). Although no overt blood loss nor malabsorption was demonstrable it is likely that a relative disparity between intake and requirements of iron had existed for some time in these patients, since Jacobs and Butler (1965) investigating the same population have demonstrated the contributory effects of excessive menstrual loss and inadequate diet in anaemia. It is thus difficult in such a population to distinguish primary from secondary gastric atrophy.

A consideration of the ages and acid output in Figure 45 shows that the younger patients had normal or low normal values and, in addition, were able to improve their acid secretion after treatment with iron. The older patients, on the other hand, were largely hypo-secretors or achlorhydric and their condition in general appeared resistant to treatment. Children with 'secondary' reduction in gastric secretion due to anaemia were shown

by Naiman and others (1964) to be capable of recovery, while no improvement was found in the older subjects of Lees and Rosenthal (1958).

The distribution of acid values within this group appears different from the other low secretory groups, gastric ulcer and gastric cancer. A large number of the anaemic patients are truly achlorhydric, while there was a definite measurable acid output of 2 - 3 mEq/hour even in the lowest ranges in gastric ulcer. Though apparently comparable with gastric cancer, the acidity in anaemia is again different, particularly in including a large number of subjects with very low output, yet of more or less normal concentration. The numbers are inadequate to justify arbitrary grouping, yet there appear to be two groups in terms of output, one normal and one achlorhydric and low, with a more continuous distribution of concentration values throughout the range 0 - 123 mEq/litre.

It remains a matter for speculation whether reversibility of hypochlorhydria is confined to the low secretors, that is those still capable of producing even a small volume of gastric acid of normal concentration.

The evidence afforded by the repeated tests, though again of limited validity in such small numbers,

and in consideration of the coefficient of variation of the test, nevertheless would support the suggestion that potential recovery is confined to the hyposecretors, the other groups - the normal and the achlorhydric - showing no change.

Summary: Gastric acid and iron-deficiency anaemia

Histamine-infusion tests were carried out on 31 patients with chronic iron-deficiency anaemia. Achlorhydria was found in 5 (16%), normal acid output in 9, and the remaining 17 (54%) had abnormally low but measurable acidity. After treatment with iron and restoration of haemoglobin to normal the tests were repeated. An improvement in acid output was found in 7 patients, and these were the younger subjects, under 30 years of age, who had initially a low acidity. Older patients and achlorhydric patients appeared to be resistant to change.

CHAPTER 11

ACID OUTPUT AND JAUNDICE

Acid output may be reduced in cirrhotic liver disease (Ostrow and others, 1960; Scobie & Summerskill, 1964). No accepted reason has been offered for this. In certain conditions of liver disease, the opposite condition of hyperacidity may arise, as Fischer and Snyder (1965) have shown in rats with portacaval shunts. Alteration in acid output appears to bear no relationship to the degree of liver damage, this being notoriously difficult to assess.

Interest in this subject arose when a few patients with jaundice were discovered to be achlorhydric for no other obvious reason. No information was available in the literature on acid output in relation to jaundice, and the present study was undertaken to explore the value of an estimation of maximal acid output by the histamine-infusion test in differentiation of hepatic from post-hepatic jaundice.

Patients and methods

Acid output was estimated in 42 patients (29 men and 13 women) being investigated for jaundice. Their ages ranged from 20 to 77 years (mean age 57). Liver function was assessed by routine clinical laboratory estimations of bilirubin, serum total protein, serum albumin and alkaline phosphatase. In 36 patients the

serum sodium and potassium were determined.

The clinical diagnoses are shown in Table 23, and of these 25 were confirmed at laparotomy. The results were compared with a control group of 15 men and 10 women, selected from the total normal group to be of comparable age.

Results

The acid output in the total group of jaundiced patients, subdivided into main pathological groups, and compared with the control group, is shown in Table 24 and Figure 46. The mean acid output in the whole group of jaundiced patients was 10.8 mEq/hour compared with 20 mEq/hour in the control group. Eighteen of the patients with jaundice (43%) were achlorhydric.

The patients with jaundice were subdivided into various diagnostic and pathological groups, and the acid output calculated for each group. No significant difference was found within these groups.

The coefficients of correlation were calculated for acid output and age, body weight, duration of jaundice, bilirubin, protein, alkaline phosphatase, sodium and potassium (Williams and others, 1968) and no significant relationship was found between any of

Table 23. Diagnosis of type of jaundice in the 42 patients.

Diagnosis	No.	Total
Haemolytic jaundice		
Sickle-cell anaemia	1	
Hereditary spherocytosis	1	2
Hepatocellular jaundice		
Infective hepatitis	4	
Portal cirrhosis	3	
Subacute hepatic cirrhosis	1	8
Hepatic cholestatic jaundice		
Intrahepatic cholestasis	5	
Drug toxicity	3	
Cholangitis	3	
Metastatic	1	12
Post-hepatic cholestatic jaundice		
Carcinoma of pancreas	9	
Gallstone obstruction	6	
Metastatic obstruction	4	
Ampullary carcinoma	1	20
		42

Table 24. Acid output in patients with jaundice. (Significance of differences from normal shown. None of the differences within the groups was significant).

Group	No.	Acid output mEq/hour Mean	± S.E.	P
Jaundice (all patients)	42	10.8	2.92	<0.01
Controls	25	20.0	1.23	
Haemolytic	2	20.4	-	
'Hepatic' (hepatocellular + intrahepatic cholestasis)	20	8.6	2.74	<0.001
Post-hepatic (extrahepatic cholestasis)	20	12.0	3.28	<0.01
Hepatocellular	8	11.5	5.50	<0.05
Cholestatic	32	10.5	2.51	<0.01

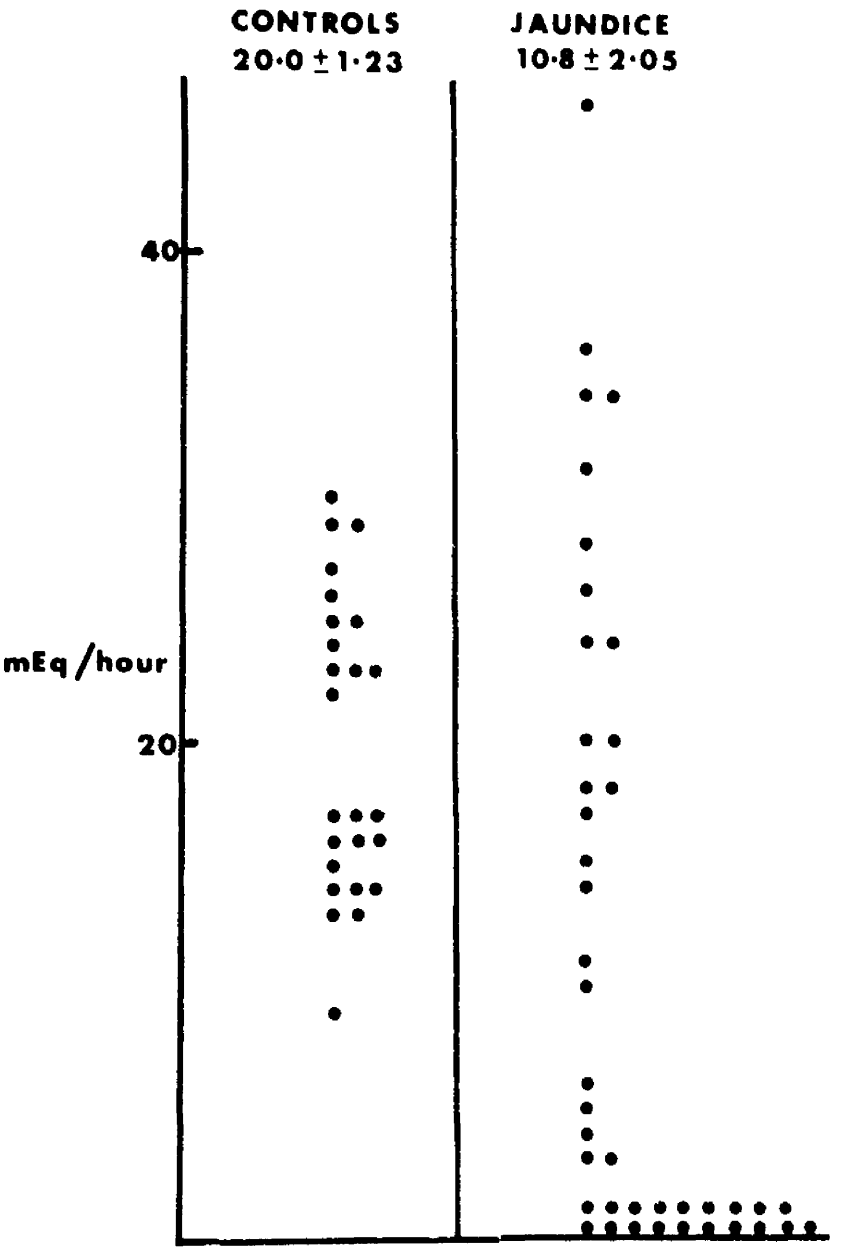


Figure 46: Distribution of acid output in 42 patients with jaundice (all types) compared with 25 control subjects.

these factors except age. Acid output diminished with increasing age ($P < 0.001$).

The jaundiced patients were then divided into two groups, those who secreted acid in any quantity and those who were achlorhydric, and the same correlations calculated. Again there was no significant relationship between acid and any of the above factors, except age, in either group.

Discussion

Acid output is significantly decreased in jaundice, regardless of the classification of the diagnosis on clinical, biochemical or pathological grounds. The classification adopted here is open to criticism, but in view of the many methods of subdivision attempted and the failure to show any difference in acid output within any of these groups, it seems reasonable to deduce that there is some factor common to all groups which is involved in gastric acid secretion and which may be abnormal in all types of jaundice. Such a factor is, at present, not known. In a large study of portal cirrhosis, Tabaqchali and Dawson (1961) found mostly normal acid output, a few hypersecretors, and none achlorhydric, but jaundice was not mentioned specifically.

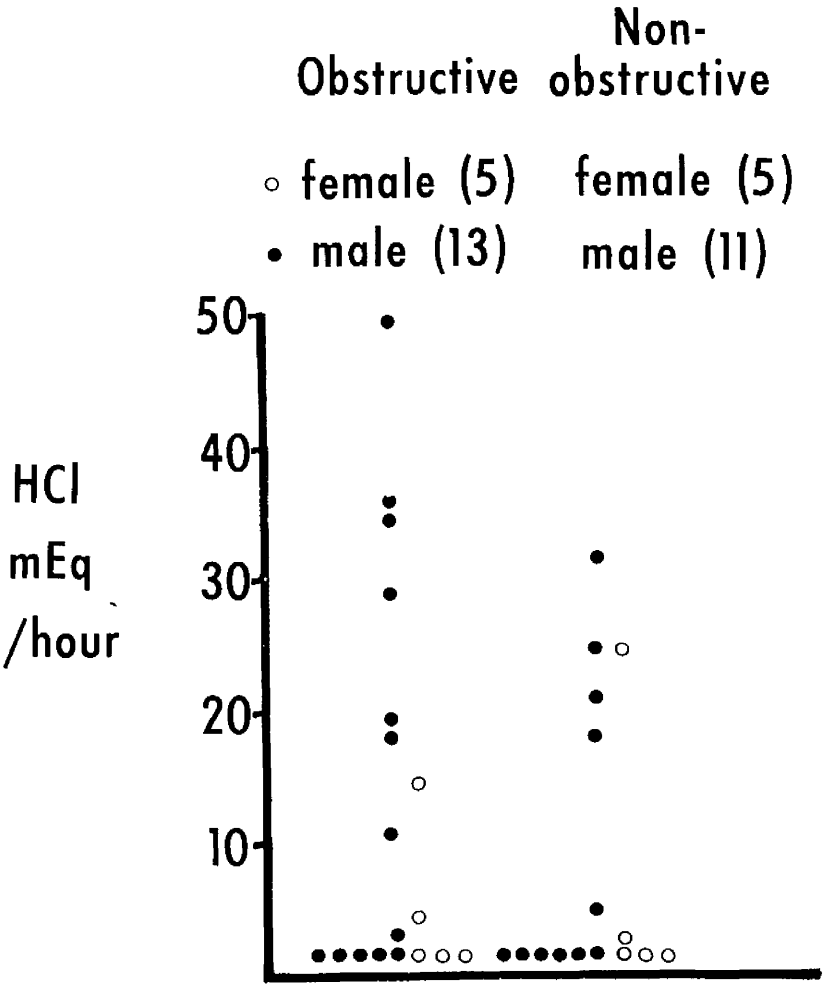


Figure 47: The acid output in the 34 patients with jaundice who could be crudely classified into 'obstructive' and 'non-obstructive' types of jaundice.

This decrease in mean acid output derives from two alterations from the normal group. One is the high incidence of achlorhydria, almost half the patients producing no acid. An attempt was made to subdivide 34 of these patients crudely into 'obstructive' and 'non-obstructive' types of jaundice to discover any possible pattern in acid secretion (Fig. 47). It can be seen that the incidence of achlorhydria is still similar in each group and in both sexes.

In addition to the high incidence of achlorhydria in the total group, which would by itself significantly reduce the mean value, the range of acid output values includes many which are abnormally low, values of 0.3, 0.7, 1.2, 2.5 and 4.4 mEq/hour occurring in the 'post-hepatic' group, and 0.3, 0.6, 3.3, 4.9 and 5.5 mEq/hour in the 'hepatic' group.

The significance of this is obscure. The marked resemblance of the acid output in jaundice to that in iron-deficiency anaemia is a matter for speculation. The mean value, the range, the incidence of achlorhydria and acidity at low levels are all remarkably similar. This observation appears to be new and worthy of further study.

CHAPTER 12

HISTAMINE AND PENTAGASTRIN (I.C.I. 50, 123)

A COMPARISON OF INFUSION TESTS

Since the extraction of pure gastrin and the demonstration of its effect as a gastric acid stimulant by Gregory and Tracy (1964) and Makhlouf and others (1964), there has developed wide interest in synthetic derivatives of gastrin as possible substitutes for histamine in gastric analysis. Through the interest of Dr. J. D. Fitzgerald and the resources of I.C.I. Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, England, the pentapeptide of gastrin, 'Pentagastrin' I.C.I. 50, 123, has become available for the investigation of patients.

Of the 17 aminoacids forming the polypeptide gastrin, only four, at the carboxyl end of the molecule, are necessary for its biological activity and these four aminoacids, tryptophane, methionine, phenylalanine and aspartic acid, are included in the pentapeptide 'pentagastrin' (N-t-butyl-oxycarbonyl-β Ala-Tryp-Met-Asp-Phe-NH_2).

The final section of this thesis is an attempt to assess pentagastrin as a stimulant of gastric acid in conditions precisely comparable with those obtaining over the past four years for the histamine tests.

Part of this work formed the Cardiff contribution to the Multicentre Pilot Study on Pentagastrin (1967).

Patients and methods

Dose-response relationship

Three patients had four pentagastrin infusion tests using increasing doses of pentagastrin. The dose rates used were 2.5, 5, 10 and 20 µg/kg/hour. The four plateaux of output resulting from these infusions in one patient are shown in Figure 48, together with the response to a single subcutaneous injection of 5 µg/kg on a fifth day on this same patient. The results of the four tests on these three patients were as follows:

Subject	Acid output mEq/hour in response to pentagastrin at dose rate (µg/kg/hour) of:			
	2.5	5	10	20
M.B.	26.2	38.0	32.2	33.3
B.H.	19.4	38.7	25.8	28.5
M.N.	52.4	59.0	57.0	35.9
Mean	32.7	45.2	38.3	32.6

These results were not analysed statistically. It was accepted that 5 µg/kg/hour would be a maximal stimulus. It was, in addition, realised that these were

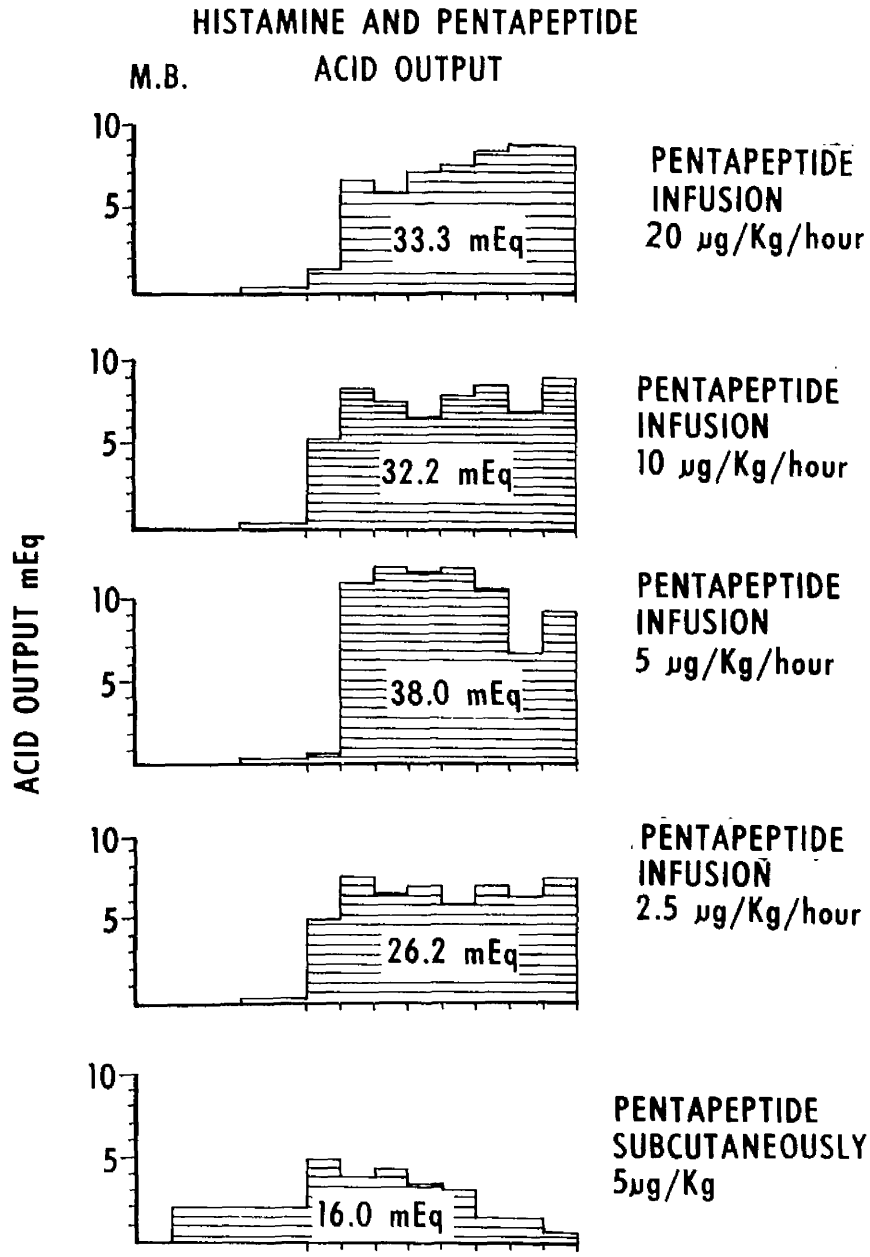


Figure 48: Acid output in one patient from 4 separate pentagastrin infusions at dose rates of 2.5, 5, 10 and 20 µg/kg/hour, together with the output resulting from a single injection of 5 µg/kg subcutaneously.

all high doses for pentagastrin and that near maximal responses might result from a dose of 0.6 µg/kg/hour from the studies of Wormsley and others (1966).

Accordingly, five patients submitted to three tests each, using the very small doses, 0.1 and 0.5 µg/kg/hour with a third test using 5 µg/kg/hour. The results are shown in Table 25. The mean acid outputs for the small doses of pentagastrin 0.1 and 0.5 µg/kg/hour are 24.2 and 29.2 mEq/hour respectively, while the dose of 5 µg/kg/hour gave again the highest mean output of 42.9 mEq/hour.

From this it was apparent that certain patients did respond to small doses of pentagastrin with a near maximal acid output, but over this group of patients, the dose rate of 5 µg/kg/hour produced again the highest mean response.

An analysis was therefore made of acid output in 5 patients using 3 infusions at doses around this apparent maximum of 5 µg/kg/hour, the other two dose rates being 2.5 and 10 µg/kg/hour. The 5 dose-response relationships, with the mean output for the 3 doses, is shown in Figure 49 and in

Table 25. The acid output in 5 patients in response to pentagastrin infusions at three different dose rates on three different occasions, 0.1, 0.5 and 5 μg/kg/hour, with the means for each dose rate.

Subject	Diagnosis	Acid output mEq/hour in response to pentagastrin in the doses (μg/kg/hour)		
		0.1	0.5	5
E.G.	Pyloric ulcer	13.0	6.5	16.6
E.B.	Duodenal ulcer	39.4	40.3	45.6
C.J.	Zollinger-Ellison	58.6	75.6	121.6
V.G.	Gastric ulcer	1.3	12.9	13.4
H.M.	Duodenal ulcer	8.6	10.8	17.6
	Mean	24.2	29.2	42.9

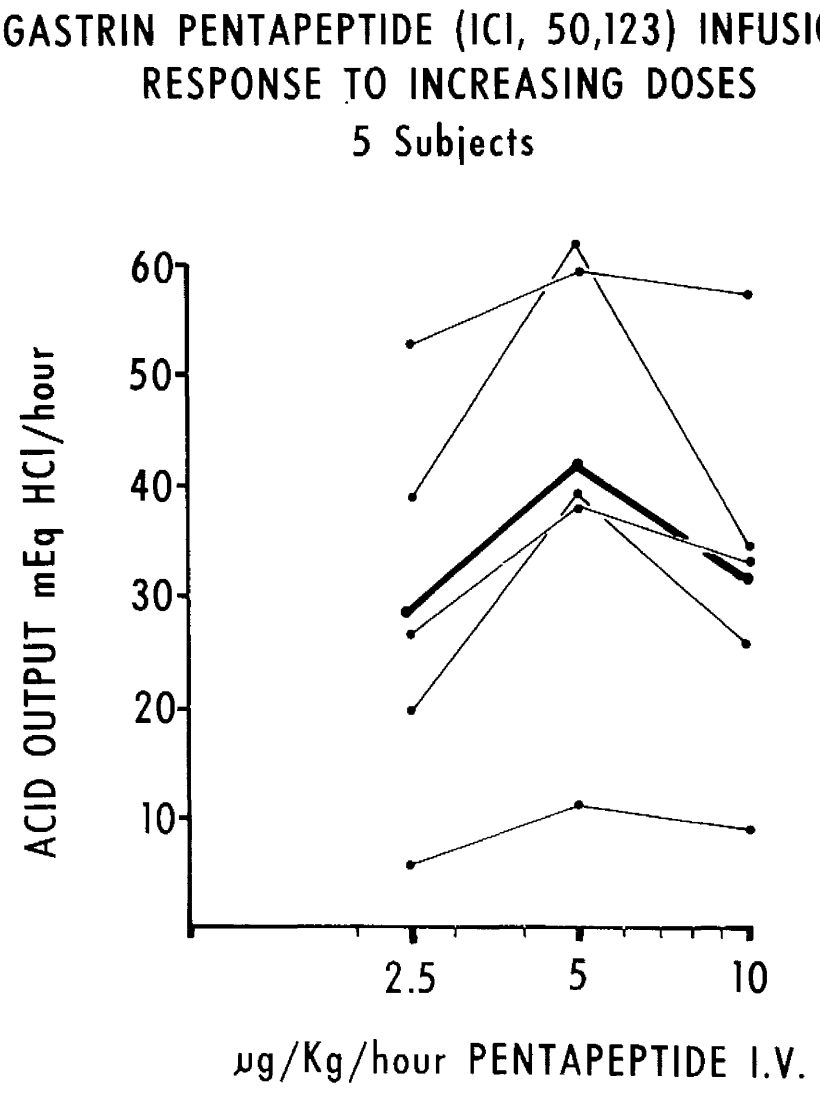


Figure 49: The acid output by 3 pentagastrin infusion tests in each of 5 patients. The dose rates used were 2.5, 5 and 10 µg/kg/hour, and these are shown on the abscissa as a logarithmic scale. The means for the 5 patients are shown by the heavy line.

the following table:

Pentagastrin dose rate µg/kg/hour	Mean acid output mEq/hour	Mean diff. ± S.E.	P
2.5	28.3	13.4 ± 3.5	<0.02
5	41.7	10.1 ± 3.8	>0.05
10	31.6		

The mean output from the dose rate of 5 µg/kg/hour is significantly higher than that from 2.5 µg/kg/hour, and also higher, though not significantly so, than that resulting from doubling the dose rate to 10 µg/kg/hour.

Results

In order to compare pentagastrin with histamine it was therefore decided to use a dose rate of 5 µg/kg/hour pentagastrin, to compare with the dose rate of histamine acid phosphate of 40 µg/kg/hour, both as continuous infusion tests, both under identical conditions of infusion, of collection and of titration.

Forty-three patients and normal subjects had both tests carried out in random order. The mean output by histamine was 31.5 mEq/hour, and by pentagastrin 30.2 mEq/hour. There is no significant difference between these means ($P > 0.7 < 0.8$).

The distribution of these results and the correlation between the two tests is shown in Figure 50. The coefficient of correlation is 0.939 ($P < 0.001$).

Side effects

Of the 84 tests in which an attempt was made to assess the side effects, there was a spontaneous complaint of headache in 14, and of nausea in 20. These symptoms were distributed throughout the various dose rates, though they could be induced by any interference with the infusion whereby a small excess of pentagastrin might be injected rapidly into the vein. The main side effects which the patients had difficulty in describing, but which impressed the author from personal experience, are those quoted by Rødbro and Køster (1967) as 'a sinking feeling, with abdominal cramps, nausea, faintness, headache and general malaise', and may be related to the effect of pentagastrin on intestinal motility (Connell & Logan, 1967).

Discussion

Pentagastrin and histamine infusions appear to give comparable and maximal acid responses when given at dose rates of 5 and 40 µg/kg/hour respectively. Whether there is a particularly critical level for the maximal stimulant, or whether there is a wide range

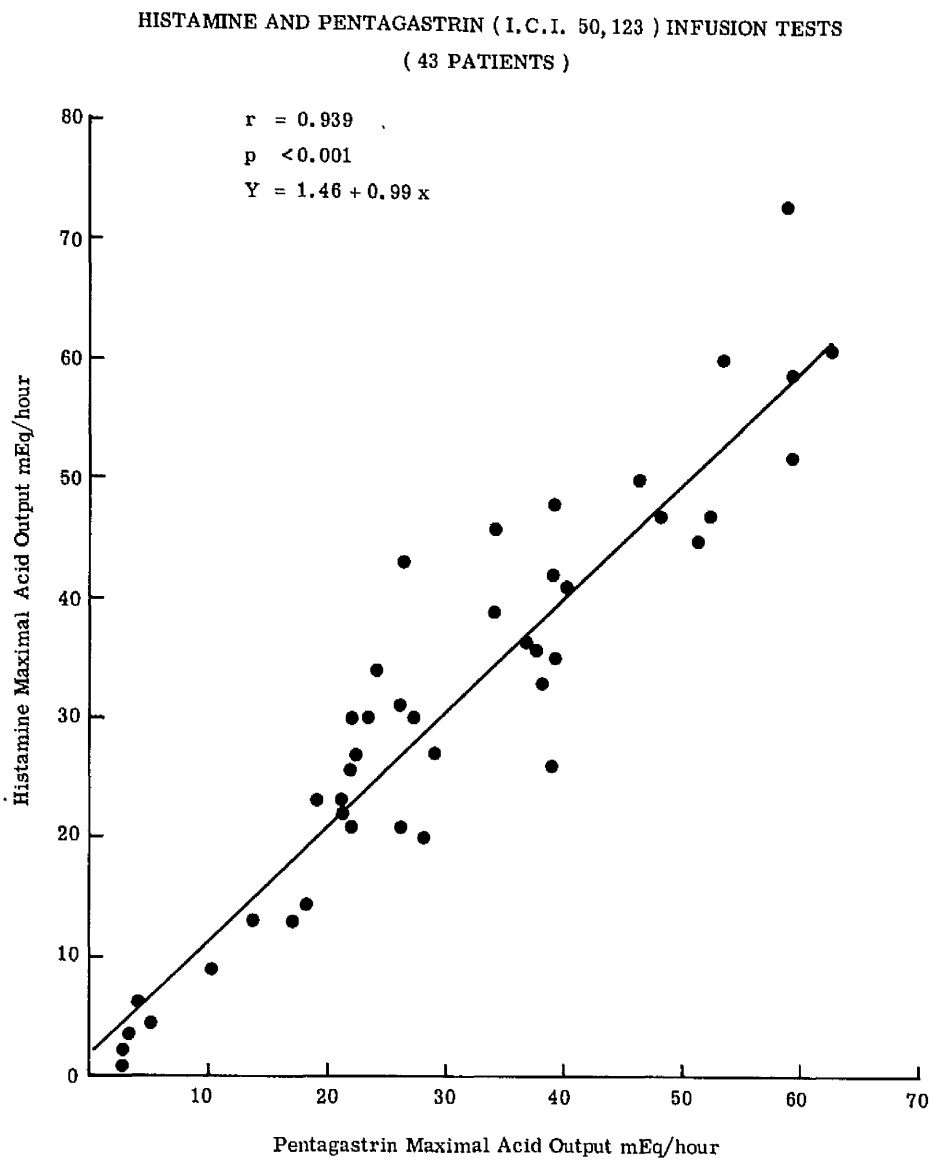


Figure 50: The correlation between maximal acid output by pentagastrin infusion (5 µg/kg/hour) and by histamine infusion (40 µg/kg/hour) in 43 patients, having the two tests carried out on different days and in random order.

of doses all of which may result in near maximal responses, is a possible deduction from the small numbers of patients in this present series. This might also explain the variety of doses from 1.5 (Konturek & Lankosz, 1967) to 6 µg/kg/hour (Aagard & Schmidt, 1967) which are claimed to elicit maximal acid responses.

Interpretation of results, however, is still obscured by different techniques. The advantages in precision afforded by an infusion seem to some extent lost when the result is calculated by extrapolation from the four best 5-minute periods, the method quoted in the above study by Konturek and Lankosz. It is likely that, given the same method, similar results will be obtained by several synthetic gastrins (Jepson and others, 1968).

Of possible relevance to routine testing is the observation of Konturek and Olesky (1967) that, although both histamine and pentagastrin will each produce an apparent maximal response, together they result in an even higher output due to a true potentiating effect.

Whether pentagastrin is 'at present the most

innocuous and most potent drug' (Wormsley, 1968) for tests of gastric acid, is difficult to substantiate. Several of our patients preferred histamine after experience of both. All were to some extent miserable. Injections and intubations are unpleasant and it would seem to be our duty, rather than define minor variations in misery, to strive to make the results of all investigations more worthwhile than they appear to be at present.

SUMMARY

The history of the evolution of tests for gastric acid secretion has been reviewed (Chapter 1), taking particular note of the changing fashions in the form of tests, the slow development of increasingly precise methods of measurement, and the continuing difficulty in deriving substantial information from the results. In this context, the value of the steady state of maximal acid secretion induced by an infusion of histamine, had been acknowledged in experimental work, but had been exploited only to a limited extent in studies in man.

Using a slow injection pump and disposable sterile equipment, a technique was evolved whereby this method of stimulation could be used to study large numbers of patients and control subjects.

Dose-response curves were determined, and from these the dose-rate of 0.04 mg histamine acid phosphate per kg body weight per hour was shown to elicit a maximal acid response. Using this dose-rate throughout, the responses were calculated to consist of a valid plateau of output, to have an acceptable reproducibility in duplicate tests, and to be consistently greater than any of the established methods of calculating the

'augmented' histamine response (Chapter 2). The test was, to some extent, self-checking, and radiological monitoring of nasogastric tube position could be obviated. Side effects were tolerable and transient. Many subjects were studied satisfactorily as out-patients.

Normal standards were determined (Chapter 3) for volume, concentration and output of acid in 54 men and 50 women. The mean output for the men, 25.3 mEq/hour, was significantly higher than that for the women, 21.7 mEq/hour. This difference was due only to the larger volumes of gastric acid secreted by men, the concentration of acid being similar in both men and women (108.4 and 110.4 mEq/litre respectively). Output declined with age in men, but not in women. There was no relationship with body weight in either men or women. The range of acid output appeared to be similar for both sexes, i.e. 9.5 - 42 and 9.7 - 47.1 mEq/hour in men and women respectively and the possible pathological significance of values outwith these ranges is discussed.

These methods and standards were applied to the study of various peptic disorders (Chapters 4 - 9). The mean acid output in 237 men with duodenal ulcer was 41.5 mEq/hour (range 19.3 - 103) and in 35 women, 31.2 mEq/hour (range 17.6 - 73.3). In both men and

women patients the volume, concentration and output of acid were all significantly greater than normal. Within the duodenal ulcer group, however, the higher male output was due only to larger volumes of gastric acid of concentration similar to that in women (121.9 and 120.3 mEq/litre respectively). In the group of patients with benign gastric ulcer (Chapter 5) the mean output in men was 21.4 mEq/hour (2.1 - 41.2) and in women 13.5 mEq/hour (4.5 - 26.8). No patient was achlorhydric, and none was above the normal range. There was no clear relationship between acid output and the site of the ulcer.

Of the patients with gastric cancer (Chapter 6) one-third were achlorhydric, while those who did secrete acid had a wide variation in concentration, from 13 - 130 mEq/litre. Acid output increased with more distally situated tumours. Prepyloric ulcers were largely associated with a normal acid output (Chapter 7).

The syndrome of dyspepsia without ulcer, and with the radiological appearance of coarse mucosal folds in the duodenum (Chapter 8) was associated with a high mean acid output of 44.3 mEq/hour. The acid levels were related to the severity of the radiological change, and

to the histological changes in the duodenal mucosa, in particular to the incidence of 'gastric-type' epithelium.

Symptomatic hiatus hernia (Chapter 9) alone, without duodenal ulceration, was associated with a normal acid output (19 mEq/hour). Patients who had both hiatus hernia and a duodenal ulcer had high acid secretion levels (39 mEq/hour) similar to those found in duodenal ulcer alone.

In a group of 31 patients with chronic iron-deficiency anaemia (Chapter 10) 5 were achlorhydric, 9 had a normal acid output, and 17 (54%) had abnormally low though measurable acidity. After treatment with iron 7 of the younger patients who had previously some acid secretion, showed an improvement in acid output. Older patients and those already achlorhydric showed no change.

In patients with jaundice (Chapter 11), regardless of the diagnosis, almost one-half were achlorhydric, and no correlation was found between acid output and any of the factors customarily associated with liver function. As in the previous group, there were many subjects who secreted very low but measurable amounts of acid.

Finally, an attempt was made to assess the synthetic pentapeptide of gastrin (I.C.I. 50,123)

(Chapter 12) in conditions precisely comparable with those obtaining for the histamine-infusion tests. Dose-response relationships showed that 5 μg/kg/hour by infusion elicited a maximal response, and this dose-rate was used to compare with the standard histamine-infusion test using 40 μg/kg/hour, in a series of 43 subjects. The mean acid output by histamine was 31.5 mEq/hour and by pentagastrin 30.2 mEq/hour. The coefficient of correlation between the two responses ($r = 0.939$) was highly significant.

ACKNOWLEDGEMENTS

The author has pleasure in recording his gratitude to Professor A. P. M. Forrest for the good years and great privilege of associating in the work of the Surgical Unit in Cardiff, of which this thesis is a small part. The inception and establishment of the Gastric Laboratory, from small resources, from which this study developed, were due to his interest, and throughout he has assisted actively in the preparation of the material for presentation to journals and societies.

During the period covered by this work, the author held appointments in the Royal Infirmary, Cardiff, and the Welsh National School of Medicine, and during 1964 was in receipt of a full-time grant from the Medical Research Council.

The study would have been impossible without the cheerful co-operation of the patients, staff and students who submitted so willingly to these tests, many having repeated investigations.

Mr. A. S. Aldis, Mr. Robert Shields and other consultant surgeons and physicians of the United Cardiff Hospitals kindly assisted by referring patients for investigation.

Other members of medical staff provided expert knowledge on special aspects of the subject and were co-authors of publications, in particular Dr. G. Martin Fraser, Dr. Allan Jacobs, Surgeon Commander James Kirkpatrick, Dr. John Rhodes, Mr. George M. R. Smith and Mr. C. Barrie Williams.

Translations from the Latin and German literature were provided by Dr. John Percival (Classics) and Mr. Alfredo Wang (Music) of University College, Cardiff.

Dr. Hubert Campbell and Dr. T. Khosla made themselves frequently accessible for discussions on statistical problems, and Miss Margaret Davies assisted in many of the calculations.

Mr. Harry Kincaid, Chief Technician to the Surgical Unit, provided invaluable supervision of the equipment and running of the Gastric Laboratory. Mrs. Glenys Davies, Mrs. Ursula Jones, Miss Lynda Moseley and Miss Gwenda Roberts assisted in carrying out the vast numbers of tests with kindness and accuracy.

The illustrations, diagrams and photographs were prepared in the Department of Medical Illustration, and the author acknowledges his debt to the Director, Mr. Ralph Marshall, Miss Gillian Eastoe and Miss Denise Griffiths for their expert advice and carefully executed work.

The typing of this thesis, its drafts and the many papers relating to it, have been the work of Miss Phyllis Robson, to whom the author is indebted for much patient co-operation.

Finally, the author acknowledges the sympathy and help of Dr. Hanne Elisabeth Lawrie who translated articles, complied lists of patients and results, and tolerated much disruption of her own life in the completion of this work.

A P P E N D I X

In the following tables age is in years, body weight in kilograms, volume in millilitres per hour, concentration in milliequivalents per litre and output in milliequivalents per hour.

Appendix Table 1

NORMAL SUBJECTS - 54 MEN

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
H.A.	30	57	243	120	26.9
S.A.	51	64	191	125	22.6
T.A.	33	54	253	86	19.5
C.B.	41	77	283	102	22.6
H.B.	23	81	260	132	32.6
R.B.	45	69	230	132	29.5
P.B.	58	56	283	74	16.3
J.B.	42	81	241	106	24.8
R.C.	41	67	286	110	30.3
H.C.	38	77	235	96	21.0
A.D.	23	75	252	106	24.9
R.D.	21	70	407	100	42.0
E.E.	56	76	145	75	10.2
B.E.	36	66	250	75	17.4
G.E.	22	58	295	100	28.4
J.F.	38	70	322	119	36.4
B.F.	30	81	265	135	30.0
G.G.	29	60	254	124	29.0
C.H.	25	72	144	96	14.5
C.H.	45	78	273	120	30.7
B.H.	34	63	305	123	36.3
I.H.	53	58	148	128	17.8
R.J.	20	78	225	119	23.1
D.J.	36	82	213	115	20.2
C.J.	30	75	219	116	24.9
A.K.	44	61	192	103	19.8
B.K.	19	63	237	116	26.0
J.L.	38	78	242	113	25.0
L.L.	14	50	245	100	20.9

Normal Subjects - 54 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
G.L.	24	77	382	120	37.6
T.L.	22	61	261	120	33.6
J.L.	22	70	283	118	29.4
H.M.	48	63	141	103	13.2
A.M.	68	42	203	87	17.0
A.M.	32	58	243	106	25.5
J.M.	32	85	292	100	27.7
R.P.	35	59	331	99	31.0
W.R.	47	64	221	128	24.4
H.R.	23	64	202	123	24.7
J.R.	28	81	240	124	28.9
C.R.	16	60	261	80	20.4
R.S.	32	59	142	84	9.5
A.T.	56	70	215	78	13.9
I.T.	22	67	278	126	32.7
R.T.	22	73	279	131	35.3
L.V.	23	82	440	73	28.6
T.V.	35	50	316	106	26.1
B.V.	22	64	211	80	15.4
F.W.	39	60	227	108	23.1
G.W.	26	72	131	113	12.9
C.W.	22	69	272	123	35.9
J.W.	22	78	255	105	25.1
A.W.	23	78	356	122	41.3
R.W.	75	85	227	133	28.1

Appendix Table 2

NORMAL SUBJECTS - 50 WOMEN

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
C.A.	18	62	308	65	18.7
I.B.	47	67	256	136	27.1
W.B.	35	45	197	68	12.6
N.B.	53	44	198	130	24.8
J.B.	23	54	251	106	23.9
I.B.	33	55	173	110	18.4
E.C.	66	52	157	116	17.0
A.C.	40	61	163	131	19.6
M.C.	42	47	255	86	17.2
A.C.	23	64	225	114	24.3
E.C.	27	56	130	130	16.6
M.D.	50	62	209	123	24.6
A.D.	54	77	131	128	16.6
M.D.	22	64	223	115	24.1
D.E.	54	49	209	126	23.2
E.E.	65	85	271	53	14.3
E.G.	38	53	262	85	20.1
S.H.	50	66	199	76	14.0
D.H.	69	49	215	128	25.8
C.H.	58	56	150	110	15.8
E.H.	44	57	212	97	20.0
J.H.	52	50	180	100	17.0
D.H.	59	64	199	134	25.9
S.H.	17	51	183	130	22.6
E.H.	43	79	198	119	21.6
E.J.	22	63	136	111	14.5
H.J.	23	61	135	130	16.3
M.J.	36	56	251	117	28.0
J.K.	29	42	274	119	30.7

Normal Subjects - 50 Women (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
P.L.	22	68	204	135	27.4
E.L.	39	82	128	122	15.2
S.L.	32	54	200	112	21.5
M.M.	30	62	399	120	47.1
L.M.	19	53	256	112	19.5
A.P.	22	64	257	108	26.3
G.P.	21	70	213	104	20.6
B.R.	40	61	175	127	21.9
H.R.	36	56	263	118	28.8
A.R.	22	54	263	94	22.4
A.R.	22	54	228	132	27.4
E.R.	22	56	300	134	37.6
A.R.	50	64	303	127	35.3
C.R.	52	56	264	38	9.7
J.R.	28	48	251	109	25.1
P.S.	22	77	201	107	19.3
M.S.	21	50	219	108	20.6
M.T.	34	66	162	109	17.0
I.W.	52	64	182	125	20.4
G.W.	27	48	224	50	10.8
B.W.	68	54	107	135	14.0

Appendix Table 3

DUODENAL ULCER - 237 MEN

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
D.A.	57	39	274	130	30.8
J.A.	48	62	329	103	31.8
R.A.	44	95	460	127	54.2
A.B.	55	79	443	137	58.2
M.B.	64	68	560	142	73.3
L.B.	38	72	297	133	37.0
B.B.	34	95	400	122	46.1
T.B.	50	65	385	134	45.1
W.B.	60	64	366	131	47.7
J.B.	47	84	383	142	51.4
M.B.	26	59	341	134	42.1
J.B.	24	69	456	129	54.3
J.B.	33	80	391	139	52.2
F.B.	54	69	417	135	52.5
F.B.	48	56	317	125	36.5
J.B.	48	74	349	110	38.0
J.B.	27	67	340	118	33.5
G.B.	34	73	360	117	41.4
A.B.	30	75	495	134	59.0
W.B.	38	76	226	127	26.2
G.B.	29	75	263	141	36.3
P.B.	79	55	265	104	25.1
L.B.	46	73	280	113	30.7
H.B.	48	55	387	136	51.2
D.B.	24	63	482	104	42.5
J.B.	47	73	297	101	29.5
T.B.	39	73	402	119	45.1
T.C.	54	64	350	105	32.7
J.C.	52	64	261	128	32.0

Duodenal Ulcer - 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
S.C.	41	73	379	118	41.2
D.C.	33	72	224	110	24.0
B.C.	44	69	585	130	75.5
J.C.	57	72	385	125	46.7
J.C.	62	78	349	142	46.8
E.C.	27	53	307	98	27.3
S.C.	40	65	354	128	43.2
G.C.	62	68	313	138	41.5
J.C.	29	71	413	118	47.0
L.C.	37	64	292	119	32.3
B.C.	56	71	398	134	49.3
W.D.	67	76	397	120	45.5
S.D.	33	89	484	128	60.4
A.D.	51	58	315	114	32.9
D.D.	31	68	458	96	41.9
D.D.	30	84	332	114	35.2
G.D.	42	77	426	111	45.0
I.D.	48	67	417	119	40.0
K.D.	46	62	320	135	42.6
R.D.	50	59	488	119	51.1
S.D.	51	59	236	117	26.8
W.D.	46	79	438	127	49.1
B.D.	34	74	282	120	41.1
A.D.	40	94	392	136	52.0
A.D.	59	63	392	142	55.5
C.D.	45	74	543	129	68.2
E.D.	42	83	295	131	38.1
W.D.	86	64	175	128	19.3

Duodenal Ulcer - 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
B.D.	37	81	341	115	38.3
J.D.	49	57	553	114	59.0
L.D.	50	86	384	119	39.3
J.D.	40	53	255	123	27.4
D.D.	29	57	393	126	45.8
P.E.	52	98	289	91	24.7
S.E.	40	65	364	124	42.8
L.E.	44	76	272	134	35.3
T.E.	32	66	354	119	38.9
W.E.	39	73	284	139	37.9
G.E.	37	64	384	144	51.6
I.E.	36	62	668	72	40.9
K.E.	40	77	299	138	39.1
K.E.	29	77	344	118	38.0
W.F.	39	62	564	117	65.1
D.F.	37	62	402	119	44.7
W.F.	45	65	440	82	33.5
T.F.	57	51	294	133	40.7
R.F.	37	73	258	100	28.6
F.F.	50	64	370	123	44.7
D.G.	34	81	334	122	35.4
D.G.	38	86	293	114	31.8
R.G.	60	51	500	136	76.2
G.G.	20	50	216	118	24.1
R.G.	39	63	289	136	38.5
E.G.	22	49	262	132	33.0
T.G.	40	67	673	142	103.0

Duodenal Ulcer - 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
J.G.	45	91	330	130	40.8
T.G.	50	68	276	93	25.8
J.G.	40	75	300	117	29.4
S.G.	35	77	464	145	65.4
J.G.	54	65	394	136	50.8
B.H.	62	56	378	88	30.1
A.H.	41	79	223	109	23.3
W.H.	45	51	439	140	72.5
R.H.	49	80	569	140	75.9
J.H.	52	77	311	114	33.4
V.H.	66	58	353	114	43.8
R.H.	40	61	339	114	35.6
T.H.	56	50	526	140	57.4
D.H.	19	54	478	137	62.9
T.H.	64	72	388	134	46.2
M.H.	56	52	482	127	61.2
J.H.	35	65	361	137	48.5
C.H.	54	64	350	146	50.6
R.H.	52	86	298	120	31.5
F.H.	50	60	328	113	36.0
S.H.	62	70	425	116	47.5
A.H.	30	63	297	143	41.7
A.J.	45	64	284	117	31.5
B.J.	54	100	246	122	29.4
E.J.	52	79	363	143	50.5
G.J.	39	67	358	107	32.5
G.J.	36	65	474	115	53.8
D.J.	68	62	206	120	23.9

Duodenal Ulcer - 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
E.J.	35	61	452	124	55.9
L.J.	46	69	344	136	46.0
F.J.	64	80	313	117	34.0
G.J.	36	73	512	139	67.9
I.J.	38	80	274	124	31.9
J.J.	44	53	326	139	40.0
L.J.	41	65	321	136	43.1
R.J.	46	78	230	135	30.4
S.J.	46	73	281	129	32.1
T.J.	66	69	691	87	54.5
T.J.	52	78	344	144	47.0
J.K.	68	78	292	110	30.3
B.K.	26	61	419	131	48.4
B.K.	28	58	276	79	21.1
L.K.	42	65	443	114	46.0
T.K.	37	69	268	115	26.3
W.K.	56	74	341	138	44.8
B.K.	16	67	351	130	43.0
R.L.	35	60	500	122	60.7
A.L.	39	49	315	100	31.2
M.L.	38	74	270	129	32.9
A.L.	35	66	375	121	39.5
E.L.	54	77	304	133	39.9
I.L.	71	62	356	110	35.9
J.L.	68	74	443	120	49.5
J.L.	68	72	263	135	34.2
P.L.	49	80	274	134	33.9
T.L.	38	77	395	125	48.0
T.L.	50	86	198	112	20.6

Duodenal Ulcer -- 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
K.L.	44	64	493	152	65.5
A.L.	45	72	386	125	47.0
J.L.	49	78	325	136	42.3
W.L.	65	98	238	124	28.5
R.M.	37	70	210	130	25.7
A.M.	28	56	228	124	26.8
W.M.	40	66	254	127	41.6
M.M.	22	53	303	133	38.9
K.M.	44	82	520	107	55.6
A.M.	54	64	460	115	48.3
T.M.	65	63	407	138	53.8
M.M.	32	79	372	111	41.7
H.M.	59	71	228	95	19.6
J.M.	39	69	300	109	31.7
L.M.	43	77	297	101	22.7
A.M.	18	73	351	133	46.4
F.M.	76	72	268	96	25.1
W.M.	39	78	451	103	44.9
R.M.	31	58	291	145	40.6
A.M.	42	82	305	121	35.2
H.Mc.C.	41	73	363	118	41.7
K.Mc.C.	34	62	348	101	34.4
H.McD.	53	73	456	106	46.8
J.Mc.K.	34	78	465	114	51.6
H.Mc.N.	25	54	335	137	42.1
E.N.	49	76	234	116	26.1
R.N.	37	57	360	129	44.9
R.N.	44	64	309	92	27.8

Duodenal Ulcer - 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
R.N.	50	73	310	129	41.0
H.N.	44	62	265	123	31.1
H.N.	55	93	197	158	30.4
W.N.	71	76	381	135	49.8
J.O'B.	67	78	330	132	42.4
D.O'C.	39	61	467	119	49.7
J.O'H.	35	68	381	136	51.2
M.O.	18	68	390	137	52.7
F.O'T.	38	77	347	129	41.3
J.R.	52	57	294	115	31.5
D.R.	25	76	408	141	56.0
D.R.	40	98	398	110	38.7
K.R.	56	78	220	127	26.3
P.R.	45	80	245	109	25.2
T.R.	55	74	249	114	27.6
K.R.	38	103	374	120	43.6
T.R.	45	69	420	124	48.2
W.R.	42	61	475	120	51.3
J.R.	62	68	460	112	48.2
A.R.	45	67	300	118	34.8
C.R.	54	50	338	102	31.5
J.R.	42	80	417	130	50.2
M.S.	28	60	266	92	22.1
E.S.	76	50	295	128	36.9
T.S.	65	62	416	114	40.2
W.S.	63	85	333	106	33.7
M.S.	47	71	256	88	20.8
A.S.	69	81	296	136	39.1
F.S.	53	56	270	130	33.2

Duodenal Ulcer - 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
I.S.	39	71	264	130	31.4
W.S.	64	91	259	100	25.1
G.S.	37	77	537	145	69.6
D.S.	30	82	334	129	42.6
R.S.	41	71	497	89	37.3
F.S.	60	68	298	109	30.3
T.S.	48	40	380	109	32.8
B.S.	23	71	410	124	50.5
G.S.	43	72	297	138	36.1
M.S.	28	71	462	134	60.3
W.S.	62	74	403	133	47.3
J.S.	60	60	293	120	29.9
K.S.	42	66	302	135	39.1
F.S.	42	62	305	138	41.5
C.S.	25	61	363	95	34.5
R.S.	38	68	356	118	41.7
B.S.	50	51	358	129	41.3
E.T.	41	60	481	142	65.6
E.T.	59	56	248	117	28.2
J.T.	50	42	238	115	25.9
G.T.	25	77	418	119	46.8
W.T.	64	54	277	127	34.2
W.T.	51	59	299	133	38.8
T.T.	68	80	388	116	39.9
E.W.	68	49	224	111	27.4
P.W.	38	68	443	133	58.0
E.W.	31	82	361	111	35.8
G.W.	32	102	276	110	25.4

Duodenal Ulcer - 237 Men (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
G.W.	45	49	338	108	35.3
S.W.	53	69	269	108	28.5
E.W.	47	87	437	141	68.1
E.W.	58	64	332	117	37.8
G.W.	57	73	339	120	39.7
O.W.	63	73	373	107	35.3
S.W.	25	70	341	116	38.1
T.W.	47	68	432	104	41.3
H.W.	56	90	390	117	40.4
J.Y.	43	77	283	83	21.3
W.Z.	43	73	750	128	84.6

DUODENAL ULCER - 35 WOMEN

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
V.A.	35	59	363	115	39.6
H.B.	18	55	266	141	34.7
J.B.	31	57	261	130	30.1
C.C.	46	47	221	112	23.7
L.C.	12	50	276	119	29.0
D.D.	63	76	205	127	25.6
E.D.	48	55	231	128	28.6
T.D.	71	43	273	110	27.3
V.D.	40	49	294	113	33.1
B.D.	44	55	342	129	39.2
E.D.	49	79	323	132	42.9
M.E.	62	73	175	129	21.3
N.F.	40	81	251	144	34.5
D.G.	39	48	241	114	27.0
M.H.	51	77	177	147	25.3
W.H.	58	51	283	107	29.7
M.H.	55	72	259	114	28.5
G.J.	62	50	295	112	28.4
A.J.	48	83	532	144	73.3
M.J.	24	56	245	105	25.2
I.K.	46	67	370	114	37.7
E.L.	54	59	213	128	25.0
M.L.	63	59	224	124	25.4
H.M.	73	54	211	102	17.6
F.Mc.A.	56	57	242	91	21.1
E.N.	45	77	276	126	33.8
L.O'D.	31	70	422	118	48.4
M.R.	49	45	265	105	25.3

Duodenal Ulcer - 35 Women (contd.)

	AGE	WEIGHT	VOLUME	CONC.	OUTPUT
W.R.	42	73	271	81	20.2
E.S.	52	65	400	96	36.2
B.T.	28	55	153	140	20.6
K.T.	52	53	347	128	41.3
E.W.	53	43	245	129	31.1
D.W.	50	76	227	129	29.5
M.W.	55	47	263	127	31.4

Table 5. The acid output in 15 men with symptomatic hiatus hernia, but without duodenal ulcer.

	AGE	ACID OUTPUT mEq/hour
H.W.	58	40.4
L.S.	51	24.2
F.H.	78	15.8
N.A.	45	15.7
J.J.	32	19.0
R.J.	76	16.4
W.A.H.	40	31.0
D.J.H.	57	19.3
P.C.	56	19.7
D.L.E.	47	24.1
F.R.P.	53	12.8
A.D.	42	27.3
L.M'C.	56	17.1
L.L.	37	27.0
H.G.	75	7.0

Table 6. The acid output in 9 men with symptomatic hiatus hernia and associated duodenal ulcer.

	AGE	ACID OUTPUT mEq/hour
J.C.	58	46.1
J.R.	42	51.0
H.Mc.K.	46	27.2
F.B.	61	36.5
H.G.C.	67	35.8
W.B.	38	26.2
A.P.	50	36.6
R.C.S.	43	45.8
J.M.R.	42	46.0

Table 7. The acid output in 19 women with symptomatic hiatus hernia, but without duodenal ulcer.

	AGE	ACID OUTPUT mEq/hour
I.W.	54	20.4
M.C.	73	13.8
C.C.	62	30.9
V.P.	42	16.9
D.M.	47	17.7
H.B.	68	18.6
C.R.	53	9.7
A.B.	72	9.1
V.I.	65	6.6
D.F.	51	23.9
A.R.	50	35.3
A.H.	71	10.8
I.A.S.	58	14.1
J.O.	43	17.1
N.B.	50	24.1
S.D.	69	18.3
P.H.	70	23.3
E.J.H.	44	19.8
D.H.	56	15.9

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THE HISTAMINE-INFUSION TEST OF GASTRIC ACID SECRETION IN MAN

Thesis for M.D.

by

James H. Lawrie

SUMMARY

SUMMARY

The history of the evolution of tests for gastric acid secretion has been reviewed (Chapter 1), taking particular note of the changing fashions in the form of tests, the slow development of increasingly precise methods of measurement, and the continuing difficulty in deriving substantial information from the results. In this context, the value of the steady state of maximal acid secretion induced by an infusion of histamine, had been acknowledged in experimental work, but had been exploited only to a limited extent in studies in man.

Using a slow injection pump and disposable sterile equipment, a technique was evolved whereby this method of stimulation could be used to study large numbers of patients and control subjects.

Dose-response curves were determined, and from these the dose-rate of 0.04 mg histamine acid phosphate per kg body weight per hour was shown to elicit a maximal acid response. Using this dose-rate throughout, the responses were calculated to consist of a valid plateau of output, to have an acceptable reproducibility in duplicate tests, and to be consistently greater than any of the established methods of calculating the

'augmented' histamine response (Chapter 2). The test was, to some extent, self-checking, and radiological monitoring of nasogastric tube position could be obviated. Side effects were tolerable and transient. Many subjects were studied satisfactorily as out-patients.

Normal standards were determined (Chapter 3) for volume, concentration and output of acid in 54 men and 50 women. The mean output for the men, 25.3 mEq/hour, was significantly higher than that for the women, 21.7 mEq/hour. This difference was due only to the larger volumes of gastric acid secreted by men, the concentration of acid being similar in both men and women (108.4 and 110.4 mEq/litre respectively). Output declined with age in men, but not in women. There was no relationship with body weight in either men or women. The range of acid output appeared to be similar for both sexes, i.e. 9.5 - 42 and 9.7 - 47.1 mEq/hour in men and women respectively and the possible pathological significance of values outwith these ranges is discussed.

These methods and standards were applied to the study of various peptic disorders (Chapters 4 - 9). The mean acid output in 237 men with duodenal ulcer was 41.5 mEq/hour (range 19.3 - 103) and in 35 women, 31.2 mEq/hour (range 17.6 - 73.3). In both men and

women patients the volume, concentration and output of acid were all significantly greater than normal. Within the duodenal ulcer group, however, the higher male output was due only to larger volumes of gastric acid of concentration similar to that in women (121.9 and 120.3 mEq/litre respectively). In the group of patients with benign gastric ulcer (Chapter 5) the mean output in men was 21.4 mEq/hour (2.1 - 41.2) and in women 13.5 mEq/hour (4.5 - 26.8). No patient was achlorhydric, and none was above the normal range. There was no clear relationship between acid output and the site of the ulcer.

Of the patients with gastric cancer (Chapter 6) one-third were achlorhydric, while those who did secrete acid had a wide variation in concentration, from 13 - 130 mEq/litre. Acid output increased with more distally situated tumours. Prepyloric ulcers were largely associated with a normal acid output (Chapter 7).

The syndrome of dyspepsia without ulcer, and with the radiological appearance of coarse mucosal folds in the duodenum (Chapter 8) was associated with a high mean acid output of 44.3 mEq/hour. The acid levels were related to the severity of the radiological change, and

to the histological changes in the duodenal mucosa, in particular to the incidence of 'gastric-type' epithelium.

Symptomatic hiatus hernia (Chapter 9) alone, without duodenal ulceration, was associated with a normal acid output (19 mEq/hour). Patients who had both hiatus hernia and a duodenal ulcer had high acid secretion levels (39 mEq/hour) similar to those found in duodenal ulcer alone.

In a group of 31 patients with chronic iron-deficiency anaemia (Chapter 10) 5 were achlorhydric, 9 had a normal acid output, and 17 (54%) had abnormally low though measurable acidity. After treatment with iron 7 of the younger patients who had previously some acid secretion, showed an improvement in acid output. Older patients and those already achlorhydric showed no change.

In patients with jaundice (Chapter 11), regardless of the diagnosis, almost one-half were achlorhydric, and no correlation was found between acid output and any of the factors customarily associated with liver function. As in the previous group, there were many subjects who secreted very low but measurable amounts of acid.

Finally, an attempt was made to assess the synthetic pentapeptide of gastrin (I.C.I. 50,123)

(Chapter 12) in conditions precisely comparable with those obtaining for the histamine-infusion tests. Dose-response relationships showed that 5 µg/kg/hour by infusion elicited a maximal response, and this dose-rate was used to compare with the standard histamine-infusion test using 40 µg/kg/hour, in a series of 43 subjects. The mean acid output by histamine was 31.5 mEq/hour and by pentagastrin 30.2 mEq/hour. The coefficient of correlation between the two responses ($r = 0.939$) was highly significant.