would seem to be supported by the consistency of the pattern of results shown by either the series as a whole or after division according to ethnic origin, or after analysis within single alcoholic units. The general pattern of an increase of group A non-secretors among the alcoholic patients and a corresponding decrease of group A secretors is maintained.

Moreover, when the patients are divided according to ethnic origin the group A secretor/non-secretor frequencies found in each ethnic group vary in such a way as to maintain about the same differential between alcoholics of a particular ethnic group and their appropriate controls. This is well shown by the percentages of non-secretors (see Table II).

There is at the present time good evidence for a number of associations between blood groups and various diseases, particularly of the alimentary tract. These have been reviewed by Roberts (1959).

Various explanations of an association between alcoholism and ABO groups and secretor status come to mind: for example, a genetically determined predisposition to the disease or the existence of an enzyme or enzymes associated with the metabolism of alcohol varying with ABO group and secretor status (cf. the association between intestinal alkaline phosphatase and ABO blood groups described by Arfors *et al.*, 1963). Such theories, however, would not be consistent with the finding of an *almost exact balance* between the increase in A non-secretors and the loss of A secretors in the series investigated.

Such a balance points to a direct effect of alcohol on the secretor status of an individual as a cause of the disturbed secretor/non-secretor distribution. Though from most points of view this would appear to be an unacceptable theory it would best fit the experimental findings. It would require that a certain number of genetically constituted group A secretors become phenotypically non-secretors through the constant imbibition of alcohol. One difficulty is the fact that the disturbed secretor/non-secretor frequency does not apparently involve group B. In addition, whatever effect the alcohol might be supposed to exert would have to be at least moderately permanent, since most of the patients were "dry" at the time of testing. Under the experimental conditions of the tests in the series no intermediate forms difficult to categorize either as secretors or as non-secretors were encountered. Moreover, since all the non-secretor alcoholic patients have the expected red cell Lewis type—that is, they are mainly Le(a+b−) and none are Le(a−b+)—it would have to be postulated that the prolonged intake of alcohol affected the uptake of Lewis antigens by the red cells as well as the secretion of group-specific substances by the salivary glands.

Family studies might offer one solution to the problem, since the production of secretor children from the mating of a group A non-secretor alcoholic with a non-secretor spouse (of any ABO group) would be very interesting indeed.

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Spontaneous Decrease in Gastric Secretory Response to Humoral Stimuli

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Summary: The gastric response to pentagastrin was studied over a period of seven months in a healthy 25-year-old man without symptoms or history of gastrointestinal disease. An abrupt impairment of the gastric response to several stimulants was observed one month after starting the tests. Periodic testing since that time has shown no reversion to the type of response seen during the initial period of testing. A second subject with proved chronic duodenal ulceration presented an identical change in pattern of gastric response to stimulants.

This study suggests that such a variation in the response to gastric stimulation in a subject with a normal stomach should be borne in mind when interpreting results of gastric secretory studies.

Introduction

Pentagastrin has been used to stimulate secretion of acid by continuous intravenous infusion (Wormsley *et al.*, 1966; Multicentre Pilot Study, 1967), subcutaneous injection (Makhlouf *et al.*, 1966; Wormsley *et al.*, 1967), and intramuscular injection (Johnston and Jepson, 1967), and also as snuff (Wormsley, 1968; Jepson *et al.*, 1968).

This study had been planned to investigate the dose-response of a normal human stomach to gastric stimuli and to examine the effect on this response of gastric secretory inhibitors. After the first few tests, however, there was a pronounced reduction in the gastric response to all stimulants

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from the original levels, which were quite normal, to levels which were abnormally low and suggestive of severe gastric dysfunction. A similar decrease in gastric secretory capacity was observed in a patient with chronic duodenal ulcer.

The secretory data of these two subjects are presented in the report below, since this type of change in gastric secretory response to stimulants has not been previously recorded.

Method

In both cases informed consent was obtained to carry out these tests. Tests were carried out in the morning after an overnight fast. A No. 14 French gauge polyethylene nasogastric tube was passed into the stomach and gastric juice aspirated at a continuous pressure of 7–10 cm. Hg subatmospheric. The position of the tube was adjusted to give continuous aspiration, and suction was interrupted frequently to blow air down the tube to keep it patent. The subject lay on his left side and a few deep breaths in each collection period assisted aspiration of the juice. Saliva was expectorated.

The resting juice was collected for a period varying from 20 to 30 minutes, after which a stimulant was given and 12 five-minute batches of gastric juice were collected. In each sample the presence of bile and mucus was noted and the volume recorded.

After filtration through gauze the acid concentration was measured by titration with 0·01 M sodium hydroxide to the phenolphthalein end-point (*p*H 6·8–8·4). The acid output was calculated by multiplying concentration by volume, and the maximal response during four successive five-minute periods was multiplied by three to give peak hourly output in mEq/hour.

Pepsin concentration was measured by the method of Hunt (1948). In one of the initial tests polyethylene glycol was used as a measure of completeness of aspiration of gastric juice. Recovery was determined by the method of Hydén (1955).

Subject 1 (myself) was a healthy man of 25 years with no gastrointestinal symptoms. Tests were carried out at intervals ranging from 24 hours to one week before the change in secretory response took place and 24 hours to four weeks after the change. Follow-up testing for several months has shown no reversion to the original secretory state. These two phases are referred to as series 1 and series 2. At no time during the course of these tests, and particularly during the interval between series 1 and 2, were there any changes in diet or intake of alcohol and salicylate.

In 14 of the 16 tests pentagastrin was given in doses shown by previous workers to stimulate maximal gastric acid secretion. The pentagastrin was injected or infused in 0·15 M sodium chloride. Intramuscular injection was given into the quadriceps femoris in a dose of 6 or 10 μg./kg. body weight and subcutaneous injection was made into the flexor aspect of the forearm in a dose of 6 μg./kg. Continuous intravenous infusion in a dose of 6 μg./kg./hour was administered through an indwelling venous cannula by means of a Palmer infusion pump. Pentagastrin snuff was given in four successive doses of 1 mg. at 10-minute intervals in both tests in which nasal insufflation was used. Ametazole (2 mg./kg. body weight) was injected subcutaneously into the flexor surface of the forearm, and soluble insulin was given intravenously in a dose of 0·2 unit/kg. body weight. All these tests were carried out personally.

Subject 2, a man aged 28 with a chronic duodenal ulcer, had five tests, comprising two with subcutaneous histamine (0·04 mg./kg.) and three with pentagastrin in a dose of 6 μg./kg. intramuscularly.

In Subject 1 the barrier to back diffusion of acid from the gastric lumen through the gastric mucosa was tested during the phase of decreased secretory response. Then 25 mEq of acid (in the form of 250 ml. of 0·1 M HCl with 0·055 M NaCl and 2·5 g. polyethylene glycol/l.) was left in the stomach for 20 minutes, and the residual gastric contents were aspirated and acid and polyethylene glycol content measured.

Antiparietal cell antibodies and antibodies to gastric intrinsic factor were estimated by Dr. D. Doniach. A biopsy of gastric fundal mucosa was obtained by means of a Crosby capsule during the phase of reduced gastric secretory response.

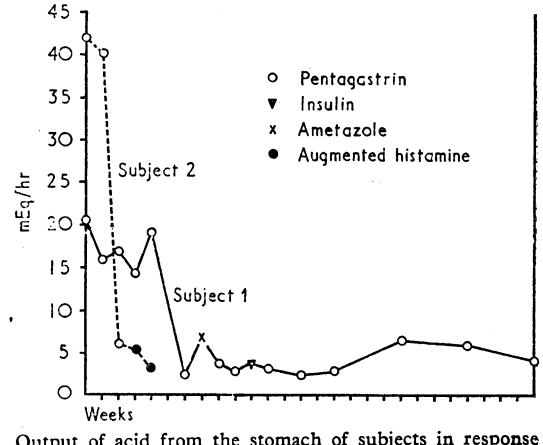
Results

Subject 1

Acid Secretion.—The acid output was significantly and consistently less in tests in series 2 (Table I and Chart) compared with series 1, owing both to decrease in volume of juice and lower concentration of acid. The change has been maintained for four and a half months (see Chart).

TABLE I.—*Result of Tests with Pentagastrin in Subject* 1

Route	Dose	Peak Acid Output (mEq/hour)		% Reduction	Total Hourly Output (mEq/hour)		% Reduction
		Series 1	Series 2		Series 1	Series 2	
Intramuscular	6 μg./kg.	24·6	2·5	90	17·8	1·7	91
Intravenous ..	6 μg./kg./hr.	20·37	4·44	79	16·5	3·5	79
Subcutaneous	6 μg./kg.	14·2	4·26	70	11·3	3·0	74
Snuff ..	4 × 1 mg.	18·3	3·85	79	15·0	2·6	83
Intramuscular	10 μg./kg.	16·62	4·39	74	15·1	2·2	85



Output of acid from the stomach of subjects in response to different stimuli, showing spontaneous decrease in response and failure of recovery in one subject over 21 weeks.

Pepsin Secretion.—The output of pepsin was less in tests of series 2 than in tests of series 1. In series 2, however, the concentration of the pepsin in the gastric juice was higher (Table II), so that the decrease in pepsin output was proportionately less than in acid.

TABLE II.—*Output of Pepsin in Subject* 1

	Peak 5-min. Concentrations	Total Hourly Output
Series 1	62 kilounits	159 kilounits
	62 ,,	111 ,,
Series 2	101 ,,	89 ,,
	110 ,,	93 ,,
	97 ,,	94 ,,

Back Diffusion.—No acid was lost across the gastric mucosa during the test. Recovery of acid was 95% and of polyethylene glycol 94·5%.

Gastric Biopsy.—This showed atrophy of the gastric mucosa, a diffuse infiltration of the mucosa by chronic inflammatory cells, a reduction in the number of parietal cells, and an occasional lymphoid follicle.

Antibody Determinations.—Gastric parietal cell antibody was present in low titre; antibodies to gastric intrinsic factor were absent.

Subject 2

The initial maximal gastric output in the patient with a chronic duodenal ulcer was high (40 mEq/hr.). One week later the response to the same stimulus was reduced, as was the response to augmented histamine stimulation (see Chart and Table III). In the interval between the two tests there had been no change in diet or ingestion of alcohol, salicylate, etc. The patient, who initially complained of symptoms typical of duodenal ulceration, became asymptomatic at the time of his later tests.

TABLE III.—*Results in Subject 2*

Route	Dose	Peak Hourly Acid Output (mEq/hour)		
		Series 1	Series 2	% Reduction
Pentagastrin: intramuscular	6 μg./kg.	42·09 40·07	5·7	73
Augmented histamine test: subcutaneous	40 μg./kg.	— —	5·2 3·7	

Discussion

In Subject 1, following five tests in which gastric secretion was stimulated by pentagastrin, with consistent reproducible results in the normal range, the secretory response of the stomach underwent a qualitative change which consisted of a decrease in basal acid secretion and a decrease in maximal acid response to all gastric stimulants used. The output of pepsin also decreased, though not as markedly as acid.

The impairment of the response to all stimulants suggested that the decreased gastric responsiveness was not selective and was not due to an immunological reaction to pentagastrin. It seemed probable that the impaired gastric secretion was either due to severe damage of the gastric mucosa (Hubel, 1966 ; Rohrer and Welsh, 1967) or that the stomach had become unresponsive to stimulants, as reported in patients with normal peptic mucosa and pancreatic adenomata, who showed markedly impaired secretory response, some of which could be reversed by treatment with steroids (Hindle *et al.*, 1964). The former cause seems more probable in Subject 1 of this study, since a gastric biopsy showed severe mucosal damage and parietal cell loss. Unfortunately no information is available about the histology of the stomach during the initial five tests, but the stomach was then functionally normal. Histological evidence of comparative sparing of the chief cells is compatible with the smaller reduction in pepsin output compared with acid. It seemed probable that the low acid output in the tests of series 2 was due to decrease in the number of parietal cells and not due to secretion and subsequent transmucosal loss of acid in view of the failure to demonstrate back diffusion of acid.

The presence of antibodies to parietal cells in Subject 1 does not, unfortunately, solve the problem of whether parietal cell damage precedes or follows the appearance of antibodies, since six months had elapsed between the change in secretory pattern and the antibody determination.

Significant impairment of the gastric secretory response to stimulants of the type noted in this study has not been reported previously, though the converse type of response has been noted with low acid output in response to stimulants followed later by greater acid output (Weir, 1967).

Gastric testing by methods in current use has been shown to produce results which are reproducible on repeated testing (Wormsley *et al.*, 1967 ; Jepson *et al.*, 1968). Indeed, this is one of the most important assumptions on which tests of gastric function are based. This study, however, has shown that the gastric response to stimulants can alter qualitatively over a period of time, and this type of reaction must be borne in mind, particularly when the assessment of gastric function depends on comparison of response to repeated stimulation—for example, after operation such as vagotomy.

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Severe Haemolytic Anaemia in Pregnancy in Nigerians Treated with Prednisolone

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Summary : Haemolytic anaemia of obscure aetiology is a common complication of pregnancy in Nigeria. Treatment with antimalarials and folic acid is usually followed by a rapid remission, but response is slow in about 25% of patients and haemolysis continues uncontrolled in about 5%. The administration of prednisolone to six patients with uncontrolled haemolysis was followed by rapid recovery in five and possible benefit in one. Risks of prednisolone therapy to the mother appear to be slight and outweighed by the risks of continued severe anaemia and frequent blood transfusions. There seemed to be no appreciable increase of fetal loss compared with that in anaemic pregnancies not treated with prednisolone.

Introduction

Severe anaemia in pregnancy is a major problem in obstetric practice in West Africa, and about 250 pregnant or recently delivered patients are seen each year at University College Hospital, Ibadan, Nigeria, with packed cell volume (P.C.V.) 23% or less. The aetiology of anaemia is complex, but two factors, haemolysis and folate deficiency, stand out as being of prime importance (Edozien *et al.*, 1961 ; Lawson, 1962). Folate

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