during apnoea, so that anoxaemia cannot by itself be held responsible. The carbon dioxide tension is, however, at its lowest during the apnoeic phase (Harrison, 1939), and, since cerebral blood flow is directly related to the carbon dioxide tension of the blood (Kety and Schmidt, 1946), reduction of blood flow from this cause may be responsible. We have no data on this aspect.

Summary

Two patients with chronic Cheyne–Stokes respiration are described in some detail. These with a further three patients were investigated, using an ear oximeter.

It has been shown that the highest arterial oxygen saturation occurs during the period of apnoea, the lowest during the hyperpnoeic interval. This is due to a delay in circulation time and has been demonstrated by means of dye time-concentration curves. The length of the apnoeic phase seems to be related to the prolongation of the circulation time.

The effects of oxygen, carbon dioxide, and aminophylline on this condition have been studied together with their effect on arterial saturation.

In our patient with chronic Cheyne–Stokes respiration a mid-brain lesion is described. The mechanism causing this form of respiration is discussed.

It is suggested that two of the factors are a prolongation of circulation time and a change in sensitivity of the respiratory centre. The latter may arise from interruption of cortical pathways to this centre.

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THE NATURE OF GASTRIC HYPERSECRETION OF ACID IN PATIENTS WITH DUODENAL ULCER

BY

J. N. HUNT, D.Sc., M.B., B.S.
Department of Physiology, Guy's Hospital, London

AND

A. W. KAY, M.D., Ch.M., F.R.C.S.Ed.
Peptic Ulcer Clinic, Western Infirmary, Glasgow

Gastric contents of high acidity are more often encountered in patients with duodenal ulcer than they are in normal persons (Enticknap and Merivale, 1954; James and Pickering, 1949). The high concentration of acid of the gastric contents in such patients is at least in part the result of an increased secretion of acid. As it is probable that a highly acid gastric content retards the healing of a duodenal ulcer, the abnormality causing the hypersecretion is a matter of clinical interest.

Gastric secretion is reflex. It depends upon the stimulation of receptors which, acting either by nervous or by hormonal channels, excite the secretory cells. The ultimate factor limiting the response of gastric secretory arcs is the maximal secretory capacity of the mucosa. If this can be measured it becomes possible to describe the gastric response to any stimulus as a percentage of the maximal secretory capacity. Viewed in this light, hypersecretion may be divided into two classes. In one, the maximal secretory capacity is normal, but the proportion of that capacity which is at work is raised. Here we may assume that there is an increase in stimulation bearing on the parietal cells. In the other, the maximal secretory capacity is abnormally high—perhaps owing to an abnormally large number of parietal cells—so, although the proportion of that capacity which is actively engaged in secretion is normal the resulting output is excessive. In this type we may conclude that the stimulus is quantitatively normal. This paper is concerned with deciding into which class the hypersecretion of patients with duodenal ulcer falls. It will be shown that patients with duodenal ulcer have an abnormally high maximal secretory capacity.

It will also be shown that the development of stenosis in duodenal ulcer patients is associated with a raised maximal secretory capacity.

A Maximal Stimulus for the Parietal Cells.—Histamine stimulates the acid-secreting cells of the stomach directly, since it is effective in isolated mucosa. It is possible to evoke from the stomach an apparent maximal output of acid by giving large doses of histamine while protecting the patient against the extragastric actions of histamine by previous administration of an antihistaminic (Kay, 1953). In the present paper this maximum is used as an index of the maximal secretory capacity of the gastric mucosa.

Methods

Material.—The augmented histamine test has been made on 27 males without a history of dyspepsia and on 152 male patients in whom duodenal ulcer was proved by subsequent operation. The basal and maximal secretions were examined and the results have provided the material for statistical analysis.

Method of Expressing the Output of the Parietal Cells.—The conventional method of assessing the activity of the parietal cells is to determine the product of the volume and the concentration of acid of the recovered gastric secretions. This is not entirely satisfactory, because other cells in the gastric mucosa secrete a varying amount of fluid which contains bicarbonate. This component neutralizes some of the acid formed by the parietal cells (Fisher and Hunt, 1950; Hunt, 1951). Thompson and Vane (1953) have shown how the volume of the secretion formed by the parietal cells may be computed as a function of the concentration of acid and the volume of the recovered gastric juice. This procedure, which minimizes the effect of neutralization of secreted acid by the non-acid component, has been applied to the results of our histamine tests.

Statistical Method.—In the discussion of the results, where it is necessary to compare mean values, the figures in brackets indicate the level of significance of the difference between the means. Thus (1/20) indicates that the observed difference between the means would arise by chance once out of twenty times if there were in fact no difference between the populations from which were drawn the samples making up the means. Correlations have been examined by fitting straight lines by the method of least squares. This method is appropriate in this context, since it allows a test of the fact that the line describing the relation between the variables passes through the origin of the abscissa and the ordinate.

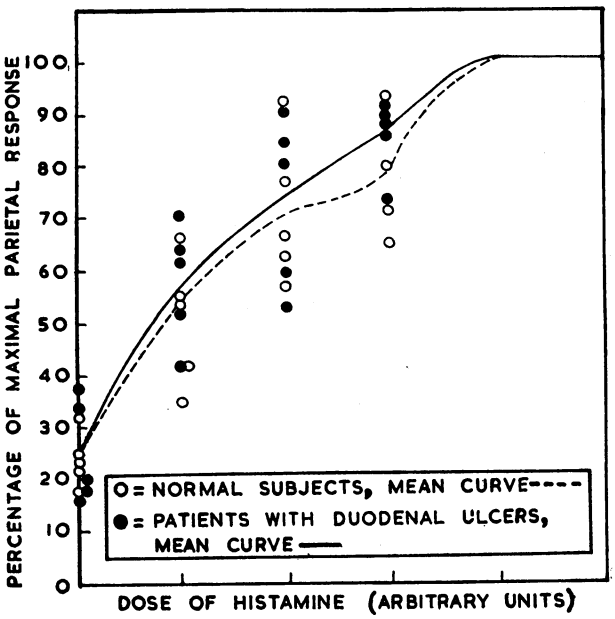

Chart showing relation between dose of histamine and parietal response.

Classification of Hypersecretion in Duodenal Ulcer

Firstly, the mean maximal parietal cell response in patients with duodenal ulcer is greater than that in normal subjects (Table I). This finding may indicate that under similar conditions of stimulation patients with ulcer will secrete more acid than will normal persons. However, it is conceivable that a proportion of the parietal cells in a mucosa with a high maximal secretory capacity may have a high threshold for stimulation; this group of cells, although responding to large doses of histamine, may not respond to stimuli of moderate intensity. This possibility has been examined by preparing dose-response curves for five normal subjects and five subjects with duodenal ulcer. The parietal cell response to increasing doses of histamine has been plotted on the ordinate as a percentage of the maximal response of the individual concerned; the dose of histamine in arbitrary units is plotted on the abscissa (see Chart). It will be seen that there is no systematic difference between the two groups. This can be shown numerically: the mean percentage of the maximal secretory capacity occupied by the response to 1 unit dose is 57 in male patients with duodenal ulcer and 53 in normal males (6/10).

Secondly, the mean basal parietal cell output in patients with duodenal ulcer is greater than in normal subjects (Table I). This would be expected from a consideration of the above argument. Thus, since the maximal secretory capacity in the duodenal ulcer group is greater than that in the normal group, and since the threshold of parietal cell excitability is similar in the two groups, it is to be expected that the ulcer group will always secrete more acid under standard conditions.

TABLE I.—*Data on the Secretion of Parietal Component by Normal Persons and Patients with Duodenal Ulcer (ml./45 min.)*

	Male Normal Persons	Male Patients with Duodenal Ulcer		
		No Stenosis	Moderate Stenosis	Severe Stenosis
No. of persons	27	81	42	29
Mean basal secretion of parietal component	23·5	50·7	69·1	59·8
Standard error of mean	±2·6	±3·8	±7·9	±6·9
Mean maximal parietal response to histamine	86·0	135·3	165·1	160·4
Standard error of mean	±9·6	±7·1	±9·7	±10·1
Mean weight (kg.)	60·8	58·5	58·0	53·0
Standard error of mean	±1·8	±1·0	±1·1	±1·0
Mean age (years)	44·1	38·3	42·9	49·1
Standard error of mean	±2·5	±1·0	±1·6	±1·4
Mean duration of symptoms (years)	—	13·1	15·0	17·2
Standard error of mean	—	±0·9	±1·3	±1·6

Thirdly, the percentage of the maximal secretory capacity occupied under basal conditions in cases with duodenal ulcer does not differ significantly from that found in normal persons. As the presence of pyloric stenosis does not alter appreciably the mean percentage of the maximal secretory power which is active under basal conditions all data for patients with duodenal ulcer have been pooled (Table II).

TABLE II.—*Percentage of the Maximal Secretory Power Active in Basal Secretion*

	Male Normal Persons	Male Patients with Duodenal Ulcer			
		No Stenosis	Moderate Stenosis	Severe Stenosis	All
Mean ratio: $\frac{\text{Basal parietal secretion} \times 100}{\text{Maximal parietal response to histamine}}$	33·7	38·4	40·1	38·2	38·9
Standard error of mean ratio	±3·3	±2·0	±3·0	±3·4	±1.42

The mean percentage of the maximal secretory power active during basal secretion in the patients with duodenal ulcer is 38.9, which is only insignificantly more than the 33.7% active in the normal persons (1/6).

This finding implies that the high basal secretion of acid in patients with duodenal ulcer can be accounted for by their high maximal secretory capacity; the influences acting on the parietal cells would therefore be similar in both groups. There is therefore no need to postulate the existence of supranormal activity of the psychic, gastric, or intestinal phases of secretion in patients with duodenal ulcer.

This finding can be confirmed from an entirely different source. Consecutive histamine and insulin tests were made in patients with duodenal ulcer and in normal subjects by Ihre (1938). An analysis of his data showed that the hypersecretion in the ulcer group in response to hypoglycaemia, which stimulates the parietal cells via the vagus, could be explained fully by the increased secretory power of the gastric mucosa (Hunt, 1950).

Influence of Onset of Stenosis on the Maximal Secretory Capacity

All patients with duodenal ulcer considered in this analysis were subjected to operation. The surgeons assessed the degree of stenosis when present as slight, moderate, or severe. The first category in particular is very liable to faulty assessment. When all the data for patients with moderate and severe stenosis are pooled, it is found that there is a rise in the maximal secretory capacity as the duration of dyspepsia increased (1/25). There is no such rise in patients having no stenosis (1/2). It is conceivable that this correlation between maximal secretory capacity and duration of symptoms of duodenal ulcer in patients developing stenosis is more closely associated with age than with duration of symptoms. This explanation is not tenable, since there is no significant increase with age in maximal secretory power in any of these groups of patients with duodenal ulcer.

Search for an explanation of this interesting observation suggests two alternatives. It is possible that scarring of the first part of the duodenum might produce, in addition to stenosis, disorganization of the duodenal receptor mechanism which normally depresses gastric secretory activity. Alternatively, the stimulus of repeated distension of the stomach associated with stenosis may induce a work hyperplasia of the parietal cells, for distension appears to be a powerful stimulus to secretion (Macdonald and Spurrell, 1953). It is known that continuous histamine stimulation of the gastric mucosa in guinea-pigs can induce parietal cell hyperplasia (Cox and Barnes, 1945). An analysis of the data of Cox (1952) reveals that his male patients with duodenal ulcer had approximately 75% more parietal cells than had his normal subjects. In our series, the maximal secretory capacity of the ulcer group was 72% greater than that of the non-ulcer group. These findings point to an association between structure and function, which is further supported by the experiments of Friedman (1953). He has shown that the weight of the stomach in mice can be increased by increasing the bulk of the diet with 50% talc. This weight increase is due mainly to an increase in the thickness of the gastric mucosa.

It seems probable that the raised maximal secretory capacity for acid in patients with duodenal ulcer who develop stenosis is due to a work hyperplasia of the parietal cells.

Discussion

There is little information regarding the mechanism which normally regulates the maximal secretory power of the parietal cells, but it certainly seems to be swayed by the vagus, although it is very stable from day to day (Kay, 1953). Oberhelman and Dragstedt (1948) made histamine tests before and after simple vagotomy in patients with peptic ulcer. From their data it is possible to assess the volume of parietal secretion formed. In 15 hospital patients the mean reduction in the volume of the parietal component secreted in response to histamine was 53% (1/1,000), whilst in 18 convict patients the mean reduction was 68% (1/1,000). In three dogs with total stomach pouches the mean reduction in the parietal response to histamine after vagotomy was 64%. It is quite clear that after the operation of vagotomy the response to histamine decreased, but it is not certain that vagotomy rather than the operation was the cause of the decrease.

Presumably there are other mechanisms regulating parietal secretory power besides the suggested vagal mechanism. Indeed, the possibility of a work hyperplasia as a result of an augmented distension stimulus in patients with pyloric stenosis has already been put forward in this paper. It is therefore necessary to be extremely cautious in interpreting the change in parietal secretory power after vagotomy. It is quite possible that the vagus enjoys no direct long-term control over the gastric mucosa at all, but that the withdrawal of cephalic excitation results in a parietal disuse hypoplasia which manifests itself in the lowered response to histamine. If vagal block were found to depress reversibly the response to histamine the question would at least be partly answered in favour of direct control of the reactivity of the parietal cells by the vagus.

It may be concluded from the experimental data examined above that the *net stimulation* bearing on the stomach during basal secretion in patients with duodenal ulcer is not abnormally high where net stimulation means excitation minus inhibition.

Summary

The results of an augmented histamine test on 27 male subjects without peptic ulcer and 152 male patients with duodenal ulcer have been expressed in terms of the volume of parietal component formed by the acid-secreting cells.

Analysis of these results shows that the maximal secretory capacity and the basal secretion of acid are both greater in the duodenal ulcer group.

Furthermore, the percentage of the maximal secretory capacity active during basal secretion is not different in the two groups. It is concluded that the basal hypersecretion of acid in duodenal ulcer can be accounted for by the increased maximal secretory capacity. There seems to be no need to postulate an increase in excitation bearing on the parietal cells in patients with duodenal ulcer during basal secretion.

In ulcer patients who develop stenosis the maximal parietal secretory capacity increases with increase in duration of symptoms.

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Once the transmission of malaria in a country has been completely stopped for three or four years there will be no more malaria parasites in the human or the mosquito host, according to E. J. PAMPANA (*Chron. Wld Hlth Org.*, 1954, **8**, 328). Malaria control can then be stopped, provided the country is protected from reimportation of parasites. Certain countries have already achieved this objective, notably Greece, and expenditure on malaria control can then be much reduced. This is of great importance in highly malarious countries. When insecticide spraying has to be stopped, various conditions must be borne in mind. First, every locality where transmission is possible should be under control. Secondly, it should be possible to determine accurately where total interruption of malaria transmission has been achieved. Thirdly, malaria control should be undertaken with the greatest technical thoroughness at one time and in as large an area as possible. The development of mosquito strains resistant to D.D.T. complicates the programme. If possible, it should be planned so that house-spraying can be safely discontinued before resistance develops. To prevent the development of resistance indiscriminate spraying and the use of the insecticide for larval control should be avoided. There are obvious dangers in the return of malaria to a community which through freedom from it for some years has lost the natural immunity conferred by endemic infection.