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THE ACTION OF HISTAMINE ON HYDROCHLORIC ACID AND PEPSIN SECRETION IN MAN

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Since the demonstration by Popielski (1920) it has been widely recognized that injection of histamine into man and animals causes a copious flow of gastric juice of high acidity. There is, however, considerable difference of opinion as to whether the liberation of pepsin into the stomach is simultaneously augmented. Gaddum (1948), for instance, in a review says that the juice is "poor in enzymes," and Kahlson (1948) makes a similar statement. This view results largely from experiments on dogs and cats in which a variety of gastric pouches and fistulae were used (see, e.g., Vineberg and Babkin, 1931; Bowie and Vineberg, 1935). Alley (1935) has even postulated an inhibitory effect of histamine on pepsin secretion. More recently, however, Bucher, Ivy, and Gray (1941) have claimed that pepsin is increased in the stomach of the dog after histamine injection; this work has been strongly criticized by Babkin (1944). In man, a number of clinical studies (e.g., Polland, 1932) suggested a stimulation of pepsin output after histamine, and Toby (1937a) found that the peptic content of human gastric juice was as high as that produced by stimulation of the vagus in the dog. Nevertheless, Toby (1937b) was unwilling to accept the idea that histamine stimulates pepsin secretion in the human stomach, and took the view that the increased pepsin found represents a washing out of pepsin as a result of the increased flow of fluid.

In this paper we report the result of a series of experiments on human subjects.

METHODS

The subjects, with the exception of two patients with gastric ulcer, were healthy medical students, male and female, aged 20–25 years. All the experiments were performed after a 12-hour fast. After a Ryle tube had been passed, continuous aspiration of the stomach contents was carried out, the receiver being changed every fifteen minutes. To reduce dilution and contamination, saliva was expectorated as completely as possible. The receiving flasks were surrounded with ice so that the samples were cooled as they were collected; after measurement and the recording of the presence of bile and excess mucus, the fluids were filtered through pleated paper and kept in the refrigerator before and after filtration and between estimations. Few samples were markedly stained with bile pigment and these were rejected.

Free and total acid were estimated by Töpfer's method (dimethyl yellow and phenolphthalein) and pepsin by digestion of 2 mg. edestin dissolved in 2 ml. of *N*/30 HCl (*p*H 1.6). Since the series of twofold dilutions employed by Fuld (see Cole, 1933) were found to cover an unsuitable range of peptic activities the quantities of gastric juice taken were modified as shown in Table I. The tubes containing the mixtures of gastric juice and edestin were placed in a water-bath kept at 16° C., and after 30 min. 1 ml. of saturated sodium chloride solution was added and the contents of the tubes thoroughly mixed; the last tube to show complete digestion (i.e., the absence of a cloud of unchanged edestin) was noted and the activity in pepsin units (the number of mg. of edestin digested in 30 min. at 16° C. by 1 ml. of juice) recorded. It will be

TABLE I

DILUTIONS OF GASTRIC JUICE USED IN PEPSIN ESTIMATIONS: 2 ML. 0.1 PER CENT EDESTIN IN *N*/30 HCl WERE ADDED TO EACH TUBE

Tube number	ml. gastric juice diluted 1/10 with *N*/30 HCl	ml. *N*/30 HCl	Pepsin units per ml.	Dilution of original gastric juice
1	1.00	0.00	20	1 in 30
2	0.50	0.50	40	1 in 60
3	0.33	0.67	60	1 in 91
4	0.25	0.75	80	1 in 120
5	0.20	0.80	100	1 in 150
6	0.16	0.84	125	1 in 187
7	0.13	0.87	154	1 in 230
8	0.10	0.90	200	1 in 300
9	0.05	0.95	400	1 in 600

noted that, except in tube 1, the dilution attained was greater than 50; according to Bucher, Grossman, and Ivy (1945) this is necessary in order to overcome the effect of inhibitors present in the juice. It seems worthy of mention that this dilution would not be attained in experiments such as those of Toby (1936, 1937) in which Mett's method was used. It is doubtful whether full peptic activity was measured under these conditions (see Le Veen, 1946).

At least two collections were made over quarter-hour periods before injection of 1.5 mg. histamine acid phosphate (= 0.54 mg. histamine) subcutaneously, the same dose being used in all experiments. In a number of experiments 1 ml. of normal saline (0.9 g. NaCl/100 ml. H_4O) was injected, and in two experiments histamine was administered after a prolonged period of aspiration of the stomach contents (Table II).

Results

The findings in fourteen experiments are shown in Fig. 1. Since no difference between the response to histamine of the ulcer patients and of the normal subjects was observed, all results have been grouped

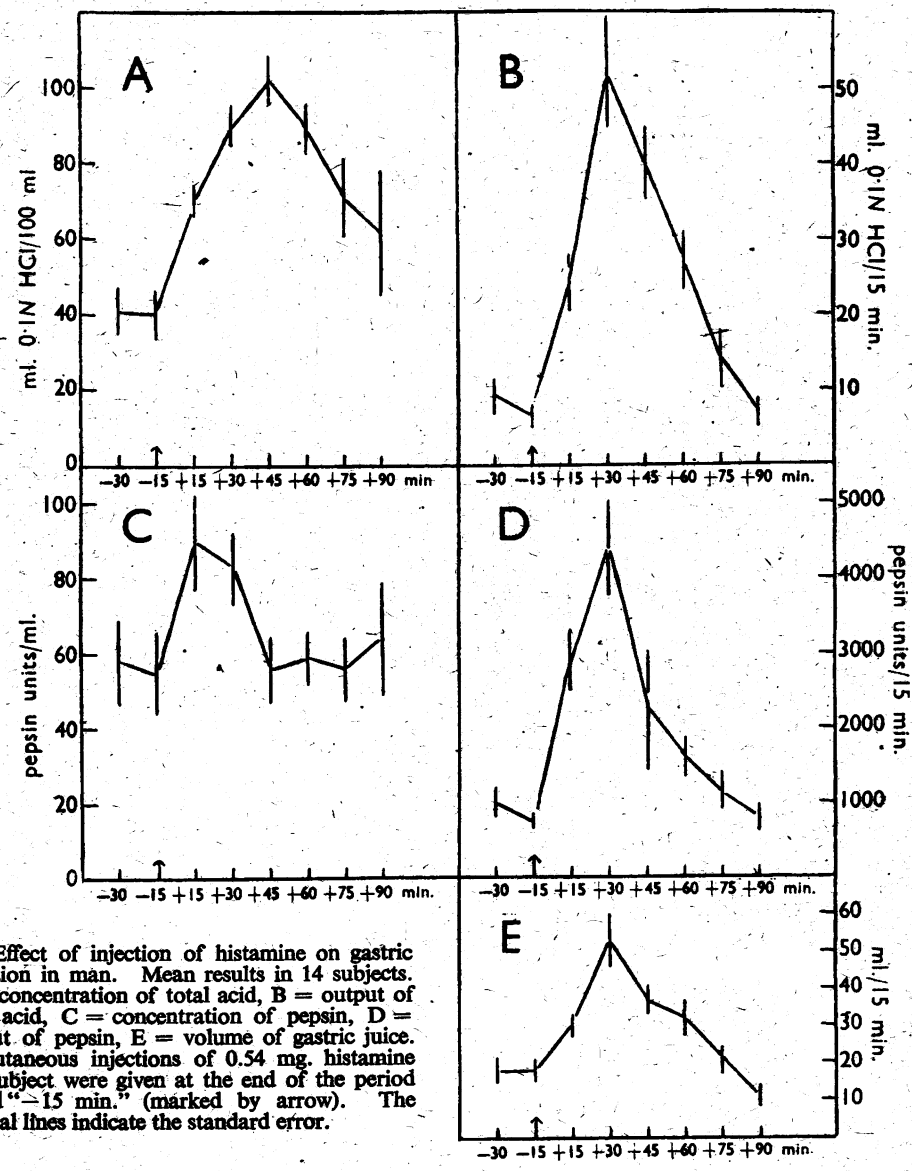

FIG. 1.—Effect of injection of histamine on gastric secretion in man. Mean results in 14 subjects. A = concentration of total acid, B = output of total acid, C = concentration of pepsin, D = output of pepsin, E = volume of gastric juice. Subcutaneous injections of 0.54 mg. histamine per subject were given at the end of the period called "−15 min." (marked by arrow). The vertical lines indicate the standard error.

together. It will be seen that in the first and second quarter-hour periods following the histamine injections, a moderate rise in pepsin concentration occurred concurrent with the rise in acid concentration. The rise in pepsin *output*, however, was more striking, reaching nearly four times the resting level in half an hour, and then declining to the resting level in the next 1¼ hours.

The "fasting contents" (=the gastric juice removed from the stomach immediately after passing the tube) were usually of considerable volume and their pepsin contents were high (Table II). It was

TABLE II

EFFECT OF INJECTION OF NORMAL SALINE ALONE, AND OF HISTAMINE INJECTION AFTER PROLONGED ASPIRATION, ON PEPSIN SECRETION IN HEALTHY SUBJECTS

No. of period (15 min.)	Subject 1 Pepsin units		Subject 2 Pepsin units		Subject 3 Pepsin units	
	per ml.	per 15 min.	per ml.	per 15 min.	per ml.	per 15 min.
"Fasting" juice	60	(6,120)	40	(3,000)	—	—
1	60	650	40	400	20	500
2	100	1,500	40	1,320	20	560
3	100	1,050	40	1,080	20	360
1 ml. normal saline injected						
4	100	1,600	20	600	40	960
5	100	1,050	20	600	20	440
6	100	1,300	20	400	20	400
7	100	1,050	20	600	40*	1,400*
8	—	—	80*	2,400*	60	6,300
9	—	—	80	5,600	—	—

*Injection of 0.54 mg. histamine per subject at beginning of these periods.

therefore thought undesirable to make comparison between the composition of the "fasting contents" and that of the juice after histamine injection, as Toby (1937b) seems to have done. In our experiment, at least two 15-minute samples were taken before injection of histamine. Table II shows that pepsin concentration and pepsin output remained reasonably steady under basal conditions. Pepsin output in some of the subjects was high. Table II shows also that an injection of normal saline had no or very little effect.

In Table III, the mean concentrations of pepsin and the outputs in the half-hour periods before and after injection of histamine are summarized. They show a rise in pepsin concentration which is significant ($t = 2.455$, $P<0.02$) and a rise in output which is highly significant ($t = 6.344$, $P<0.001$). It may be noted that the rises shown in subjects 2 and 3 (Table II) after prolonged aspiration were greater than those shown in Fig. 1; it is doubtful, however, whether any significance should be attached to these observations which were only two in number.

TABLE III

COMPARISON BETWEEN PEPSIN CONCENTRATION AND OUTPUT DURING THE HALF-HOUR PERIOD BEFORE AND THE HALF-HOUR PERIOD AFTER THE INJECTION OF 0.54 MG. *HISTAMINE

	Pepsin units ± S.E. of mean of 14 observations	
	Mean concentration (units/ml.)	Mean output (units/30 min.)
Before histamine	55 ± 10	1894 ± 333
After histamine	90 ± 10	7381 ± 802

Discussion

Notwithstanding a large volume of published work and Babkin's (1944) detailed discussion of the subject, there is no general agreement as to whether histamine stimulates the secretion of pepsin into the stomach. In the dog, surgically prepared in various ways for the collection of gastric juice, there seems to be little doubt that sham-feeding and pilocarpine (Toby, 1936) are more potent stimuli than histamine, while Goodman (1938) showed that choline esters and pilocarpine were more efficacious than histamine, which nevertheless caused an increase in peptic output. Babkin (1944) and others have argued that since the histamine-stimulated secretion of pepsin may be low and since repeated injections may cause a further fall in concentration, the histamine secretion represents only a washing out of pepsin from the gastric pits. Goodman (1938), however, found a rise in pepsin on repeated injection, while Bucher and Ivy (1941) have criticized the deductions made from the "double histamine" method (see, e.g., Gilman and Cowgill, 1931), and Bucher, Ivy, and Gray (1941) suggest that histamine, like such substances as pilocarpine, should be regarded as a stimulant for pepsin. More recently, Björkman, Norden, and Uvnäs (1943), using anaesthetized cats with the pylorus ligated, failed to find a rise in pepsin activity and indeed found a decline after histamine injection, whereas vagal stimulation caused a marked rise. They considered pepsin concentration only and not the total output. It would thus appear that in animals the gastric secretion produced by histamine has a low concentration of pepsin and that, with the greatly increased flow of fluid produced by histamine, the concentration may fall although the total output may be greater than the "resting" output.

It may well be that a species difference exists between the action of histamine on the human stomach and that of the cat and the dog. This difference may be connected with the finding (Bloomfield and Polland, 1933) that a steady flow of gastric juice of fairly high peptic activity appears to occur in the fasting state in man. We also have observed in all our experiments comparatively high peptic activity in "resting" samples, and it is clear that this fact tends to mask the response to histamine if concentration and not total output is considered. It is therefore even less easy to accept Babkin's "washing out" hypothesis in man, since a fall in pepsin concentration would be expected to result from the greatly increased flow of juice which follows all injections of histamine. Toby (1937b), using a high dose of histamine (1 mg. per subject), did find such a fall, but failed to do so at a lower dosage (0.5 mg.) ; with both doses, however, pepsin *output* was increased. In none of our experiments, in which 0.54 mg. of histamine was given, was a fall of pepsin concentration observed. A probable explanation of Toby's results is as follows : Wang (1936) obtained a maximum secretion of acid (139 m. equiv./l., equivalent to an acidity of 139 ml. 0.1*N* hydrochloric acid/100 ml.) and fluid by the injection of 1 mg. of histamine into human subjects. Our figures for acid secretion with a lower dose, like those of Toby with the lower dosage, are less than this. If at the higher dosage the rates of fluid and acid formation increased more than the rate of pepsin secretion, an apparent dilution would be the result. This assumption receives further support from the findings of Blakeley and Wilkinson (1933), who at a lower dosage still (0.25 mg. per subject) found an increase of pepsin output *and* concentration which was equal to or often greater than that produced by 6 mg. pilocarpine.

It seems clear that pepsin secretion is more easily provoked in man than in animals. Nevertheless great weight has been attached to the results of those animal experiments which indicated a low peptic secretion and less attention paid to the very extensive series of experiments carried out on human subjects by, e.g., Osterberg, Vanzart, Alvarez, and Rivers (1936), who concluded that human peptic glands are stimulated by histamine. Our results are in agreement with their findings. It may be mentioned that many authors (e.g., Ihre, 1939) have only considered pepsin concentration and not output. It is probable indeed that too great consideration of pepsin concentration, which may not be markedly increased, is the root cause of the differences in the interpretation of results by various authors.

Summary

In a series of fourteen experiments on twelve normal subjects and two with gastric ulcers, it was found that injections of 0.54 mg. histamine caused a moderate rise in mean pepsin concentration concurrent with the rise in acid concentration and fluid volume ; there was, however, a marked rise in pepsin output as compared with that in the previous resting period.

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