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The possible role of histamine in the cortisone induced gastric acid hypersecretion of the guinea-pig

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1. The effects of cortisone treatment combined with agents influencing histamine metabolism were studied on the free and total acid output in pylorus ligated guinea-pigs.

2. It was found that reduction in the synthesis of histamine produced by the administration of α-methylDOPA significantly inhibited the acid response to cortisone.

3. Enhancement of the oxidative deamination of histamine brought about by the administration of diamine oxidase or heparin inhibited cortisone induced acid hypersecretion significantly.

4. Inhibition of the oxidative deamination of histamine by aminoguanidine and iproniazid resulted in a significant increase of the cortisone induced acid hypersecretory response.

5. Inhibition of the methylation of histamine by chlorpromazine or 1,4-methylhistamine inhibited the cortisone induced hypersecretory response significantly.

6. Studies with labelled histamine indicated that cortisone increases the sequestration of histamine to the stomach.

It has been reported by Heisler & Kovacs (1967) that administration of cortisone to guinea-pigs resulted in a decrease in gastric histamine content, while gastric acid secretory activity was increased. The results suggested that an interrelationship between cortisone treatment, gastric histamine release and acid secretion might be the underlying sequence of events in the cortisone induced secretory process. Consequently, studies were designed to suppress the synthesis and enhance or suppress the inactivation of endogenous histamine and to test the effect of these pharmacological alterations on the cortisone induced gastric secretory response. The results presented here suggest that in the guinea-pig cortisone induced acid hypersecretion might be mediated by histamine.

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Methods

Animals

Male guinea-pigs weighing 300–340 g at the start of the experiments were used. They were of the multi-coloured shorthaired variety obtained from the Quebec Breeders Association (Canada). The guinea-pigs were fed with a diet of Purina guinea-pig chow, water and hay *ad libitum*. Before experiments they were fasted for 24 hr in cages with wide mesh wire bottoms ; water was allowed at all times.

Collection and analysis of gastric juice

The method previously described (Heisler & Kovacs, 1967) was used with the difference that guinea-pigs were subjected to pylorus ligation for 3 hr. Those gastric juice samples that contained 2 ml. or more of solid particles were discarded.

Extraction and assay of histamine-2-^{14}C in guinea-pig stomach

Guinea-pigs (two animals per group) were anaesthetized with pentobarbitone sodium (32 mg/kg intraperitoneally) and injected with histamine-2-^{14}C intracardially. The injections were made slowly over a 1 min period. The animals were killed 15 min after the injection. The stomachs were then blotted dry on filter paper, pooled and the wet weight determined. The extraction and assay of labelled histamine was carried out according to the method of Snyder & Axelrod (1964). The radioactivity was measured with a Nuclear Chicago gas flow detector. The efficiency of the counter for ^{14}C was 33%.

Treatments

Cortisone acetate (Cortone ; Merck, Sharp & Dohme) in a suspension of 50 mg/ml. was used. All animals receiving cortisone were injected three times subcutaneously with 100 mg/kg ; injections were made 48 hr and 24 hr before and immediately following pyloric ligation.

Other substances used were: aminoguanidine sulphate (Eastman Organic Chemicals) ; chlorpromazine hydrochloride (Poulenc Ltd.) ; diamine oxidase (Nutritional Biochemicals Corp.) ; heparin sodium (Nutritional Biochemicals Corp.) ; histamine-2-^{14}C dihydrochloride (The Radiochemical Centre, Amersham, England) ; iproniazid phosphate (Hoffmann-La Roche Ltd.) ; α-methylDOPA (Merck, Sharp & Dohme) ; and 1,4 methylhistamine dihydrochloride (Calbiochem). 1,4 Methylhistamine is expressed in terms of the base ; all other agents were calculated as salts. The substances were administered in a volume of 0.2 ml. distilled water/100 g body weight, with the exception of histamine-2-^{14}C dihydrochloride, injected in 0.1 ml. distilled water/100 g body weight. Control animals were injected with physiological saline solution in volumes equal to those administered to treated guinea-pigs.

Statistical analysis

For statistical evaluation of the results, Student's two-tailed *t* test was used.

Results

Inhibition of histamine synthesis

Effect of α-methylDOPA on cortisone induced acid hypersecretion

α-MethylDOPA has been shown by Lorenz, Pfleger & Werle (1967) to inhibit the *in vitro* decarboxylation of histidine by the non-specific histidine decarboxylase (aromatic L-amino-acid decarboxylase) in the guinea-pig stomach. α-MethylDOPA seems to be capable of blocking the enzyme *in vivo* as well: we found that it reduced gastric histamine concentrations of the guinea-pig significantly and inhibited histidine induced acid hypersecretion while histamine induced acid hypersecretion was not affected (unpublished data).

α-MethylDOPA was administered intraperitoneally in a dose of 200 or 300 mg/kg to two groups of animals. Injections were made 24 hr and 16 hr before and immediately following pyloric ligation. Cortisone was administered as described in **Methods** to a third group of animals. Another two groups of guinea-pigs received α-methylDOPA and cortisone in conjunction according to the treatment schedules described.

The results obtained are described in Table 1. α-MethylDOPA did not alter free and total acid output and concentration in comparison with respective values obtained in control animals. Cortisone produced a significant increase in free and total acidity. The lower dose of α-methylDOPA, when administered in conjunction with cortisone, decreased free and total acid output significantly. The higher dose also reduced the cortisone stimulated gastric acidity to control levels, but probably because of the large standard errors, these reductions were not statistically significant.

Enhancement of the inactivation of histamine

Effect of diamine oxidase (histaminase) on cortisone induced acid hypersecretion

Diamine oxidase was administered subcutaneously in a dose of 2, 5 or 8 mg/kg to three groups of guinea-pigs. Injections were made immediately following pyloric ligation. A fourth group of animals was injected with cortisone as described in **Methods**. Diamine oxidase was administered in conjunction with cortisone to three groups of guinea-pigs ; treatment schedules described above were used.

The results obtained in this experiment are described in Table 2. Diamine oxidase administered by itself in a dose of 2, 5 or 8 mg/kg did not significantly alter secretory volume or free and total acid output in comparison with the volume and respective acid outputs in control animals. Cortisone produced significant increases in both free and total acid outputs, but not in secretory volume. The administration of the enzyme in the lowest dose, in conjunction with cortisone, did not affect cortisone stimulated acid hypersecretion. On the other hand, the two higher doses of diamine oxidase produced significant decreases in cortisone stimulated free and total acid outputs without altering the volume of gastric juice.

Effect of heparin on cortisone induced acid hypersecretion

Hansson, Holmberg, Tibbling, Tryding, Westling & Wetterquist (1966) reported that heparin produced an increase in the activity of plasma diamine oxidase. This action of heparin may explain its inhibitory effect on histamine induced acid hyper-

TABLE 1. *Effect of α-methylDOPA on cortisone-induced acid hypersecretion in pylorus ligated guinea-pigs*

Treatment	No. of animals	Volume of gastric juice	Free HCl m-equiv.	*P* compared with	Total acid m-equiv.	*P* compared with
(a) Control	19	8·89±0·66	0·51±0·05		0·68±0·06	
(b) α-MethylDOPA 200 mg/kg 24 hr and 16 hr before and at ligation	6	8·75±0·95	0·48±0·09		0·66±0·08	
(c) α-MethylDOPA 300 mg/kg 24 hr and 16 hr before and at ligation	6	8·08±1·32	0·49±0·15		0·61±0·16	
(d) Cortisone, 100 mg/kg 48 hr and 24 hr before and at ligation	17	9·17±0·60	0·79±0·07	(a): 0·05	0·96±0·07	(a): 0·05
(e) α-MethylDOPA (as in b)+cortisone (as in d)	6	7·58±0·59	0·56±0·07	(d): 0·05	0·68±0·07	(d): 0·01
(f) α-MethylDOPA (as in c)+cortisone (as in d)	6	6·54±1·43	0·54±0·14	(d): N.S.	0·65±0·17	(d): N.S.

Duration of ligation: 3 hr. Values are means and standard errors. N.S., Not significant.

TABLE 2. *Effect of diamine oxidase on cortisone induced acid hypersecretion in pylorus ligated guinea-pigs*

Treatment	No. of animals	Volume of gastric juice	Free HCl m-equiv.	*P* compared with	Total acid m-equiv.	*P* compared with
(a) Control	11	7·67±0·83	0·42±0·04	(e) =0·001 (f) =0·01	0·55±0·06	(e) =0·01 (f) =0·01
(b) Diamine oxidase, 2 mg/kg at ligation	6	7·15±0·45	0·37±0·03	(f) =0·01	0·51±0·01	(f) =0·01
(c) Diamine oxidase, 5 mg/kg at ligation	6	7·45±0·84	0·42±0·04	(g) =N.S.	0·56±0·05	(g) =N.S.
(d) Diamine oxidase, 8 mg/kg at ligation	6	7·18±1·02	0·45±0·04	(h) =N.S.	0·58±0·12	(h) =N.S.
(e) Cortisone, 100 mg/kg 48 hr and 24 hr before and at ligation	9	8·52±0·72	0·70±0·04	(h) =0·01	0·85±0·05	(h) =0·01
(f) Diamine oxidase (as in b)+cortisone (as in e)	6	9·27±0·78	0·77±0·10	(g) =0·05	0·96±0·10	(g) =0·05
(g) Diamine oxidase (as in c)+cortisone (as in e)	6	7·77±0·45	0·50±0·05	(e) =0·01	0·66±0·05	(e) =0·02
(h) Diamine oxidase (as in d)+cortisone (as in e)	6	6·83±0·90	0·39±0·08	(f) =0·02	0·52±0·09	(f) =0·01

Duration of ligation: 3 hr. Values are means and standard errors. N.S., Not significant.

secretion in dogs (Thompson, Lerner & Tramontana, 1963) and guinea-pigs (Watt, Eagleton & Marcus, 1966).

Heparin was administered intracardially to three groups of six guinea-pigs each in a dose of 10, 20 or 50 mg/kg. Injections were made immediately following pyloric ligation. Six guinea-pigs were injected with cortisone (see **Methods**). Another three groups of animals consisting of six guinea-pigs each received both agents in conjunction according to dose schedules described above.

Results obtained in this experiment are illustrated in Fig. 1. Heparin administered by itself at three different dose levels did not produce statistically significant alterations in free or total acid output. Cortisone increased both free and total acid outputs significantly ($P<0.02$ in both cases) in comparison with the respective control outputs. When administered in conjunction with cortisone, heparin in all doses significantly reduced cortisone stimulated acid hypersecretion. Compared with animals receiving cortisone alone, heparin in the middle dose reduced cortisone stimulated free acid output by 62.5% ($P<0.001$) and total acid output by 52.7% ($P<0.01$). The highest dose reduced cortisone stimulated free acid output by 70.8% ($P<0.001$) and total acid output by 67.0% ($P<0.001$).

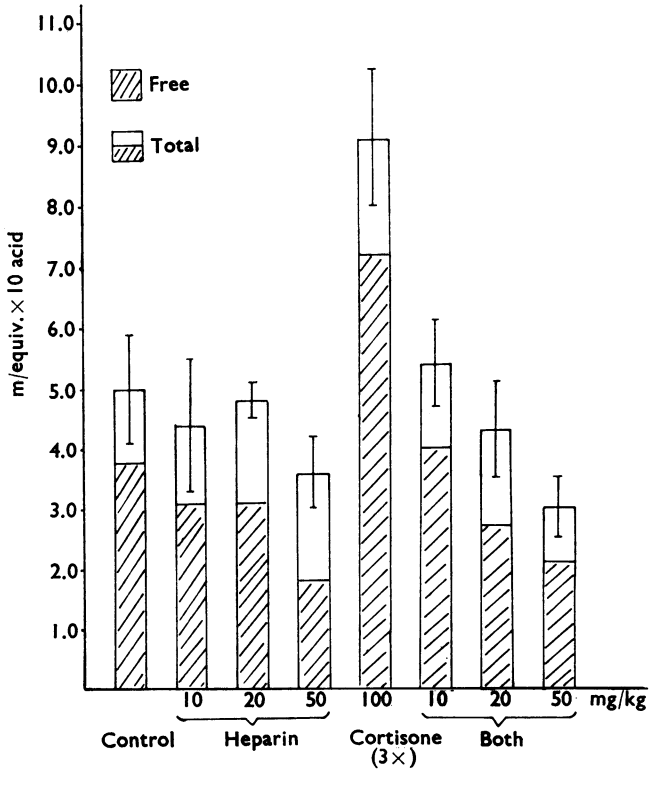

FIG. 1. Effect of heparin on cortisone induced acid hypersecretion in pylorus ligated guinea-pigs. Duration of pylorus ligation, 3 hr. Vertical bars=standard errors of total acidity.

TABLE 3. *Effect of aminoguanidine on cortisone induced acid hypersecretion in pylorus ligated guinea-pigs*

Treatment	No. of animals	Volume of gastric juice	Free HCl m-equiv.	*P* compared with	Total acid m-equiv.	*P* compared with
(a) Control	19	8·89±0·66	0·51±0·05		0·68±0·06	
(b) Aminoguanidine, 2 mg/kg 24 hr before and at ligation	6	9·82±0·64	0·71±0·09	(a) N.S.	0·89±0·11	(a) N.S.
				(f) 0·01		(f) 0·01
(c) Aminoguanidine, 5 mg/kg 24 hr before and at ligation	6	14·68±1·40	1·15±0·14	(a) 0·001	1·36±0·15	(a) 0·001
				(g) 0·05		(g) 0·05
(d) Aminoguanidine, 10 mg/kg 24 hr before and at ligation	6	12·78±0·95	1·22±0·09	(a) 0·001	1·45±0·12	(a) 0·001
				(h) 0·01		(h) 0·02
(e) Cortisone, 100 mg/kg 48 hr and 24 hr before and at ligation	17	9·17±0·60	0·79±0·07	(a) 0·01	0·96±0·07	(a) 0·01
(f) Aminoguanidine (as in b)+cortisone (as in e)	9	16·40±1·80	1·70±0·22	(a) 0·001	1·97±0·26	(a) 0·001
				(e) 0·01		(e) 0·01
(g) Aminoguanidine (as in c)+cortisone (as in e)	6	17·20±1·65	1·77±0·24	(a) 0·001	2·09±0·27	(a) 0·001
				(e) 0·001		(e) 0·001
(h) Aminoguanidine (as in d)+cortisone (as in e)	6	17·23±1·43	1·86±0·16	(a) 0·001	2·11±0·19	(a) 0·001
				(e) 0·001		(e) 0·001

Duration of ligation: 3 hr. Values are means and standard errors. N.S., Not significant.

Inhibition of the inactivation of histamine

Effect of aminoguanidine on cortisone induced acid hypersecretion

The inactivation of histamine by oxidative deamination was inhibited by treating guinea-pigs with aminoguanidine, a well known inhibitor of diamine oxidase.

Three groups of guinea-pigs were injected with aminoguanidine in a dose of 2, 5 or 10 mg/kg. Injections were made 24 hr before and immediately following pyloric ligation. A fourth group of animals received three cortisone injections (see **Methods**). Aminoguanidine was administered in conjunction with cortisone to three groups of guinea-pigs using the same treatment schedules as described above.

The results obtained in this experiment are summarized in Table 3. Only the two higher doses of aminoguanidine produced statistically significant increases both in secretory volume and in free and total acid output. The highest dose of aminoguanidine, however, did not substantially stimulate gastric secretion above the levels obtained following injection of the middle dose. Cortisone also significantly increased free and total acid outputs in comparison with the respective control outputs. Aminoguanidine (in all three dose levels) when used in conjunction with cortisone, stimulated acid secretion maximally as seen from the fact that the volume as well as the free and total acid outputs recorded following the administration of the different doses of aminoguanidine were similar and not significantly different from each other.

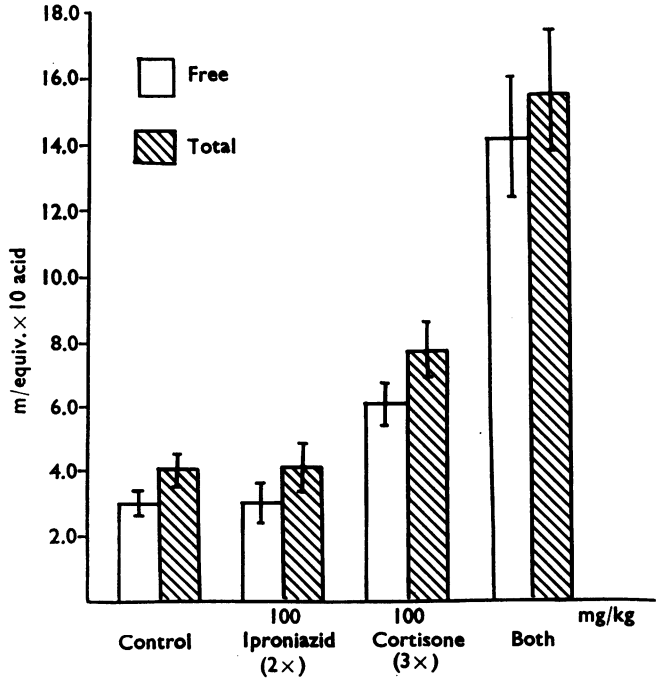

FIG. 2. Effect of iproniazid on cortisone induced acid hypersecretion in pylorus ligated guinea-pigs. Duration of pylorus ligation, 3 hr. Vertical bars=standard errors of total acidity.

TABLE 4. *Effect of chlorpromazine on cortisone induced acid hypersecretion in pylorus ligated guinea-pigs*

Treatment	No. of animals	Volume gastric juice	Free HCl m-equiv.	*P* compared with	Total acid m-equiv.	*P* compared with
(a) Control	9	7·26±0·76	0·34±0·06		0·49±0·05	
(b) Chlorpromazine, 5 mg/kg, 24 hr before and at ligation	8	5·36±0·58	0·18±0·02	(a) 0·05 (e) 0·001	0·27±0·03	(a) 0·01 (e) 0·001
(c) Chlorpromazine, 10 mg/kg, 24 hr before and at ligation	6	4·80±0·43	0·12±0·01	(a) 0·01 (f) 0·01	0·25±0·03	(a) 0·01 (f) 0·02
(d) Cortisone, 100 mg/kg, 48 hr and 24 hr before and at ligation	9	10·1 ±0·98	0·87±0·03	(a) 0·01 (e) 0·05	1·07±0·13	(a) 0·001 (e) N.S.
(e) Chlorpromazine (as in b)+cortisone (as in d)	6	8·45±0·61	0·60±0·06	(a) 0·01	0·87±0·08	(a) 0·01
(f) Chlorpromazine (as in c)+cortisone (as in d)	6	6·68±1·09	0·39±0·06	(d) 0·01 (e) 0·05	0·55±0·09	(d) 0·01 (e) 0·05

Duration of ligation: 3 hr. Values are means and standard errors. N.S., Not significant.

TABLE 5. *Effect of* 1,4 *methylhistamine on cortisone induced acid hypersecretion in pylorus ligated guinea-pigs*

Treatment	No. of animals	Volume of gastric juice	Free HCl m-equiv.	*P* compared with	Total acid m-equiv.	*P* compared with
(a) Control	9	7·07±0·67	0·32±0·04		0·44±0·05	
(b) 1,4 Methylhistamine, 1 mg/kg, at ligation	6	7·23±0·83	0·31±0·04	(a) =N.S. (c) =0·001	0·45±0·07	(a) =N.S. (c) =0·01
(c) Cortisone, 100 mg/kg, 48 hr and 24 hr before and at ligation	9	8·83±1·95	0·59±0·04	(a) =0·001 (d) =0·01	0·74±0·03	(a) =0·001 (d) =0·01
(d) 1,4 Methylhistamine (as in b)+cortisone (as in c)	6	7·18±0·73	0·40±0·04	(a) =N.S. (b) =N.S.	0·52±0·06	(a) =N.S. (b) =N.S.

Duration of ligation: 3 hr. Values are means and standard errors. N.S., Not significant.

Effect of iproniazid on cortisone induced acid hypersecretion

Six guinea-pigs were injected with iproniazid 100 mg/kg intraperitoneally 24 hr before and immediately following pyloric ligation. Six animals received cortisone as described in **Methods**, and six guinea-pigs were injected with both agents according to the same treatment schedules as above.

Data obtained in these experiments are illustrated in Fig. 2. Administration of iproniazid produced no changes in free or total acid output in comparison with the respective control outputs. Cortisone treatment increased free and total acid outputs by 103.3% ($P<0.01$) and 87.8% ($P<0.01$) respectively. Iproniazid administered in conjunction with cortisone produced a further increase in cortisone stimulated acid hypersecretion. Increases of 373% ($P<0.001$) in free acid output and 281% ($P<0.001$) in total acid output were observed in comparison with the respective control outputs. Free and total acid outputs were increased by 133% ($P<0.01$) and 102% ($P<0.01$) in comparison with the respective outputs in the animals injected with cortisone alone.

Effect of chlorpromazine on cortisone induced acid hypersecretion

Chlorpromazine has been shown to inhibit the metabolism of histamine by imidazole-N-methyltransferase both *in vitro* (Code, 1965; Lorenz *et al.*, 1967) and *in vivo* (Snyder & Axelrod, 1964).

Chlorpromazine was injected intraperitoneally into two groups of guinea-pigs in a dose of 5 or 10 mg/kg respectively. Injections were made 24 hr before and immediately following pyloric ligation. A third group of animals was injected with cortisone (see **Methods**) and two groups of guinea-pigs received chlorpromazine in conjunction with cortisone, following the same treatment schedule as with the individual agents.

The data obtained in these experiments are summarized in Table 4. Chlorpromazine administered by itself produced at both dose levels a significant decrease in free and total acid output in comparison with the respective outputs observed in the control group. Secretory volume was significantly lower only in that group of animals which had received the higher dose of chlorpromazine. Cortisone treatment increased both free and total acid output significantly. When given in conjunction with cortisone, the cortisone stimulated acid outputs were significantly reduced in animals which received the higher dose of chlorpromazine.

Effect of 1,4 methylhistamine on cortisone induced acid hypersecretion

To determine whether chlorpromazine blocked cortisone induced acid secretion specifically by the inhibition of imidazole-N-methyltransferase or non-specifically

TABLE 6. *Effect of cortisone on the sequestration of histamine-2-^{14}C to the guinea-pig stomach*

Treatment	Total radioactivity c.p.m./g	Histamine-2-^{14}C c.p.m./g
Control	5,985	4,383
Cortisone, 100 mg/kg for 3 days	22,849	9,246

Animals were injected intracardially with histamine-2-^{14}C 20 μc/kg and killed 6 hr after the last cortisone (or saline), and 15 min after the histamine-2-^{14}C injection. Values are single estimations representing two animals in each group. Counts per minute corrected for background.

by one of its many actions, the effect of another inhibitor of imidazole-N-methyltransferase, 1,4 methylhistamine (Kapeller-Adler & MacFarlaine, 1963 ; Haverback, Sturbin & Dyce, 1965) was also investigated in conjunction with cortisone.

Guinea-pigs were injected with 1,4 methylhistamine 1 mg/kg intraperitoneally immediately following pyloric ligation, or cortisone (see **Methods**) or both agents in conjunction.

The results obtained are summarized in Table 5. 1,4 Methylhistamine treatment did not alter significantly the secretory volume or the free and total acid output compared with the values obtained in the control group ; cortisone treatment significantly increased acid outputs. The administration of 1,4 methylhistamine in conjunction with cortisone significantly reduced cortisone stimulated acid hypersecretion.

Studies with histamine-2-^{14}C

Groups of guinea-pigs were injected with cortisone or saline, once daily for 3 days, subcutaneously. The animals were killed 6 hr after the last injection. Fifteen minutes before they were killed, the guinea-pigs were injected intracardially with histamine-2-^{14}C 70 μg/kg (20 μc/kg). In both groups, stomachs were removed, pooled, extracted and the radioactivity determined. The results obtained in a typical experiment are summarized in Table 6. The data in this table indicate that cortisone markedly increased the sequestration of the radioactive label to the guinea-pig stomach. Total radioactivity in the stomach of cortisone pretreated animals was 3.82 times greater than that in control stomachs. Free histamine-2-^{14}C in the stomachs of the cortisone treated group was 2.11 times greater than free labelled histamine in control stomachs.

Discussion

Cortisone in stimulating acid secretion in the guinea-pig must act on the parietal cell mass either directly or indirectly through the vagus, gastrin or histamine. It appears that changes in the parietal cell mass *per se* are poor indices of gastric secretory activity because acid secretion in response to cortisone can proceed regardless of a concomitant increase (Clarke, Neill & Welbourn, 1960 ; Reid, Hackett & Welbourn, 1961) or decrease (Goksen & Hardy, 1967) in the absolute number of parietal cells. It is unlikely that cortisone stimulates acid secretion by a vagal or gastrin-linked dependence, because vagotomy in dog (Goksen & Hardy, 1967) and man (Gray, Benson, Reifenstein & Spiro, 1951 ; Gray, Ramsey, Reifenstein & Benson, 1953) or antrectomy in dog (Zubiran, Kark & Dragstedt, 1952) do not significantly alter the acid hypersecretory response to cortisone. Atropine, which was found to reduce greatly the acid secretory response to gastrin (Grossman, 1961 ; Gregory & Tracy, 1961), did not significantly alter cortisone induced acid secretion in our experiments (unpublished).

It has been suggested previously (Heisler & Kovacs, 1967) that histamine might be involved in the acid hypersecretory response to cortisone in guinea-pigs. Results described in this paper seem to substantiate this suggestion.

One of the best known agents used for the inhibition of the non-specific histidine decarboxylase *in vitro* is α-methylDOPA (Mackay and Shepherd, 1960 ; Weissbach, Lovenberg & Udenfriend, 1961). Lorenz *et al.* (1967) have shown that this com-

pound inhibits *in vitro* the non-specific histidine decarboxylase in guinea-pig stomach, which has a high non-specific histidine decarboxylase activity (Hakanson & Owman, 1966). In the present experiments, the inhibition of gastric histamine forming capacity in guinea-pigs by α-methylDOPA inhibited the hypersecretory response to cortisone.

Roth & Horton (1940) reported that the injection of diamine oxidase to man prevented the gastric acid response to histamine. The administration of this enzyme to dogs also markedly reduced the secretory response to histamine (Grossman & Robertson, 1948). It was expected that if histamine were involved in the acid hypersecretory response to cortisone, an increase in its catabolism would result in a reduction of the cortisone effect. Enhancement of the oxidative deamination of histamine by administration of diamine oxidase indeed led to this alteration in the cortisone induced acid response.

Heparin might have blocked cortisone induced acid hypersecretion by the same mechanism as exogenous diamine oxidase, for it has been reported that the injection of heparin into guinea-pigs (Schmutzler, Giertz, Hahn, Seseke & Bernauer, 1964; Hahn, Bernauer, Giertz, Schmutzler & Seseke, 1965) or man (Hansson *et al.*, 1966) is followed by an increase of diamine oxidase activity in the plasma. Recent work by Green (1967) and Uvnäs (1967), however, has suggested that histamine in mast cells is bound to heparin. If heparin can also bind free histamine, it may block the gastric hypersecretory response to cortisone also by binding free histamine in the body.

The inhibition of the oxidative deamination of histamine by aminoguanidine and iproniazid brought about a marked increase in the cortisone induced acid hypersecretion. In the guinea-pig stomach, oxidative deamination is not a significant pathway for the removal of gastric histamine (Code, 1965), so diamine oxidase inhibitors probably exert their main inhibitory effect on diamine oxidase outside the gastric mucosa in this species, thereby extending the half-life of circulating histamine.

Methylation of histamine in the ring is the principal pathway of histamine destruction in the stomach of guinea-pigs (Liepins, Ivy & Suzuki, 1958). Our finding that the inhibition of ring-N-methylation of histamine by chlorpromazine and 1,4 methylhistamine inhibited the hypersecretory response to cortisone was rather unexpected. These results suggested to us that these agents may inhibit the formation of one or more methylated metabolites of histamine which may be essential in the secretory responses to cortisone. Indeed it was found (Kovacs & Heisler, to be published) that cortisone promotes the formation of a metabolite of histamine in the guinea-pig stomach, which is capable of exerting a marked hypersecretory effect.

Experiments with labelled histamine showing that total radioactivity and free histamine-2-^{14}C were increased in the stomachs of guinea-pigs pretreated with cortisone indicate that cortisone increases the sequestration of histamine to the gastric mucosa.

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