J. Physiol. (1967), **190**, *pp.* 261–272
With 3 *text-figures*
Printed in Great Britain

GASTRIC SECRETION DURING PREGNANCY AND LACTATION IN THE RAT

BY B. LILJA AND S. E. SVENSSON
From the Institute of Physiology, University of Lund, Sweden

(*Received* 12 *July* 1966)

SUMMARY

1. Gastric acid secretion has been studied in the rat before, during and after pregnancy using different types of stomach preparation. During the same periods the histamine-forming capacity (HFC) has been determined in gastric mucosa and mammary gland.

2. In rats with a whole stomach fistula interdigestive acid secretion is increased during pregnancy and lactation.

3. In rats with a denervated chronic pouch secretory response to stimulation with gastrin and histamine is augmented during pregnancy and lactation.

4. The histamine forming capacity (HFC) of the gastric mucosa is increased 2–3 times during the last days of pregnancy and also during lactation.

5. The HFC of the mammary gland is increased 2–3 times during lactation as compared with the fully developed gland in pregnancy.

INTRODUCTION

It has long been known that peptic ulceration during human pregnancy is uncommon. This had focused interest on gastric secretion during this period. In the rat, an increased resistance to experimentally induced gastric ulceration during the last days of pregnancy and the first days of lactation has been reported (Kahlson, Lilja & Svensson, 1964). Furthermore, an increase in the interdigestive acid secretion during the second half of pregnancy was observed by these authors. The opinion maintained by some workers that in humans the gastric acid secretion is reduced during pregnancy is based on experiments with a fractional analysis technique in combination with different secretory stimuli. However, the limitation of this type of test procedure has been emphasized (see Crean, 1963). Clark & Tankel (1954), using continuous aspiration of gastric contents, found that in a group of nine pregnant women acid secretion was increased

in three cases, decreased in one and unchanged in five. Murray, Erskine & Fielding (1957), employing a histamine test involving subcutaneous injection of a large dose of histamine, the undesired side effects of which were abolished by pre-treatment with a histamine antagonist, found that both basal and histamine-stimulated gastric secretion were reduced during pregnancy, but, as Crean (1963) has pointed out, the difference was not striking.

Both McCarthy, Evans & Dragstedt (1954) and Clark (1957) found no consistent change in gastric acid secretion during pregnancy in dogs, but a striking increase during lactation. Furthermore, Clark (1957) showed that there was no increase if lactation was suppressed by prevention of suckling and the administration of stilboestrol. In this connexion it appears noteworthy that a hypertrophy of the parietal cells has been observed in the rat during lactation (Fell, Smith & Campbell, 1963), and a hypertrophy of the gastric mucosa with hyperplasia of the parietal cells has been found in the sheep during the same period (Fell, Campbell & Boyne, 1964).

The changes in gastric mucosal histamine, the mobilization and accelerated rate of formation on re-feeding and the bearing of these findings on acid secretion have been reported by Kahlson, Rosengren, Svahn & Thunberg (1964). Further, pertinent to the present study, is the discovery that foetuses of various species are known to produce histamine at high rates: rat, (Kahlson, Rosengren, Westling & White, 1958), man (Kahlson, Rosengren & White, 1959; Lindberg, Lindell & Westling, 1963), and mouse (Rosengren, 1963). The main object of the present report is to investigate whether, and to what extent, histamine produced by the foetuses may influence the state of activity of the parietal cells. To this end, gastric acid secretion was studied during pregnancy and lactation using different types of rat stomach preparation.

METHODS

Animals. Female rats from a closed colony bred at this Institute were used, except in the radioactive experiments in which albino rats obtained from a commercial dealer were used. The body weights of the rats were 180–230 g.

Diet. The rats were fed a standard pellet diet (Anticimex 210) and tap water was freely available. A partly synthetic, histamine-free paste (Kahlson, Rosengren & Westling, 1958) was given to rats in the test-meal experiments.

Mating. Vaginal smears were taken every day and stained with methylene blue. The females were allowed to mate when in pro-oestrus, by transferring them for 12 hr to an ordinary cage containing a male rat kept on the same diet. The day of removal from the male was counted as the first day of pregnancy.

Drugs. In experiments using the test-meal technique, gastrin prepared from hog antral mucosa, a gift from Professor R. A. Gregory, was used and in the experiments with total stomach fistulas and denervated pouches, 'Gastrin II' (Gregory & Tracy, 1963) was used. In acid secretory potency, which was determined on the denervated rat pouch, 4 units of

the former gastrin preparation was equally active with 0·87 μg 'Gastrin II' (Kahlson, Rosengren *et al.* 1964). Histamine was used in the form of the diphosphate dissolved in 0·9 % NaCl and doses are expressed in terms of the base. Aminoguanidine sulphate (AMG) was used as a histaminase inhibitor in a dosage of 20 mg/kg body weight once daily. All injections were subcutaneous.

Test-meal technique. Acid secretion was measured in the unanaesthetized rat every other day by a test-meal procedure described by Thornton & Clifton (1959). The animals were given a semi-synthetic, histamine-free diet and fasted for 15 hr before the tests. Sucrose-phenol red solution, 5 ml., was introduced into the stomach through a rubber tube (Nelaton no. 9). The gastric contents were aspirated 30 min later through the reintroduced catheter and analysed for total acid by titration with 0·01 N-NaOH. The decrease in amount of phenol red during the test was determined colourimetrically to correct for the fraction of gastric contents having passed the pylorus. Acid secretion was stimulated by histamine and gastrin, the histamine test being followed in the same rat 2 hr later by a gastrin test. Histamine was injected 10 min before, and gastrin simultaneously with, inserting the test meal.

Stomach preparations. The secretory response to injected agents is altered by the presence in the stomach of the test meal (Kahlson, Rosengren *et al.* 1964). Moreover, this procedure is unsuitable for gastric juice collection over a period of several hours. Consequently, two types of rat stomach preparation were used; the whole stomach fistula, which is fully described as concerning variability of response and consistency of results during several weeks of testing by Lane, Ivy & Ivy (1957), and the denervated gastric pouch devised by Alphin & Lin (1959). Rats provided with a whole stomach fistula were not mated until at least 3 weeks after the operation and in rats provided with a denervated pouch 4–7 weeks elapsed between operation and mating. As a rule every rat was tested about 5 times before being pregnant. Animals were tested every third day. They were fasted for 15 hr before the tests and were kept unanaesthetized in Bollman-type restraining cages during the tests. During the first week of lactation the animals were fasted and tested in specially adapted Bollman-type restraining cages, so that lactation could continue. In the whole stomach preparation gastric juice was collected at 30 min intervals and analysed for total acid by titration with 0·1 N-NaOH using phenol red as indicator, In the denervated pouch total acid output was followed by perfusing the pouch with 0·9 % NaCl through a two-way plug in the cannula at a rate of 6 ml./hr. In this report, the expression 'denervated pouch' implies that at operation the pouch was deprived of vagal fibres passing along the main stomach wall.

Prevention of body fluid disturbance. Animals with whole stomach fistulas lose water and electrolytes during the collection of gastric juice, and in animals with denervated pouches there is a continuous loss of gastric secretion. Tap water and Tyrode solution were freely available to the latter animals. In the former group 5 ml. 0·9 % NaCl was injected at the onset of the collection period of 4 hr.

Determination of histamine-forming capacity (HFC) in vitro. Gastric mucosa was obtained from pregnant, lactating and non-pregnant rats. The glandular layers were removed by scraping with a scalpel after the stomach has been cleaned and pinned flat. The inguinal mammary glands were removed at different stages of pregnancy and lactation. The rate of histamine formation, in this laboratory referred to as histamine-forming capacity (HFC), was measured by incubating 100–200 mg tissue, finely cut, with 40 μg [^{14}C]histidine and by determining the amount of [^{14}C]histamine formed. The procedure as currently employed has been described by Kahlson, Rosengren & Thunberg (1963).

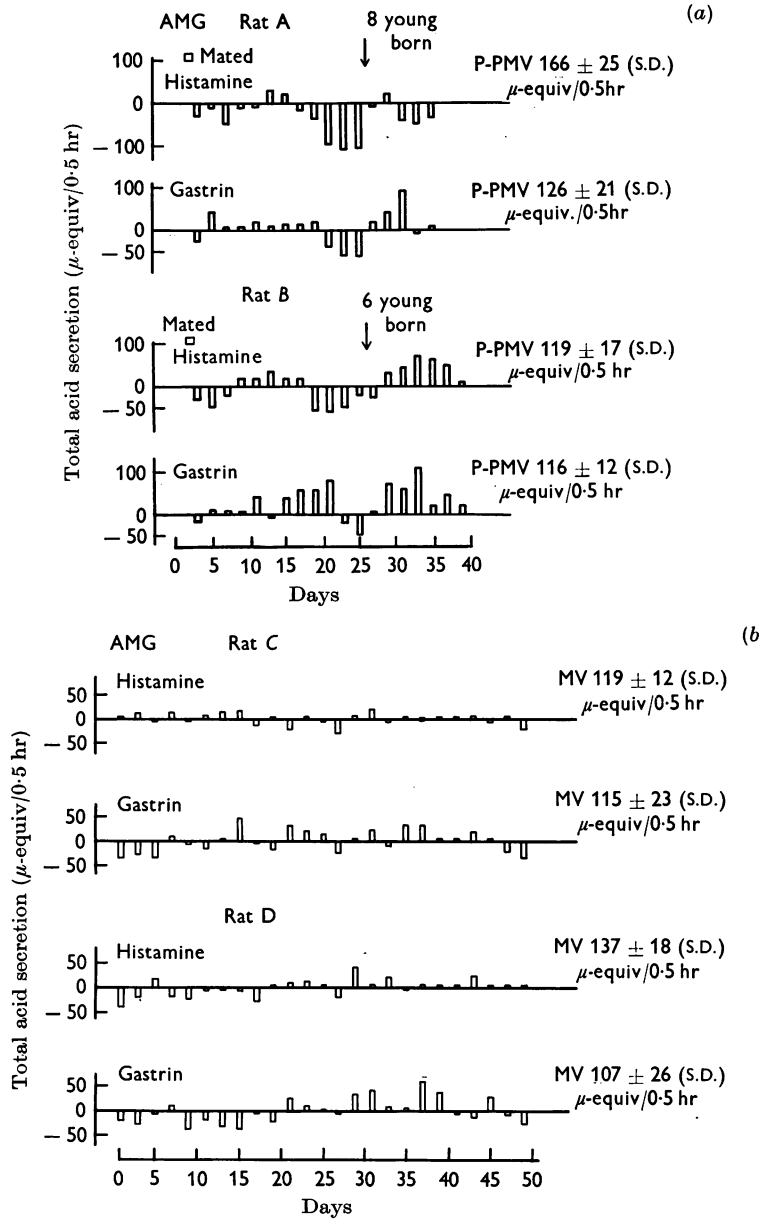

Fig. 1. Total acid secretion followed by the test-meal technique in two rats (*A* and *B*) before, during and after pregnancy (*a*). For comparison, the results are also given in the two control rats (*C* and *D*) (*b*). All rats were stimulated with 0·2 mg histamine (in terms of the base) and 2 units of gastrin. Rats *A* and *C* were under the influence of AMG. In the pregnant rats the results are given as differences from a pre-pregnant mean value (P-PMV), obtained from six observations, in the control rats as differences from the mean value. The rats were not lactating.

RESULTS

Acid secretion during pregnancy and lactation

Test-meal technique. Acid secretion was studied in six pregnant and two non-pregnant rats. Dose–response curves were established for histamine and gastrin in individual rats and the two substances were administered in doses calculated to give a submaximal response. Four experiments are presented in Fig. 1. The results are given as differences from a pre-pregnant mean value (P-PMV) and in the non-pregnant rats from the mean value. Secretory responses to histamine or gastrin are unchanged or slightly increased during the first 2 weeks of pregnancy, while there is a decrease during the third week. In all six pregnant rats the same pattern was noticed. The rats were not lactating.

Whole stomach fistula. Twenty-three rats were investigated. The animals were injected either with histamine or gastrin. In one group of seventeen the animals were under the influence of AMG. Results from two rats are presented in Fig. 2, values being given as variations from P-PMV. In pregnancy there is a steep increase in the basal secretion from the first week onwards, and this increase reaches a maximum during the third week. This is in agreement with earlier observations (Kahlson, Lilja & Svensson, 1964). When pregnancy is followed by lactation the high basal acid secretion observed during pregnancy persists, and in some rats even higher values are registered (Fig. 2 and Table 1). The increase in interdigestive secretion, as compared with the pre-pregnant values is 1·5–2 times during the second week of pregnancy, 2–3 times during the third week, and 2–3·5 times during lactation. The administration of AMG did not seem to affect the rate of secretion in the interdigestive phase. The secretory responses to both histamine and gastrin are increased during pregnancy and lactation, the highest response being noted during lactation. Following weaning there is a slow decrease. No difference in rate of secretion was noted between animals with and without AMG.

Denervated pouch. Six rats were injected first with histamine, and 2 hr later with gastrin. Results are shown in Fig. 3 and Table 2. The interdigestive secretion of the pouches was absent or very scanty, thus confirming the observations of Alphin & Lin (1959), and did not change measurably during pregnancy and lactation. In one rat, not included in the series, there was a conspicuous increase in basal secretion during lactation, presumably due to reinnervation of the pouch. A typical experiment from the series of six is presented in Fig. 3, which shows an increase in the secretory response to both histamine and gastrin, with peak values during the third week of pregnancy and during lactation. Following weaning, the secretory responses to histamine and gastrin decreased steadily but

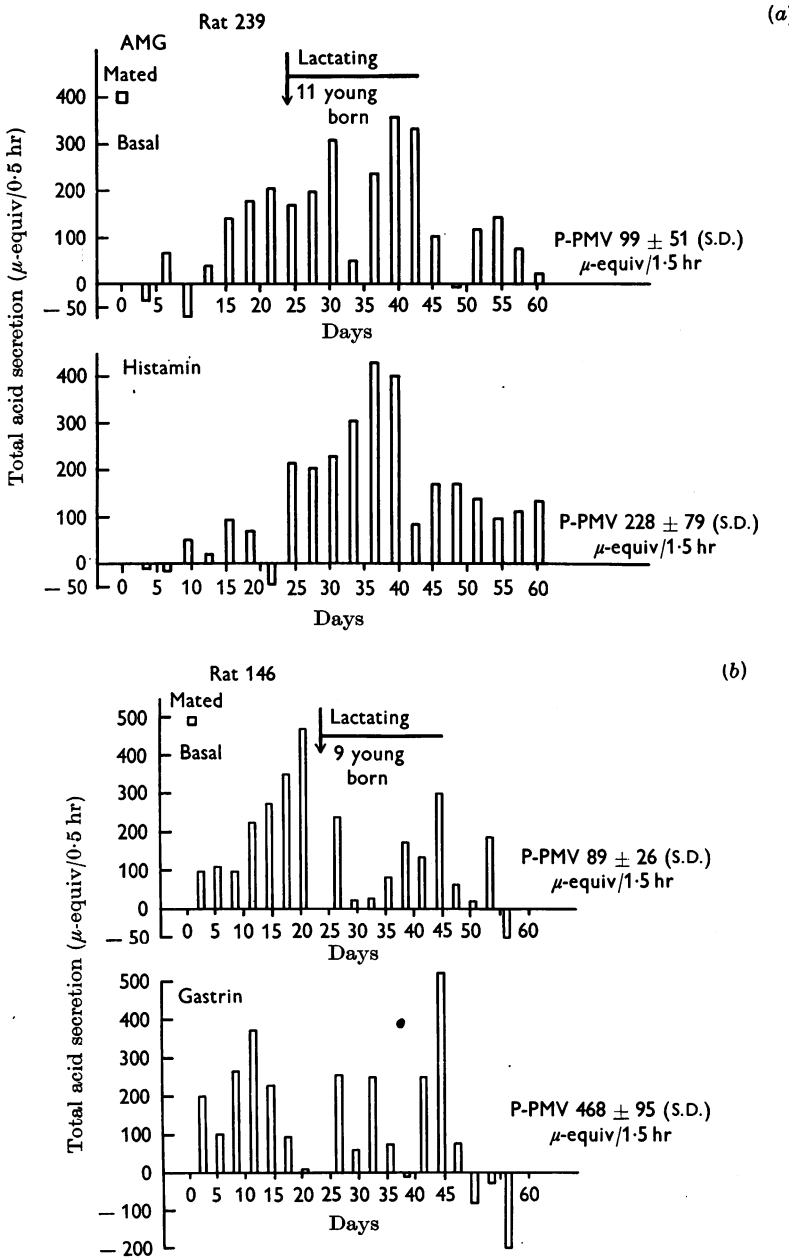

Fig. 2. Basal and histamine (1 mg in terms of the base) or gastrin (0·5 μg) stimulated acid secretion during pregnancy and lactation in two rats each provided with a whole-stomach fistula. Rat 239 was under the influence of AMG (*a*). Rat 146 was not (*b*). The results are given as differences from a pre-pregnant mean value (P-PMV), obtained from five observations in rat 239 and seven in rat 146.

TABLE 1. Basal, histamine (1 mg in terms of the base)—and gastrin (0·5 μg)—stimulated acid secretion during pregnancy and lactation in two groups of rats provided with whole stomach fistulas. The animals in the (*b*)-part of the table were under the influence of AMG. The figures with S.E. of the mean represent multiples of the P-PMV value. Pre-pregnant mean values (P-PMV) with S.E. of mean are expressed in μ equiv/1·5 hr. The increase in basal secretion has been verified by applying the Student's *t*-test to the results

Period	Basal secretion	No. of rats	Histamine-stimulated secretion	No. of rats	Gastrin-stimulated secretion	No. of rats
			(*a*)			
P-PMV	169 ± 24	6	286 ± 23	5	346 ± 32	1
Pregnancy						
1st week	1·2 ± 0·11*	6	1·1 ± 0·25	5	1·7	1
2nd	1·7 ± 0·43**	6	1·5 ± 0·37	5	1·3	1
3rd	2·8 ± 0·37**	6	1·6 ± 0·39	5	0·9	1
Lactation						
1st week	2·4 ± 1·05**	6	1·8 ± 0·49	5	1·3	1
2nd	2·2 ± 0·71**	5	2·1 ± 0·23	4	1·3	1
3rd	3·3 ± 0·42**	4	2·1 ± 0·59	3	1·8	1
After weaning						
1st week	1·9 ± 0·30**	4	1·3 ± 0·08	3	0·5	1
			(*b*)			
P-PMV	115 ± 14	17	273 ± 38	6	330 ± 29	11
Pregnancy						
1st week	1·5 ± 0·71**	17	1·2 ± 0·29	6	1·1 ± 0·42	11
2nd	1·9 ± 0·60**	17	1·3 ± 0·32	6	1·3 ± 0·32	11
3rd	3·2 ± 1·34**	17	1·3 ± 0·44	6	1·2 ± 0·35	11
Lactation						
1st week	2·7 ± 1·44**	8	1·7 ± 0·26	4	1·6 ± 0·49	4
2nd	2·4 ± 0·50**	5	2·8 ± 0·30	3	1·8 ± 0·43	3
3rd	3·5 ± 0·78**	5	2·8 ± 1·02	2	1·9 ± 0·55	3
After weaning						
1st week	1·7 ± 0·34**	4	1·53	1	1·3 ± 0·30	3

* $P < 0·05$; ** $P < 0·01$.

TABLE 2. Secretory responses to histamine (1 mg in terms of the base) and gastrin (0·3 μg), in terms of multiples of the pre-pregnant responses, in rats provided with a denervated pouch. Pre-pregnant mean values (P-PMV) with S.E. of mean are expressed in μ-equiv/1·0 hr. The increase has been verified in most cases by applying the Student's *t*-test to the results

Period	Histamine-stimulated secretion	Gastrin-stimulated secretion	No. of rats
P-PMV	18 ± 3	70 ± 13	6
Pregnancy			
1st week	1·3 ± 0·52*	1·3 ± 0·45*	6
2nd week	1·7 ± 0·64**	1·9 ± 0·85**	6
3rd week	2·1 ± 0·92**	2·3 ± 0·96**	6
Lactation			
1st week	3·6 ± 1·75**	3·6 ± 1·59**	4
2nd week	5·0 ± 2·91**	3·3 ± 1·66**	4
3rd week	4·2 ± 2·61**	3·9 ± 1·31**	3
After weaning			
1st week	2·5 ± 1·87*	2·8 ± 2·08*	2

* $P < 0·05$; ** $P < 0·01$.

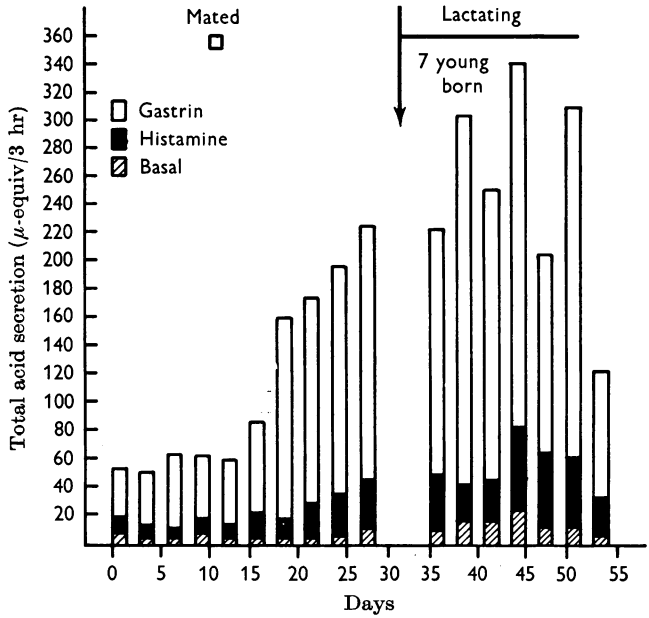

Fig. 3. Acid secretion before, during and after gestation in a rat provided with a denervated pouch. The columns represent a 3 hr collection, composed of 1 hr inter-digestive secretion (the cross-hatched part), followed by 1 hr of histamine (1 mg in terms of the base) stimulated secretion (the filled part), and finally 1 hr of gastrin (0·5 μg) stimulated secretion (the open part).

TABLE 3. Mucosal HFC on different days of pregnancy and lactation

Day of pregnancy	HFC (μg/g. 3 hr) (fasting)	Mean	HFC (μg/g. 3 hr) (free access to food)	Mean
7	1·1, 1·6	1·4	—	—
13	2·3, 3·3, 4·9	3·5	6·2, 34·8	20·5
15	3·5, 4·0	3·8	15·0, 44·2	29·6
17	1·9, 2·1, 3·3, 4·3 5·6	3·4	43·1, 57·5	50·3
19	4·3, 4·8, 6·4	5·2	31·2, 58·2, 60·4	49·9
21	4·6, 9·1, 9·7	7·8	16·9, 42·8	29·9
Day of lactation				
1	3·0, 6·7	4·9	—	—
3	6·8, 15·2	11·0	—	—
7	3·5, 4·8, 6·5, 6·8 11·3, 11·7, 13·4	8·3	—	—
14	4·0, 5·7, 7·5 7·7, 12·4, 13·9	8·5	—	—
21	4·7, 6·5, 6·7 8·8 10·4	7·4	—	—
Non-pregnant controls	1·7, 2·2, 3·8, 4·4 4·4, 4·5, 5·8	3·8	11·7, 13·3, 19·8 20·9, 31·0	19·3

remained augmented even after one month. This is in agreement with the finding that the secretory response of denervated pouches is less in the first month than in the sixth month following operation (Kahlson, Rosengren *et al.* 1964).

Mucosal HFC during pregnancy and lactation. Code & Hallenbeck (1961) using a non-isotopic *in vitro* method have reported a three- to four-fold increase in the rate of histamine formation in the rat gastric mucosa during the 17th to 21st day of pregnancy. Since in later work the state of feeding has been shown to affect mucosal histidine decarboxylase activity (Kahlson, Rosengren *et al.* 1964) two groups of animals were studied, one with free access to food and the other fasted for 24 hr before determination of mucosal HFC. The former group was investigated during pregnancy, the latter during both pregnancy and lactation. The results are shown in

TABLE 4. HFC of the rat inguinal mammary gland (ng/g.3 hr)

Day of pregnancy	HFC (ng/g.3 hr)	Mean HFC (ng/g.3 hr)
7	34, 42	
13	34	
16	56	
17	18, 32	34
19	34	
20	34	
21	28	
Day of lactation		
1	10, 12	11
3	32, 52	42
7	26, 40, 56, 90, 94, 112	70
14	50, 90, 90, 92, 144, 150	102
21	36, 44, 52, 76, 114	64

Table 3. In the fasted group the mucosal HFC during the last days of pregnancy was about 2 times higher than in the non-pregnant controls. During lactation this increase persists with mean values about 2–3 times those of the controls. In the group with free access to food the increase during the last days of pregnancy was about the same as in the fasted group. During lactation a few determinations were done on animals with free access to food and the increase was 2–3 times as against the controls.

HFC of the mammary gland

During the second half of pregnancy and during lactation the inguinal glands are easily recognized and removed. In the non-pregnant animal the recognition of the glands is difficult, and controls were not obtained. As seen from Table 4, the variations in HFC are small during the course of pregnancy and the mean value for this group is 34 ng/g tissue.3 hr.

During lactation the HFC was elevated, and after 7 days lactation the HFC was twice that found in the pregnant group. This increase persists for the whole period of lactation.

DISCUSSION

The present observations on rats with a whole stomach fistula show that during pregnancy and lactation the interdigestive acid secretion and the acid secretory response to injected gastrin and histamine are increased. As to the acid secretory response to gastrin and histamine, it appears uncertain whether the figures in Table 1 represent a genuine increase. On subtracting the basal secretion from the amount of acid obtained by gastrin and histamine stimulation it appears that the increase is presumably largely due to a greater interdigestive secretion. However, in rats with denervated pouches, where basal secretion is absent or scanty, a striking increase in acid secretory response to both histamine and gastrin is easily demonstrated during pregnancy and lactation. Since the interdigestive acid secretion in the pregnant rat with a whole stomach fistula is probably near the maximal secretory capacity, injection of histamine or gastrin is not likely to augment secretion further, a circumstance which may account for the discrepancy in the results given by the two methods. The maximal secretory capacity was not estimated during pregnancy. The high basal secretion during pregnancy and lactation is dependent on intact vagal innervation, since the secretion is absent in the denervated pouch. Pregnancy and lactation influence the gastric mucosa to give an increased acid response to histamine and gastrin even without vagal innervation. The results obtained with the test-meal technique are at variance with those seen with the stomach preparations. As mentioned earlier, Kahlson, Rosengren *et al.* (1964) found that 'the secretory response to injected agents was altered by the presence of the test-meal itself', an observation which renders further discussion of the results with the test-meal technique unprofitable. As to the mechanism of the increase in acid secretion during lactation it should be mentioned that Fell *et al.* (1963), and Campbell & Fell (1964) showed that, in rats during this period, a hypertrophy of the parietal cells occurred, which was related to an increased food intake and could be inhibited by subjecting the animals to a restricted diet.

The HFC of the rat gastric mucosa increases on re-feeding and after injections of gastrin, but no increase occurs after histamine stimulation (Kahlson, Rosengren *et al.* 1964). Under the influence of vagal excitation the mucosal HFC is likewise elevated (G. Kahlson, E. Rosengren & R. Thunberg, unpublished). There is a continuous increase in the interdigestive secretion during pregnancy, but the increase in HFC, determined

after 24 hr starvation, is seen only during the last days of pregnancy and persists for the whole period of lactation. Significantly, the increase in basal hydrochloric acid secretion coincides with the increasingly high rate of foetal histamine formation. The present results reinforce the conclusion that histamine produced by the foetus is, at least in part, responsible for the high rate of interdigestive secretion during the last week of pregnancy (Kahlson, Lilja & Svensson, 1964). A further secretory stimulus is presumably provided by the elevated mucosal HFC.

During lactation histamine cannot be responsible for the increase in interdigestive secretion as there is no or only slight increase in urinary histamine during this period (B. Lilja, unpublished). In non-pregnant and pregnant rats the basal urinary excretion of histamine is increased 3–4 times by AMG. Long-term treatment with AMG, however, does not seem either to increase the interdigestive secretion or to enhance the responses to injected histamine or gastrin in rats with whole stomach fistula, as can be seen from Table 1. This is contrary to the findings obtained with single doses of AMG (Ghosh & Schild, 1958; Amure & Ginsburg, 1964). It appears that the increase in blood histamine concentration under the influence of AMG is not sufficient to give a measurable increase in interdigestive acid secretion. In pregnant rats high values of histamine excretion are found during the last period of pregnancy, corresponding to about 2–6 mg foetal histamine entering the maternal bloodstream in 24 hr (Kahlson, Rosengren & Westling, 1958). It is reasonable to assume that the high blood concentration of histamine during this period provides for stimulation of acid secretion during the interdigestive phase in the preparation with intact vagal innervation.

The HFC in lactating mammary glands is increased in relation to those of pregnant ones but the increase is too small to explain the high rate of interdigestive secretion. However, the association of mammary gland activity with an elevation of HFC of the gland appears noteworthy.

From the present results it is apparent that the factors imparting protection against mucosal ulceration are other than alterations in acid secretion. A clue to the problem has been found by the demonstration that the foetus produces an agent imparting such protection (Kahlson, Lilja & Svensson 1964). Nevertheless, further work on gastric secretion during pregnancy in the rat and other species appears desirable.

We should like to thank Professor R. A. Gregory, Liverpool, for generous gifts of gastrin preparations and Professor Georg Kahlson for encouragement and advice. This work was supported by National Institute of Health Grant No. 5 R01 HD00255-06 (to G.K.), and by grants from the medical faculty of the University of Lund, Sweden (B.L. and S.E.S.).

REFERENCES

ALPHIN, R. S. & LIN, T. M. (1959). Preparation of chronic denervated gastric pouches in the rat. *Am. J. Physiol.* **197**, 257–259.

AMURE, B. O. & GINSBURG, M. (1964). Effects of chlorpromazine and bromolysergic acid diethylamide on gastric secretion of acid induced by histamine in rats. *Br. J. Pharmac. Chemother.* **22**, 520–526.

CAMPBELL, R. M. & FELL, B. F. (1964). Gastro-intestinal hypertrophy in the lactating rat and its relation to food intake. *J. Physiol.* **171**, 90–97.

CLARK, D. H. (1957). Gastric acid secretion in dogs during pregnancy and lactation. *Scott. med. J.* **2**, 392–395.

CLARK, D. H. & TANKEL, H. I. (1954). Gastric acid and plasma-histaminase during pregnancy. *Lancet* ii, 886–887.

CODE, C. F. & HALLENBECK, G. A. (1961). Effect of pregnancy on the histidine decarboxylase activity of the rat's stomach. *J. Physiol.* **159**, 66–67*P*.

CREAN, G. P. (1963). The endocrine system and the stomach. *Vitams Horm.* **21**, 215–280.

FELL, B. F., CAMPBELL, R. M. & BOYNE, R. (1964). Observations on the morphology and nitrogen content of the alimentary canal in breeding hill sheep. *Res. vet. Sci.* **5**, 175–185.

FELL, B. F., SMITH, K. A. & CAMPBELL, R. M. (1963). Hypertrophic and hyperplastic changes in the alimentary canal of the lactating rat. *J. Path. Bact.* **85**, 179–188.

GHOSH, M. N. & SCHILD, H. O. (1958). Continuous recording of acid gastric secretion in the rat. *Br. J. Pharmac. Chemother.* **13**, 54–61.

GREGORY, R. A. & TRACY, H. J. (1963). Constitution and properties of two gastrins extracted from hog antral mucosa. *J. Physiol.* **169**, 18–19*P*.

KAHLSON, G., LILJA, B. & SVENSSON, S. E. (1964). Physiological protection against gastric ulceration during pregnancy and lactation in the rat. *Lancet* ii, 1269–1272.

KAHLSON, G., ROSENGREN, E., SVAHN, D. & THUNBERG, R. (1964). Mobilization and formation of histamine in the gastric mucosa as related to acid secretion. *J. Physiol.* **174**, 400–416.

KAHLSON, G., ROSENGREN, E. & THUNBERG, R. (1963). Observations on the inhibition of histamine formation. *J. Physiol.* **169**, 467–486.

KAHLSON, G., ROSENGREN, E. & WESTLING, H. (1958). Increased formation of histamine in the pregnant rat. *J. Physiol.* **143**, 91–103.

KAHLSON, G., ROSENGREN, E., WESTLING, H. & WHITE, T. (1958). The site of increased formation of histamine in the pregnant rat. *J. Physiol.* **144**, 337–348.

KAHLSON, G., ROSENGREN, E. & WHITE, T. (1959). Formation of histamine by the foetus in the rat and man. *J. Physiol.* **145**, 30–31*P*.

LANE, A., IVY, A. C. & IVY, E. K. (1957). Response of the chronic gastric fistula rat to histamine. *Am. J. Physiol.* **190**, 221–228.

LINDBERG, S., LINDELL, S. E. & WESTLING, H. (1963), The metabolism of ^{14}C-labelled histamine injected into the umbilical artery. *Acta obstet. gynec. scand.* **42**, suppl. 1, 35–47.

MCCARTHY, J. D., EVANS, S. O. & DRAGSTEDT, L. R. (1954). Gastric secretion in dogs during pregnancy and lactation. *Gastroenterology* **27**, 275–280.

MURRAY, F. A., ERSKINE, J. P. & FIELDING, J. (1957). Gastric secretion in pregnancy. *J. Obstet. Gynaec. Br. Commonw.* **64**, 373–381.

ROSENGREN, E. (1963). Histamine metabolism in the pregnant mouse. *J. Physiol.* **169**, 499–512.

THORNTON, G. H. M. & CLIFTON, J. A. (1959). Estimation of gastric hydrochloric acid secretion in rats by a test meal technique. *Am. J. Physiol.* **197**, 263–268.