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HYPERPLASIA OF THE GASTRIC MUCOSA DURING PREGNANCY AND LACTATION IN THE RAT

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SUMMARY

1. The growth of the gastric mucosa during pregnancy and afterwards has been studied by comparing the stomachs of rats, killed at weekly intervals after impregnation, with the stomachs of virgin rats of the same age and starting weight. The rate of growth of the gastric mucosa in both groups was determined from the changes observed in the weight of the whole stomach, the weight and surface area of the fundus, the volume (mass) of the fundic mucosa and the total parietal and total peptic cell populations.

2. Hyperplasia of the gastric mucosa occurred during pregnancy and lactation, the effect being characterized by increases in the surface area and volume (mass) of the gastric mucosa, and in the total parietal and total peptic cell populations.

3. The data suggest that the effect developed shortly after conception. Hyperplasia of the gastric mucosa continued throughout pregnancy and reached maximal values after the second week of lactation and waned thereafter; the maximal changes obtained for individual observations such as surface area and the total parietal and total peptic cell populations represented increases of the order of 40% above corresponding control values.

4. From the observations that were made on food intake it seemed unlikely that the hyperplasia of the gastric mucosa was due to hyperphagia. It also seemed unlikely that the effect could be accounted for by the increase that occurred in body weight during pregnancy.

INTRODUCTION

Fell and his colleagues (Fell, Smith & Campbell, 1963; Campbell & Fell, 1964; Fell, Campbell & Boyne, 1964) have established that the growth of the alimentary tract is accelerated during lactation in several species such as the rat, mouse and sheep, and they, amongst others, have suggested that the mechanism responsible for this effect is the increased food consumption that occurs at this time. However, it has yet to be clearly established that this effect is restricted only to the period of lactation; it seemed possible that it might occur during pregnancy also since the growth of the liver is increased during both pregnancy and lactation in rats and mice (Campbell, Innes & Kosterlitz, 1953; Kennedy, Pearce & Parrott, 1958).

The problem has been re-examined in the present study using the rat as an experimental model, the rate of growth of the gastric mucosa during pregnancy and lactation being determined from the changes observed in the weight of the whole stomach, the weight, surface area and volume (mass) of the gastric mucosa, and the total parietal and total peptic cell populations. An attempt has been made to relate the changes observed in the growth of the gastric mucosa to the changes that occurred in body weight and to food consumption during pregnancy and lactation.

The experiment was designed to compare the stomachs of impregnated rats, killed at different time intervals throughout the course of pregnancy, lactation and afterwards, with the stomachs of unmated control rats of the same age and starting weight.

METHODS

Experimental design

A population of virgin female rats, within the weight range 240–260 g, was obtained from the closed Wistar colony maintained at the Clinical Endocrinology Unit. The animals were ranked in pairs of similar age and body weight, one animal from each pair being selected at random for impregnation, while the other was designated as its unmated control. Each pair was then allocated according to a predetermined random order to one or other of eight sample groups which were killed at weekly intervals corresponding to different stages of the pregnancy and lactation of the impregnated rat in each pair (Table 1). The animals in each pair were caged together in the same cage throughout the experiment except for the period of lactation when the dam was housed in a separate cage with her pups.

Originally, six pairs of rats were allocated to each sample group and six additional pairs were kept in reserve to replace those that might be lost to the experiment because of infertility. For the purpose of mating two females were housed in a single cage with a fertile male. Vaginal smears were examined each morning and impregnation was considered to have occurred on the day that spermatozoa were first observed; if no sperms had been detected after seven days the female was deemed infertile and removed with its unmated control from the experiment. In the event, fourteen out of the total of fifty-six rats proved infertile and as a result the number of pairs available for allocation to groups 5–8 were reduced (Table 2).

The period of gestation for all impregnated rats was found to be 21 days to the nearest day and lactation was permitted for 21 days following delivery. The animals were killed by exposure to chloroform and the dead body weight and litter size were recorded.

Body weight

Final body weight was regarded as the weight of each animal recorded immediately after death. In the case of the pregnant animals (i.e. those in groups 1, 2 and 3) final body weight was estimated as the difference between dead body weight and the wet weight of the uterus and its contents, the uterus being removed immediately after death; no allowance was made for the weight of the uterus in any of the other groups.

TABLE 1. Sample groups which were killed at weekly intervals corresponding to different stages of the pregnancy and lactation of the impregnated rat in each pair

Sample group	Time interval after impregnation (days)
1	7; end of 1st week of pregnancy
2	14; end of 2nd week of pregnancy
3	21; at term, end of 3rd week of pregnancy
4	28; end of 1st week of lactation
5	35; end of 2nd week of lactation
6	42; at weaning, end of 3rd week of lactation
7	49; end of 1st week after lactation
8	56; end of 2nd week after lactation

Food consumption

Food consumption was estimated throughout pregnancy and afterwards in three rats which had been impregnated on the same day and in their unmated controls. The animals selected for this purpose were housed in individual cages which were equipped with food baskets constructed of fine wire to minimize the scattering of food particles. The food baskets were weighed at the same time each day and the food intake of each rat was calculated from the difference in the weight of the food basket from day to day. In order to assimilate daily fluctuations in the food intake of this small number of animals, the results were calculated as the average food intake per rat per three days.

Observations on the gastric mucosa

The stomach was removed as quickly as possible after death and the following observations were made on each organ after it had been processed; the weight of the whole stomach, the weight of the fundus, the surface area, height and volume of the fundic mucosa, and the total parietal and total peptic cell populations of the stomach. The methods used to obtain these estimates have been described previously (Cox & Barnes, 1945; Card & Marks, 1960; Crean, 1968; Crean, Marshall & Rumsey, 1969). Briefly, the stomach was opened along the greater curvature and placed serosal surface downwards on a sheet of unexposed X-ray film; the organ was pinned to the X-ray film in such a way as to eliminate mucosal folds, and fixed in the flattened position by immersion in 10% formol-saline. After fixation the whole stomach was weighed after being swabbed dry. The antrum and rumen were then separated from the fundus by cutting along the appropriate junction lines with fine scissors and the

weight of the fundus itself was recorded (Crean, Hogg & Rumsey, 1969). The surface of the fundus was measured with a planimeter from its outline on the X-ray film (Card & Marks, 1960; Crean, 1968). The parietal and peptic cell populations were estimated from the counts of each cell type made on histological sections cut at right angles to the surface of the mucosa. Cell counts were carried out at a magnification of approximately × 1500, using a calibrated graticule on the screen of a projecting microscope. A single cell 'count' represented all the parietal and peptic cell nuclei seen in a column of tissue 0·1 mm broad extending from the base to the surface of the mucosa; such a column would underlie a unit of the surface area of the mucosa with dimensions represented by the width of the column and the thickness of the section under observation. An 'average count per unit area' (i.e. the average number of parietal or peptic cells underlying a unit of the surface area of mucosa) was calculated for each animal after the observed values had been corrected for section thickness, nuclear overestimation and tissue shrinkage (Abercrombie, 1946; Card & Marks, 1960; Crean, 1968), the correction factors required being derived from direct measurements (Marengo, 1944; Card & Marks, 1960). The average count per unit area was then referred to the total surface area of the fundus to give an estimate of the total parietal and peptic cell populations of the stomach. The volume of the fundic mucosa was calculated as the product of the surface area and the mean height of the mucosa; since the density of a cell is about unity, mucosal volume approximates mucosal mass. In order to eliminate subjective bias each rat was coded by a third party according to a set of random numbers, so that all observations were made without knowledge of the identity of the stomachs or tissues under consideration.

RESULTS

The mean and standard error for the individual observations in the impregnated and control animals in each group are given in Table 2. The difference between the individual rats in each pair was calculated, and the mean difference in each group was tested for statistical significance by the Student t test.

(*i*) *Stomach weight*

There was an increase in the weight of the whole stomach during pregnancy and the early stages of lactation followed by a decrease during the later stage of lactation and afterwards. There was no such rise and fall in stomach weight in the control rats and, moreover, stomach weight tended to be greater in the impregnated animals than it was in the controls at almost all time intervals. Thus, after the first week of the experiment the mean values for stomach weight were 1422 ± 30 mg and 1406 ± 39 mg in the impregnated and control groups respectively (N.S.) while after the second week the value for the impregnated animals had increased to 1645 ± 76 mg compared to 1341 ± 68 mg in the controls ($P < 0{\cdot}001$); thereafter, stomach weight increased in the impregnated animals to reach a maximum value of 1962 ± 56 mg after the second week of lactation, at which point the corresponding control value was 1433 ± 25 mg ($P < 0{\cdot}01$).

TABLE 2. The effects of pregnancy and lactation

	Pregnancy			Lactation				
Groups of rats ...	1	2	3	4	5	6	7	8
Number of pairs ...	6	6	6	6	3	4	5	4
Initial body weight (g)								
Impregnated	245 ± 4*	234 ± 7	249 ± 5	238 ± 8	241 ± 5	247 ± 8	246 ± 8	243 ± 3
Control	243 ± 4	233 ± 7	245 ± 5	237 ± 7	238 ± 9	243 ± 6	244 ± 6	239 ± 4
Final body weight (g)								
Impregnated	257 ± 7 (257 ± 7)†	261 ± 4 (263 ± 5)†	275 ± 6 (328 ± 8)†	284 ± 10	301 ± 11	307 ± 16	263 ± 12	264 ± 3
Control	246 ± 3	241 ± 8	253 ± 6	238 ± 5	255 ± 6	259 ± 6	262 ± 7	247 ± 6
Value for P	< 0·05	< 0·001	< 0·001	< 0·005	< 0·05	< 0·025	N.S.‡	N.S.
Total stomach weight (mg)								
Impregnated	1422 ± 30	1645 ± 76	1725 ± 81	1931 ± 78	1962 ± 56	1774 ± 47	1713 ± 107	1703 ± 151
Control	1406 ± 39	1341 ± 68	1749 ± 91	1572 ± 198	1433 ± 25	1674 ± 119	1620 ± 26	1590 ± 146
Value for P	N.S.	< 0·001	N.S.	< 0·05	< 0·01	N.S.	N.S.	N.S.
Weight of fundus (mg)								
Impregnated	765 ± 22	996 ± 51	1052 ± 52	1196 ± 65	1198 ± 41	1077 ± 60	1059 ± 71	1013 ± 127
Control	740 ± 27	787 ± 51	1042 ± 69	956 ± 89	866 ± 31	1003 ± 93	961 ± 27	906 ± 106
Value for P	N.S.	< 0·005	N.S.	< 0·05	< 0·025	N.S.	N.S.	N.S.
Surface area of fundus (cm^2)								
Impregnated	10·5 ± 0·2	11·2 ± 0·4	12·4 ± 0·4	14·2 ± 0·4	13·7 ± 0·3	12·8 ± 0·7	12·6 ± 0·9	11·5 ± 0·4
Control	10·6 ± 0·3	10·3 ± 0·4	11·0 ± 0·2	11·2 ± 0·5	10·2 ± 0·7	11·0 ± 0·4	11·1 ± 0·8	11·4 ± 2·0
Value for P	N.S.	< 0·01	< 0·01	< 0·005	< 0·05	N.S.	N.S.	N.S.
Height of fundus mucosa (mm)								
Impregnated	0·394 ± 0·009	0·499 ± 0·010	0·513 ± 0·023	0·517 ± 0·020	0·526 ± 0·010	0·475 ± 0·026	0·504 ± 0·053	0·509 ± 0·030
Control	0·378 ± 0·016	0·462 ± 0·016	0·443 ± 0·018	0·452 ± 0·025	0·469 ± 0·017	0·496 ± 0·012	0·473 ± 0·062	0·457 ± 0·028
Value for P	N.S.	< 0·05	< 0·05	N.S.	< 0·05	N.S.	N.S.	N.S.
Volume of fundus (mm^3)								
Impregnated	414 ± 11	558 ± 26	631 ± 23	735 ± 38	721 ± 26	606 ± 49	630 ± 32	589 ± 53
Control	399 ± 17	476 ± 23	486 ± 23	509 ± 43	480 ± 50	544 ± 17	522 ± 30	526 ± 19
Value for P	N.S.	< 0·025	< 0·01	< 0·01	< 0·05	N.S.	< 0·05	N.S.
Total parietal cell population (millions)								
Impregnated	38·7 ± 1·0	42·7 ± 2·4	49·2 ± 2·3	59·3 ± 4·0	53·3 ± 2·4	52·3 ± 3·3	54·8 ± 3·0	48·8 ± 3·2
Control	39·8 ± 1·0	40·3 ± 1·8	43·3 ± 0·6	43·5 ± 2·6	43·7 ± 5·8	46·5 ± 2·6	44·0 ± 1·9	44·0 ± 1·9
Value for P	N.S.	N.S.	< 0·01	< 0·01	N.S.	N.S.	< 0·05	N.S.
Total peptic cell population (millions)								
Impregnated	58·6 ± 2·8	68·3 ± 4·1	81·3 ± 3·3	93·3 ± 11·4	92·7 ± 2·0	81·0 ± 6·3	82·2 ± 7·3	74·0 ± 6·2
Control	60·2 ± 1·0	61·5 ± 2·3	62·2 ± 3·0	68·3 ± 6·7	61·7 ± 4·7	6·98 ± 5·8	67·8 ± 5·6	62·3 ± 2·8
Value for P	N.S.	< 0·05	< 0·01	< 0·05	< 0·01	N.S.	N.S.	< 0·05

* Mean ± S.E. of mean.
† Values in parentheses ( ) denote total dead body weight, including weight of uterus and contents.
‡ N.S. = not significant.

Stomach weight declined during the further course of lactation and afterwards, and while the values tended to be greater in the impregnated group than they were in the controls at all subsequent time intervals, the effect was no longer significant.

The weight of the fundus showed the same general pattern of change, increasing during pregnancy and the early stages of lactation and declining subsequently; like the effect on the weight of the whole stomach the increase in the weight of the fundus became significant after the second week of pregnancy.

Surface area and mucosal height

The dimensions of the stomach also increased during pregnancy and the early stages of lactation and decreased during the latter stages of lactation and afterwards. Thus, after the first week of the experiment the mean values for the surface area of the fundus were $10{\cdot}5 \pm 0{\cdot}2$ cm^2 and $10{\cdot}6 \pm 0{\cdot}3$ cm^2 in the impregnated and control groups respectively (N.S.), while after the first week of lactation the value for the impregnated animals had increased to $14{\cdot}2 \pm 0{\cdot}4$ cm^2 compared to the control value of $11{\cdot}2 \pm 0{\cdot}5$ cm^2 ($P < 0{\cdot}005$). The mean values for the height (or thickness) of the mucosa were $0{\cdot}394 \pm 0{\cdot}009$ mm and $0{\cdot}378 \pm 0{\cdot}016$ mm in the impregnated and control animals respectively after the first week of the experiment (N.S.); however, mucosal height increased to a value of $0{\cdot}526 \pm 0{\cdot}010$ mm after the second week of lactation, compared to the corresponding control value of $0{\cdot}469 \pm 0{\cdot}017$ mm ($P < 0{\cdot}05$).

Mucosal volume

Mucosal volume was calculated as the product of surface area and height (or thickness) of the fundic mucosa and varied with the previously described dimensional changes throughout the experiment. After the first week of the experiment the mean values for mucosal volume were 414 ± 11 mm^3 and 399 ± 17 mm^3 in the impregnated and control groups respectively (N.S.), while after the second week of pregnancy the value for the impregnated animals had increased to 558 ± 26 mm^3 compared to 476 ± 23 mm^3 in the controls ($P < 0{\cdot}025$). Mucosal volume increased thereafter in the impregnated animals to reach a maximum value of 735 ± 38 mm^3 after the first week of lactation at which point the corresponding control value was 509 ± 43 mm^3 ($P < 0{\cdot}01$). Mucosal volume declined during the further course of lactation and afterwards, and while the values tended to be greater in the impregnated group than they were in the controls at all subsequent time intervals the effect was no longer significant.

Total parietal and total peptic cell populations (illustrated in Fig. 1)

The two cell populations increased progressively during pregnancy and the early stages of lactation and decreased subsequently, the values observed in the impregnated animals being greater than those in the controls at almost all time intervals. After the first week of the experiment the mean values for the peptic cell population were $58{\cdot}6 \pm 2{\cdot}8$ and $60{\cdot}2 \pm 1{\cdot}0$ millions in the impregnated and control groups respectively (N.S.), while

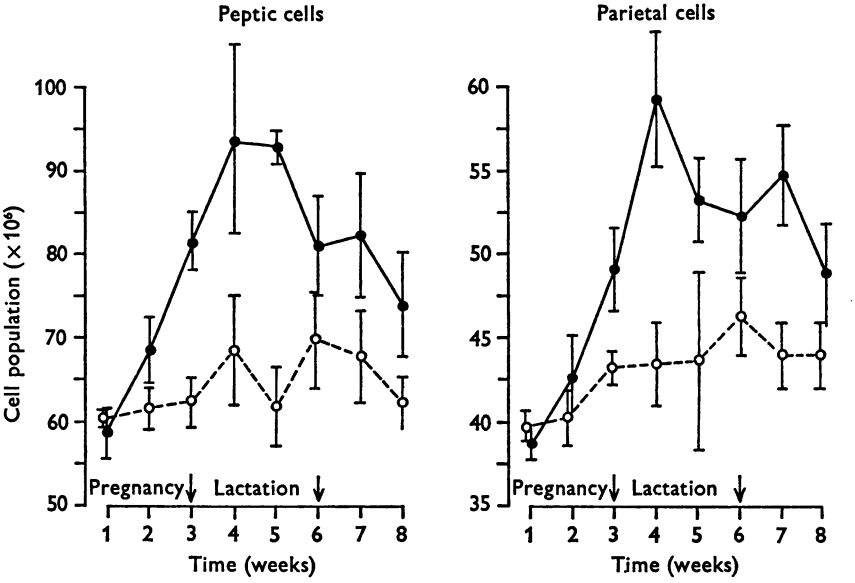

Fig. 1. Mean values for the total parietal and total peptic cell populations in the impregnated (●) and control (○) rats in each group; the points represent the mean values and the bars represent the S.E. of the mean.

after the second week of pregnancy the value for the impregnated animals was $68{\cdot}3 \pm 4{\cdot}1$ compared to $61{\cdot}5 \pm 2{\cdot}3$ millions in the controls ($P < 0{\cdot}05$). The peptic cell population increased thereafter in the impregnated animals to reach a maximum value of $93{\cdot}3 \pm 11{\cdot}4$ millions after the first week of lactation, at which point the corresponding control value was only $68{\cdot}3 \pm 6{\cdot}7$ millions ($P < 0{\cdot}05$). This maximum value was maintained during the second week of lactation, after which the peptic cell population declined; although the effect was no longer significant, the mean values for the peptic cell population tended to remain greater than those for the control animals during the subsequent course of the experiment. The parietal cell population showed the same general trend as the peptic cells, increasing during pregnancy to reach a maximum value after one

week of lactation and declining subsequently. The changes that occurred in the parietal and peptic cell populations with time during pregnancy and lactation could be described in terms of simple quadratic functions as illustrated in Fig. 2.

The maximum change in both cell populations represented an increase of the order of 30–40% above the corresponding control levels. The mean growth rates calculated from the regression of each cell population against

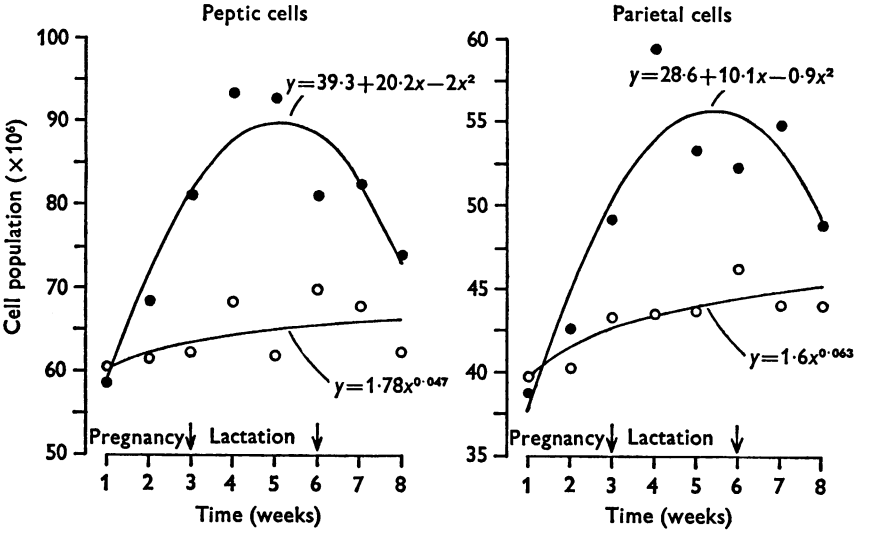

Fig. 2. Mean values for the total parietal and total peptic cell populations obtained in the impregnated (●) and control (○) rats in each group. Simple quadratic functions have been fitted to the mean values for impregnated rats and simple logarithmic functions have been fitted to the data for the control animals, viz. $y = 39{\cdot}3 + 20{\cdot}2x - 2x^2$ and $y = 28{\cdot}6 + 10{\cdot}1x - 0{\cdot}9x^2$ for the peptic and parietal cell populations of the impregnated rats; $y = 1{\cdot}78x^{0{\cdot}047}$ and $y = 1{\cdot}6x^{0{\cdot}063}$ for the peptic and parietal cell populations of control animals.

time for the first four weeks of the study were 7·9 million parietal cells per week and 12·7 million peptic cells per week in the impregnated animals, compared to 1·2 million parietal cells per week and 1·6 million peptic cells per week in the control group. The mean ratio between the two cell populations was approximately 1:1·5 for both the impregnated animals and the controls; this value is of the same order as the ratio found between the total parietal and peptic cell populations over a wide range of stomach size in normal rats (Crean, Hogg & Rumsey, 1969; Bralow, Brown, Gruenstein & Shimkin, 1967). Moreover, the increases that occurred in the parietal and peptic cell populations in the impregnated animals were proportional to the increases that occurred in mucosal volume: thus the correlation

coefficients for the relationship between the individual cell populations and mucosal volume were $r = 0{\cdot}88$ in the case of the parietal cells and $r = 0{\cdot}95$ in the case of the peptic cells.

The influence of somatic growth

The results discussed above establish that hyperplasia of the gastric mucosa occurred during pregnancy and lactation. Since the growth of the gastric mucosa is largely determined by somatic growth (Crean, 1967*a*),

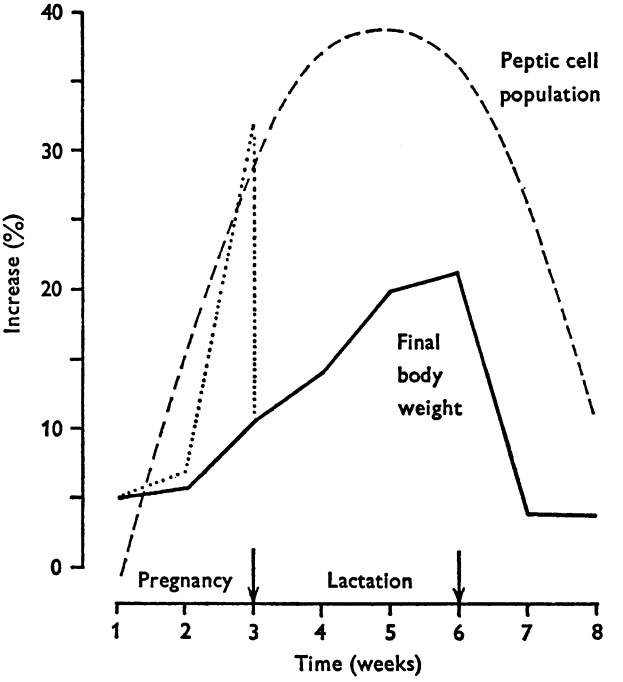

Fig. 3. The percentage increases obtained in the impregnated rats compared to the unmated controls for peptic cell population (- - -) and final body weight (—) on the same time scale. Final body weight represents dead body weight minus the weight of the uterus and its contents; total body weight (...) represents dead body weight, including the weight of the uterus and its contents.

it seemed possible that the effect could be accounted for simply by the increase that occurred in body weight during pregnancy. This possibility was tested by comparing the percentage increase that occurred in body weight with the percentage increase in the growth of the gastric mucosa, taking the changes in the peptic cell population to exemplify the changes that occurred in the gastric mucosa as a whole. For the purpose of analysis the percentage changes in the peptic cell population were calculated from

the regression line for the peptic cell population against time as shown in Fig. 2. The percentage changes in body weight were calculated from the differences between the actual values observed for the impregnated animals and the regression line calculated for body weight against time in the controls. During pregnancy the increase that occurred in the peptic cell population was similar both in time and magnitude to the increases that occurred in body weight (Fig. 3); during lactation, however, this similarity was lost since body weight continued to increase while the cell population declined. The data for the percentage changes in the parietal cell population, mucosal volume and surface area all showed similar trends when plotted against body weight in the same way. The results suggest that there is no simple relationship between body weight and the over-all course of hyperplasia of the gastric mucosa during pregnancy and they support Spencer's conclusion (1967) that the increase in the growth of the intestinal tract during lactation is in excess of the growth that might be predicted from the allometric equation.

The influence of food intake

Food intake was greater in the impregnated animals than it was in the controls at all time intervals, with the most marked difference occurring during lactation. Thus the percentage increase in food consumption was of the order of 20 % in the first week of pregnancy and 50 % in the third week, whereas it increased to approximately 250 % in the third week of lactation. Food intake returned rapidly to normal levels very shortly after weaning. In order to examine the relationship between food intake and the growth of the gastric mucosa the 3-day means for food consumption were plotted against the percentage changes that occurred in the peptic cell population (Fig. 4). There was no close temporal relationship between the changes in food intake and changes in the peptic cell population during the experimental period; indeed the maximum value for the peptic cell population was reached almost 7 days before the maximum increase in food intake, and the cell population was declining during lactation while food intake was actually increasing. Although the measurement of food intake is notoriously difficult in rats, the values obtained in the present experiment are of the same order as those previously recorded for food intake during lactation in this species (Fell *et al.* 1963; Anderson & Turner, 1963). If our observations are correct, it seems unlikely therefore that food intake *per se* can account for the hyperplasia of the gastric mucosa that occurred in the experiment.

As previously reported (Fell *et al.* 1963) the size of litters bore no discernible relationship to the degree of hyperplasia of the gastric mucosa.

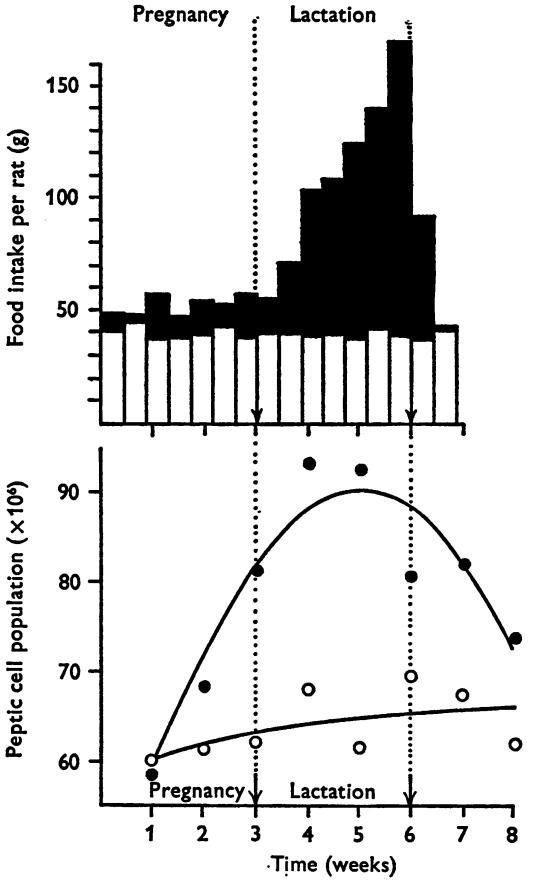

Fig. 4. The values obtained for food intake compared to the values obtained for the peptic cell population on the same time scale. Each block represents the mean food intake per rat for 3-day periods; open blocks represent the values for the unmated controls, and the hatched blocks represent the values for the impregnated rats. The peptic cell population is represented in the same way as in Fig. 2.

DISCUSSION

The results confirm that hyperplasia of the gastric mucosa occurs during pregnancy and lactation in the rat, the effect being characterized by dimensional changes as well as by increases in the actual mass of the secretory cells; thus there were increases in the surface area of the fundus and in the height (thickness) of the fundic mucosa as well as in the volume (mass) of the gastric mucosa and in the total parietal and peptic cell populations. The effect developed very shortly after conception, and had become statistically significant after the second week of pregnancy.

Hyperplasia continued to develop until the early stages of lactation and waned thereafter, although the values for almost all the observations made on the gastric mucosa still tended to remain greater in the impregnated animals than they were in the controls for as long as 5 weeks after the pups had been delivered. The effect was of considerable magnitude; during the first and second weeks of lactation when hyperplasia was maximum the increases observed for most of the gastric parameters were of the order of 30–40% above the appropriate controls. Calculation of the data suggests that the hyperplasia observed represents an acceleration of the normal growth of the gastric mucosa. Thus the parietal and peptic cell populations increased in the ratio of 1:1·5 which compares to the ratio found between these two cell populations over a wide range of stomach size in normal rats (Crean, Hogg & Rumsey, 1969; Bralow *et al.* 1967). Moreover, the increase that occurred in the cell populations was proportional to the increase that occurred in mucosal volume, and this in turn could be accounted for by the increases observed in the surface area of the fundus and in the height or thickness of the fundic mucosa. These observations suggest that there was an increase in the actual number of the gastric glands as well as in the cellular populations of the individual glands. Thus the hyperplasia of the gastric mucosa during pregnancy compares with the hyperplasia induced by partial obstruction to the gastric outflow, which is also characterized by an increase in surface area as well as by increases in mucosal volume and in the total parietal and peptic cell populations (Crean, Hogg & Rumsey, 1969).

The mechanisms responsible for the accelerated growth of the gastric mucosa during pregnancy are unknown. The secretory cells of the stomach are highly differentiated and are believed to be incapable of cell division (Hunt & Hunt, 1962) so that any increase in the parietal or peptic cell populations can only occur as a result of proliferative activity in the germinal cells of the mucosa some time previously. The recent work of Ragins, Wincze, Liu & Dittbrenner (1968) with mice suggests that the time lag between proliferation in the germinal cells and the development of new secretory cells in the gastric mucosa is of the order of 7–16 days. If the same time scale obtained during pregnancy it would appear that the stimulus responsible for hyperplasia must have been applied very shortly after conception. On the same analogy, it might be argued that the stimulus to hyperplasia ceased at about the time of delivery, since the cell population began to decline between 1 and 2 weeks later during the early stages of lactation. This interpretation of the data implies that the stimulus responsible for hyperplasia of the gastric mucosa was directly associated with pregnancy *per se*; moreover, since the accelerated growth of the gastric mucosa was maintained for several weeks it follows that the stimulus,

whatever its nature, must have operated continuously at least for some of this period.

This line of argument suggests the hypothesis that the responsible stimulus might be hormonal in nature, originating either in the maternal organism or from the foeto-placental unit. Although there is no critical evidence for or against the possibility that the maternal hormones are involved, this seems an unlikely explanation since none of the hormones that characteristically increase during pregnancy is known to exert any specific effects on the growth of the alimentary tract. Thus the oestrogens, progesterone and the pituitary gonadotrophins exert no stimulating effect on the growth of the stomach or alimentary tract in intact or hypophysectomized animals (Souders, 1955; Campbell & Fell, 1964; Crean, 1965; and see Crean, 1963), whereas the corticosteroids and ACTH appear to inhibit the growth of the gastric mucosa in intact animals (Myhre, 1960; Crean, 1967*b*). The corticosteroid and thyroid hormones, however, potentiate the effects of prolactin and growth hormone in stimulating the regrowth of the intestinal tract after hypophysectomy (Bates, Miller & Garrison, 1962). While growth hormone and prolactin exert powerful effects in restoring the growth of the stomach and alimentary tract after hypophysectomy, both these hormones exert only modest effects in intact animals even when administered at very high dose levels (Bates *et al.* 1962; Bates, Milkovic & Garrison, 1964; Crean, 1965; G. P. Crean, R. D. E. Rumsey & S. Wheeler, unpublished observations). However, the possibility that the maternal hormones are in some way responsible for the effect cannot be excluded on the evidence available, since the effect could be due not to any single hormone but rather to the interaction of several hormones coming into play in critical combinations or at critical time intervals during the course of pregnancy.

A placental mechanism requires to be considered if only because the time course for the evolution of hyperplasia of the gastric mucosa appears to coincide with the development and presence of this organ. Moreover, there is evidence that the placenta is capable of exerting direct growth-promoting properties on the maternal organism. For example, the increase in body weight during pregnancy depends at least in part on viable placental tissue, and the increase in protein synthesis in the maternal liver during pregnancy is also dependent on the placenta (Campbell *et al.* 1953). Since human placental lactogen is known to exert growth-promoting properties (Josimovich & MacLaren, 1962; Friesen, 1965; Kaplan & Grumbach, 1964) it is interesting to speculate whether this hormone could be responsible for the hyperplasia of the gastric mucosa observed; it remains to be shown, however, whether rat placenta elaborates a hormone with the same biological properties as the hormone extracted from the human placenta.

Other explanations to account for hyperplasia of the alimentary tract during pregnancy and lactation attribute the effect either to increased food intake (Fell *et al.* 1963; Campbell & Fell, 1964) or to an increase in somatic growth (Bullough, 1962). However, neither of these explanations would satisfactorily account for the results obtained in the present study. Although food intake increased slightly during pregnancy, the main increase in food consumption occurred during lactation, long after hyperplasia of the gastric mucosa had been established. Moreover, while hyperplasia induced under conditions such as hypothermia (Heroux & Gridgeman, 1958), experimental lesions of the hypothalamus (Brobeck, Tepperman & Long, 1943; Mayer & Yannoni, 1956), administration of insulin or thyroid extract (McKay, Callaway & Barnes, 1940; Levin & Smyth, 1963), intermittent starvation (Holeckova & Fabry, 1959) or high-bulk feeding with agents such as alfalfa or talcum (Addis, 1932; Wierda, 1950; Friedman, 1953) produces hypertrophy of the alimentary tract in rats and mice, the increase in food intake required to achieve this effect is far greater than the modest increase in food consumption that occurs early in pregnancy.

It seems unlikely also that the hyperplasia of the gastric mucosa could be accounted for by the increase in body weight during the experiment, since the time courses for the two effects were so different. During pregnancy the increases in the dimensions and in the mass of the secretory cells in the stomach paralleled the increase in body weight; during lactation, however, this similarity was lost since hyperplasia started to decline while body weight actually increased. Although the growth of the gastric mucosa is allometric with body weight under normal conditions (Crean, 1967*a*) the relationship does not apply universally; thus hyperplasia of the entire gastric mucosa may be induced by gastric outlet obstruction, and hyperplasia of the parietal cells alone may be induced by chronic administrations of pentagastrin without alteration in body weight in either circumstance (Crean, Hogg & Rumsey, 1969; Crean, Marshall & Rumsey, 1969).

It is interesting to note that gastric secretion increases progressively during pregnancy in the rat and is maintained at high levels throughout lactation (Kahlson, Lilja & Svensson, 1964; Lilja & Svensson, 1967; Long, 1969). These secretory changes develop at a rate which is roughly similar to the rate of development of hyperplasia of the gastric mucosa in the present experiment, suggesting that the increase in the population of the secretory cells may well account for the hypersecretion. It is of interest also that active peptic ulcers are virtually unknown during pregnancy, and that ulcers previously giving rise to symptoms become clinically quiescent shortly after conception (Clark, 1953; and see Crean, 1963). These very striking clinical features have led to the widely held view that active ulcers

heal during pregnancy; if so, it seems at least possible that such an effect could be due to the increased epithelial-cell turnover which must accompany the hyperplasia of the gastric mucosa demonstrated in the present experiments.

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