PEPTIC ULCER IN WOMEN.

DOUGLAS H. CLARK, M.B., Ch.M.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

CONTENTS.

PART II.

GASTRIC ACID SECRETION AND PLASMA HISTAMINASE DURING PREGNANCY.

PART III.

URINARY EXCRETION OF PEPSINOGEN IN LATE PREGNANCY AND THE EARLY PUERPERIUM.

PART IV.

GASTRIC ACID SECRETION IN DOGS DURING PREGNANCY AND LACTATION.

PART V.

THE EFFECT OF CASTRATION ON THE GASTRIC ACID SECRETION OF FEMALE DOGS.

INTRODUCTION.

The study of peptic ulcer has largely been confined to the disease as it occurs in men. This is not surprising since its victims are mainly men. A treatise on the disease as it occurs in women, therefore, begs explanation for, in many respects, its behaviour in the two sexes is similar. The interest, however, lies with the differences, which are especially notable and, at the same time, unexplained.

The history of peptic ulcer as it occurred in women during the 19th Century has no male counterpart. During the 19th Century, according to the only reliable information available, viz., the incidence of perforation (JENNINGS 1940), the disease was still relatively uncommon and was almost as frequent and, in some localities, more frequent in women than in men. Furthermore, this ulcer in women was most often situated in the upper part of the body or in the fundus of the stomach. This form of the disease disappeared by the end of the First World War and, since then, there has been much speculation regarding its cause; nutritional, psychical - and even sartorial factors being suggested. Probably the main inference to be drawn, however, is that it demonstrated that environment has played, and may still play, an important role in the etiology of peptic ulcer. During the present century,

the incidence of peptic ulcer in women has remained considerably less than in men and especially so in the tendency to perforation. Whether this can be interpreted as resulting from less exposure of women to "ulcer" environment, or resulting from protection by biological factors in their constitution, remains to be seen.

When one studies the natural history of the disease in women, further interesting features emerge. Whereas in men ulcers seem, in most instances, to appear, remit and relapse without obvious cause, encouragement or provocation, in women, on the other hand, there are events in their lives which can be associated with the onset of ulcer, with the healing of ulcer or with the extension of the ulcer.

The present investigation was embarked upon to study certain aspects of the epidemiology of peptic ulcer in women; to study the natural history of the disease in women with special reference to menstruation, pregnancy, lactation and the menopause, and the effects of those events on the course of the disease; and, finally, to investigate several of the factors arising from the natural history.

Some of these factors have been the subject of previous investigation e.g., gastric acid secretion in pregnancy has been studied on several occasions using "sampling" test-meal methods. This subject is re-investigated, using more modern "continuous suction" methods with, at the same time, estimation of the enzyme histaminase. The other factors at the outset of this work had not previously been investigated. The investigations performed are:

1. Gastric acid secretion and plasma histaminase during pregnancy. (Part II.).
2. Urinary excretion of Pepsinogen in late pregnancy and the puerperium. (Part III.).
3. Gastric acid secretion in dogs during pregnancy and lactation. (Part IV.).
4. The effect of castration on gastric acid secretion of female dogs. (Part V.).

PART I.

EPIDEMIOLOGY AND NATURAL HISTORY OF PEPTIC ULCER IN WOMEN.

A. REVIEW OF THE LITERATURE.

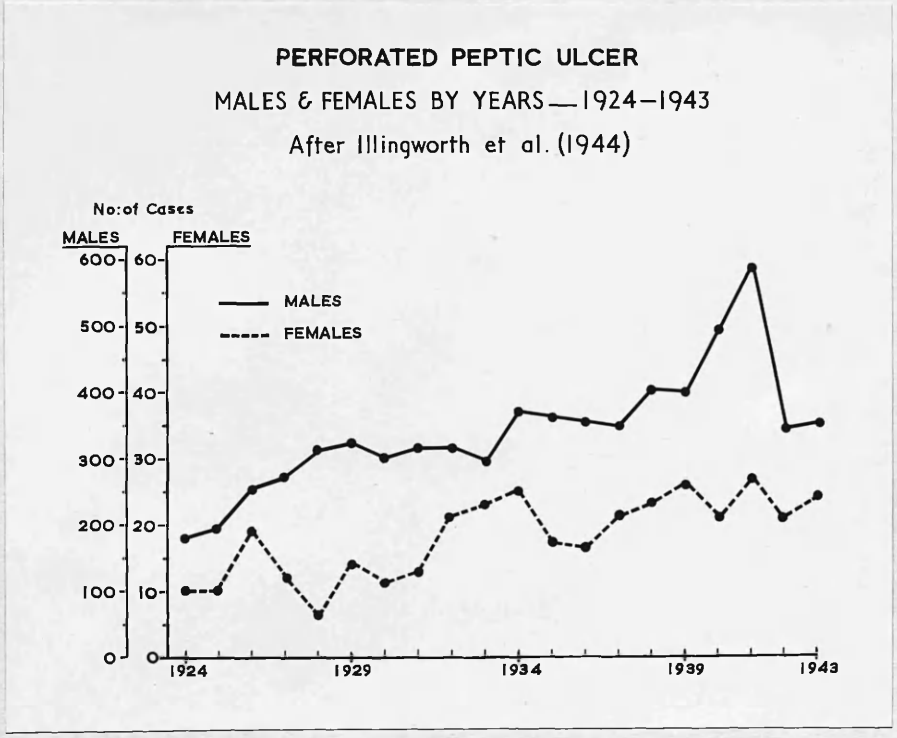
1. EPIDEMIOLOGY.

There is now abundant evidence indicating that peptic ulcer is more common in males, the ratio being of the order of 4 males to 1 female. AVERY JONES and POLLACK (1945); JAMIESON et al (1949). More recently DOLL and AVERY JONES (1951) have made a further painstaking survey by making an individual field study of a large "sample" of the population. They interviewed over 6000 workers in a number of factories in the London area. When allowance was made for special features of age and sex in the groups interviewed, the results gave an incidence for men (aged 15-64) of 5.8 per cent and for women of 1.9 per cent.

Not only is the disease more common in males, but judged, for example, by the incidence of perforation in the two sexes, it would appear to be more severe in the male. De BAKEY (1940) in a collected series of 14,339 perforations found that more than 90 per cent occurred in males. A similar sex distribution has been noted here

in the West of Scotland. ILLINGWORTH et al (1944). It may well be that the factors causing perforation are not the same as those which cause ulcer per se, and that women are less exposed to, or more resistant, to the former. JAMIESON et al (1949), for example, noted that in duodenal ulcer in males the ratio of perforation to haemorrhage was 1.5 to 1, and that in females, it was 1 to 5. If it be accepted that the duodenal ulcers which perforate are situated anteriorly, and those which bleed are mainly posterior, it would seem that women must have a relative immunity from ulcer of the anterior wall of the duodenum. In their study, ILLINGWORTH et al (1944), of acute perforated peptic ulcer in the West of Scotland, these authors have produced interesting facts concerning the sex distribution which seem further to emphasise this relative immunity. Their survey which covered the twenty-year period from 1924 to 1943 inclusive, indicated that the incidence rate of perforation in both sexes was increasing, but that the ratio of 19 males to 1 female was maintained.

Fig. 1.



Moreover, as will be seen in Fig. 1, the dramatic rise in incidence of 1940-1941, and the dramatic fall of 1942-1943, was confined to males. The sudden upsurge in the incidence of perforation in men has been ascribed to post-Dunkirk overtime working, fear of invasion and air-raids. The stability of the incidence in women seems all the more remarkable in view of the great changes that were taking place, especially since 1939, in their habits, working conditions and wartime stresses.

This relative immunity to peptic ulcer which the female enjoys has caused a great deal of speculation. It is not surprising that the sex hormones should be invoked as the probable protective factors. Further to support this probability SALTZSTEIN et al (1940) studied the sex incidence of peptic ulcer in children. It seemed to them that if the sex hormones endowed this protection, then it should be absent in children before puberty, when the sex hormones have little or no activity. They collected 99 cases of peptic ulcer in children up to 12 years of age from the literature and added a further 6 cases. The incidence was 1 female to 1.18 males. Following the observations of OESTING et al (1938) that the male sex hormone appears as early as 3 and gradually increases, and that the oestrogenic hormone in females appears about 10 years of age, rapidly increasing to puberty, they observed the incidence in the age groups 1-6 and 7-12. Their findings are shown in the following table.

Table 1. SEX INCIDENCE OF PEPTIC ULCER IN CHILDREN. AFTER SALTZSTEIN et al (1940).

AGE.	MALES.	FEMALES.
1 - 6	8	11
7 - 12	49	37.

These findings seemed to indicate that when the female hormone began to appear, the sex incidence began to approach adult figures. The rarity of the disease in children and the equal sex distribution was also shown by THEILE in 1919. In his series there were 89 males and 98 females.

From the foregoing epidemiological findings it would appear that a difference in the overall sex incidence of peptic ulcer exists, and that this difference is especially notable concerning perforations. This difference becomes very definite after the age of 14. It may well be due to environmental, rather than constitutional factors. The statistics of ILLINGWORTH et al (1944) showing that the great rise in male perforations was not paralleled by the female incidence suggest that constitutional factors may be more important. Further evidence in support of this is adduced by GAINSBOROUGH and SLATER (1946). In their psychiatric appraisal of peptic ulcer patients, they found that their female patients formed a much more neurotic and emotionally unstable group than the males. This seemed to suggest to them "that as regards liability to ulcer, a woman must have a constitution altogether inferior to that of a man, and, therefore, in her case, there is some protection afforded by biological and constitutional factors".

2. NATURAL HISTORY.

The first suggestion that there might be some connection between peptic ulcer and the sex hormones has been attributed to BORRI (1904). As long ago, however, as 1837-38, the LANCET, commenting on the perforated peptic ulcer in young women prevalent at that time, noted that "all of these cases occurred in young girls in whom there was a disordered state of uterine function" and that it occurred rarely in married women. PRITCHARD (1842-43) expressed a similar conviction. BORRI was more precise. He noted the common occurrence of peptic ulcer, at or shortly after, the menopause. Since then there have been in the literature many contributions to the natural history of the disease in women. Most of these have been based on clinical impressions or on case reports. A few have referred to the influence of menstruation, pregnancy, lactation and the menopause on the onset and course of peptic ulcer.

(a) Menstruation.

TAUSSIG (1908) noted gastric disorders associated with menstruation in his gynaecological practice, and quotes similar observations by others. SUTHERLAND (1910) observed that recurrent haematemeses from ulcers seemed to occur with greater frequency during the mentrual period

and attributed this to increased nervous tension. Nevertheless, a study of a large series has not been carried out.

(b) Pregnancy.

Until 1939, there were approximately 10 references in the literature alluding to the effect of pregnancy on the symptoms of peptic ulcer. The beneficial effect was noted, for example, by CROHN (1927) and HURST and STEWART (1929). The rarity of active ulcer during pregnancy was stressed by SCZENES (1924) who was able to collect from the literature only 12 gastric ulcers and 7 duodenal ulcers in pregnant women. This author, on the basis of those few cases and observations in his own Clinic, concluded that nulliporous patients came to operation for ulcer at an earlier age than those who had one or more pregnancies, and that patients who did not gain relief during pregnancy were usually those who suffered from pregnancy vomiting in severe form. Records of complicated ulcer during pregnancy in the literature are extremely rare, and such an occurrence is still sufficiently unusual to warrant comment. MULSOW and BROWN (1936) recorded a case of haemorrhage from peptic ulcer during pregnancy - the first in the literature.

The first worthwhile study of the behaviour of peptic ulcer during pregnancy was performed by SANDWEISS and his associates in 1939. They selected their female ulcer patients who had been pregnant. In their series there were 46 patients with proved peptic ulcer: 25 had had one or more pregnancies, totalling 52. Their findings are summarised in the following Table:-

Table 2.

INCIDENCE OF ACTIVE ULCER SYMPTOMS DURING PREGNANCY
(After SANDWEISS et al., 1939)

	On Basis of Patients	On Basis of Pregnancies
Total Number	25	52
Known to be free of all gastro-intestinal symptoms during 9 months.	20	37
Known to have had 'gas;' 'nausea','vomiting' in first 3 months; symptoms free thereafter.	4	14
Known to have had ulcer symptoms.	+1	+1

+ This patient gave birth to a premature child.

They furthered their investigations in another direction by reviewing the records of 70,310 consecutive admissions of pregnant women to 5 Detroit hospitals. Only one proved case of peptic ulcer was recorded, that of death due to a perforation of a duodenal ulcer. At one of these hospitals (HARPER HOSPITAL, DETROIT) during

during a 10-year period (1928-1937 inclusive), 95 operations of necessity during pregnancy were performed on the gastro-intestinal tract alone. Not one was for peptic ulcer. MUSSEY (1927) who scrutinised the 370 general surgical operations of necessity during pregnancy over a 10-year period, found only 2 operations for peptic ulcer - both gastro-jejunostomies. ADAIR and STIEGWITZ (1934) discussing the incidence of active peptic ulcer during pregnancy state that "in 20 years at the MINNESOTA GENERAL HOSPITAL, no case of peptic ulcer in pregnancy had to be treated". AVERY JONES (1947) found only one slight haematemesis but without confirmed ulceration in approximately 10,000 confined women in London. Among over 2,000 women admitted with abortions, only one had haematemesis associated with renal failure. AVERY JONES also states that the acute anxiety of pregnancy in unmarried women does not precipitate gastro-duodenal haemorrhage.

These statistics derived from obstetric records emphasise the rarity of complicated peptic ulcer during pregnancy. They probably underestimate, however, the true incidence of ulcer during pregnancy, since obstetrical records are not unduly concerned with digestive ailments.

Since it has become established that pregnancy exerts a beneficial effect on peptic ulcer, and that complicated peptic ulcer during pregnancy is rare, there have been sporadic and timely warnings in the form of case reports, indicating that perforations do occasionally occur, sometimes with fatal result, due to delayed diagnosis.

It is natural that a great deal of clinical and experimental work should stem from these observations in pregnancy. A discussion of this work does not belong in this chapter, and is more germane to the study of gastric function, which will be dealt with later.

(c) Lactation.

CROHN (1927) first noted that ulcer patients who had been well during pregnancy, relapsed very soon during and after lactation. This clinical observation soon had experimental interest in the fortuitous findings of KLEIN (1933) and HOLLANDER (1930) that during lactation in dogs the ulceration of the skin around the gastric pouch stoma increased. They noted an increase in the volume and acidity of the gastric juice. WINKELSTEIN (1935) confirmed these findings and was able to produce regression of the ulceration by the administration of oestrogens, though antiutrin - S aggravated the ulcerative

tendency. Despite these observations, there is no well-developed study of the number of patients who relapse after pregnancy, nor of the time in relation to the foregoing pregnancy, at which the relapse most commonly takes place.

(d) Menopause.

BORRI (1904) first drew attention to the relationship between the menopause and peptic ulcer. In 1908, TAUSSIG in his contribution on the "uterus and stomach" observed that 23 per cent of his 44 gynaecological conditions associated with gastric upset were in women at the menopause. Since then there have been several references based mainly on clinical impressions, for example, by SZENES (1924), CROHN (1927) and HURST AND STEWART (1929). FRIEDENWALD (1932) studied the gastric disturbances incident to the menopause and in gastric analyses found subacidity and achlorhydria. SANDWEISS et al (1939) found 18 of 30 patients at the time of examination either presented signs and symptoms of the menopause, or had passed the climacteric. They further noted that in 4 cases the onset coincided with the menopause, and that in the remaining 14 who had passed the climacteric, their symptoms had been aggravated by the change. WINKELSTEIN'S (1940) experience at the

MOUNT SINAI HOSPITAL, NEW YORK, impressed on him the incidence of ulcer or ulcer-like symptoms occurring at the menopause. During a 5-year period, 40-44% of 90 female ulcer patients experienced the onset of their ulcer symptoms at the time of the menopause, whether natural or artificially induced. His impressions of ulcer behaviour, both at the menopause and during lactation, encouraged him to formulate an attractive hypothesis suggesting that the anterior pituitary, which is probably hyperactive during lactation and uninhibited by oestrogens or progesterone during and after the menopause, may play an important part in the cause or aggravation of what he calls "this ductless gland peptic ulcer".

B. OBSERVATIONS ON THE NATURAL HISTORY OF PEPTIC ULCER IN WOMEN.

The following investigation was undertaken and designed to test the validity of many of the foregoing observations. The PEPTIC ULCER CLINIC at the WESTERN INFIRMARY, GLASGOW, provides ample material for study. The patients attending this Clinic are referred by practitioners outside the hospital, or by physicians and surgeons from the Out-Patient Department of the Hospital. The tendency is as a result for the more severe and intractable cases to be referred, and this series is,

therefore, not truly representative of the general female ulcer population. For the purposes of this investigation which is concerned mainly with ulcer behaviour, this tendency seemed not to be of undue importance. It was thought that the information from a large group of women suffering from peptic ulcer would help to substantiate and clarify previous impressions.

1. METHOD OF INVESTIGATION.

(a) Clinical Material.

The evidence here presented was obtained by interviewing 400 women in whom peptic ulcer had been demonstrated either by radiology or at operation. The ulcer was duodenal in 330 cases, gastric in 70. The patients' ages ranged from 21 to 74 years, and in most cases the symptoms were of more than 5 years' duration.

(b) Marital State.

Of the 400 women, 328 were married and 72 single. It has been noted by GAINSBOROUGH and SLATER (1946) among others, that peptic ulcer is more common in unmarried women. This is not borne out by the present series. Among the 357 women of this group between the ages of 20 and 64, the unmarried amounted to 68 (19 per cent). This figure is considerably lower than the proportion of

unmarried women in the general population; for women aged 20-64, the 1931 census for England and Wales gives the proportion of unmarried as 3,747,699 to 11,743,965 or 32 per cent.

(c) Method of Interview.

In a disease which remits and relapses with such facility, the manner of eliciting and correlating the evidence is, obviously, of importance. During the interviews, every effort was made to eliminate the element of suggestion. Most of the evidence was volunteered; much was obtained by questioning, as indirect as possible; some had to be obtained by direct questioning. All of these women had already been interviewed at least once previously, and the standard case record of the Peptic Ulcer Clinic had been completed, so that information was already available on such relevant points as year of birth, age at onset of symptoms, and age at which complications had occurred. At the interview for the present investigation, these points were confirmed. Thereafter inquiry was made into the gynaecological and obstetrical history - for example, age at menarche, age at which pregnancies occurred, the number of pregnancies, whether pregnancies were normal or abnormal, admissions to hospital during pregnancies, age at menopause, etc.

Finally, the effect of these events on the ulcer history was correlated.

Often the patient volunteered some information. If not, the standard questions were asked, "Have you noticed any relationship between your ulcer and menstrual period/pregnancy/menopause?". "Was your ulcer made better, or worse, or did it remain the same?". Apart from paraphrasing these questions according to the patients' understanding of them, no further attempt was made to elaborate a correlation.

According to the patients' answer, "Better", "Worse", or "No change noted", the results were assessed. If a relationship had been noticed, inquiry was made into the time relationship and the quality and quantity of the worsening or improvement.

2. RESULTS.

(a) Menstruation.

Of the 400 patient, 291 had had ulcer symptoms before the menopause. In this group 81 (28%) claimed to have noticed some relationship between menstruation and the occurrence of ulcer symptoms. In all these cases the symptoms were worse for a few days or a week before the onset of menstruation. In 8, the ill-effect

persisted during the menstrual period. In one had the symptoms been noted to increase in the post-menstrual phase.

In interpreting these findings, it must be remembered that the symptoms of quite unrelated diseases may be aggravated in the pre-menstrual phase - the result perhaps of psychic influences, or of the general malaise which many young women experience at that time. This pre-menstrual state is known to gynaecologists as "pre-menstrual tension". In those patients who had noted premenstrual increase of symptoms, there was no evidence to indicate whether the exacerbation was due to such causes, or to factors directly related to the menstrual cycle, or even to the use of aspirin and similar analgesics. On the whole, however, it may be concluded from the present series that the effect of menstruation on ulcer symptoms is inconsiderable.

(b) Pregnancy.

In assessing the effect of this state on the symptoms of peptic ulcer, it must be remembered that normal pregnancy in healthy women is commonly associated with symptoms not unlike those of peptic ulcer. Many women who normally have no hint of gastric disorder suffer

during pregnancy, from such digestive symptoms as nausea, vomiting and heartburn, to a varying degree, and for a variable time. Indeed, these symptoms occur so often as to be accepted by the patient and her attendant as normal accompaniments of pregnancy. DOUGRAY (1949) found these digestive accompaniments during the first 3 months of pregnancy in 49 per cent of 1816 pregnancies. Occasionally they may persist until term. Sometimes more severe dyspepsia occurs, and its resemblance to ulcer is heightened by the relief afforded by antacids. Rarely hyperemesis gravidarum may lead to confusion.

In attempting to decide whether such symptoms were attributable to the ulcer, attention was paid to their severity and to the patients' own view regarding their origin. With their previous experience of peptic ulcer, most of the patients with heartburn, nausea and vomiting during the early months, attributed the symptoms to pregnancy, and regarded the ulcer as "cured". In cases with more severe pain, relieved by alkalis, the patients were unable to distinguish it from previous ulcer dyspepsia. These patients were considered not to be improved, as were those in whom symptoms persisted throughout the pregnancy.

Of the total of 400 women, 118 had been pregnant.

Table 3.

EFFECT OF PREGNANCY

Total No: of Women.	400
Women who had been pregnant.	118
Total No: of Pregnancies	344
No: of Pregnancies after onset of ulcer symptoms.	313
Free from symptoms.	140 (44.8 %)
Improved.	136 (43.4 %)
Not improved.	37 (11.8 %)

The total number of pregnancies was 344. Of these 313 had occurred subsequent to the onset of peptic ulcer. On the criteria laid down above, it is believed that pregnancy was associated with a remission of ulcer in 276 pregnancies (88.2%). More than half of these patients claimed to have been completely free of all symptoms during the whole pregnancy; the remainder had minor symptoms which they regarded as unconnected with ulcer. In the remaining 37 pregnancies (11.8%) symptoms persisted which were indistinguishable from those of ulcer.

Thus, it would appear that in almost 90% of ulcer patients symptoms are in abeyance during pregnancy. In

some of the cases the ulcer had been inactive immediately before conception, and in them remission persisted. In others, the symptoms cleared up dramatically at an early stage of pregnancy. 4 of the patients, who had considerable experience both with ulcer and pregnancy, claimed that they were able to diagnose pregnancy before the first "missed" period. In still others they improved gradually or became obscured by minor symptoms attributed to the pregnancy itself. Several patients averred that their successive pregnancies had been their only eupeptic respites and that they had enjoyed the pregnant state for the wellbeing it afforded.

(c) Toxaemia of Pregnancy.

In 37 pregnancies, symptoms persisted and were indistinguishable from those of ulcer. In some of these, the symptoms were much worse than previously, relief being obtained with the birth of the child. These 37 pregnancies involved 15 women, 14 of whom were admitted to hospital because of the severity of their digestive symptoms, or for other reasons. It is worthy of note that in 15 pregnancies, in 4 women, signs of toxaemia, such as albuminuria and hypertension were present. Three of these women blamed such a pregnancy for the onset of

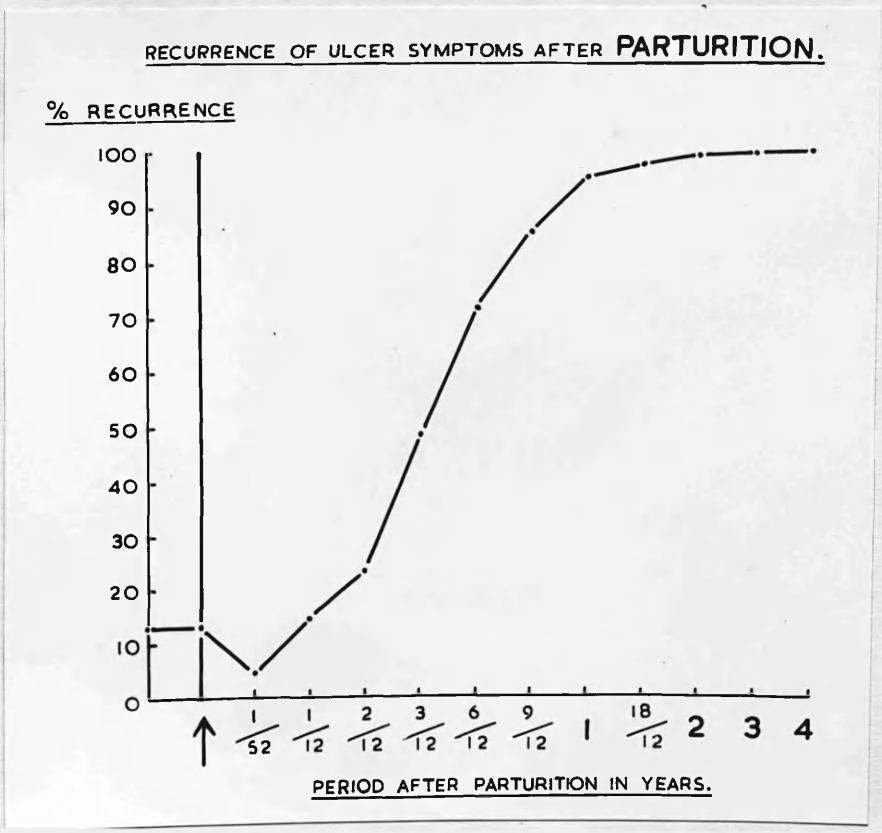
their ulcers. This high incidence of "toxaemia" in the "not improved" group is in striking contrast to one case of mild albuminuria in the remaining 276 pregnancies in which the patients were either "improved" or "free from ulcer symptoms". The significance of this finding is not immediately obvious, but the suggestions of HOFFBAUER (1926) and KAPELLER-ADLER (1941 and 1943) implicating histamine, one of the most potent stimulants of acid secretion known, as a cause of toxaemia, is interesting.

In no case did a complication of ulcer (haemorrhage or perforation) occur during pregnancy.

(d) Lactation.

The benefit derived from pregnancy is generally short-lived as Fig. 2 shows.

Fig. 2.



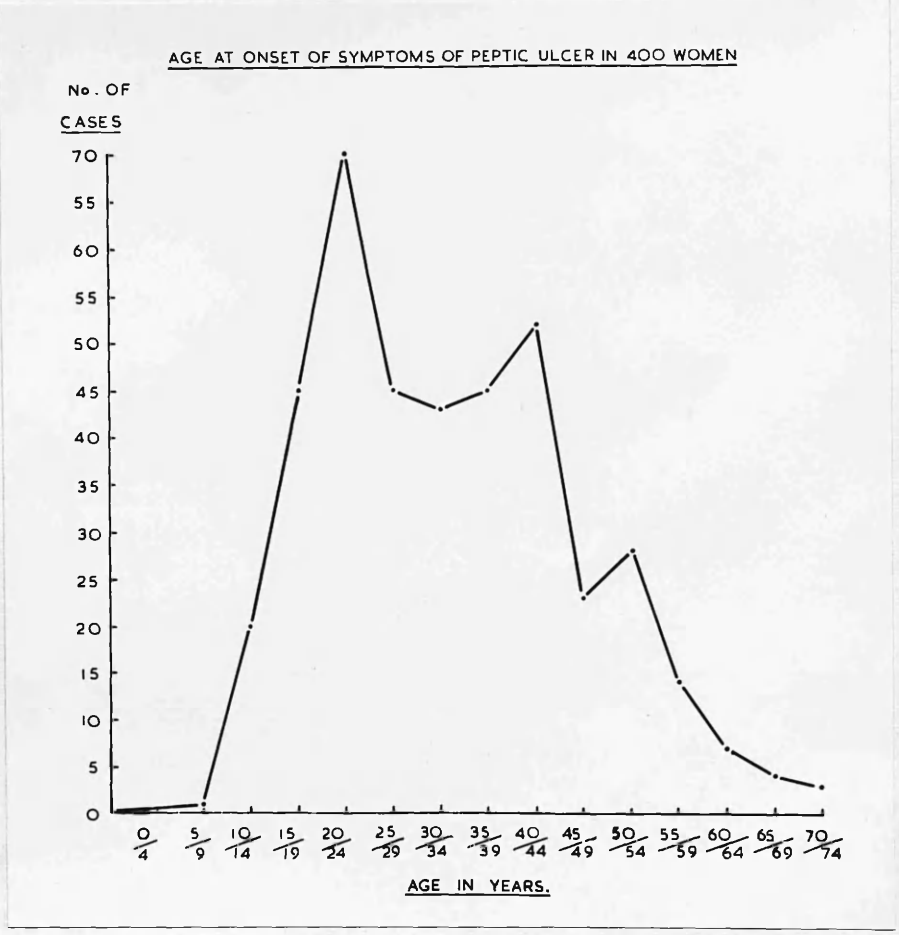
By the end of the third month after parturition symptoms had recurred in almost half the cases, and by the end of the sixth month in three-quarters. At the end of two years, almost every patient had suffered a recurrence. Unfortunately, during the interviews for this investigation, the significance of lactation at that time not being fully appreciated, no notes were made regarding the number of patients who breast-fed their babies, and for what period of time. Nevertheless, as Fig. 2 shows, there is a remarkable incidence of recurrence during the first 3-6 months (75%) after what has been a fairly prolonged period of wellbeing and, probably, although this is not certain, healing of the ulcer. This incidence of recurrence would tend to suggest that during the lactation phase there are certain agencies at work which have an ulcerogenic effect.

This idea seems all the more tenable when the incidence of complications during the first few months is noted. Although no complications occurred in any of these pregnancies, within 10 weeks after term there were 6 episodes of haematemesis and 2 perforations involving 8 patients.

(e) Menopause.

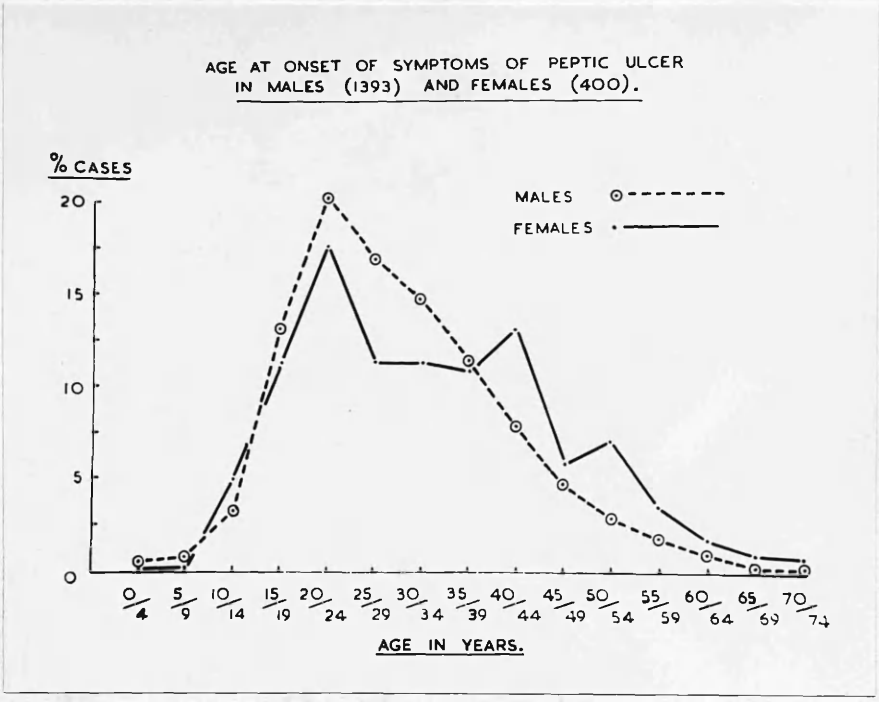
The distribution curve of the ages of the 400 patients at the onset of ulcet symptoms is shown in Fig. 3.

Fig. 3.



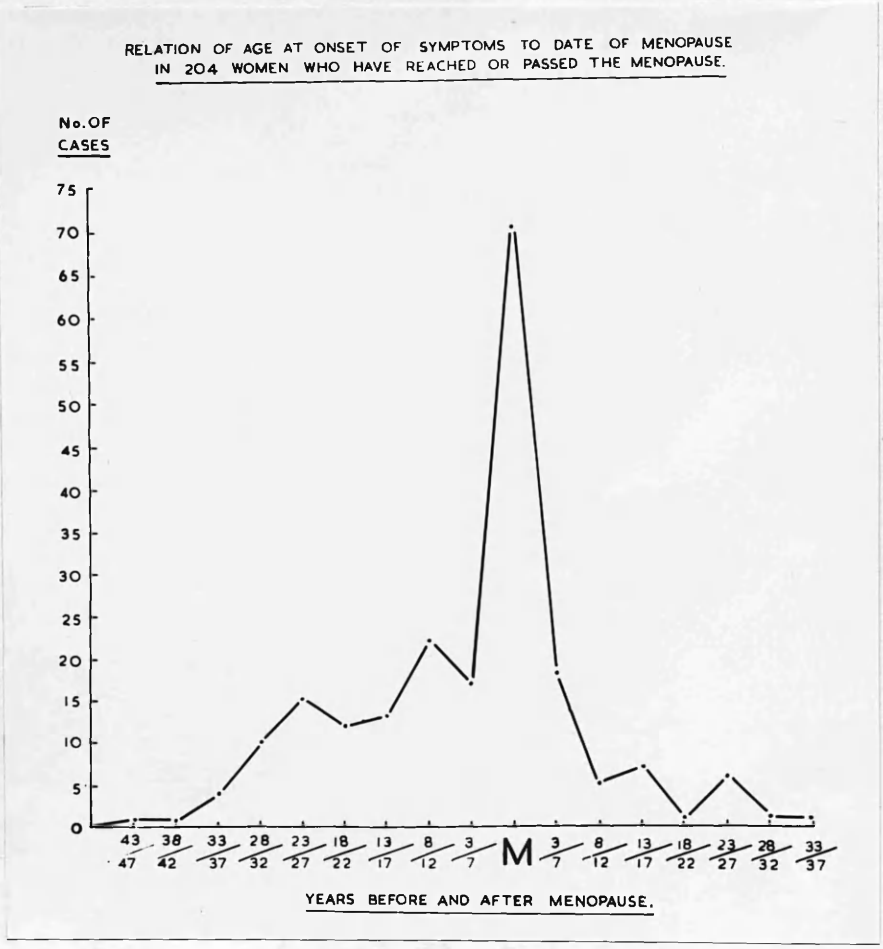
It is compared with a similar curve for male patients based upon figures derived from 1,393 cases from the Peptic Ulcer Clinic in Fig. 4.

Fig. 4.



It will be seen that while in both sexes there is a steep rise of incidence between the ages of 15 and 24 years, thereafter there is a difference in that in females there is a deficit during the age period 25-40 years, followed by a secondary rise of incidence between 40-50 years. These features suggest a possible relation to the child-bearing period and the menopause. In order to explore this possibility, the time relationship between the onset of ulcer and the menopause has been noted in the 204 women in whom the date of the menopause was known.

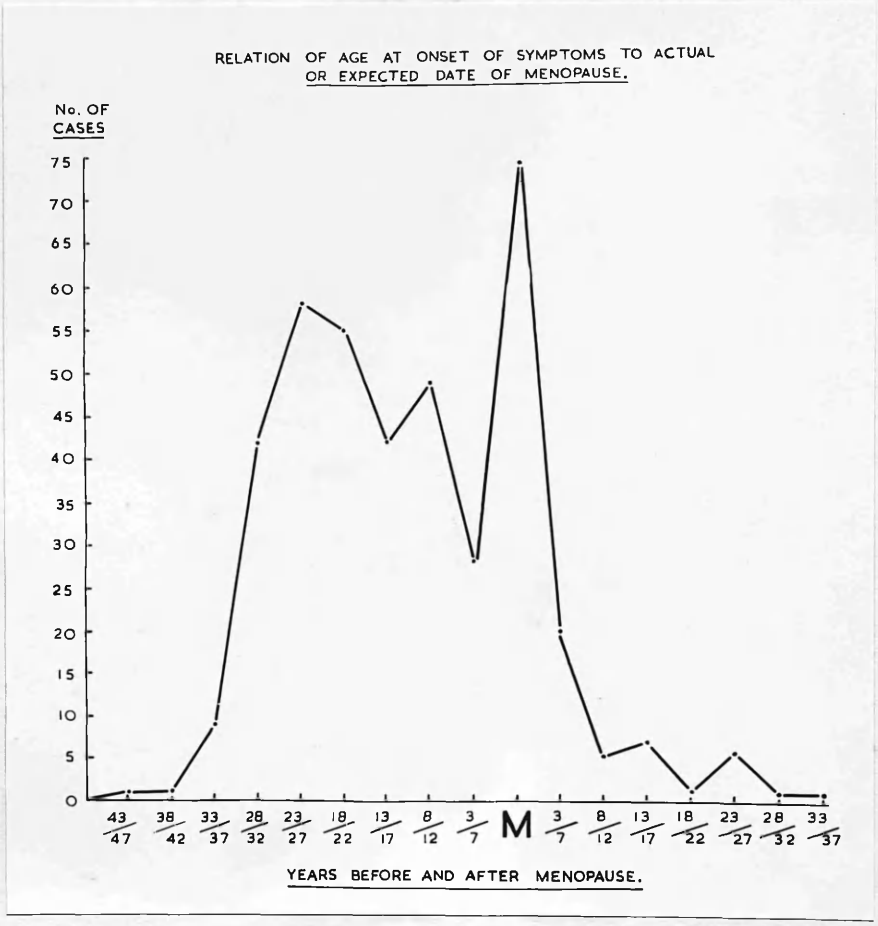
Fig. 5.



In Fig. 5 these cases have been plotted in 5-year groups according to whether the ulcer began to produce symptoms before or after, or about, the time of the menopause. It will be seen that there is a striking peak of incidence at, or about, the time of the menopause.

The remaining 196 women have not yet attained the menopause. In order to produce a composite curve, comparable with Fig. 3, relating 400 cases to the menopause, the onset of ulcer symptoms in this remaining group has been related to the expected age for that event. On the information available for the 204 cases, the age of the menopause ranged from 37 and 56 years with over 90 per cent between 40 and 50 years; the average was 45 years, and this figure was treated as the expected age of the menopause in the remaining 196 cases.

Fig. 6.



Working on this basis, Fig. 6 shows the time relationship of the onset of ulcer symptoms to the actual or expected age of menopause in the whole series of 400 cases. It will be seen that it again emphasises the two peaks of incidence in women, the former occurring in later adolescence and early adult life, the latter at about the time of the menopause.

In this series of 400 there were 330 patients with duodenal ulcer and 70 with gastric ulcer.

Fig. 7.

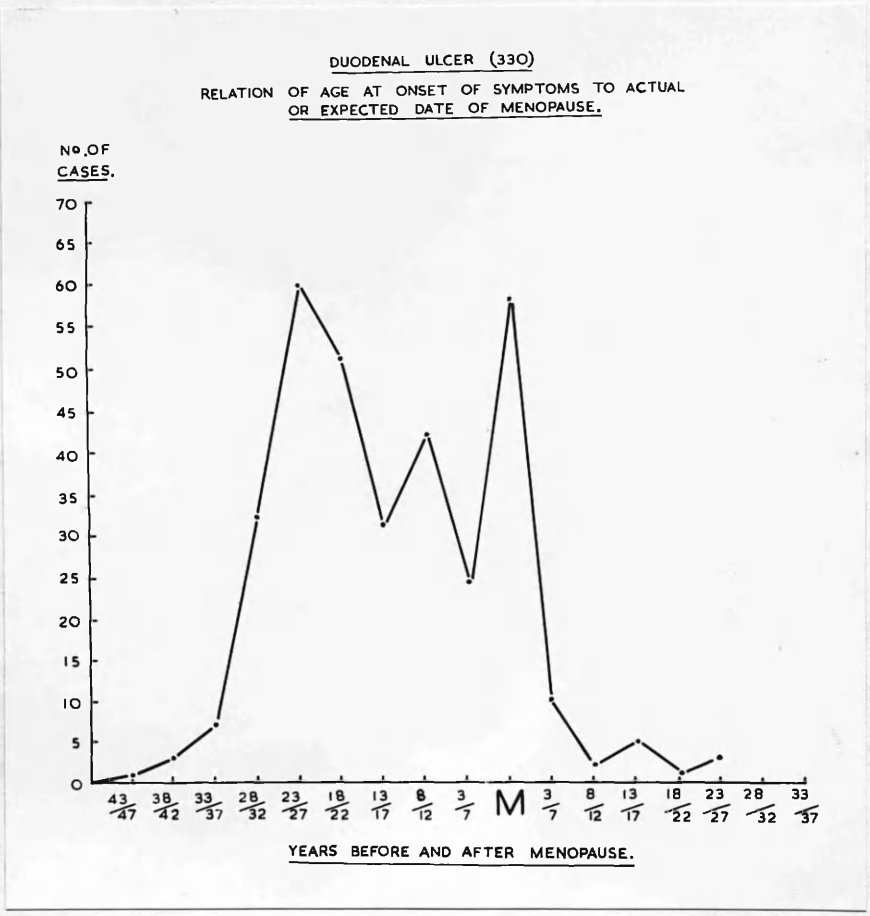
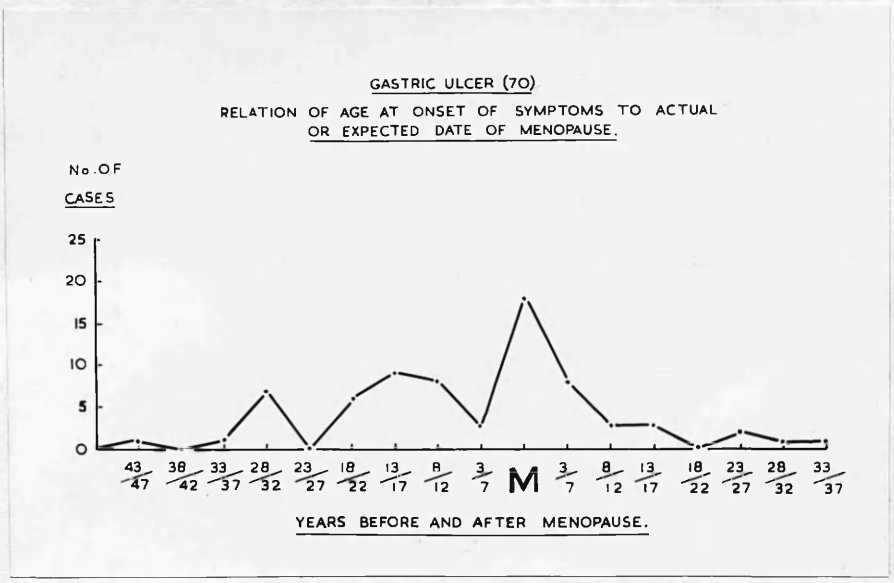


Fig. 8.



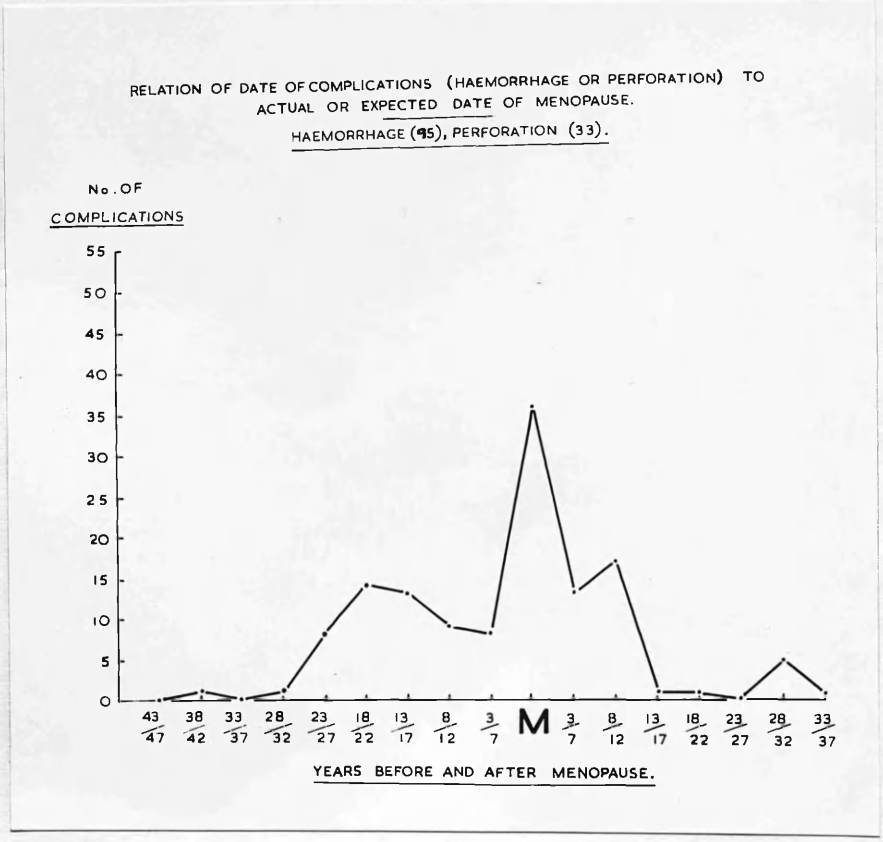
In Figs. 7 and 8 the two types have been treated seprately in the manner described above for the series as a whole. It will be seen that the menopausal rise in incidence is not confined to one type, though, perhaps owing to the paucity of numbers, the peak is less evident in the case of peptic ulcer. In the latter too it will be noted that the post-pubertal increase in incidence is not so marked, gastric ulcer being more commonly nowadays a disease of older age groups.

In those women who had ulcer symptoms before reaching the menopause, inquiry was made concerning the progress of the symptoms at that time. There were 92 in this

group, and 41 (45%) of them either volunteered, or agreed, on indirect questioning that their symptoms had worsened at or about that time. This trend was confirmed by the fact that a large number of them were then constrained to attend hospital for the first time on account of ulcer symptoms.

The incidence of complications of ulcer gives added evidence of the harmful effect of the menopause on the activity of the lesion. Among the total series of 400 patients, there was a history of 128 complications (95 haemorrhages and 33 perforations.

Fig. 9.

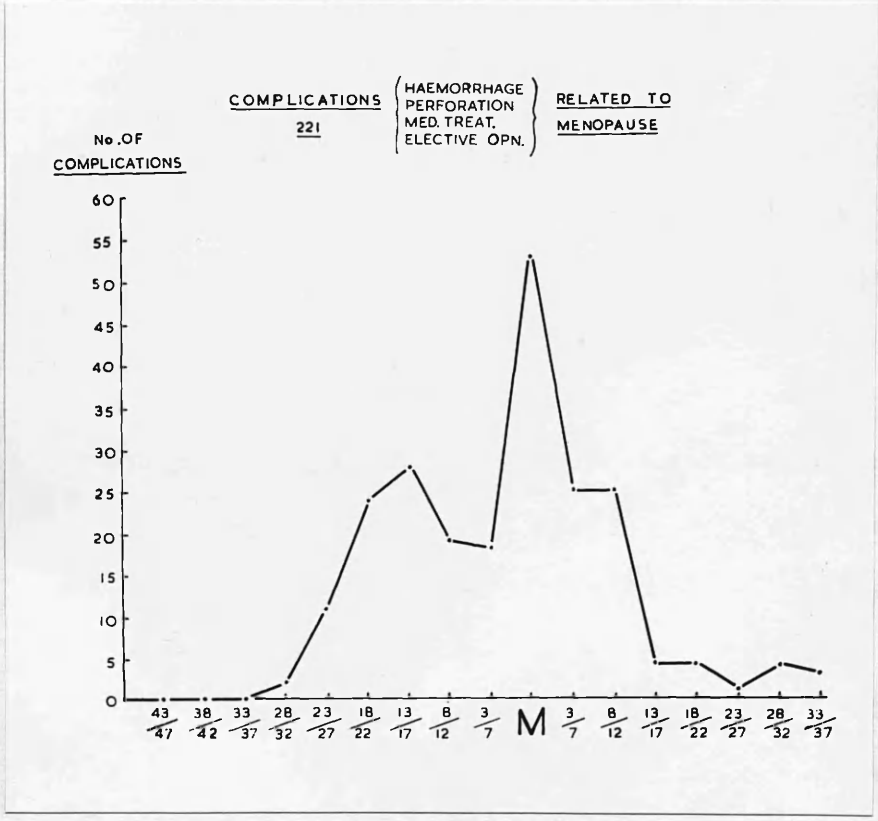


In Fig. 9 it will be seen that again there is a striking correlation, the number of complications occurring in the 5-year period centered on the year of the menopause being more than double that of any earlier or later period. Study of individual case records seems to give emphasis to this correlation, for several patients had more than one complication within a short time of the menopause.

One patient, for example, had two haematemeses and two perforations within the actual 5-year period. Another patient had three haematemeses and a perforation within the 5-year period of the menopause. Both these patients were thereafter without complications for 10 years and 15 years respectively. Yet another patient had four severe haematemeses within two years, the year of the menopause and the year after, her fourth haematemesis necessitating an emergency gastrectomy.

If admission to hospital for medical treatment and elective operation is considered as an indication of severity of the lesion, it will be seen from Fig. 10 that these "complications" further increase the peak of incidence of complications at the time of the menopause.

Fig. 10.


COMPLICATIONS
221
HAEMORRHAGE
PERFORATION
MED. TREAT.
ELECTIVE OPN.
RELATED TO
MENOPAUSE
No. OF
COMPLICATIONS
60
55
50
45
40
35
30
25
20
15
10
5
0
43/47
38/42
33/37
28/32
23/27
18/22
13/17
8/12
3/7
M
3/7
8/12
13/17
18/22
23/27
28/32
33/37

3. Discussion of the Results.

An epidemiological survey of peptic ulcer emphasises that women enjoy a relative immunity to the disease. From the statistical evidence available concerning the incidence of the disease in children, in whom it is uncommon, it would appear that the sex ratio before puberty is almost equal. Thereafter, however, there is a rapid increase in the incidence of the disease in both sexes, with males predominating in a ratio of 4 to 1.

The survey brings to light two further interesting features concerning the disease in women. Firstly, whereas haemorrhage from ulcer is equally common in both sexes, perforation is much less frequent in women. Indeed, the disparity is sufficiently striking to postulate in women a resistance of the anterior duodenal mucosa to ulceration. The second feature of interest is the remarkable stability of the perforation incidence in females throughout the 1939-1945 War years. The dramatic increase in perforation in 1940-1941, and decrease in 1942-1943, which was noted both in London and the West of Scotland, was confined solely to men. This is all the more surprising considering the large numbers of women who were employed in factories, munitions, shipyards, the Services, etc.

Both environment and constitution are important factors in determining the incidence of disease. They are undoubtedly concerned in the sex difference, though difficulty arises in deciding which plays the dominant role. Masculine conceit, for example, would demand that the incidence difference in the sexes is probably explained by the differences in environment, and that the female is less exposed to the go-getting, striving, worrying and often frustrating climate of masculine endeavour. (OGILVIE, 1949). The incidence of ulcer in professional women is not known. In the group of 400 women here presented, the proportion of professional women was very small. It seems to the author, however, that the failure of the great upheaval of the environment of many women during the years 1939-1945 to produce any striking change in their incidence of perforation, places the greater emphasis on constitution.

The psychiatric studies of GAINSBOROUGH and SLATER (1946) support this. They indicated that the female pattern is conducive to ulcer, and this led them to postulate that biological factors in the constitution of the female were important in protecting them against ulcer.

The nature of these biological factors is not known, nor are their benign effects confined to peptic ulcer: coronary thrombosis is a further notable example. Indeed, throughout life, the vulnerability of the male is a biological truism. The sex hormones have naturally been implicated, and a consideration of the natural history of peptic ulcer in women lends support to this hypothesis.

Since peptic ulcer is prone to spontaneous remissions, great caution is necessary in attributing variations in symptoms to internal or external events. However, the regularity with which remission of symptoms occurs in pregnancy, the rapid onset of relapse during lactation and the frequency with which ulcers start, flare up and undergo complications at, or about, the time of the menopause, give no justification for concluding that these states do influence the activity of the ulcer.

The manner in which they do so is uncertain, but two lines of speculation merit consideration. Firstly, the effect of psychical disturbances on gastric function has been known for a long time, and has been demonstrated convincingly in recent years by many workers, notably MITTELMANN and WOLFF (1942) and WOLF and WOLFF (1943).

It may well be that the remission of ulcer symptoms in pregnancy is related to the general feeling of wellbeing, success and fulfilment characteristic of that state; it may also be that lactation is a time of new responsibilities and anxiety which may promote ulcer activity; finally, the mental stresses, irritability and emotional imbalance of the menopause may account for the new, or renewed, ulcer activity at that time.

Secondly, the mechanism may possibly be a hormonal one. It is well-established that pregnancy is a period of increased hormonal activity with a marked increase in the gonadotrophic, luteal and oestrogenic hormones. During lactation there is increased activity of the anterior pituitary, in particular in the production of lactogenic, growth and possibly other hormones. The menopause is associated with a diminution in the sex hormones, particularly in the level of oestrogens.

In attempting to justify any theory concerning those events and their impact on the course of peptic ulcer, it must be remembered that the ability to demonstrate a "positive correlation" between two sets of happenings does not, in itself, prove a correlation between the two. The balance of evidence concerning the parts played by psychical disturbances and sex hormones would

would tend to suggest that the latter are the more important, although, despite much research, it should be emphasised from the outset that there is still no clear proof of a relationship between sex hormones and peptic ulcer.

A considerable amount of clinical and experimental data anent this subject has accumulated during the past 20 years, and though the author has perused most of it, only the more apposite contributions will be quoted.

There have been numerous clinical trials of sex hormones in the treatment of peptic ulcer and, in the opinion of the author, in many instances, unjustifiable conclusions have been inferred from them. Nowadays the importance of design in a clinical therapeutic trial in peptic ulcer is well appreciated for the difficulty in appraising the effect of any drug or set of circumstances in peptic ulcer is notorious. The clinical trial requires to be well-controlled, the follow-up sufficiently long and the results independently judged. Those trials of sex hormones in the treatment of peptic ulcer reported in the literature fail to satisfy these requirements. The most instructive are those reported by SANDWEISS et al (1939) using chorionic gonadotrophin, WINKELSTEIN (1940) and ABRAHAMSON et al (1942) using

oestrogens. The results produced were neither better nor more prolonged than the orthodox measures of diet and antacids. Clinical trials to date, therefore, have failed to produce results either indicating a relationship between sex hormones and peptic ulcer, or warranting their therapeutic use in patients. It should be observed, however, that these hormones are present in pregnancy in much larger amounts than can be given therapeutically.

In the experimental field, the presumed relationship between sex hormones and peptic ulcer and, especially, the beneficial effect of pregnancy on the course of the disease, have stimulated a great deal of endeavour and produced a large volume of literature. These experiments can be classified into two main groups, and it is the author's intention to mention only the more noteworthy contributions.

(1) Attempts have been made to ascertain the effect of pregnancy and the hormones known to be associated with, or increased, during pregnancy on experimental animal "ulcer" preparations. Pregnancy was found by FARBMANN, SANDWEISS and SALTZSTEIN (1939) not to protect animals against cinchophen ulcers; by WANGENSTEEN (1943) not to protect against the effects of

continuous histamine stimulation; and by SHAY and his associates (1945) not to protect rats against the ulcer whichrapidly develops with simple ligature constriction of the pylorus. SIRCUS (1956), on the other hand, on his study of the resistance to digestion of stomach-implanted dog's colon, noted the remarkable protective properties of pregnancy. With a preparation in which ulceration of the transplanted colon invariably occurred, the only exception was in one animal which was pregnant.

With regard to the effect of hormones SANDWEISS et al (1938, 1939 and 1949) have attempted to measure their anti-ulcer effect, using the MANN-WILLIAMSON dog preparation (1923). In this preparation, by reason of deviation of duodenal, bile and pancreatic secretions away from the upper jejunum, ulcers develop at the gastro-enterostomy stoma in a large proportion of cases, usually within 10 weeks. These authors found that chorionic gonadotrophin of human pregnancy urine (the luteinising hormone), the chorionic gonadotrophin of pregnant mares' serum (the follicle-stimulating hormone) and progesterone appeared to have significant value in the prevention or healing of these ulcers. Oestrogens were apparently without effect. On the other hand, NASIO (1946) found that synthetic oestrogens prevented

cinchophen ulcers in 100 per cent of male dogs, although only 22 per cent of the females were protected.

The importance of these observations is difficult to evaluate and, more especially, in view of the lack of similarity between "experimental ulcer" and chronic peptic ulcer in man.

2. The second group of experimental data concerns the effect of sex hormones on gastric secretion, and stems from the belief that acid is invariably depressed during pregnancy. The investigators in this field have studied mainly the extracts of human pregnancy urine. Thus CULMER and his associates (1939) reported significant depression of the gastric secretory response of Pavlov pouch dogs to standard meals. The active substance was contained in the A.P.L. fraction of human pregnancy urine, though its nature and mechanism of action was, and is, still unknown. This observation, and others, concerning pregnancy and peptic ulcer, stimulated research into gastric secretory inhibitary substances present in the urine, not only of pregnant women, but of normal women, and of men with, and without, duodenal ulcer. The efforts in this field and, particularly, those of GRAY, WIECZOROSKI and IVY (1939), NECHELES et al (1939) and FRIEDMAN et al (1939) resulted in the

identification of an active principle in urine which was named UROGASTRONE.

This active principle urogastrone has been found both in the extracts of normal persons and in the urine of pregnant women (FRIEDMAN et al 1939, and GRAY et al 1939). Both these authorities have demonstrated its presence in the urine of patients with peptic ulcer but the amount, they state, is less than in normal persons. It has not been shown, however, to be present in significantly increased amounts in pregnant women (SIRCUS 1956), and its part in promoting the remission of ulcer in pregnancy is probably not important.

A further substance in the extracts of human pregnancy urine noted by SANDWEISS and his associates (1938, 1939 and 1941), and one which may have greater significance in pregnancy than urogastrone, was the active principle which they later named ANTHELONE. This substance was shown to have prophylactic and therapeutic effects on the Mann-Williamson "ulcer" preparations by virtue of enhanced fibroblastic proliferation, new formation of blood vessels and epithelialisation of the mucosa. These histological changes were not due to the inhibition of gastric secretion since the extract in the doses administered to these dogs had no inhibitory

effect. (SANDWEISS and FRIEDMAN, 1940; SANDWEISS et al, 1941; FRIEDMAN and SANDWEISS, 1941; SANDWEISS and FRIEDMAN, 1942). These authors also noted that the principle was present in greatest amounts in the urine of pregnant women; present, though to a lesser degree, in normal patients; and almost absent in patients with duodenal ulcer.

It will be seen, therefore, that clinical and experimental study of sex hormones and allied substances associated with pregnancy has so far failed to reveal a relationship between any one of them and peptic ulcer. Pregnancy, however, has a complicated hormone pattern, and a combination of hormones may be more effective than a single hormone. The active principles of pregnancy urine seem to hold promise, though their study is beset with difficulties, e.g., in extraction, in assaying their activities and in isolating and identifying them in pure form.

Mention must be made of ACTH and cortisone. HENCH'S (1938) original observation of the ameliorating influence of pregnancy on rheumatoid arthritis stimulated interest in these hormones in relation to peptic ulcer. There is evidence (JAILER and KNOWLTON, 1950; VENNING, 1946) that adrenocortical activity is increased during

pregnancy, certainly as far as corticoids which are concerned with carbohydrate and protein metabolism. (VENNING, 1946). In the light of these observations SANDWEISS and his colleagues (1950) tested these hormones on their Mann-Williamson dogs, noting that the survival time was longer than the controls. Practical results, however, have not fulfilled the original theoretical promise of these hormones. They have now been shown (GRAY et al 1951) to be dangerously ulcerogenic, deaths from perforation and haemorrhage occurring with a frequency which precludes their use in patients who suffer, or have suffered, from peptic ulcer. GRAY et al 1951 also demonstrated an increase in gastric acid and pepsin secretion. On the basis of their clinical and experimental evidence these authors formulated a theory of causation of peptic ulcer, subserved by a hormonal mechanism through the "hypothalamic-pituitary-adrenal-gastric axis" and initiated by stress. This theory readily fits into SELYE'S (1946) concept of General Adaptation and reinforces the recurring theme of the psychosomatic basis of peptic ulcer. The paradox thus arises that of all the hormones known to be increased during pregnancy, only one has been shown to have a relationship to peptic ulcer - and that a deleterious one.

The consistent behaviour of peptic ulcer during pregnancy, lactation and the menopause, though still not amenable to clinical or experimental elucidation, is sufficiently remarkable to warrant speculation. In searching for a common endocrinological factor which would explain real or apparent healing of ulcers in pregnancy and recurrence of, and increased ulceration, during lactation and the menopause, the anterior pituitary hormones seem the most likely. During pregnancy anterior pituitary activity is overshadowed and probably supplanted by hormones of the chorioplacental system which produces oestrogens, progesterone and gonadotrophins. During lactation and the menopause, the anterior pituitary and its hormones play a dominant role. This dominant role of the anterior pituitary formed the basis of WINKELSTEIN'S (1940,1946) hypothesis concerning what he called "this ductless gland peptic ulcer". This theory, however attractive, remains purely speculative.

In this connection, one further point concerning the menopause is worthy of comment. The endocrine pattern would appear to be one of pituitary hyperfunction between the time of the failing ovary and the time when adrenocortical function supervenes as a "gonad", reducing and stabilising pituitary function at a lower

(though still higher than pre-menopausal) level. This increase in anterior pituitary activity seems to coincide with the acute peak of incidence both of onset of ulcer and of complications in the menopausal 5-year period. (See figs. 6 and 9). Does the ulcerogenic effect of the menopause diminish with adrenal stabilisation? Several case records suggest that the storm abates somewhat when the climacteric has ended.

One interesting finding in the present study of the behaviour of peptic ulcer during pregnancy, and one which has not previously been reported, is the effect of toxaemia of pregnancy on the course of the disease. Of the 37 pregnancies in which no remission of ulcer symptoms occurred, there was a large proportion of toxaemias. In the 90% of pregnancies in which remission occurred, no toxaemia states were recorded. This phenomenon is not readily explained, since the cause of toxaemia of pregnancy is not known. Two theories are worthy of comment.

PARKS (1941 and 1943) suggested that extra adrenocortical secretion arising, for example, from the foetal adrenal glands or possibly from the placenta, may contribute to the cause of toxaemia by disturbing the water and electrolyte balance. Such a theory is of

interest in the light of the findings of GRAY et al (1951), and the known clinical effect of those hormones on peptic ulcer. However, the behaviour of acid secretion in pre-eclamptic states is not known and, obviously, merits investigation.

The second theory concerns histamine and the enzyme histaminase. This enzyme is normally present in high concentration in the plasma of pregnant women (HOFBAUER 1926; KAPELLER-ADLER, 1941, 1943; AHLMARK,1944) though its purpose is not known. It has been suggested that it protects the foetus from the effects of histamine, which, it is claimed by some authorities, also increases during pregnancy. KAPELLER-ADLER and others have reported data indicating a deficiency of the enzyme in toxaemia of pregnancy which complication, it is suggested, may result from "histamine intoxication". This possibility, implicating histamine, would provide a ready explanation for the failure of remission in toxaemic patients. Furthermore, the indirect effect of histaminase on gastric acid secretion during pregnancy may be of considerable importance. So far, a correlation of acid secretion and histaminase concentration in plasma during pregnancy has not been reported. This correlation has been investigated by the author and forms the subject of Part II.

C. SUMMARY OF PART I.

1. The literature concerning the epidemiology of peptic ulcer in females is reviewed. The following striking features emerge.

   (a) Prior to puberty there is no sex difference in the incidence of ulcer. Thereafter, however, the female incidence is approximately one-third of the male incidence.

   (b) While haemorrhage from peptic ulcer occurs frequently in females, perforation is remarkably uncommon. Moreover, there appears to be a remarkable stability of the female perforation incidence, which was unaffected by the "stresses" which caused the great increase in male perforations during 1940-1941.

2. The literature concerning the natural history of peptic ulcer with special reference to menstruation, pregnancy, lactation and the menopause is reviewed.

3. The results of personal interview of 400 women in the Peptic Ulcer Clinic, Western Infirmary, Glasgow, concerning the effect of those events on the course of the disease are reported.

   (a) The evidence concerning the effect of menstruation is too difficult to assess and insufficient to warrant conclusions being drawn.

(b) The beneficial effect of pregnancy is confirmed, and appears to happen, in about 90 per cent of pregnancies.

(c) In the remaining 10 per cent of pregnancies where relief is not obtained, there is a high proportion of pre-eclamptic toxaemias.

(d) Lactation appears to be a phase of ulcerogenic activity as witnessed by the rapid onset of relapse, and the not infrequent occurrence of complications (haemorrhage and perforation).

(e) At about the time of the menopause there is again evidence of ulcerogenic activity, ulcers frequently appearing, relapsing, if already present or undergoing complications.

4. The role of environment and constitutional factors in relation to ulcer activity is discussed in the light of the evidence provided by the study of its epidemiology and natural history in female patients. The evidence, so far as it goes, would seem to indicate that the relative immunity which women enjoy is due mainly to biological factors in their constitution.

5. The biological factors generally implicated are the sex hormones, and the evidence concerning them in relation to human peptic ulcer and experimental peptic ulcer in

animals is presented and discussed. Though the effect of pregnancy, lactation and the menopause on peptic ulcer is substantial, there is still no clear-cut evidence demonstrating a relationship between sex hormones and peptic ulcer. Only A.C.T.H. and cortisone, which are not sex hormones, but which are increased during pregnancy, lactation and the menopause, have been shown to have an effect, viz., ulcerogenic.

6. The interesting substances identified in the extracts of human pregnancy urine viz. urogastrone and anthelone are mentioned, and the pertinent experimental evidence is discussed. Though interest in these substances has waned in recent years, they seem to hold considerable promise, especially in view of the fact that they are also present in the urines of normal men and women, but are deficient in patients suffering from duodenal ulcer.

7. An interesting observation, not previously reported, is the failure of remission of symptoms in patients suffering from pre-eclamptic toxaemias. Two current theories anent the etiology of toxaemia viz. increased adrenocortical activity and the deficiency of the enzyme plasma histaminase are briefly mentioned since both these disorders are theoretically capable of increasing ulcer activity.

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PART II.

GASTRIC ACID SECRETION AND PLASMA HISTAMINASE DURING PREGNANCY.

A. REVIEW OF THE LITERATURE.

1. Effect of Pregnancy on Gastric Acid Secretion.

The observations that pregnancy may exert a beneficial effect on the course of peptic ulcer stimulated investigation into the level of gastric secretion during pregnancy. The work of NAKAI (1925), ARZT (1926), MASON (1931) and STRAUSS and CASTLE (1932) has shown that the level of acid gastric secretion is depressed during pregnancy. The manner in which this reduction is brought about is uncertain, but it was presumed that the sex hormones played a part. The evidence has been reviewed and discussed in Part I. IVY et al (1950) and SANDWEISS (1951) mooted the possibility that the enzyme histaminase - an enzyme which inhibits histamine - may play an important role in depressing gastric acid secretion.

2, Role of Histaminase.

The enzyme histaminase was discovered by BEST in 1929. It is normally present in considerable amounts in the mucosa of the small intestine and the kidneys, but apart from pregnancy, no condition has been encountered

in which histaminase could be detected in human blood. ANREP et al (1947), MARCOU et al (1938) have shown that the plasma histaminase level rises during pregnancy, the enzyme being derived from the placenta, particularly the decidua SWANBERG (1948). This plasma level may rise to one thousand, or even two thousand times the normal level AHLMARK (1944). A considerable increase of enzyme activity is observed as early as the 7th week of pregnancy, reaching a high level around the 30th week and lessening somewhat in the latter part of pregnancy. The highest levels were found in twin pregnancies, suggesting a relationship to placental size, whilst significantly low results were obtained in cases of pre-eclamptic toxaemia, the severe cases showing a very small histaminase activity KAPELLER-ADLER (1951). Several authors have stressed the importance of the metabolism of histamine when intoxications occur during pregnancy, and histamine has been looked upon as being one of the causes FELBERG and SCHILF (1930), WESTBERG (1941), KAPELLER-ADLER (1941) and KAPELLER-ADLER and ADLER (1943) found that during pregnancy histidine normally present in the urine decreases or disappears in severe cases of toxaemia of pregnancy, and the latter authors showed that histamine appears in the urine in these pathological states.

They assumed that the histaminase metabolism was disturbed in cases of toxaemia. ZELLER (1941) noted smaller quantities of histaminase in patients with hyperemesis gravidarum while WERLE and EFFKEMAN (1940) stated that the histaminolytic power in cases of toxaemia was decreased in comparison with that of healthy pregnant women. AHLMARK (1944), on the other hand, investigating the same problem, found that in at least one-third of the patients studied, there were abnormally low values; as many had normal values; and the remainder had values higher than normal. In his small series, therefore, he could find no correlation between the degree of enzyme and the histaminolytic power.

It should be noted that histaminolysis has not been found to occur to any remarkable extent in the blood of the pregnant or non-pregnant animals. Studies can therefore be performed only on the human subject.

These findings seem to emphasise the importance of the presence of histaminase in the blood during human pregnancy. Nothing is known as to the possible function of the large amounts appearing in the blood and placenta. It has been suggested that the placental histaminase may offer a protection to mother or foetus against histamine, though the significance of the low histaminolytic

power in pathological pregnancies is unknown. It is of interest, however, to note that both the pregnancy toxaemias and also the high histaminolytic power in pregnancy plasma occur only in human beings.

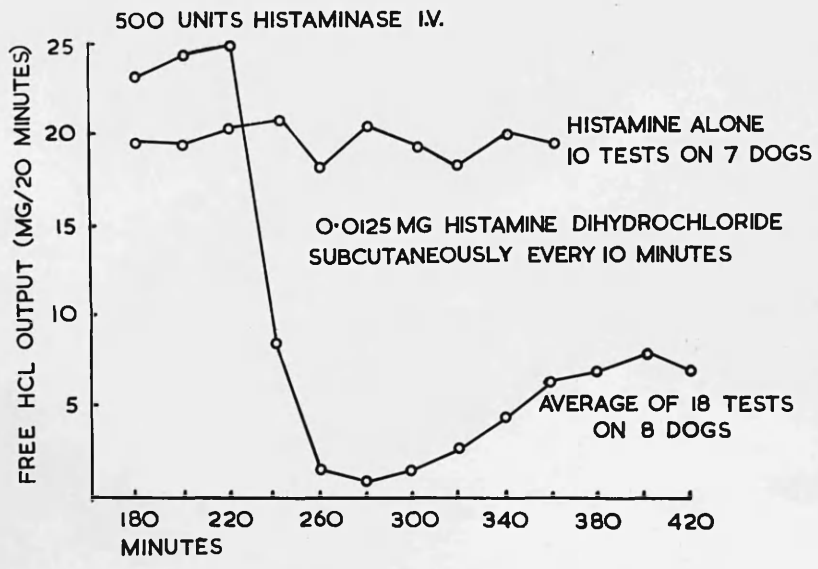
Eighteen years ago interest in the therapeutic use of histaminase in peptic ulcer was stimulated by several reports indicating its efficacy in peptic ulcer and allergic states. KARADY and BROWN (1939) showed that histamine and anaphylactic shock were effectively prevented by the pre-administration of histaminase to guinea pigs. Similar findings in the symptomatic relief of serum sickness were reported by FOSHAY and HAGENBUSCH (193) and also by LAYMAN and CUMMING (1939) in the prevention and treatment of urticaria. NAKADA (1939) reported successful results in the treatment of duodenal ulcer. Clinical and laboratory reports, however, were controversial. ROTH and HORTON (1939) found that in man gastric acid secretion provoked by cold and by histamine, could be suppressed by histaminase. On the other hand, ATKINSON and IVY (1938), using their own preparation of the enzyme, failed to find any effects on the secretion of gastric pouches in dogs when stimulated with histamine. These varied reports culminated in the appraisal of this enzyme (proprietarily known as "Torantil", an extract

of hog's small intestine and kidney) by the American Council on Pharmacy and Chemistry (1940). The Council decided that the evidence was so conflicting, and insufficient, to warrant the use of the preparation under examination. BEST and McHENRY (1940), for example, were unable to confirm the findings of KARADY and BROWNE (1939). NECHELES and OLSON (1941) further discredited the commercial preparation (TORANTIL). They found it to have no effect on acid gastric secretion, or gastric motility, and suggested that a number of the clinical and laboratory findings reported in the literature have been due to the side-effects of unknown or non-specific agents in the samples of the preparation. Certain reports claiming good histamine inhibition by the oral administration of histaminase seem dubious in the light of the knowledge that it is destroyed by pepsin as well as trypsin. BEST and McHENRY (1940). Moreover, NECHELES and OLSON (1941) doubted if the small amount administered would make much difference to the already large store present in the body.

When more pure and more potent extracts became available ROSTORFER and LASKOWSKI (1945) and GROSSMAN and ROBERTSON (1948) working with "pouch" dogs confirmed that histaminase could antagonise the effect of histamine

on acid secretion. The results of the experiments of the latter authors are shown in Fig. 11.

Fig. 11. AFTER GROSSMAN & ROBERTSON (1943).



AVERAGE SECRETORY RESPONSE of dogs with pouches of entire stomach to histamine alone and to histaminase plus histamine.

These authors, however, were unwilling to discard the possibility that the effect was non-specific, for example, due to a pyretic agent in the extract.

B. PRESENT INVESTIGATION.

1. AIM OF INVESTIGATION.

The reports mentioned deal solely with extracts of the enzyme from hog tissue. There are no reports of any attempts at a correlation of the naturally circulating enzyme in human pregnancy with the gastric acid secretion during pregnancy. The purpose of the present study is to report observations on the gastric acid secretion and the plasma histaminase level, during and after pregnancy. The intention was to find whether the acid secretion (spontaneous or histamine-induced) is regularly diminished during pregnancy, and whether any such change is related to the plasma histaminase level.

2. CLINICAL MATERIAL.

Volunteers for this investigation were sought in an ante-natal clinic, and an effort was made to obtain them as early as possible in pregnancy. The nature of the investigation was explained, and its objects were outlined. The aim was to study gastric acid secretion (spontaneous and histamine-induced) and to estimate the plasma-histaminase level on several occasions during pregnancy and, again, after parturition. As was to be expected, many of the volunteers failed to stay the course.

Some had to give up because pregnancy sickness precluded intubation; others lost interest, or were prevented by their domestic duties from attending. The 9 patients who submitted to the full investigation deserve high praise for their considerable sacrifice in the cause of medical science. Two of them were former patients of the Peptic Ulcer Clinic of the Western Infirmary, Glasgow; but the remaining 7 gave no history of ulcer.

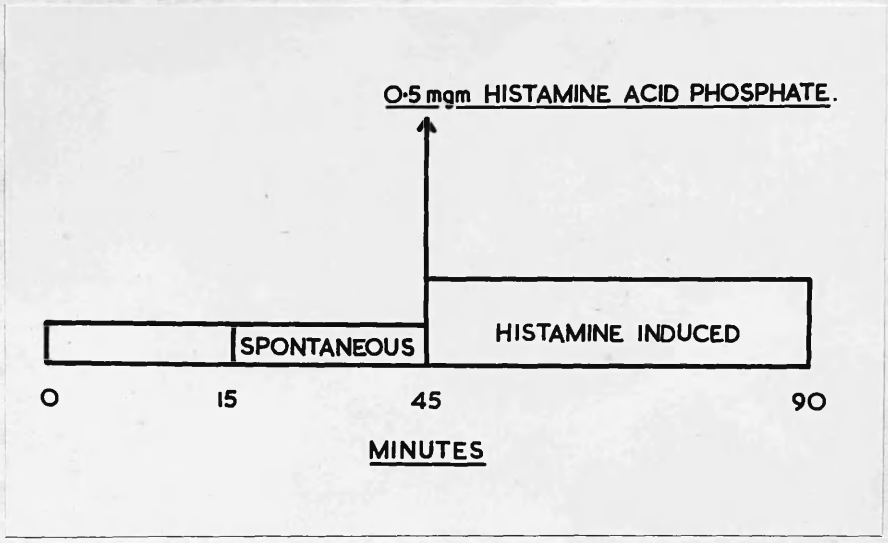
3. METHODS.

(a) Gastric Acid Secretion.

The patients were tested after a twelve-hour fast, and 10 ml. of venous blood was withdrawn for estimation of the plasma-histaminase level, care being taken to avoid haemolysis. The patients gargled with 3 ml. of 2% tetracaine hydrochloride (Anethaine), which they also swallowed. This amount of anethaine has no effect on gastric secretion. A No. 10 stomach tube with multiple perforations at its tip was passed, and continuous aspiration with an electric suction pump was started. The tube and the patient were both moved to ensure that the best position for the collection of juice was found.

The plan for the collection of juice is shown in Fig. 12.

Fig. 12. PLAN FOR COLLECTION OF GASTRIC JUICE.



The fasting juice was withdrawn and discarded. Spontaneously secreted juice was next collected for 30 minutes and then 0.5 mg. of histamine acid phosphate was injected subcutaneously, and the collection of juice continued during the subsequent 45 minutes. This dose of histamine was not exceeded. Though the effect of histamine on the pregnant human uterus is probably insignificant, it was considered unwise to attempt the augmented histamine test as described by KAY (1953). A longer period of collection for both the spontaneous and histamine-induced secretion would have been desirable; however, the test had to be kept within the limits of time which the volunteers could spare.

The volume and titrable free acidity of both collections were measured, and the final results expressed as mg. of hydrochloric acid.

This was done about every four weeks during pregnancy from about the 14th week onwards, and on several occasions after parturition. No readings were available for the first trimester of pregnancy in any of the 9 cases. It was impossible to obtain specimens during the early weeks of the puerperium owing to the patients' domestic duties.

(b) Histaminase.

The various methods of estimating histaminase are reviewed by KAPELLER-ADLER (1951). These are mainly chemical or biological. The method used was a volumetric method described by that author and which has the great advantage of simplicity, and seems to agree very closely with the more accurate biological methods. Where possible, controls and test sera were examined in triplicate. The procedure is as follows:

Reagents required:

1. M/15 phosphate buffer (Sorensen) ph. 7.2.
2. Histamine solution in m/15 - phosphate buffer, containing 10 mg. of histamine dehydrochloride/ml.

3. Indigo disulphate solution. Indigo carmine (200 mg.) is dissolved in ~~300~~ 300 ml. water and the solution stored in a brown bottle.

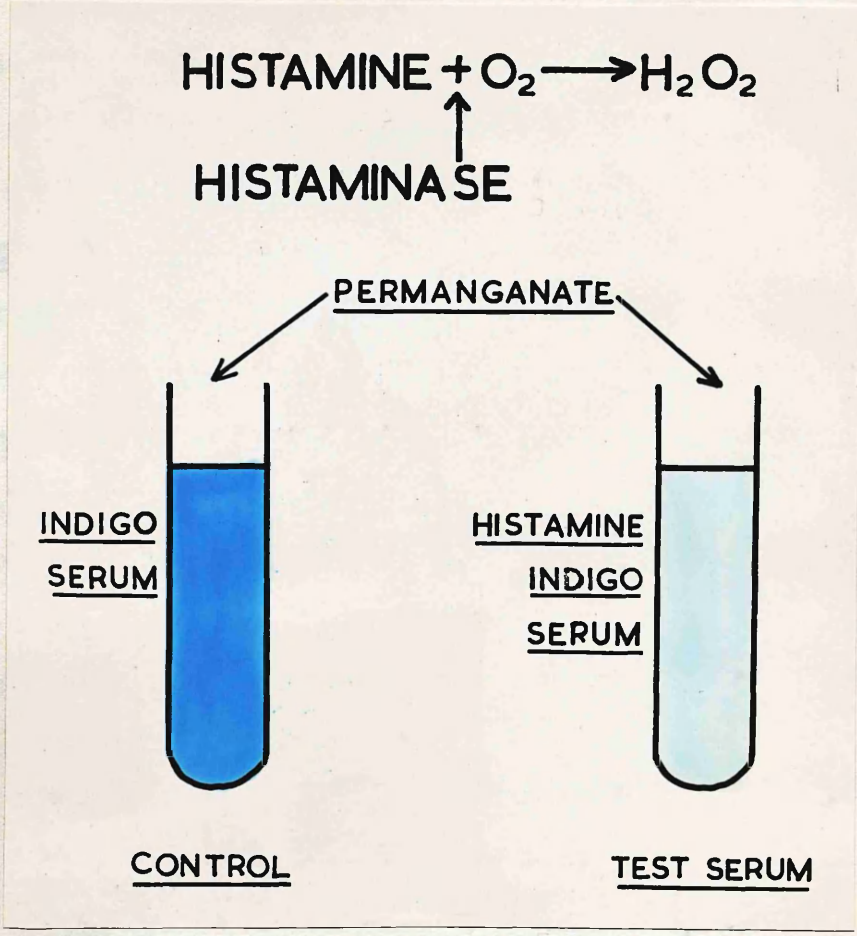
4. 0.002 N KMNO4 ~~M-K & M-0/4~~ solution.

5. $CHCl_3$

ESTIMATION.

Add to 1 ml. of non-haemolysed serum 2.5 ml. of phosphate buffer pH 7.2, 0.1 ml. of the histamine solution, 0.5 ml. of the indigo solution and 1 drop of $CHCl_3$. O_2 is passed through the fluid for 1 minute, the test-tube is closed with a rubber stopper, the solution well-mixed by shaking and incubated for 24 hours at 37°C. A control for each individual test without the addition of histamine is always carried out simultaneously with the test. After 24 hours the controls and the tests containing an excess of the indigo compound are titrated with 0.002-KMNO/4, until the end-point of titration is reached, when the blue colour has just disappeared and a pink colour just appears and persists for a few seconds. The amount of KMNO/4 utilised in the assay is subtracted from the amount taken up by the control. The difference indicates the amount of H_2O_2 formed by the action of histaminase on histamine and thus the enzyme activity. The method is graphically presented in Fig. 13.

Fig. 13. METHOD OF ESTIMATION OF HISTAMINASE.



The histaminase unit of activity is conveniently called a Permanganate Unit (P.U.), and it represents the amount of enzyme which, after an incubation of 24 hr. at 37° and PH. 7.2., in an atmosphere of oxygen with 1 mg.

of histamine hydrochloride as substrate and with an aqeous solution of indigo desulphonate takes up 0.1 ml. 0.002M - potassium permanganate.

4. RESULTS.

(a) Gastric Acid Secretion.

For each of the 9 patients about 7 sets of readings were made during pregnancy, and 4 sets after parturition. The results for each of the 9 patients are shown in the Appendix.

The results are summarised in the accompanying Table 4.

COMPARISON OF SPONTANEOUS AND HISTAMINE-INDUCED ACID SECRETION BEFORE AND AFTER PREGNANCY

CASE NO:	SPONTANEOUS GASTRIC SECRETION mgm. HCl.			HISTAMINE INDUCED GASTRIC SECRETION mgm. HCl.		
	Post-pregnancy (Average)	Pregnancy (Average)	Percentage rise (+) or fall (−) of level during pregnancy	Post-pregnancy (Average)	Pregnancy (Average)	Percentage rise (+) or fall (−) of level during pregnancy
I	90.1	54.2	− 40	267.3	236.0	− 11
II	33.8	38.9	+ 15	274.4	320.9	+ 17
III	27.4	28.5	+ 4	250.4	219.7	− 12
IV	24.9	23.0	− 8	281.8	156.1	− 45
V	20.4	14.2	− 30	115.4	130.3	+ 13
VI	43.5	93.5	+ 115	281.9	498.5	+ 70
VII	9.1	37.2	+ 308	40.5	114.5	+ 183
VIII	0.3	8.4	+2700	2.5	44.2	+1668
IX	31.8	7.9	− 75	161.9	107.8	− 33

This table shows for each patient (1) the average amount of spontaneous secretion obtained on the seven occasions duringpregnancy: (2) the corresponding figure after parturition; (3) the average amount of histamine-induced secretion obtained during pregnancy; and (4) the corresponding figure after parturition.

The post-partum figures are presumed to be the patients' normal. A difference of 50% during pregnancy has been taken arbitrarily as indicating a significant rise or fall.

It will be seen that in 5 patients (cases 1 - 5) there was no significant difference in the level of either spontaneous or histamine-induced secretion. In 3 patients (cases 6 - 8) there was a significant rise during pregnancy. Only in 1 patient (case 9) was there a significant fall during pregnancy: the average of the readings of spontaneous secretion fell 75% during pregnancy; the fall in histamine-induced secretion was only 33%.

To illustrate the degree of consistency of the readings in successive estimations in individual cases, charts are presented giving the detailed findings in 3 patients. Fig. 14 gives the details of case 7 in which both the spontaneous and histamine-induced secretions were higher on every occasion during pregnancy than after parturition.

Fig. 14. PATIENT No. 7.

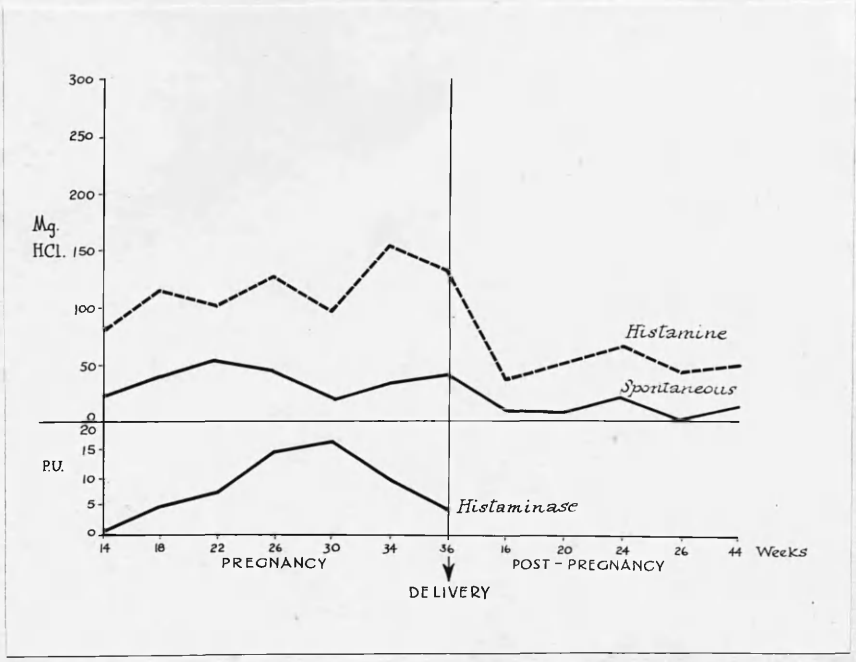


Fig. 15 gives the details of Case 9, the only patient whose readings showed a lowered secretion during pregnancy.

Fig. 15. PATIENT No. 9.

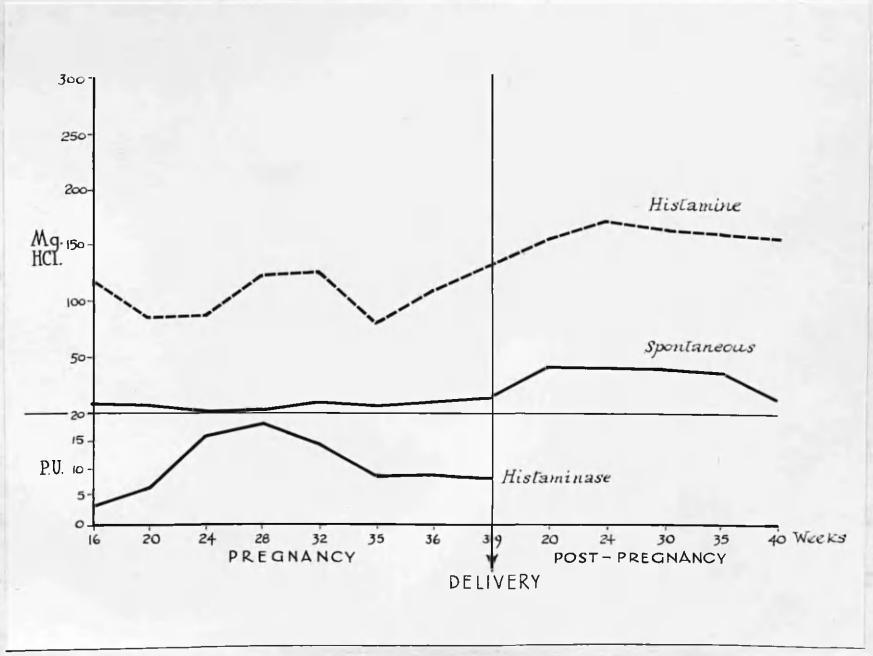
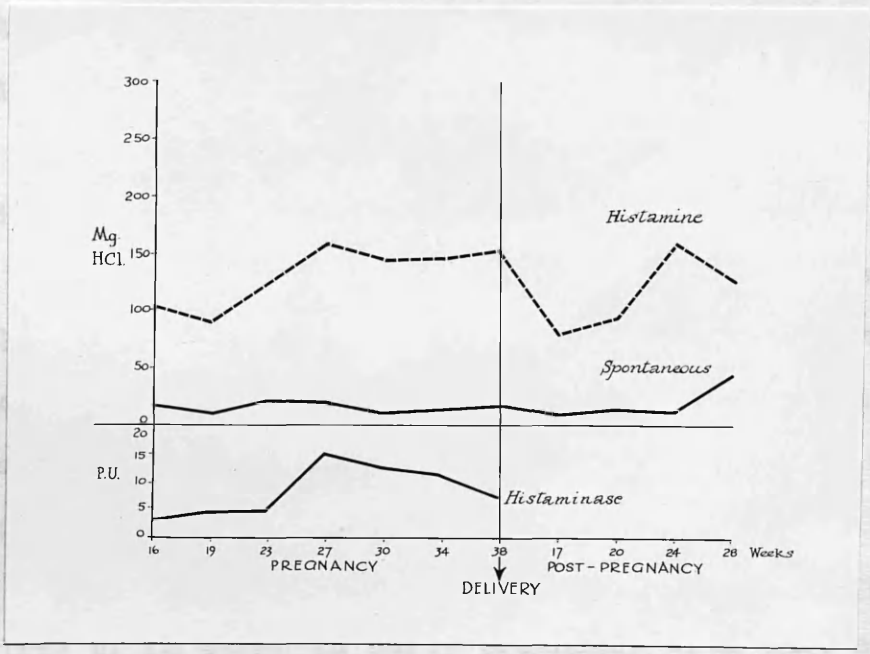


Fig. 16 gives the details of Case 5, one of the 5 patients in whom no significant change was noted; this group included the 2 patients with duodenal ulcer.

Fig. 16. PATIENT No. 5.



(b) Plasma Histaminase.

The plasma histaminase level was estimated in all 9 cases. It was consistently raised during pregnancy, the highest levels usually being found about the 27th-30th weeks. The level regularly returned to zero after parturition. Figs. 14-16 show the entire absence of correlation between the plasma-histaminase level and the amount of either spontaneous or histamine-induced gastric secretion.

7. DISCUSSION.

The observations reported here make it clear that there is no justification for the belief that the acid secretion of the stomach diminishes during pregnancy. This happened indeed in only 1 of the 9 cases studied; by contrast, in 3 of the 9 cases the acid secretion showed a significant increase during pregnancy.

In view of these findings, it is interesting to review the previous work on which this belief was based.

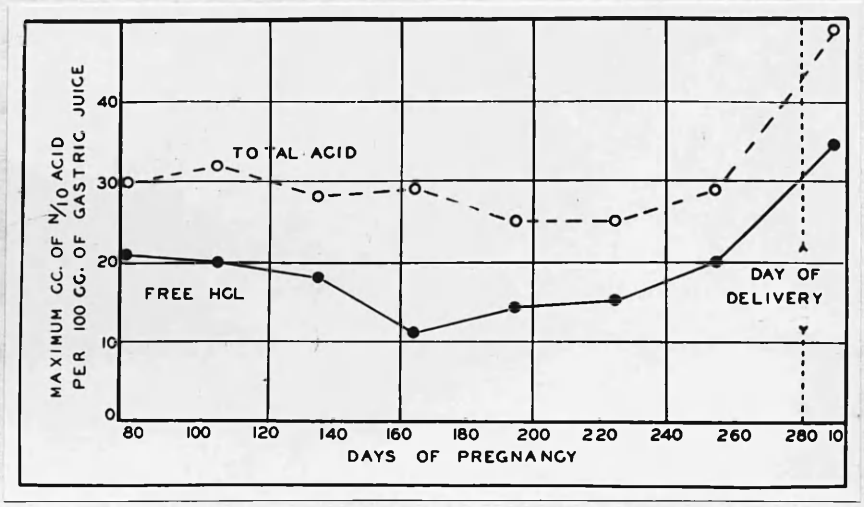
NAKAI (1925) compared the secretion of a gastric acid in 14 pregnant women with that of non-pregnant women reported by other Japanese workers. The conclusion that acidity was reduced during pregnancy was based on a single reading in each of these women.

ARZT (1926), using test meals, compared the gastric acidity of 18 women in early pregnancy with that of 6 of the same women in late pregnancy. He concluded that there is a low acidity throughout pregnancy, particularly in the early months.

MASON (1931) reported an acidity in 2 patients and low acidity in 4 patients during the first trimester of pregnancy. He made no observations on the normal level of acidity in these patients.

The most adequate study to date is that of STRAUSS and CASTLE (1932), who analysed the gastric juice of 24 apparently normal pregnant women about monthly during pregnancy and, again, on one occasion only, 7-10 days after delivery, and on this basis concluded that acidity is lowered during pregnancy. A graphical representation of their results is shown in Fig. 17.

Fig. 17. AFTER STRAUSS and CASTLE (1932).



From what is now known of the limitations of sampling methods of gastric analysis, it is clear that a comparison of this sort, based upon a single estimate of the "normal" is not free from fallacy. This is especially so when the "normal" reading is a single estimate so soon after

parturition. Experimental evidence will be presented and quoted later in this study which indicates that during the phase of lactation, the acid gastric secretion is raised in dogs, and may well be raised in humans.

Apart from showing that the gastric acidity is usually maintained in pregnancy, the results of the present investigation underline some points of interest about the plasma-histaminase level. They confirm the findings of previous workers that this level is regularly raised during pregnancy, but they do not provide any evidence that histaminase has any significant effect on either spontaneous or histamine-induced gastric secretion. During this investigation it was also our impression that such histamine effects as flushing and headaches are no less in pregnant women than in others. WICKSELL (1949) made a study of histamine sensitivity in pregnancy. Using the vascular reaction of the skin to intradermal histamine injections, his experiments gave no indication that the sensitivity of the skin vessels to injected histamine was altered in pregnancy.

The finding of this investigation contrasts with those of ROSTORFER and LASKOWSKI (1945), and GROSSMAN and ROBERTSON (1948) who countered the effects of histamine on gastric acid secretion in pouch dogs by administering

histaminase. The secretory response to food and to parasympathomimetic drugs was also inhibited. The latter authors, however, could not decide whether the gastric secretory depressant activity was due to histaminase or to some other constituent of the extract. They found that the thermal stability of the histaminase activity and that of the gastric secretory depressant factor were the same, but admitted that this did not prove that they were identical. They concluded that their results were suggestive, but could not be construed as evidence in favour of histaminase inhibiting acid gastric secretion. The difference in the results of this investigation and that of the GROSSMAN and ROBERTSON may be due to a difference in dosage, since these authors gave doses far in excess of those present in the plasma of pregnant humans.

In view of the clinical finding of peptic ulcer being not improved and occasionally worsened in toxaemia of pregnancy, and in view of the reported low histaminase levels in those pathological pregnancies, it would be of interest to study the acid gastric secretion in such cases.

C. SUMMARY OF PART II.

1. The previous observations on the level of gastric acid secretion during pregnancy are quoted. These, though not numerous, were unanimous in stating that gastric acid secretion was consistently depressed during pregnancy.

2. The possibility that histaminase, an enzyme which inhibits histamine and which is increased during pregnancy, may play an important role in depressing gastric acid secretion was mooted, but had never been investigated.

3. The literature concerning histaminase in normal and toxaemic pregnancies is reviewed. Though there is no uniform concensus of opinion, there is a considerable weight of evidence indicating that theenzyme is deficient in toxaemia.

4. In 1939, and for several years thereafter, when a commercial preparation of the enzyme became available for therapeutic use, there were many reports of its effect on clinical conditions attributed to histamine, "intoxication". Thus, it was used in serum, sickness, skin conditions and also in duodenal ulcer because of the known association of the latter condition with hyperchlorhydria. The literature concerning these clinical trials is briefly mentioned and discussed.

5. Previous work has demonstrated that the enzyme extract could inhibit histamine-stimulated acid secretion in dogs.

6. The intention of the presentinvestigation was to find whether acid secretion (spontaneous or histamine-induced) was regularly diminished duringpregnancy, and whether any such change is related to the plasma histaminase level.

7. In 9 women (2 of whom were known to suffer from duodenal ulcer) the acid secretion of the stomach, both spontaneous and histamine-induced, was estimated repeatedly during pregnancy and after parturition. The plasma histaminase level was also estimated.

8. Contrary to previous belief, there is no significant reduction (50 per cent) in acid secretion during pregnancy. Such a finding was observed in only 1 of the 9 patients, whereas in 3 the acid secretion was significantly and consistently increased. The remainder showed no change.

9. The plasma-histaminase level was consistently raised during pregnancy, but showed no correlation with the gastric secretion of acid.

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PART III.

URINARY SECRETION OF PEPSINOGEN IN LATE PREGNANCY AND THE EARLY PUERPERIUM.

The value of the conventional method of studying gastric function by the withdrawal of gastric juice is limited to some extent by its unpleasantness. This is so when numerous readings are desired, and more especially when the subjects concerned are not suffering from a gastric disorder. The investigation of acid gastric secretion described in Part II. was frequently jeopardised by this difficulty, many of the volunteers indicating their unwillingness to continue.

In attempting further to study gastric function it was decided to use the urinary pepsinogen secretion rate, since the estimation of this entails no unpleasantness for the patient.

A. REVIEW OF THE LITERATURE.

The pro-enzyme pepsinogen, which is manufactured by the peptic cells of the stomach, is largely excreted into the lumen of the stomach. A small portion of it, however, finds its way into the blood stream when it is excreted in the urine as uropepsinogen. On acidification this pro-enzyme is converted into a proteolytic enzyme

with properties identical with gastric pepsin. The peptic glands of the stomach seem, therefore, to have an endocrine as well as an exocrine status. The portion entering the blood stream is extremely small and has been estimated to be of the order of 1 per cent of the output of the peptic cells. JANOWITZ and HOLLANDER (1951).

BUCHER (1947) has shown that the enzyme is capable of assay, the method being based on the haemoglobin method of peptic assay of ANSON and MIRSKY (1932). Evidence has been presented by several authors, particularly JANOWITZ and HOLLANDER (1951) and AITKEN et al (1954), showing that a reciprocal relationship exists between the gastric secretion of pepsin and the level of excretion of uropepsinogen. A similar, though rough, relationship may also exist between the level of acid gastric secretion and that of urinary pepsinogen. AITKEN et al (1954) and SIRCUS (1954). Certainly it would appear that in conditions where gastric acid secretory activity is increased as in duodenal ulcer, the urinary pepsinogen excretion is generally raised; in conditions where low acids are encountered, the excretion level tends to be low; in normal individuals and in those suffering from gastric ulcer where the acid level is within the normal range, the excretion level is within a "normal" range.

However, dissociation between the level of gastric acid secretion and the uropepsinogen excretion rates do occur. This is especially notable in the following circumstances.

(1) The hyperacidity following histamine injection is not accompanied by an increase in the urinary excretion of the enzyme. (ASHER, 1955).

(2) Vagotomy does not result in lower levels of uropepsinogen excretion. GRAY et al (1954).

(3) Gastric resection, unless total, may not affect the level of excretion.

Thus, though the levels may be considered to reflect gastric pepsin activity, they probably do not accurately indicate gastric acid secretion.

It has been noted previously, and is obvious in the data to be presented, that there are considerable day-to-day variations in the excretion levels. Current opinion on these day-to-day variations correlates them with the stress situation of the patient. The stress need not be emotional, although it is often the case. It may be physical or hormonal. The observations of GRAY et al (1954) and ASHER (1955) support this.

ASHER (1955) considered that these variations may indicate the gastro-intestinal response of the patient

to stress in a manner that can be measured. In this respect, uropepsinogen would resemble the eosinophile count, 17-KETOSTEROID excretion levels, blood pressure determinations and other tests of the responses of specific of specific organ systems to stress. Though isolated estimations would appear, on this account, to have little value, there would appear to be little doubt that daily estimations over a period of weeks would determine the pattern of uropepsinogen excretion for an individual patient, reflecting the gastric secretory activity and its response to the immediate stress situation.

Published work on this subject is unanimous in many respects. For example, it is well-established that in gastric ulcer, the urinary pepsinogen excretion rate is within normal limits, and that in duodenal ulcer in men it is consistently and considerably raised. In duodenal ulcer in women, on the other hand, there have been divergent findings. Thus, HIRSCHOWITZ (1953) found that females excrete normal amounts of urinary pepsinogen irrespective of the presence of ulcer. EASCOTT et al (1953) and SIRCUS (1954) have shown that when an ulcer was present, the level was proportionately raised, though not to the levels found in male D.U. patients.

B. PRESENT INVESTIGATION.

1. AIM OF INVESTIGATION.

The purpose of the present investigation was to compare gastric secretory activity in late pregnancy with that in the early puerperium, using daily urinary pepsinogen excretion estimations. The scope of the investigation had to be limited to these periods because of the need for accurately measured 12 or 24-hour urine collections. The patients studied were, therefore, in-patients. Though the period of time covered is short, it was hoped that any trend of change in gastric secretory activity would be noticeable. It is also arguable that hospital conditions more nearly approach the "basal" conditions ideal for a stress sensitive indicator.

In order to assess the level of the gastric secretory activity during late pregnancy and the early puerperium, it seemed advisable to compare these results with those of controls in which the level of activity was known. Data was, therefore, collected concurrently in males and females with and without duodenal ulcer. This plan seemed to have the added advantage that the "yardstick" of measurement was derived at the same time, with the same method, using the same substrate and the same reagents.

interest in the levels of gastric secretory activity in pregnancy and the puerperium was further stimulated by the work of SPIRO et al (1950) who showed that the rate of excretion of the enzyme was an index of adrenocortical activity, a finding which has been confirmed by EASCOTT et al (1953). Since considerable hormone changes occur in pregnancy and the puerperium, and probably include increased adrenocortical activity, their effects on urinary pepsinogen excretion rates were, therefore, worthy of study.

2. METHOD.

The method followed is that described by FAWCETT (1951).

Urine is collected during the overnight 12 hours, or for 24 hours. The volume of urine voided per hour is calculated.

Urine is incubated with a human haemoglobin substrate for 30 minutes at 37°C, the PH being adjusted to 1.5-1.8. Excess haemoglobin is precipitated by trichloracetic acid, and the degree of proteolysis is measured by the FOLIN and CIOCALTEAU procedure. A blank determination in which the enzyme is inactivated accounts for chromogenic substances present in urine and substrate.

The difference between the extinction coefficient of "test" and "blank" interpreted on a calibration curve is a measure of proteolysis due to uropepsin activity. The unit of uropepsin is the same as that of MIRSKY et al (1948) who define it as "that quantity which, during a 10-minute incubation of the Standard assay, releases 1 mg. of "tyrosine-like substance". Correcting for dilution and for the 30-minute incubation period 1 unit/100 ml. of urine = 0.0015 mg. of tyrosine".

The results are expressed in units/hour.

3. MATERIAL AND RESULTS.

(a) Controls.

The excretion rates of urinary pepsinogen were estimated in the following four groups of patients for an average of 10-12 days in each patient.

1. In 12 males with no clinical evidence of peptic ulcer, the mean excretion rate was found to be 4.37 units/hour.

2. In 10 males with proven duodenal ulcer of more than 5 years' duration, 9 of whom subsequently underwent gastrectomy, the mean excretion rate was considerably higher, 9.41 units/hour.

3. In 10 females of child-bearing age with no clinical evidence of peptic ulcer, the mean excretion rate was 3.86 units/hour.

4. In 10 females of childbearing age with proven duodenal ulcer of more than 5 years' duration, the mean excretion rate was higher than in normal women, 5.95 units/hour. This difference is less than occurred in the two groups of males.

The mean excretion rates are shown in Table 5.

Table 5.

COMPARISON OF MEAN EXCRETION OF URINARY PEPSINOGEN IN UNITS/HR. IN MALES AND FEMALES WITH AND WITHOUT DUODENAL ULCER, AND IN FEMALES BEFORE AND AFTER PARTURITION

Type	No: of Patients	Days Observed	Mean Excretion of Urinary Pepsinogen Units / hour	Standard Error of Mean
MALES				
1. Normal	12	11	4.37	± 0.34
2. Duodenal Ulcer	10	10	9.41	± 1.26
FEMALES				
1. Normal	10	12	3.86	± 0.41
2. Duodenal Ulcer	10	11	5.95	± 0.81
1. Before Parturition	25	14	5.87	± 0.53
2. After Parturition	25	14	4.83	± 0.43

The distribution of mean values for the patients in each group are shown in Figs. 18 and 19.

Fig. 18.

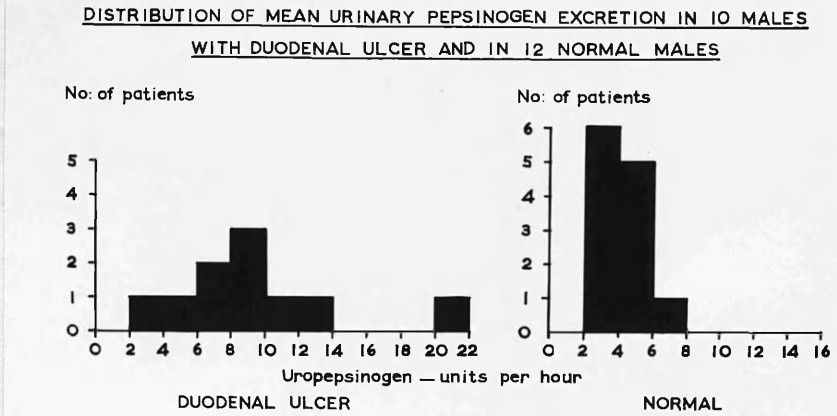
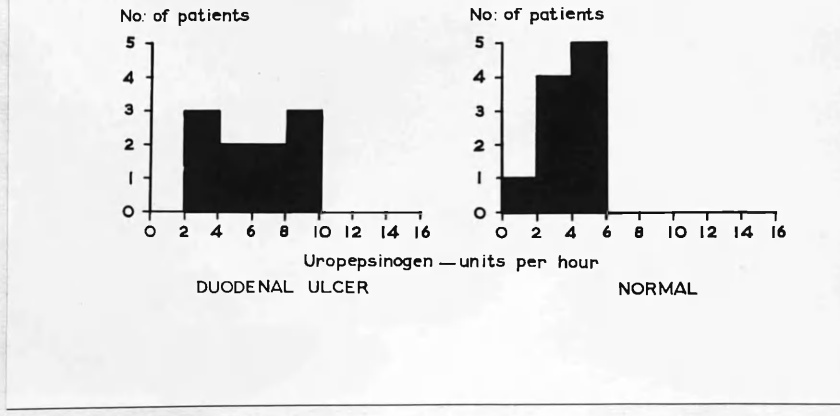

DISTRIBUTION OF MEAN URINARY PEPSINOGEN EXCRETION IN 10 MALES
WITH DUODENAL ULCER AND IN 12 NORMAL MALES
No: of patients
No: of patients
0 2 4 6 8 10 12 14 16 18 20 22
0 2 4 6 8 10 12 14 16
Uropepsinogen — units per hour
DUODENAL ULCER
NORMAL

Fig. 19.


DISTRIBUTION OF MEAN URINARY PEPSINOGEN EXCRETION IN 10 FEMALES
WITH DUODENAL ULCER AND IN 10 NORMAL FEMALES
No: of patients
No: of patients
0 2 4 6 8 10 12 14 16
0 2 4 6 8 10 12 14 16
Uropepsinogen — units per hour
DUODENAL ULCER
NORMAL

. These rates are similar to those reported by EASCOTT et al (1953).

(b) Pregnancy and Puerperium.

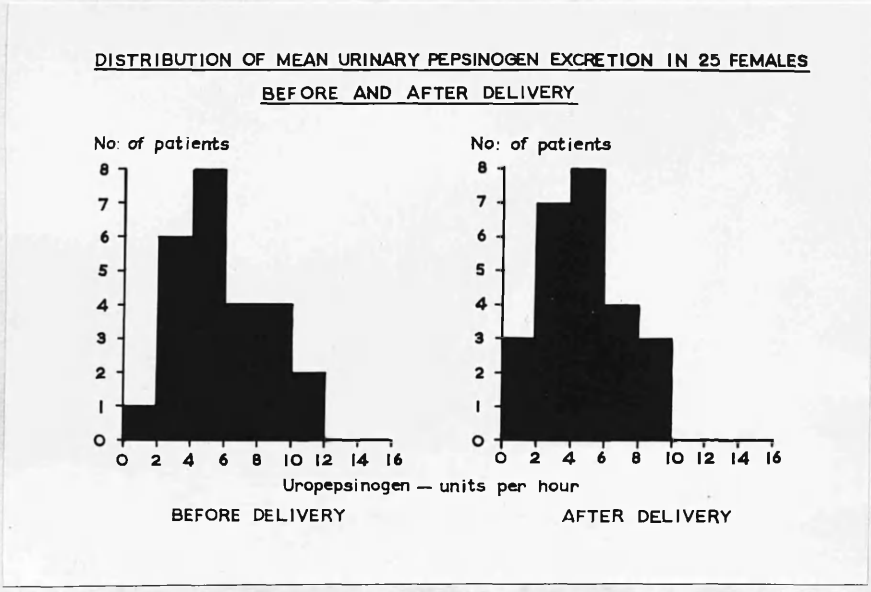
The uropepsinogen excretion rates were estimated in 25 patients. Most of the pregnancies were essentially normal, the admissions being attributed to deformed pelvis, older primiparae and twin-pregnancies. The rates were estimated for an average of 17 days before delivery and for an average of 16 days after delivery. For comparison with the control groups, the mean excretion rates have been calculated on the 14 days preceding, and the 14 days succeeding, delivery.

Before delivery, the mean rate was 5.87 units/hour, and after delivery 4.83 units/hour. A comparison between the means is made by an analysis of variance, when the variability between patients can be eliminated. This yields an F value of F=7.23, which indicates a significant difference between "before" and "after" parturition. The results are shown in Table 5 where they are compared with the mean rates for the four control groups.

It will be seen from Table 5 that the mean rates of excretion during the periods of investigation are at a higher level than the mean rate in normal female controls.

Also, the level in the pre-parturition phase is of the order found in women suffering from duodenal ulcer and greater than in normal man. The distribution of each patient "before" and "after" is shown in Fig. 20.

Fig. 20.

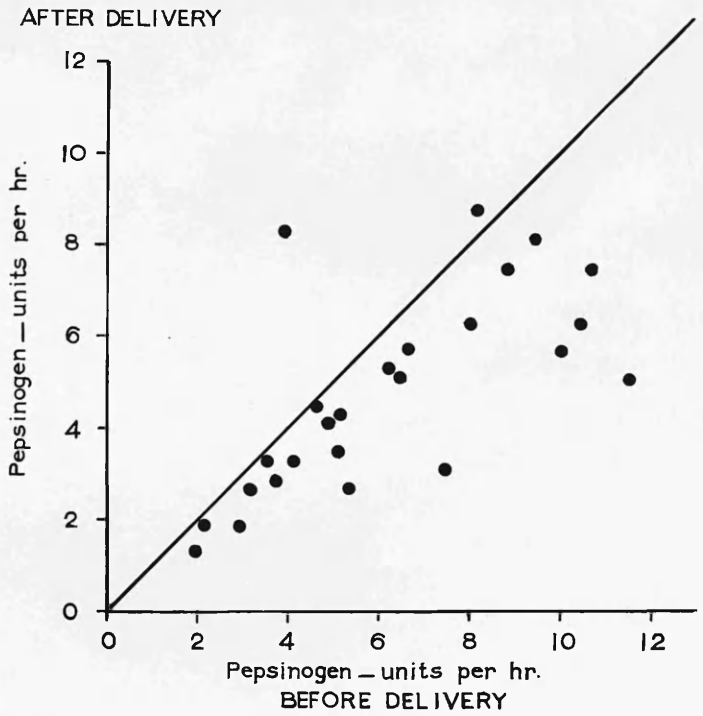


The scatter diagram in Fig. 21 demonstrates the higher values in the majority of patients before delivery, compared with after delivery.

Fig. 21.

MEAN URINARY PEPSINOGEN EXCRETION IN 25 FEMALES BEFORE AND AFTER DELIVERY

(Observations for 14 days per patient before and after delivery)



The daily estimations for the 4 control groups and the 25 pregnant patients are shown in the Appendix. The wide day-to-day variations can be seen.

5. DISCUSSION.

The estimation of the excretion of urinary pepsinogen would appear to be a reliable reflection of the gastric secretion of pepsin. That it may also

reflect the acid secretion is less certain though the range of low, normal and increased rates in conditions where the acid secretion is respectively low, normal and increased at least suggests that a relationship exists. On those grounds, this method has been used as a measure of gastric secretory activity in patients for as long as they remained in hospital before and after parturition. The method has the advantage that data could be collected daily for as long as 34 days - a period of observation hardly feasible with intubation. The scope is limited to hospital, however, by the need for accurately measured urinary output.

It would be unreasonable to infer too much from this data which covers such a short period of time. Nevertheless, it is evident that during the last two weeks of pregnancy and the two weeks following delivery, gastric function and, especially the activity of the peptic glands, is not depressed, and is, indeed, in the range to be expected in non-pregnant women suffering from active duodenal ulcer. If it can be inferred that a relationship between acid and urinary pepsinogen excretion exists, the results indicate that during pregnancy

gastric secretory activity far from being depressed, is elevated to levels higher than those expected in normal women and, in many instances, to levels encountered in women suffering from duodenal ulcer. Statistical analysis of the data indicates a slightly higher level before parturition.

It has been shown by SPIRO et al (1950) and EASCOTT et al (1953) that the uropepsinogen secretion rate is an index of adrenocortical activity. The higher rates of excretion found during this investigation may be an indication of this activity which has been noted by previous authors.

C. SUMMARY OF PART III.

1. The study of gastric function in normal pregnant women by the conventional methods of intubation is difficult for the investigator, and unpleasant for the volunteer. These women are generally outpatients and busy housewives. Because of this, it was decided to use urinary pepsinogen excretion as a measure of gastric function.

2. Though the level of excretion of urinary pepsinogen fairly reflects the gastric secretion of pepsin, its relationship to gastric acid secretion is much less reciprocal. High secretion rates, however, are found in patients with duodenal ulcer and low rates where the acid secretion is normal or low as in gastric ulcer.

3. It is obvious from the data presented that there are large day-to-day variations in the excretion levels in the same patient. As a result, a solitary reading is without value. Daily readings over a period of time, however, will be a reasonable measure of a particular patient's gastric secretory activity. It is the opinion of several authors that those day-to-day variations indicate the gastrointestinal response of the patient to stress.

4. The purpose of the investigation was to compare gastric secretory activity in late pregnancy with that

in the early puerperium using daily urinary pepsinogen excretion estimations. The need for accurately measured 24-hour urine collections limited the study to hospital patients.

5. The method used for estimation is described.

6. Mean excretion rates were estimated in 4 groups of controls - normal males and females, and males and females suffering from duodenal ulcer.

7. Uropepsinogen excretion rates were estimated in 25 patients during the 17 days before parturition and for about 16 days afterwards.

8. The results show that during this period, gastric secretion of pepsin, as measured by the excretion of urinary pepsinogen is greater than in normal women and, as far as the last 14 days of pregnancy are concerned, of the order found in non-pregnant women suffering from duodenal ulcer.

9. The raised excretion may indicate increased adrenocortical activity during those periods.

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PART IV.

GASTRIC ACID SECRETION IN DOGS DURING PREGNANCY AND LACTATION.

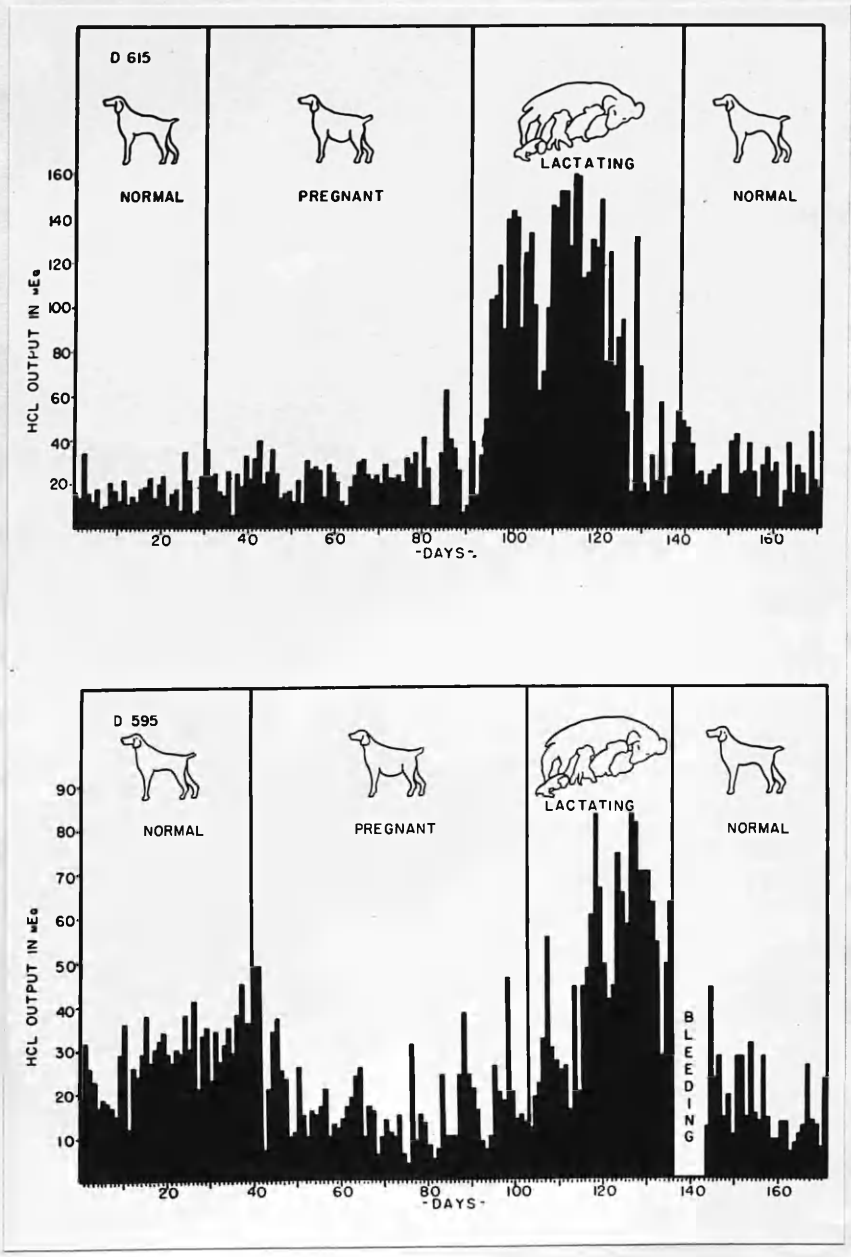
A. REVIEW OF THE LITERATURE.

The wellknown effect of pregnancy on the behaviour of peptic ulcer has stimulated research into gastric acid secretion during pregnancy in humans and in dogs. The work in pregnant women has been reviewed in Part II. Whereas previously it was believed that gastric acid secretion in pregnant women was consistently depressed, it has been shown that there was no uniform pattern in the 9 patients studied. Indeed, more patients showed a rise than a fall. There have been no secretory studies performed in women during lactation.

The first definite data concerning gastric acid secretion in pregnant dogs was published in 1954 by McCARTHY et al. They concluded that pregnancy had no consistent effect in either stimulating or inhibiting acid secretion. 6 periods of pregnancy in 5 dogs were compared with the gastric secretion in the same animals during control periods of similar length when the animals were not pregnant. During three pregnancies the total output of free HCl was greater than during the control period and in the remaining 3 it was less.

A most interesting feature rediscovered by McCARTHY et al (1954), was the remarkable rise in the level of gastric acid secretion during lactation. This was noted in both the dogs in which this phase was measured.

Fig. 22. GASTRIC ACID SECRETION DURING PREGNANCY AND LACTATION IN TWO DOGS. AFTER McCARTHY et al (1954).



These findings confirmed the previous observations of HOLLANDER (1930), KLEIN (1933) and WINKELSTEIN (1935). These observers noted hypersecretion during lactation and that it was frequently accompanied by extension of the ulcerative process around the gastric stoma. KLEIN (1933) further reported that in one case in which all the puppies died, and there was no period of lactation, no increase in secretion was observed.

B. PRESENT INVESTIGATION.

The present investigation was performed as a companion study to that in humans described in Part II. In pregnant women, it is difficult to obtain frequent readings. In dogs, on the other hand, using the methods outlined by DRAGSTEDT et al (1950) daily collections of gastric juice can readily be obtained over a prolonged period.

1. AIM OF INVESTIGATION.

The aim of this investigation was to study the acid secretion (a) during pregnancy, (b) during lactation, (c) when lactation is suppressed.

2. METHOD.

Heidenhain pouches were prepared in 3 dogs, nylon plastic cannulae being inserted for the collection of the secreted juice. The juice was collected daily in rubber

bags, the animals being free to run in pens. The diet was the normal mixed kennel fare throughout the test. The daily output of juice was calculated in millequivalents. Dog I. was found to be pregnant when the pouch was made, so no pre-pregnancy control is available. In Dogs II and III, pre and post-pregnancy control periods are available. In Dog I the pups were allowed to suckle and were weaned after 28 days. In Dogs II and III, the pups were not allowed to suckle, and lactation was suppressed by Stilboestrol given daily for 12 days in the following dosage - (mgm. 10.10.10. 5.5.5. 3.3.3. 1.1.1.)

3. RESULTS.

The results are summarised in Table 6 and graphically illustrated in Figs. 23, 24 and 25.

Table 6. RESULTS IN DOGS I, II and III.

	PREPARATION	GASTRIC ACID SECRETION	
		Days Observed	Average daily Output mEq.
DOG I	Pre-pregnancy control	—	—
	Pregnancy	59	1.13
	Lactation	28	5.24
	Post-pregnancy control	33	1.96
DOG II	Pre-pregnancy control	137	1.44
	Pregnancy	63	2.03
	Suppressed lactation	28	1.07
	Post-pregnancy control	40	1.11
DOG III	Pre-pregnancy control	53	0.92
	Pregnancy	61	1.26
	Suppressed lactation	28	0.81
	Post-pregnancy control	19	0.17

Fig. 23. DAILY ACID OUTPUT IN DOG I.

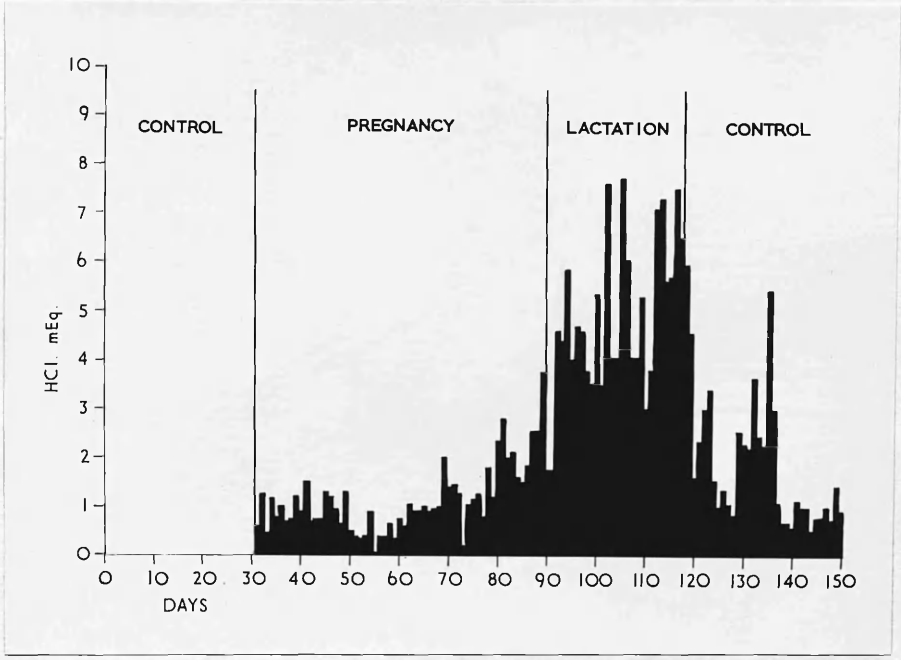


Fig. 24. DAILY ACID OUTPUT IN DOG II.

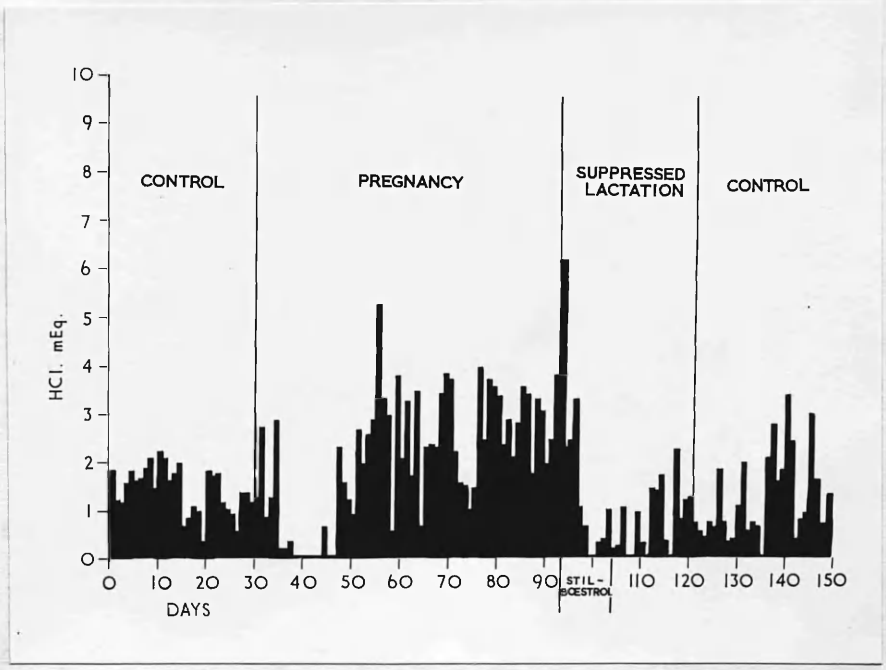
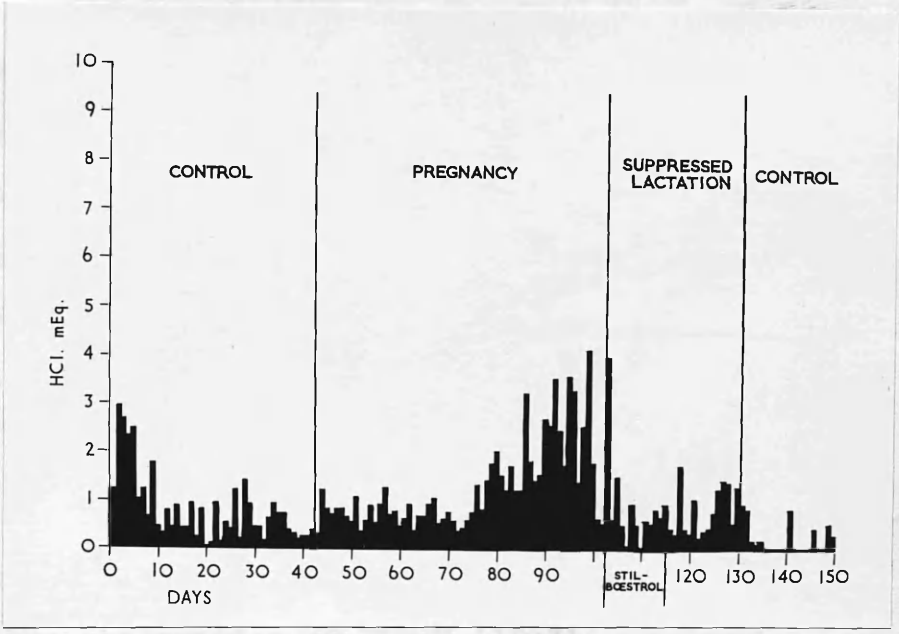


Fig. 25. DAILY ACID OUTPUT IN DOG III.



The daily readings for each dog are shown in the Appendix.

(a) Pregnancy.

It will be seen that in Dog I (where no pre-pregnancy control is available), the output of acid is less during pregnancy than in the post-pregnancy control period. In Dogs II and III the output during pregnancy is greater than the control periods obtained before and after pregnancy.

It will be noted that in Dog II, the rise in acid secretion during pregnancy appeared at an early phase and was sustained until parturition. In Dogs I and II, on the other hand, the output remained at a low level throughout the greater part of pregnancy but rose progressively during the terminal 10-20 days.

(b) Lactation.

Natural lactation was observed in Dog I for a period of 28 days, at the end of which period, the pups were weaned. There is an obvious and consistent increase in output of gastric acid secretion during this period, the average output being almost three times as great as the control period. These findings confirms the previous observations noted above.

(c) Suppressed Lactation.

In Dogs II and III where lactation was suppressed there was no increase in secretion, confirming the single previous observation of KLEIN (1933).

4. DISCUSSION OF THE RESULTS.

The effects of pregnancy on gastric acid secretion in dogs in these experiments confirm those of McCARTHY et al (1954) in demonstrating again that there is no consistent depression of secretion. In one dog the secretion was less, and in two it was greater than the control periods. These findings also conform to the pattern of secretion in pregnant women (Part II.) where a rise in output was noted more often than a fall.

All observers who have measured acid secretion during lactation in dogs, have noted a remarkable increase in output HOLLANDER (1930), KLEIN (1933), WINKELSTEIN (1935)

and McCARTHY et al (1954). One is, naturally, hesitant to accept a conclusion based on so few dogs were it not that the results fit in so well with the few previous reports in the literature. The cause of this increase is a matter for conjecture.

Theoretically it might be due to increased appetite and increased intake of food. This has not been noted by previous observers and, in the present experiment, the impression was gained that the lactating dog did not eat in excess of the two dogs in which lactation was suppressed. However, the food intake was not measured, and this simple explanation remains a possibility.

The increase might be due to some factor concerned with, or resulting from, the loss of fat, calcium and other constituents of milk. Those factors are not accurately known, but the main influence would appear to be hormonal. YOUNG (1947) has stressed that milk secretion, as well as growth and diabetogenic activity, are processes which involve a restraint on the oxidation of metabolites which are thus made available for other purposes such as milk formation. These phenomena, he claims, are under hormonal control.

The recently accumulated knowledge of the hormonal control of female mammary growth and function has made it

possible to reproduce in the male gland the various growth and secretory phases. In this way it has been shown that the important hormones for mammary growth are oestrogens and progesterone and for secretion lactogenic, growth and adrenocortical hormones. The thyroid hormone in some species may also be essential. The stimulation and maintenance of lactation is dependent to a considerable extent on the neurohumoral reflex, activated by suckling and mediated via the posterior pituitary gland and the oxytocic hormone (BENSON and FOLLEY (1956).

Of the hormones involved in lactation only the adrenocortical hormone is known to stimulate gastric secretion GRAY et al (1951). McCARTHY et al (1954) failed to promote an increase in gastric secretion in 2 dogs by giving lactogenic hormone in doses sufficient to stimulate and promote lactation in post-partum human females. The influence of other pituitary hormones such as growth hormone and oxytocic hormone has not been investigated.

The original observations by KLEIN (1933) and the findings in Dogs II and III in the present experiment would appear to indicate that if lactation is not fulfilled, the increase in acid does not take place. In Klein's case, the absence of the suckling stimulus was the only

factor suppressing lactation. In the present experiment Stilboestrol was also given as in present-day obstetrical practice.

The influence of oestrogenic hormones on gastric acid secretion is uncertain, and may depend on the species studied. OJHA and WOOD (1950) have demonstrated almost complete inhibition of histamine-stimulated acid secretion in anaesthetised cats. ATKINSON and IVY (1938), on the other hand, found no effect on dogs, though CULMER, ATKINSON & IVY (1939) later suggested that the doses used were low compared with the amounts of oestrogens produced during pregnancy. It is now known, however, that in both dogs and humans, when oestrogens are high during pregnancy, viz. approaching term, the acid secretion may be raised rather than depressed. The present author has failed to produce consistent and significant depression of acid secretion by the administration of large doses of Stilboestrol to non-pregnant female dogs (unpublished). The part played by Stilboestrol in preventing the lactational rise in secretion is, therefore, undertain, and its effect in instances where the pups were allowed to suckle would be of great interest.

The importance of the suckling neuro-humoral reflex in the initiation and maintenance of lactation is wellknown. Is it possible that the same reflex may also stimulate gastric secretion?

C. SUMMARY OF PART IV.

1. The quantitative daily estimations of gastric secretion in dogs during pregnancy has been reported by only one group of workers who performed their studies at the same time as the present author. By means of Heidenhain pouches, gastric juice can be totally and accurately collected daily for a very long time covering a pre-pregnancy control period, pregnancy, lactation and a post-pregnancy control period. The advantages in this method compared to human intubation methods are obvious.

2. The previous reports on gastric secretion in dogs during pregnancy and lactation are reviewed.

3. The purpose of the present investigation was to study acid secretion (a) during pregnancy (b) during lactation and (c) when lactation is suppressed.

4. Heidenhain pouches were made in three dogs, indwelling nylon plastic cannulae being used by daily collections of secreted juice.

5. In one dog the pouch was made during the first four days of pregnancy. In the other two dogs pre-pregnancy controls were obtained.

6. Natural lactation was observed in one dog and suppressed in the remaining two by the prevention of suckling and the administration of Stilboestrol.

7. There was no consistent depression of gastric acid secretion during pregnancy.

8. A marked and sustained rise in the output of acid was observed in one dog where natural lactation was allowed.

9. When lactation was suppressed in 2 dogs by the prevention of suckling and the administration of Stilboestrol, no rise in output occurred.

10. The implications of the findings during lactation and when lactation is suppressed is discussed. It is suggested that the suckling neuro-humoral reflex which is important in initiating and maintaining lactation may also stimulate gastric secretion.

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PART V.

THE EFFECT OF CASTRATION ON THE GASTRIC ACID SECRETION OF FEMALE DOGS.

A. REVIEW OF THE LITERATURE.

The remarkable effect of the menopause on the behaviour of peptic ulcer, surprisingly, has not led to much clinical or experimental inquiry.

There are very few reports on the level of acid secretion in the menopausal state in human subjects. These reports are couched mainly in general terms such as "subacidity"; TAUSSIG (1908), "hypochlorhydria"; WINKLER (1905) and "achlyia"; FRIEDENWALD (1932). There are, to the author's knowledge, no data comparing the output of gastric acid secretion before and after castration in females, although this operation is frequently performed.

A fairly exhaustive search of the literature has also failed to reveal any reported work on acid secretion in animals before and after castration.

B. PRESENT INVESTIGATION.

1. AIM OF INVESTIGATION.

The present investigation was designed to compare the gastric acid output from Heidenhain pouches in female dogs before, and immediately after, castration.

2. METHOD.

Heidenhain pouches with nylon plastic indwelling cannulae were prepared in 11 female mongrel dogs. Free drainage of the pouches was allowed for 3 weeks following the preparation of the pouches. Thereafter, the juice was collected in rubber bags attached to the cannulae, the six-hour output of acid being calculated in milli-equivalents. After a control period varying from 17 - 28 days, castration was performed in seven of the dogs - (Nos. 1 - 7) - through a lower midline abdominal incision. In the remaining four animals - (Nos. 8 - 11) - a similar incision was made, the ovaries being brought into the wound and then returned to the abdomen. Dogs 8 - 11 were intended to serve as controls so that the effect of the "stress" of operation and of any probable adrenocortical stimulation of gastric secretion could be noted and offset. Collections were restarted the day after operation.

The dogs were allowed to run free in pens and received ordinary kennel rations.

3. RESULTS.

The results are based on the acid output for at least 20 days after castration, and for 7 days after simple laparotomy, since the "stress" effect would be maximal in the first 7 days.

The results for the two groups of dogs with statistical analysis of the data are shown in Tables 7 and 8.

Table 7.

COMPARISON OF ACID SECRETION FROM HEIDENHAIN POUCHES IN FEMALE DOGS BEFORE AND AFTER CASTRATION

DOG NO:	BEFORE CASTRATION		AFTER CASTRATION		t.	n.	p.
	Days	Mean daily output mEq.	Days	Mean daily output mEq.			
I	17	25.9 ± 7.44	20	11.7 ± 8.65	5.1478	35	< 0.001
II	28	22.6 ± 9.56	20	12.4 ± 10.57	3.4246	46	0.01-0.001
III	25	10.9 ± 4.61	20	7.5 ± 3.62	2.6217	43	0.02-0.01
IV	18	6.5 ± 2.52	28	9.7 ± 3.85	3.8264	44	< 0.001
V	17	4.5 ± 2.57	22	4.0 ± 1.62	0.6032	37	0.6 - 0.5
VI	20	3.1 ± 1.11	20	2.3 ± 0.57	2.6695	33	0.02-0.01
VII	20	3.7 ± 1.35	20	3.5 ± 2.10	0.5727	38	0.7 - 0.6

Table 8.

COMPARISON OF ACID SECRETION FROM HEIDENHAIN POUCHES IN FEMALE DOGS BEFORE AND AFTER LAPAROTOMY

DOG NO:	BEFORE CASTRATION		AFTER CASTRATION		t.	n.	p.
	Days	Mean daily output mEq.	Days	Mean daily output mEq.			
VIII	17	4.5 ± 2.57	7	8.6 ± 2.94	3.2449	22	0.01-0.001
IX	12	5.7 ± 1.53	7	6.4 ± 2.18	0.7226	17	0.5 - 0.4
X	26	3.3 ± 1.55	7	3.5 ± 2.64	0.2610	31	0.8 - 0.7
XI	19	7.2 ± 2.74	7	12.1 ± 6.81	2.4986	24	0.02-0.01

In the group of seven castrated dogs it will be seen that during the period of observation after castration, in four animals (Nos. 1,2, 3 and 6) there was a significant depression of acid output,in two of them (Nos. 1 and 2) the depression being highly significant. In two dogs (Nos. 5 and 7) there was no significant change. In one dog (No. 4), however, there was a highly significant increase. No explanation can be offered for the distinctly different behaviour of secretion in this animal.

In the control group of 4 dogs which had undergone laparotomy, two dogs (Nos. 8 and 11) showed a significant rise in output, the increase being highly significant in No. 8. In the remaining two animals (Nos. 9 and 10) there was no change.

Though one hesitates to draw conclusions from the results in this small group,the impression gained is that the "stress" of laparotomy tends to increase acid output. Castration, which also involves laparotomy, tends to diminish acid secretion. It may, therefore, be reasonably, though very tentatively, suggested that if the stimulus to acid secretion provoked by laparotomy could be removed from the castrated group, the acid depressing effect of castration might become more evident.

4. COMMENT.

In the absence of other reports with which to compare these results, and cognisant of their rather inconclusive nature, little more than brief comment is needed. Gastro-enterologists tend to correlate increased ulcer activity with increased acid secretion. If results similar to those obtained in the above experiments can be shown to obtain in human subjects, the paradoxical situation of ulcerogenic activity associated with diminished acid output would, indeed, be an interesting one. It would emphasise again the often forgotten factor of mucosal resistance.

It also seems to the author that this should be a profitable field for research in that it might be possible to correlate acid secretion with the pituitary gonadotrophins. which increase rapidly in the urine after castration, (HELLER et al (1944)), and with oestrogens by replacement therapy. The author has investigated the effect of large doses of diethylstilboestrol on gastric acid secretion in both castrated and normal female dogs. In neither group was there any significant effect. In these investigations, however, the level of urinary gonadotrophins was not monitored, and it is known, (HELLER et al (1944)), that large doses of stilboestrol may suppress completely the urinary output of gonadotrophins.

C. SUMMARY.

1. There has been surprisingly little enquiry, either clinical or experimental, into gastric acid secretion during the menopause.

2. The present investigation was designed to compare the gastric acid output from Heidenhain pouches in female dogs before and immediately after castration.

3. In four of the castrated dogs there was significant depression of acid secretion; in two there was no significant change; in one there was a highly significant rise.

4. In the four control dogs, two showed a significant rise in the output of acid, while in the remaining two no significant change occurred.

5. It is suggested that the tendency for the acid to increase in the control dogs is due to the "stress" of operation. It is also suggested that since the operation of laparotomy is also involved in the castrated group, the acid depressing effect of castration is, thereby, less evident.

6. The implications of these results are briefly discussed.

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GENERAL SUMMARY.

Peptic ulcer, in common with several other diseases, has notable sex differences in incidence and in behaviour. These sex differences have been used in attempts to elucidate the etiology of peptic ulcer and to determine those factors which protect the patient, and those which promote the disease. While the periodicity of the disease in men is too elusive for research, the behaviour of the disease in women during menstruation, pregnancy and the menopause is amenable to study and investigation.

The prominent sex differences both in the incidence of the disease and its complications is presented and discussed with reference to the importance of environment and constitution. The sex incidence of perforations during the recent war years, and the stability of the female perforation rate during the years 1940-1943 are emphasised and produced as evidence that biological factors in the female constitution play an important role in protecting them against the disease.

Further evidence anent those biological factors is forthcoming from a study of the natural history of peptic ulcer in women. The behaviour of the disease in 400 women with reference to menstruation, pregnancy, lactation and the menopause, is presented. Though the effect of menstruation was difficult to assess and deemed to

be slight, the beneficial influence of pregnancy and the ulcerogenic effects of lactation and the menopause are notable and confirm, in a large series of cases, previous reported impressions.

Previous clinical and experimental work concerning sex hormones and peptic ulcer is reviewed and criticised. Despite several attractive hypotheses there is as yet no substantial proof of a relationship between sex hormones and peptic ulcer, though the extracts of pregnancy urine and, especially, the anthelone group of substances, are worthy of continued investigation.

Attention is drawn to the failure of toxaemic pregnancies to promote remission of ulcer symptoms. This phenomenon has not previously been reported, and the relevant theories are discussed.

Previous investigations have indicated that gastric acid secretion is consistently depressed during pregnancy. This subject is reinvestigated using "continuous suction" methods, and an attempt is made to correlate the acid findings with the histaminolytic power of plasma during pregnancy in 9 patients. The acid output was not found to be consistently and significantly depressed in the small number investigated, being more often unchanged or increased. There was no correlation with plasma histaminase.

Rather than rely on gastric analysis alone, a further study using urinary pepsinogen excretion rates as an indication of gastric secretory function, was performed during late pregnancy and the early puerperium in 25 women. The results indicate that during those periods gastric secretory function is increased.

As a companion study to that in women, the acid output from Heidenhain pouches in female dogs before, during and after pregnancy in 3 animals was observed. Acid secretion was greater in 2 animals during pregnancy than during the control periods. A remarkable rise in acid output during natural lactation and the absence of this rise in suppressed lactation was observed. The implications of these phenomena is discussed.

The lack of clinical and experimental investigation on the effect of castration on gastric function is noted. The results of an experiment measuring the output of acid from Heidenhain pouches in 7 female dogs before and after castration are reported, using simple laparotomy in 4 dogs as controls. The results, though inconclusive, suggest that gastric acid secretion tends to be depressed immediately after castration.

The one solid incontrovertible fact to which gastroenterologists cling in the field of peptic ulcer

-investigation and therapy is summed up in the wellknown aphorism, "No acid: no ulcer", and treatment both conservative and radical is designed towards this end. So ingrained is this thought process that increased ulcer activity is regarded as almost synonymous with increased acid secretion and vice versa. Previous reports indicating depressed acid secretion during pregnancy fell naturally into line. From the "acid-ulcer" point of view, the results of the investigations herein reported are disturbingly out of line in that they indicate acid and pepsin secretion not to be depressed and commonly increased during pregnancy. Furthermore, if the results in dogs are repeated in humans, increased ulcer activity of the menopause may be found to be associated with depressed acid secretion. Only during lactation is there a suggestion that increased acid secretion may be associated with increased ulcer activity.

There are other factors concerned with the integrity of the gastroduodenal mucosa and which protect it in many normal individuals in the presence of high levels of acid - protective factors e.g., which may be recouped during pregnancy and lost, or impaired, at the menopause. These factors, e.g., mucus barriers, vascularity, etc., can be mentioned only in general terms since little is

known regarding them.

The general conclusion of this thesis, therefore, is to stress once again the need for investigation into the protective factors.

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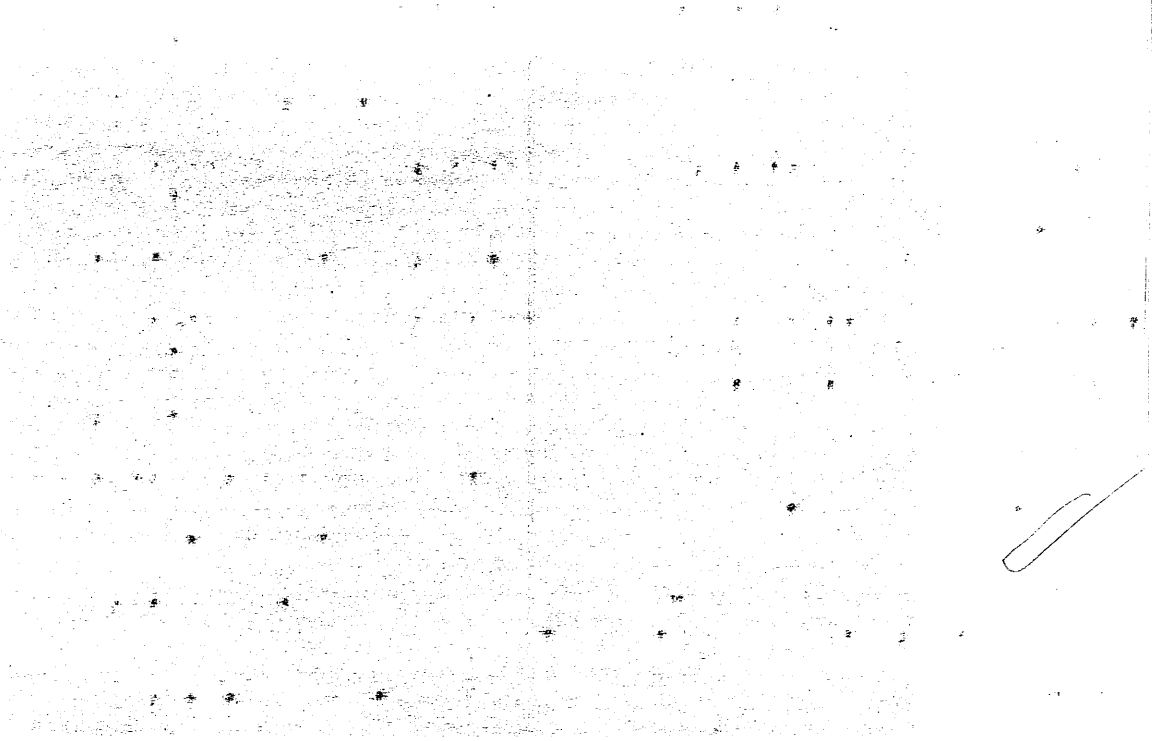

APPENDIX.

APPENDIX TO PART II.

GASTRIC ACID SECRETION AND PLASMA HISTAMINASE DURING PREGNANCY.

ESTIMATIONS OF SPONTANEOUS AND HISTAMINE INDUCED ACID SECRETION AND PLASMA HISTAMINASE IN 9 WOMEN DURING AND AFTER PREGNANCY.

Patient No. 1. (Duodenal Ulcer).

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
		PREGNANCY.	
15th	81.10	124.21	4.3
19th	56.13	257.02	11.5
23rd	47.32	256.93	12.0
26th	31.93	195.45	11.9
30th	43,34	235.46	9.3
35th	59.04	301.73	10.6
39th	60.66	287.96	5.4
		POST-PREGNANCY.	
18th	130.00	321.00	0
25th	65.85	224.84	0
30th	70.32	237.76	0
36th	94.16	285.55	0

Patient No. 2.

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
		PREGNANCY.	
15th	5.48	158.41	1
19th	55.66	271.18	1.5
23rd	34.38	352.58	5.8
27th	13.14	375.76	6.2
30th	27.04	352.16	7.0
34th	31.16	360.60	7.5
38th	105.77	375.82	9.0
		POST-PREGNANCY.	
17th	48.20	219.66	0
22nd	35.46	274.39	0
25th	26.34	309.73	0
30th	25.45	293.85	0

Patient No. 3.

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
		PREGNANCY.	
13th	52.99	221.81	3.4
16th	21.07	196.00	5.0
20th	33.31	205.42	4.4
23rd	23.34	244.68	6.0
27th	10.68	256.67	7.17
31st	42.36	260.73	7.07
35th	18.07	186.54	14.0
39th	26.43	185.96	9.3
		POST-PREGNANCY.	
18th	25.62	220.77	0
22nd	20.63	236.50	0
26th	29.78	276.08	0
30th	33.58	268.27	0

Patient No. 4. (Duodenal Ulcer).

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
		PREGNANCY.	
14th	68.53	199.79	2.5
18th	42.48	210.67	2.8
22nd	42.34	141.04	2.3
26th	7.74	200.60	3.3
30th	6.57	119.72	3.8
34th	10.84	152.86	2.8
36th	2.04	90.88	3.9
39th	3.65	132.86	4.2
		POST-PREGNANCY.	
17th	26.86	293.86	0
21st	31.09	285.44	0
23rd	23.74	301.53	0
34th	17.86	245.44	0

Patient No. 5.

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
	PREGNANCY.		
16th	14.60	103.11	3.2
19th	9.46	89.33	4.0
23rd	23.72	120.41	4.3
27th	18.06	158.33	9.0
30th	7.56	144.93	8.3
34th	10.51	145.81	11.3
38th	15.32	150.40	7.1
	POST-PREGNANCY.		
17th	7.61	79.29	0
20th	14.31	94.90	0
24th	12.78	160.60	0
28th	46.72	126.95	0

Patient No. 6.

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
		PREGNANCY.	
12th	74.31	476.40	1.3
16th	102.63	563.39	2.5
20th	64.07	425.51	3.7
24th	156.73	518.58	9.0
28th	83.25	516.04	7.8
32nd	77.05	505.51	3.0
38th	96.34	483.74	4.8
		POST-PREGNANCY.	
20th	37.93	296.41	0
24th	46.74	301.73	0
30th	24.07	205.53	0
36th	65.53	364.16	0

Patient No. 7.

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
		PREGNANCY.	
14th	23.73	77.56	0.5
18th	39.97	115.41	2.3
22nd	54.20	100.52	3.6
26th	44.72	127.60	3.2
29th	23.58	95.81	5.1
33rd	33.58	154.83	5.0
36th	40.84	130.31	4.8
		POST-PREGNANCY.	
16th	10.95	36.94	0
20th	9.64	50.26	0
24th	20.26	64.49	0
26th	0	43.07	0
44th	0	0	0
46th	13.51	48.36	0

Patient No. 8.

Week	Spontaneous Secretion mgm. HCl.	Histamine Secretion mgm. HCl.	Histaminase P.U.
	PREGNANCY.		
17th	2.99	15.47	2.5
20th	0.99	7.44	4.9
24th	23.72	83.79	7.2
27th	6.90	57.15	6.2
31st	4.96	30.84	6.6
35th	1.09	18.03	4.0
39th	18.07	96.94	3.8
	POST-PREGNANCY.		
16th	0	0	0
21st	0	0	0
24th	1.04	10.31	0
30th	0	0	0

Patient No. 9.

Week	Spontaneous Secretion mgm. HCl.	Histamine Response mgm. HCl.	Histamine.
	PREGNANCY.		
16th	10.36	120.08	3.6
20th	7.85	83.92	6.7
24th	1.60	85.63	15.7
28th	4.38	123.43	18.3
32nd	8.97	126.67	14.6
35th	6.93	81.06	8.9
36th	10.41	111.63	9.0
39th	12.47	129.74	8.6
	POST-PREGNANCY.		
20th	39.42	156.40	0
24th	36.50	171.55	0
30th	36.13	164.79	0
35th	34.52	160.56	0
40th	12.22	156.36	0

APPENDIX TO PART III.

UROPEPSINOGEN OUTPUT IN

(a) 12 NORMAL MALES.

(b) 10 MALES WITH DUODENAL ULCER.

(c) 10 NORMAL FEMALES.

(d) 10 FEMALES WITH DUODENAL ULCER.

(e) 25 FEMALES BEFORE AND AFTER DELIVERY.

STATISTICAL COMPARISON OF UROPEPSINOGEN OUTPUTS BEFORE AND AFTER DELIVERY.

UROPEPSINOGEN OUTPUT IN 12 NORMAL MALES.

Patients No.

Days	1	2	3	4	5	6	7	8	9	10	11	12
1.	2.9	2.2	7.5	4.8	5.0	4.6	7.3	5.3	7.0	4.7	6.1	2.9
2.	2.4	2.9	6.1	2.3	2.1	4.0	6.4	5.2	4.6	2.3	4.6	3.0
3.	2.9	2.9	8.2	2.9	1.9	2.1	7.1	4.8	4.8	4.5	6.0	4.6
4.	2.9	4.2	8.6	7.8	2.3	1.9	4.8	1.9	5.1	4.6	3.9	4.9
5.	11.8	2.3	6.2	6.0	3.6	1.8	3.9	2.7	7.3	3.1	7.0	5.1
6.	2.5	2.5	6.2	8.0	3.4	2.2	5.0	2.1	6.0	3.0	6.9	5.5
7.	2.3	4.3	5.4	4.8	2.9	3.9	2.8	2.0	6.8	1.5	5.8	4.0
8.	2.8	2.9	5.5	7.2	3.8	4.6	2.9	3.4	7.2	3.7	4.7	4.6
9.	2.2	2.9	6.4	7.1	3.9	5.1	3.1	2.5	5.3	2.4	5.6	5.3
10.	5.6	6.1	3.7	2.6	2.7	2.8	4.4	4.8	5.5	2.6	6.6	5.8
11.	3.0	2.7	6.0	1.9	2.0	2.8	4.5	4.4	5.4	3.0	4.9	6.0

Uropepsinogen Units/Hour.

UROPEPSINOGEN OUTPUT IN 10 MALES WITH DUODENAL ULCER.

Patient's No.

Days.	1	2	3	4	5	6	7	8	9	10.
1.	3.3	11.1	7.1	2.5	8.3	7.0	12.1	8.5	13.2	8.1
2.	3.1	4.9	6.3	3.1	5.5	7.5	6.7	5.9	13.0	8.3
3.	5.0	6.8	11.4	4.9	5.9	6.5	6.8	13.4	6.1	8.4
4.	4.9	6.8	14.0	4.7	10.9	7.4	9.9	17.9	6.7	7.6
5.	4.8	6.0	8.2	3.4	7.2	10.2	11.6	15.3	6.4	6.6
6.	4.2	5.8	10.8	10.2	4.7	10.5	22.2	24.8	6.9	16.5
7.	3.6	5.7	6.4	2.7	2.8	10.8	38.8	10.3	5.8	10.3
8.	3.1	6.9	6.7	3.6	12.4	9.8	20.6	16.3	11.6	7.7
9.	2.2	7.0	13.1	7.4	7.2	11.1	40.2	8.4	10.3	21.2
10.	4.0	6.8	11.1	10.1	5.2	10.3	36.1	8.6	10.3	7.1

Uropepsinogen Units/Hour.

UROPEPSINOGEN OUTPUT IN 10 NORMAL FEMALES.

Patient's No.

Days.	1	2	3	4	5	6	7	8	9	10
1.	0.9	3.6	6.0	4.1	5.1	7.0	5.3	5.7	2.9	4.2
2.	0.8	5.0	6.3	2.6	4.7	6.1	2.1	6.8	0.9	3.0
3.	1.6	4.1	3.1	4.0	5.0	4.8	4.7	7.3	2.0	2.6
4.	2.5	4.3	4.8	3.8	3.4	6.4	4.5	7.0	1.4	2.7
5.	0.9	4.7	4.6	4.3	4.2	2.3	3.9	2.9	3.6	2.9
6.	3.1	4.0	5.2	2.9	4.6	5.1	4.0	6.4	3.1	3.4
7.	3.4	3.9	5.7	5.0	3.8	5.6	6.1	5.1	1.0	1.9
8.	1.2	5.3	2.9	3.9	3.7	5.8	2.8	5.0	1.2	2.1
9.	1.8	4.8	3.8	3.1	2.9	3.7	2.0	5.8	1.4	4.0
10.	2.1	2.4	6.1	3.7	4.0	6.4	3.7	7.3	1.0	3.4
11.	2.9	3.9	6.3	3.6	4.4	2.9	2.9	6.9	0.9	4.1
12.	3.0	2.8	4.7	2.1	3.8	3.5	4.8	5.7	3.1	2.8

Uropepsinogen Units/Hour.

UROPEPSINOGEN OUTPUT IN 10 FEMALES WITH DUODENAL ULCER.

Patient's No.

Days	1	2	3	4	5	6	7	8	9	10.
1.	4.7	11.3	4.5	5.5	1.0	6.1	5.3	3.9	10.0	2.8
2.	9.0	3.1	5.3	9.8	1.8	4.8	3.9	3.2	9.2	2.9
3.	11.5	11.5	1.7	10.4	2.3	4.0	7.1	2.9	9.1	3.4
4.	3.5	6.3	1.9	6.7	1.4	10.0	6.4	4.0	8.7	5.1
5.	6.7	9.6	0.8	8.8	3.1	4.5	6.7	4.6	10.3	4.6
6.	9.9	5.8	3.9	11.9	2.6	8.3	6.5	5.1	11.0	5.0
7.	4.5	7.4	4.1	10.6	3.0	9.1	9.0	2.8	5.8	2.8
8.	3.9	10.0	3.2	20.1	4.4	11.6	4.5	3.4	4.9	3.4
9.	4.5	13.7	1.1	4.3	2.9	10.2	3.7	2.9	6.2	6.4
10.	6.2	8.7	3.4	9.7	1.7	5.9	5.0	6.3	6.5	3.6
11.	9.3	9.8	1.4	6.7	1.8	7.3	6.1	5.4	7.4	2.7
12.	9.0	10.0	5.2	5.4		6.2	5.8	2.3	5.1	2.4

Uropepsinogen Units/Hour.

Before Delivery.		After Delivery.	
Day.	Urobilin/litre.	Day.	Urobilin/litre.
24.	14.1	1.	1.0
23.	20.8	2.	1.6
22.	14.0	3.	2.0
21.	8.4	4.	0.9
20.	8.4	-	-
19.	10.2	16.	1.7
18.	8.8	17.	1.0
17.	8.8	18.	1.2
16.	8.5	19.	1.0

UROPEPSINOGEN OUTPUT IN 25 FEMALES BEFORE AND AFTER DELIVERY.

Patient No. 1.

Before Delivery		After Delivery.	
Day	Uropeps. Units/Hour.	Day	Uropeps. Units/Hour.
24.	14.1	1.	6.0
23.	20.4	2.	2.8
22.	12.0	3.	3.9
21.	12.3	4.	10.8
20.	15.1	5.	5.4
19.	12.0	6.	7.6
18.	11.7	7.	9.3
17.	12.3	8.	10.9
16.	9.8	9.	9.8
15.	9.6	10.	6.4
14.	9.6	11.	5.7
13.	10.1	12.	9.8
12.	10.5	13.	10.7
11.	9.3	14.	6.1
10.	11.4	15.	6.9
9.	10.3	16.	9.7
8.	9.5	17.	6.2
7.	8.2	18.	6.3
6.	8.5	19.	7.8
5.	11.4	20.	6.4
4.	12.3		
3.	8.5		
2.	11.3		
1.	11.4		

Patient No. 2.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour.	Day	Uropeps. Units/Hour.
17.	4.4	1.	3.8
16.	6.0	2.	5.6
15.	7.3	3.	5.5
14.	6.2	4.	9.2
13.	5.0	5.	3.8
12.	12.3	6.	7.4
11.	6.4	7.	7.3
10.	7.4	8.	4.9
9.	8.9	9.	4.0
8.	9.7	10.	5.7
7.	10.4	11.	5.6
6.	13.5	12.	7.3
5.	11.8	13.	7.7
4.	11.4	14.	5.8
3.	9.2	15.	5.6
2.	9.5		
1.	10.1		

Patient No. 3.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour.
22.	10.2	1.	3.2
21.	9.1	2.	4.8
20.	6.3	3.	10.2
19.	7.3	4.	8.0
18.	8.1	5.	10.4
17.	6.4	6.	9.8
16.	7.5	7.	10.6
15.	11.0	8.	9.3
14.	5.1	9.	13.6
13.	6.8	10.	5.7
12.	8.6	11.	13.1
11.	9.3	12.	11.3
10.	6.1	13.	5.9
9.	5.8	14.	7.6
8.	6.5	15.	5.4
7.	5.5	16.	7.1
6.	6.7		
5.	7.3		
4.	14.8		
3.	7.1		
2.	8.7		
1.	5.8		

Patient No. 4.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour.
21.	6.4	1.	1.0
20.	5.4	2.	2.3
19.	5.3	3.	2.5
18.	7.8	4.	1.9
17.	7.3	5.	3.6
16.	3.5	6.	7.2
15.	4.0	7.	3.5
14.	3.6	8.	6.8
13.	3.8	9.	7.4
12.	4.5	10.	8.3
11.	4.3	11.	3.3
10.	2.7	12.	2.1
9.	3.6	13.	1.0
8.	4.1	14.	0.8
7.	11.7	15.	0.9
6.	8.3	16.	0.8
5.	4.1	17.	1.5
4.	4.5	18.	2.1
3.	4.6	19.	0.9
2.	7.3		
1.	3.4		

Patient No. 5.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
23.	8.2	1.	2.9
22.	11.0	2.	3.1
21.	7.3	3.	2.3
20.	3.1	4.	4.0
19.	6.7	5.	2.7
18.	6.6	6.	3.9
17.	5.1	7.	1.5
16.	6.8	8.	1.7
15.	3.9	9.	3.0
14.	3.0	10.	2.8
13.	4.0	11.	1.9
12.	6.5	12.	1.4
11.	3.8	13.	3.7
10.	3.9	14.	4.6
9.	4.0	15.	2.5
8.	3.7	16.	2.9
7.	5.1	17.	3.0
6.	4.4	18.	4.0
5.	7.2	19.	1.9
4.	4.4	20.	2.5
3.	6.1	21.	2.6
2.	6.7		
1.	7.0		

Patient No. 6.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
24.	2.3	1.	4.9
23.	2.6	2.	4.6
22.	4.5	3.	5.0
21.	10.1	4.	5.3
20.	8.3	5.	5.4
19.	4.6	6.	4.3
18.	7.1	7.	4.1
17.	6.0	8.	6.6
16.	5.6	9.	7.4
15.	7.5	10.	6.6
14.	4.7	11.	6.8
13.	5.0	12.	6.6
12.	4.7	13.	6.7
11.	4.8	14.	3.1
10.	5.3	15.	5.3
9.	6.7	16.	6.3
8.	5.5	17.	4.7
7.	4.3	18.	4.8
6.	4.8	19.	5.1
5.	7.2		
4.	6.4		
3.	7.3		
2.	8.0		
1.	6.4		

Patient No. 7.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
20.	5.1	1.	3.0
19.	4.8	2.	4.6
18.	5.3	3.	2.5
17.	4.4	4.	2.7
16.	3.7	5.	3.1
15.	3.9	6.	2.8
14.	4.0	7.	4.6
13.	2.0	8.	5.0
12.	2.9	9.	4.9
11.	3.1	10.	7.3
10.	4.7	11.	6.1
9.	5.4	12.	4.5
8.	6.0	13.	6.0
7.	3.9	14.	2.9
6.	4.7	15.	5.4
5.	4.2	16.	3.1
4.	6.3		
3.	4.0		
2.	2.6		
1.	6.1		

Patient No. 8.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
22.	1.5	1.	1.3
21.	1.7	2.	1.2
20.	1.3	3.	1.9
19.	1.9	4.	2.9
18.	3.1	5.	2.7
17.	2.0	6.	1.6
16.	1.9	7.	3.1
15.	1.5	8.	2.8
14.	1.0	9.	1.9
13.	3.4	10.	1.6
12.	2.5	11.	1.7
11.	2.1	12.	1.0
10.	2.8	13.	0.9
9.	1.9	14.	2.7
8.	1.6	15.	2.3
7.	2.3	16.	1.1
6.	1.7	17.	1.6
5.	1.5	18.	1.4
4.	1.0		
3.	3.1		
2.	2.6		
1.	1.6		

Patient No. 9.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
22.	6.0	1.	1.2
21.	5.4	2.	6.4
20.	6.1	3.	3.1
19.	6.3	4.	3.0
18.	5.9	5.	2.9
17.	10.5	6.	2.6
16.	8.3	7.	5.4
15.	6.1	8.	6.1
14.	6.9	9.	5.8
13.	7.3	10.	6.2
12.	4.6	11.	3.8
11.	5.0	12.	4.4
10.	6.2	13.	4.6
9.	7.2	14.	3.9
8.	5.0	15.	4.0
7.	3.6	16.	5.0
6.	4.1	17.	4.6
5.	3.8	18.	3.1
4.	2.1	19.	6.5
3.	6.0	20.	5.4
2.	3.5		
1.	3.6		

Patient No. 10.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
22.	2.7	1.	1.1
21.	2.5	2.	1.0
20.	3.7	3.	3.6
19.	2.7	4.	3.2
18.	3.3	5.	1.2
17.	3.0	6.	1.5
16.	3.2	7.	1.9
15.	3.6	8.	3.1
14.	3.9	9.	1.8
13.	3.5	10.	1.6
12.	3.4	11.	1.6
11.	3.6	12.	5.2
10.	4.0	13.	6.6
9.	2.5	14.	5.1
8.	3.6	15.	5.0
7.	4.4	16.	5.9
6.	3.4	17.	3.9
5.	3.5	18.	2.6
4.	3.7	19.	6.1
3.	1.0	20.	5.0
2.	1.2	21.	3.3
1.	1.5		

Patient No. 11.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
24.	7.9	1.	8.6
23.	7.0	2.	6.4
22.	7.1	3.	6.3
21.	4.6	4.	6.3
20.	9.9	5.	4.2
19.	7.5	6.	5.4
18.	7.6	7.	6.6
17.	10.5	8.	4.6
16.	12.2	9.	5.0
15.	6.3	10.	1.2
14.	8.5	11.	4.3
13.	6.3	12.	4.4
12.	3.1	13.	5.4
11.	6.9	14.	6.3
10.	6.1	15.	6.2
9.	6.5	16.	3.5
8.	7.2	17.	1.1
7.	7.5	18.	5.2
6.	9.1	19.	5.1
5.	2.1		
4.	2.6		
3.	4.4		
2.	5.0		
1.	5.9		

Patient No. 12.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
17.	2.1	1.	1.6
16.	5.1	2.	2.5
15.	4.0	3.	4.4
14.	4.5	4.	4.6
13.	6.3	5.	2.6
12.	10.6	6.	2.9
11.	9.3	7.	4.4
10.	6.7	8.	1.2
9.	6.8	9.	0.5
8.	9.1	10.	1.9
7.	11.3	11.	6.8
6.	3.4	12.	1.6
5.	5.9	13.	1.5
4.	9.6	14.	7.0
3.	10.1	15.	7.1
2.	5.3	16.	6.3
1.	3.4	17.	3.2
		18.	3.7

Patient No. 13.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
22.	3.3	1.	0.3
21.	3.6	2.	1.6
20.	4.2	3.	2.5
19.	3.2	4.	0.7
18.	2.5	5.	4.5
17.	3.7	6.	1.2
16.	3.6	7.	3.8
15.	3.8	8.	1.7
14.	6.2	9.	3.1
13.	5.0	10.	0.9
12.	5.4	11.	2.9
11.	3.6	12.	5.3
10.	3.7	13.	6.3
9.	5.1	14.	5.7
8.	3.2	15.	5.8
7.	3.6	16.	5.1
6.	6.2	17.	2.8
5.	3.4	18.	5.5
4.	0.9	19.	6.7
3.	1.1	20.	6.3
2.	1.2		
1.	1.4		

Patient No. 14.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
16.	5.6	1.	5.1
15.	7.1	2.	5.0
14.	7.2	3.	5.6
13.	8.3	4.	6.7
12.	14.6	5.	6.3
11.	13.1	6.	9.0
10.	9.0	7.	8.2
9.	8.5	8.	6.7
8.	10.5	9.	2.2
7.	7.3	10.	5.3
6.	7.6	11.	7.4
5.	7.5	12.	7.5
4.	10.6	13.	6.1
3.	10.9	14.	8.1
2.	11.0		
1.	11.3		

Patient No. 15.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
20.	6.3	1.	4.6
19.	6.6	2.	4.5
18.	7.6	3.	3.1
17.	8.5	4.	4.9
16.	6.3	5.	5.1
15.	5.4	6.	3.4
14.	8.7	7.	3.6
13.	9.8	8.	3.9
12.	9.9	9.	4.9
11.	10.7	10.	3.7
10.	11.3	11.	12.8
9.	10.4	12.	5.4
8.	8.6	13.	6.8
7.	9.3	14.	7.3
6.	11.4	15.	4.6
5.	11.7	16.	9.1
4.	12.8	17.	7.6
3.	13.1		
2.	13.0		
1.	12.4		

Patient No. 16.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
17.	2.9	1.	1.5
16.	1.6	2.	1.0
15.	1.9	3.	1.7
14.	1.7	4.	2.8
13.	2.8	5.	3.5
12.	5.4	6.	3.2
11.	4.3	7.	4.6
10.	6.7	8.	6.0
9.	6.2	9.	4.5
8.	4.8	10.	3.6
7.	3.1	11.	2.8
6.	2.9	12.	2.9
5.	3.0	13.	3.1
4.	5.4	14.	4.6
3.	2.1		
2.	4.7		
1.	3.5		

Patient No. 17.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
19.	3.1	1.	1.0
18.	2.5	2.	3.4
17.	1.1	3.	4.1
16.	1.6	4.	4.0
15.	1.6	5.	3.8
14.	3.4	6.	2.9
13.	3.2	7.	3.0
12.	1.6	8.	5.4
11.	4.7	9.	3.2
10.	5.4	10.	3.4
9.	3.6	11.	4.1
8.	3.0	12.	2.7
7.	3.4	13.	3.0
6.	2.7	14.	2.8
5.	1.6	15.	1.6
4.	4.7	16.	5.7
3.	2.9	17.	5.0
2.	3.0	18.	4.1
1.	4.6		

Patient No. 18.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
19.	13.8	1.	1.7
18.	14.0	2.	7.3
17.	6.4	3.	9.1
16.	7.5	4.	9.3
15.	8.3	5.	14.2
14.	9.1	6.	6.4
13.	3.2	7.	4.2
12.	3.7	8.	5.1
11.	6.5	9.	4.3
10.	6.7	10.	6.2
9.	12.0	11.	9.1
8.	6.5	12.	4.1
7.	7.3	13.	3.2
6.	6.9	14.	3.8
5.	7.0	15.	7.6
4.	11.1		
3.	9.3		
2.	7.2		
1.	6.5		

Patient No. 19.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
21.	4.2		1.0
20.	3.4		0.7
19.	3.1		0.5
18.	8.6		1.2
17.	4.1		0.8
16.	3.0		0.9
15.	4.6		3.2
14.	1.6		2.8
13.	1.7		0.9
12.	3.6		1.0
11.	2.3		2.6
10.	1.7		2.3
9.	3.6		1.7
8.	3.9		0.6
7.	4.1		0.4
6.	1.4		0.9
5.	0.5		1.1
4.	0.5		1.4
3.	0.6		0.9
2.	1.3		
1.	0.9		

Patient No. 20.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
18.	8.5		1.8
17.	8.5		0.9
16.	7.9		1.3
15.	7.1		1.0
14.	8.2		2.9
13.	4.1		3.1
12.	4.3		1.9
11.	2.3		2.4
10.	4.1		1.9
9.	2.0		0.7
8.	2.9		1.8
7.	3.0		1.6
6.	1.7		3.0
5.	1.5		2.3
4.	2.1		1.3
3.	1.6		1.6
2.	1.9		2.0
1.	0.7		2.1

Patient No. 21.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
16.	5.7	1.	7.6
15.	5.0	2.	7.8
14.	4.9	3.	7.3
13.	5.2	4.	7.9
12.	5.1	5.	10.6
11.	4.7	6.	6.2
10.	4.2	7.	5.2
9.	5.1	8.	3.06
8.	4.9	9.	10.6
7.	4.3	10.	9.1
6.	3.4	11.	8.4
5.	3.3	12.	10.6
4.	2.9	13.	10.2
3.	2.1	14.	10.8
2.	3.6		
1.	0.5		

Patient No. 22.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
21.	1.5	1.	3.5
20.	1.2	2.	4.7
19.	0.5	3.	3.8
18.	1.9	4.	5.0
17.	2.1	5.	5.8
16.	1.5	6.	2.7
15.	5.2	7.	2.9
14.	5.1	8.	2.6
13.	3.3	9.	5.7
12.	4.6	10.	3.1
11.	4.3	11.	4.0
10.	5.4	12.	2.8
9.	3.9	13.	4.5
8.	6.3	14.	6.0
7.	6.6	15.	6.1
6.	4.1	16.	4.6
5.	4.7	17.	2.9
4.	6.6	18.	4.2
3.	6.9	19.	4.1
2.	2.2		
1.	5.3		

Patient No. 23.

Before Delivery		After Delivery	
Day	Uropeps. Units/Hour	Day	Uropeps. Units/Hour
19.	6.5	1.	3.4
18.	5.9	2.	9.7
17.	6.0	3.	10.1
16.	6.3	4.	9.2
15.	7.8	5.	8.8
14.	9.1	6.	9.3
13.	12.8	7.	10.7
12.	14.2	8.	11.2
11.	5.1	9.	8.4
10.	9.2	10.	6.1
9.	12.2	11.	5.0
8.	12.3	12.	4.9
7.	9.4	13.	5.3
6.	13.1	14.	11.1
5.	9.7	15.	10.2
4.	11.9	16.	9.7
3.	11.8		
2.	10.5		
1.	9.7		

Patient No. 24.

Before Delivery		After Delivery	
Days	Uropeps. Units/Hour	Days	Uropeps. Units/Hour
17.	8.5	1.	6.0
16.	2.6	2.	8.6
15.	2.9	3.	8.3
14.	8.3	4.	8.9
13.	6.6	5.	9.2
12.	8.6	6.	6.4
11.	6.9	7.	7.3
10.	7.1	8.	13.4
9.	7.4	9.	7.3
8.	7.5	10.	2.6
7.	13.7	11.	6.9
6.	7.9	12.	6.7
5.	8.0	13.	6.6
4.	10.4	14.	7.5
3.	10.5	15.	4.8
2.	8.1	16.	10.3
1.	8.0		

Patient No. 25.

Before Delivery		After Delivery	
Days	Uropeps. Units/Hour	Days	Uropeps. Units/Hour
20.	6.1	1.	4.6
19.	5.7	2.	4.6
18.	6.3	3.	5.0
17.	7.1	4.	5.3
16.	7.4	5.	6.2
15.	9.0	6.	5.9
14.	9.3	7.	4.7
13.	4.2	8.	9.3
12.	4.6	9.	10.1
11.	5.1	10.	3.4
10.	5.0	11.	6.2
9.	9.6	12.	6.7
8.	11.1	13.	5.9
7.	10.3	14.	6.0
6.	4.8	15.	8.2
5.	7.3	16.	9.1
4.	6.2		
3.	3.5		
2.	2.1		
1.	2.0		

25 WOMEN. BEFORE AND AFTER DELIVERY.

Uropepsinogen (units per hour).

	Before Delivery		After Delivery		
Patient	Mean	Standard Error of Mean	Mean	Standard Error of Mean	
1	11.32	+0.53	7.43	+0.52	**
2	8.79	-0.65	5.95	-0.40	**
3	7.72	0.47	8.50	0.76	
4	5.25	0.25	3.05	0.57	**
5	5.57	0.35	2.81	0.19	**
6	5.71	0.35	5.45	0.26	
7	4.36	0.26	4.28	0.37	
8	2.00	0.14	1.87	0.17	
9	5.61	0.40	4.40	0.33	*
10	3.09	0.19	3.35	0.40	
11	6.74	0.49	5.06	0.41	*
12	6.68	0.69	3.54	0.50	**
13	3.54	0.32	3.64	0.48	
14	9.38	0.61	6.37	0.46	**
15	9.69	0.54	5.61	0.60	**
16	3.71	0.39	3.27	0.36	
17	3.04	0.28	3.51	0.28	
18	8.05	0.67	6.37	0.82	
19	2.80	0.42	1.31	0.19	**
20	4.02	0.65	1.87	0.24	**
21	4.06	0.34	8.24	0.62	**
22	3.80	0.41	4.16	0.29	
23	8.85	0.67	8.32	0.63	
24	7.82	0.62	7.55	0.60	
25	6.34	0.58	6.33	0.48	

One * denotes significant difference.
Two *'s denote highly significant difference.
Thus of the 25 patients 11 showed positive differences which were significant, 1 showed a significant negative difference, and 13 showed differences which were not significant.

APPENDIX TO PART IV.

GASTRIC ACID SECRETION FROM HEIDENHAIN POUCHES IN DOGS DURING PREGNANCY AND LACTATION.

DAILY READINGS OF VOLUME, CONCENTRATION IN CLINICAL UNITS AND OUTPUT IN MEq.

GASTRIC ACID SECRETION IN DOGS DURING PREGNANCY AND LACTATION.

DOG I.

Day	Vol.	C.U.	MEq.	Day	Vol.	C.U.	MEq.
	NO PRE-PREGNANCY CONTROL.			28	25	26	0.65
				29	30	12	0.36
				30	29	27	0.78
	PREGNANCY.			31	25	25	0.62
				32	39	27	1.05
1	30	20	0.60	33	31	29	0.89
2	51	55	1.20	34	30	30	0.90
3	29	15	0.44	35	40	25	1.00
4	45	25	1.13	36	25	37	0.92
5	35	27	0.95	37	23	42	0.96
6	51	20	1.02	38	25	41	1.02
7	33	22	0.73	39	26	62	2.01
8	33	23	0.76	40	27	51	1.37
9	40	30	1.20	41	28	52	1.45
10	45	20	0.90	42	25	50	1.25
11	63	25	1.50	43	20	11	0.22
12	35	20	0.70	44	26	41	1.06
13	26	28	0.73	45	29	40	1.16
14	27	29	0.74	46	31	40	1.24
15	43	30	1.29	47	29	27	0.78
16	40	36	1.20	48	35	52	1.82
17	30	31	0.93	49	30	40	1.20
18	26	25	0.65	50	32	74	2.36
19	40	32	1.28	51	33	85	2.80
20	26	19	0.49	52	34	58	2.00
21	25	15	0.38	53	30	70	2.10
22	30	12	0.36	54	35	45	1.57
23	25	15	0.38	55	34	44	1.49
24	45	20	0.90	56	29	64	1.86
25	30	2	0.06	57	37	69	2.55
26	35	10	0.35	58	42	61	2.56
27	32	12	0.38	59	47	80	3.76

Day	Vol.	C.U.	MEq.	Day	Vol.	C.U.	MEq.
	DELIVERY.				PUPS WEANED.		
	Lactation.				Post-Pregnancy control		
60	34	52	1.77	88	60	90	5.94
61	62	28	1.74	89	50	91	4.55
62	82	56	4.59	90	25	63	1.51
63	74	62	4.39	91	32	74	2.37
64	83	70	5.84	92	34	88	2.99
65	50	80	4.00	93	38	90	3.42
66	60	78	4.68	94	26	76	2.03
67	52	89	4.62	95	22	45	0.99
68	63	60	3.78	96	23	59	1.35
69	50	70	3.50	97	35	30	1.05
70	85	63	5.36	98	25	34	0.85
71	44	79	3.48	99	42	61	2.56
72	95	80	7.60	100	42	55	2.31
73	50	81	4.05	101	48	46	2.20
74	50	81	4.05	102	58	63	3.65
75	66	114	7.52	103	50	49	2.45
76	71	85	6.04	104	50	45	2.25
77	54	75	4.05	105	77	72	5.45
78	53	76	4.03	106	52	58	3.00
79	64	83	5.31	107	37	35	1.19
80	42	71	2.98	108	40	17	0.68
81	55	69	3.80	109	35	20	0.70
82	75	94	7.05	110	40	18	0.62
83	80	91	7.28	111	40	29	1.16
84	74	76	5.62	112	50	20	1.00
85	60	95	5.70	113	49	20	0.98
86	84	90	7.56	114	20	25	0.50
87	64	101	6.50	115	25	30	0.75
				116	30	26	0.78
				117	35	28	0.98
				118	38	20	0.76
				119	36	47	1.69
				120	38	25	0.95

GASTRIC ACID SECRETION IN DOGS DURING PREGNANCY AND LACTATION.

DOG II.

Day	Vol.	C.U.	MEq.	Day	Vol.	C.U.	MEq.
	PRE-PREGNANCY CONTROL.				PREGNANCY.		
1	70	25	1.75	32	60	44	2.64
2	50	33	1.16	33	40	20	0.80
3	50	22	1.10	34	55	22	1.21
4	50	30	1.50	35	50	56	2.80
5	55	32	1.76	36	30	5	0.15
6	35	44	1.54	37	55	4	0.22
7	45	36	1.62	38	54	5	0.27
8	45	40	1.80	39	53	0	0
9	50	40	2.00	40	50	0	0
10	38	40	1.42	41	82	0	0
11	50	43	2.15	42	50	0	0
12	45	45	2.03	43	63	0	0
13	35	44	1.54	44	50	0	0
14	60	28	1.68	45	60	10	0.60
15	45	42	1.89	46	55	0	0
16	50	12	0.60	47	60	0	0
17	50	15	0.75	48	80	28	2.24
18	45	22	1.00	49	50	30	1.50
19	90	10	0.90	50	52	22	1.14
20	60	5	0.30	51	50	17	0.85
21	88	20	1.76	52	54	48	2.59
22	65	10	0.65	53	45	42	1.89
23	85	8	0.68	54	56	45	2.52
24	80	14	1.12	55	58	48	2.78
25	60	16	0.96	56	81	64	5.18
26	56	15	0.84	57	60	54	3.24
27	50	10	0.50	58	58	50	2.90
28	60	22	1.32	59	50	10	0.50
29	55	24	1.32	60	80	46	3.68
30	40	28	1.12	61	50	40	2.00
31	55	22	1.21	62	60	54	3.24

Day	Vol.	C.U.	MEq.
63	55	32	1.66
64	65	52	3.38
65	30	21	0.63
66	50	45	2.25
67	55	42	2.31
68	50	45	2.25
69	70	48	3.36
70	75	50	3.75
71	70	52	3.64
72	40	54	2.16
73	50	30	1.50
74	45	32	1.44
75	32	30	0.96
76	50	28	1.40
77	72	54	3.89
78	60	40	2.40
79	75	48	3.60
80	70	50	3.50
81	63	52	3.28
82	50	46	2.30
83	62	45	2.79
84	45	45	2.03
85	55	50	2.75
86	70	50	3.50
87	70	48	3.36
88	53	32	1.70
89	60	54	3.24
90	50	60	3.00
91	60	32	1.92
92	48	50	2.40
93	47	80	3.76
DELIVERY.			
Suppressed Lactation.			
94	140	44	6.16
95	70	32	2.24
96	60	40	2.40
97	75	50	3.75
98	50	20	1.00
99	58	10	0.58
100	60	0	0
101	45	0	0
102	50	5	0.25
103	45	8	0.36
104	48	20	0.96
105	28	5	0.14
106	20	10	0.20
107	50	20	1.00
108	18	0	0
109	60	0	0
110	92	10	0.92
111	53	5	0.26
112	78	0	0
113	58	24	1.38
114	68	20	1.36
115	69	24	1.66
116	61	5	0.31
117	74	0	0
118	91	24	2.18
119	73	10	0.73
120	94	12	1.15
121	80	15	1.20
POST-PREGNANCY CONTROL.			
122	70	10	0.70
123	68	8	0.52
124	80	5	0.40
125	73	10	0.73
126	71	8	0.57
127	89	20	1.78
128	71	10	0.71
129	32	10	0.32
130	30	12	0.36
131	68	15	1.04
132	70	28	1.96
133	60	8	0.48
134	70	10	0.70
135	90	7	0.63
136	40	0	0
137	79	26	2.05
138	81	34	2.75
139	60	26	1.56
140	72	25	1.80
141	80	42	3.36
142	60	40	2.40
143	70	5	0.35
144	85	9	0.77
145	60	15	0.90
146	90	33	2.97
147	63	25	1.58
148	65	10	0.65
149	85	8	0.68
150	65	20	1.30

GASTRIC ACID SECRETION IN DOGS DURING PREGNANCY AND LACTATION.

DOG III.

Day	Vol.	C.U.	MEq.	Day	Vol.	C.U.	MEq.
PRE-PREGNANCY CONTROL.				PREGNANCY.			
1	30	40	1.20	42	30	12	0.36
2	60	49	2.90	43	28	10	0.28
3	55	48	2.64	44	37	30	1.21
4	50	46	2.30	45	40	20	0.80
5	40	61	2.44	46	35	20	0.70
6	55	20	1.00	47	26	30	0.78
7	60	20	1.20	48	28	29	0.81
8	63	10	0.63	49	30	22	0.66
9	45	40	1.75	50	31	17	0.53
10	70	6	0.42	51	35	30	1.05
11	53	6	0.32	52	23	16	0.37
12	75	10	0.75	53	27	20	0.54
13	40	10	0.40	54	34	25	0.85
14	35	25	0.85	55	26	20	0.52
15	40	10	0.40	56	30	30	0.90
16	40	10	0.40	57	38	32	1.22
17	45	20	0.90	58	27	25	0.67
18	56	4	0.22	59	29	26	0.75
19	45	18	0.81	60	13	36	0.46
20	47	0	0	61	28	22	0.62
21	25	4	0.10	62	30	30	0.92
22	45	20	0.90	63	25	14	0.35
23	12	10	0.12	64	32	20	0.64
24	50	10	0.50	65	29	26	0.65
25	30	14	0.42	66	30	31	0.91
26	30	40	1.20	67	34	30	1.02
27	20	10	0.20	68	25	20	0.50
28	30	46	1.38	69	28	22	0.62
29	40	22	0.88	70	20	36	0.72
30	35	12	0.42	71	28	20	0.56
31	30	14	0.42	72	35	10	0.35
32	35	4	0.14	73	28	14	0.39
33	30	20	0.60	74	28	20	0.56
34	30	30	0.90	75	24	30	0.72
35	34	20	0.68	76	50	26	1.30
36	35	20	0.70	77	30	26	0.78
37	36	10	0.36	78	50	28	1.40
38	30	10	0.30	79	40	44	1.76
39	37	5	0.18	80	50	40	2.00
40	30	8	0.24	81	35	30	1.50
41	25	10	0.25	82	50	24	1.20

Day	Vol.	C.U.	MEq.
83	50	35	1.70
84	48	25	1.20
85	40	30	1.20
86	50	40	2.20
87	70	46	3.20
88	50	36	1.80
89	48	30	1.42
90	50	30	1.50
91	65	40	2.60
92	60	42	2.52
93	61	50	3.50
94	48	50	2.40
95	30	56	1.68
96	52	68	3.54
97	50	65	3.25
98	30	44	1.34
99	50	50	2.50
100	60	68	4.08
101	48	36	1.73
102	30	20	0.60
103	35	15	0.53
	DELIVERY.		
	Suppressed Lactation.		
104	62	71	3.95
105	24	24	0.58
106	40	36	1.44
107	38	12	0.46
108	10	5	0.05
109	32	28	0.90
110	30	16	0.48
111	8	0	0
112	20	28	0.56
113	20	25	0.50
114	30	26	0.78
115	25	26	0.66
116	35	25	0.87
117	40	10	0.40
118	60	5	0.30
119	65	26	1.69
120	48	8	0.38

Day	Vol.	C.U.	MEq.
121	30	10	0.30
122	50	20	1.00
123	40	5	0.20
124	50	7	0.35
125	48	8	0.38
126	40	18	0.72
127	65	18	1.17
128	50	28	1.40
129	40	34	1.36
130	43	12	0.52
	POST-PREGNANCY CONTROL.		
132	45	20	0.90
133	20	40	0.80
134	20	8	0.16
135	18	5	0.09
136	30	5	0.15
137	20	0	0
138	25	0	0
139	15	0	0
140	25	0	0
141	28	0	0
142	40	20	0.80
143	60	0	0
144	18	0	0
145	20	0	0
146	30	0	0
147	36	10	0.36
148	15	0	0
149	39	0	0
150	35	0	0

APPENDIX TO PART V.

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION OF FEMALE DOGS.

DAILY READINGS OF VOLUME, CONCENTRATION IN CLINICAL UNITS AND OUTPUT IN MEq.

(a) IN 7 DOGS BEFORE AND AFTER CASTRATION.

(b) IN 4 DOGS BEFORE AND AFTER LAPAROTOMY (CONTROLS).

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION.

DOG. No. 1.

BEFORE CASTRATION				AFTER CASTRATION			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	Output MEq.
17	206	108	21.65	1	150	135	20.25
16	158	115	18.17	2	157	126	19.78
15	68	136	9.13	3	194	134	25.99
14	235	123	28.99	4	219	129	28.25
13	192	124	24.05	5	120	140	16.80
12	151	120	18.12	6	159	132	20.99
11	171	131	22.40	7	114	129	14.71
10	257	135	34.69	8	68	99	6.73
9	287	134	38.46	9	191	121	23.11
8	252	138	34.77	10	80	100	8.00
7	200	144	28.80	11	95	109	10.35
6	255	134	33.97	12	45	70	3.15
5	250	123	30.75	13	35	110	3.85
4	225	94	21.15	14	35	120	4.20
3	192	131	25.15	15	43	107	4.60
2	191	121	23.11	16	42	143	6.01
1	200	130	26.20	17	60	100	6.00
				18	76	82	6.23
				19	51	29	1.48
				20	42	74	3.11

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION.

DOG No. 2.

BEFORE CASTRATION				AFTER CASTRATION			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	MEq.
28	120	96	11.52	1	250	121	30.25
27	170	118	20.26	2	225	115	25.88
26	137	104	14.25	3	220	117	25.74
25	202	121	34.44	4	140	75	10.50
24	162	113	18.30	5	286	117	38.46
23	195	112	21.84	6	163	94	15.32
22	295	125	36.87	7	177	90	15.93
21	230	108	24.84	8	153	77	11.78
20	242	117	28.31	9	105	67	7.04
19	84	58	4.87	10	164	108	17.71
18	88	94	8.27	11	82	95	7.79
17	120	105	12.60	12	136	100	13.60
16	159	93	14.79	13	68	61	4.15
15	153	96	14.69	14	67	77	5.16
14	166	96	15.94	15	60	71	4.26
13	183	106	19.40	16	45	33	1.48
12	180	100	18.00	17	54	89	4.81
11	195	105	20.47	18	58	93	5.39
10	206	91	18.74	19	24	47	1.13
9	200	90	18.00	20	32	42	1.34
8	230	122	40.26				
7	248	113	28.02				
6	267	120	32.04				
5	267	121	32.31				
4	179	115	20.58				
3	231	127	29.34				
2	268	140	37.50				
1	300	124	37.20				

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION.

DOG No. 3.

BEFORE CASTRATION				AFTER CASTRATION			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	MEq.
25	96	126	12.10	1	108	125	13.50
24	37	118	4.37	2	70	108	7.56
23	49	103	5.05	3	41	95	3.89
22	80	126	10.08	4	42	93	3.91
21	49	124	6.08	5	49	96	4.70
20	114	132	15.07	6	67	101	6.77
19	63	105	6.62	7	25	80	2.00
18	80	126	10.08	8	43	104	4.47
17	91	100	9.10	9	92	106	9.75
16	176	118	20.77	10	45	100	4.50
15	142	107	15.19	11	143	117	16.73
14	164	109	15.69	12	68	91	6.19
13	70	93	6.51	13	70	100	7.00
12	104	115	11.96	14	84	90	7.56
11	44	70	3.08	15	108	97	10.48
10	82	110	9.02	16	109	104	11.34
9	104	121	12.58	17	100	99	9.90
8	100	111	11.10	18	77	100	7.70
7	91	100	9.10	19	53	88	4.66
6	91	101	9.19	20	76	92	6.99
5	160	121	19.36				
4	159	117	18.50				
3	79	108	8.52				
2	100	112	11.20				
1	101	110	11.11				

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION.

DOG No. 4.

BEFORE CASTRATION				AFTER CASTRATION			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	Output MEq.
18	45	80	3.60	1	55	89	7.90
17	84	47	9.83	2	36	95	3.42
16	68	105	7.14	3	38	85	3.23
15	71	100	7.10	4	73	114	8.32
14	82	97	7.95	5	71	105	7.46
13	45	65	2.93	6	83	114	9.46
12	74	90	6.66	7	76	122	9.27
11	92	100	9.20	8	112	122	13.66
10	69	72	4.64	9	65	106	6.89
9	62	96	5.95	10	120	120	14.40
8	60	63	3.78	11	117	125	14.63
7	45	65	2.93	12	79	115	9.09
6	44	61	2.70	13	89	105	9.35
5	78	84	6.55	14	68	96	6.53
4	89	96	8.54	15	127	117	14.86
3	101	107	10.81	16	125	119	14.88
2	81	99	8.02	17	110	124	13.64
1	55	89	7.90	18	165	120	19.80
				19	85	104	8.84
				20	92	113	10.40
				21	106	114	12.08
				22	99	105	10.39
				23	64	101	6.46
				24	63	102	6.43
				25	74	108	7.99
				26	83	108	8.96
				27	65	108	7.02
				28	53	103	5.46

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION.

DOG No. 5.

BEFORE CASTRATION				AFTER CASTRATION			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	MEq.
17	35	99	3.47	1	53	92	4.88
16	42	113	4.85	2	22	79	1.74
15	66	86	5.68	3	50	88	4.40
14	65	93	6.05	4	47	82	3.85
13	39	97	3.78	5	52	82	4.26
12	50	88	4.40	6	63	102	6.43
11	36	56	2.02	7	50	88	4.40
10	42	94	3.95	8	69	103	7.11
9	36	104	3.74	9	57	92	5.24
8	49	107	4.95	10	74	99	7.33
7	50	82	4.10	11	55	96	5.28
6	33	67	2.21	12	41	91	3.73
5	46	116	5.34	13	38	83	3.15
4	38	67	2.55	14	37	71	2.63
3	42	115	4.83	15	34	84	2.86
2	23	48	1.10	16	37	77	3.00
1	122	106	12.95	17	53	84	4.45
				18	44	71	3.12
				19	30	40	1.20
				20	85	50	4.25
				21	72	31	1.30
				22	51	97	4.45

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION.

DOG No. 6.

BEFORE CASTRATION				AFTER CASTRATION			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	Output MEq.
20	101	31	3.13	1	82	43	3.53
19	100	37	3.70	2	45	40	1.80
18	80	41	3.28	3	45	35	1.58
17	80	36	2.88	4	50	35	1.75
16	76	36	2.74	5	53	50	1.75
15	80	34	2.82	6	60	37	2.22
14	75	34	2.55	7	50	42	2.10
13	85	58	4.93	8	50	41	2.05
12	110	51	5.67	9	55	53	2.92
11	96	31	2.98	10	45	38	1.71
10	100	47	4.70	11	55	45	2.42
9	100	48	4.80	12	55	55	3.13
8	80	28	2.24	13	55	36	1.98
7	50	32	1.60	14	72	34	2.45
6	62	35	2.17	15	77	37	2.85
5	60	31	1.86	16	52	40	2.08
4	65	29	1.89	17	75	51	3.83
3	70	41	2.87	18	63	38	2.39
2	70	45	3.15	19	47	44	2.07
1	72	40	2.88	20	75	52	3.90

EFFECT OF CASTRATION ON GASTRIC ACID SECRETION.

DOG No. 7.

BEFORE CASTRATION				AFTER CASTRATION			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	Output MEq.
20	97	63	6.01	1	118	29	3.42
19	96	50	4.80	2	85	22	1.87
18	83	40	3.32	3	75	20	1.50
17	95	50	4.75	4	86	59	5.07
16	90	44	3.96	5	120	86	10.32
15	120	41	4.92	6	70	32	2.24
14	90	37	3.33	7	70	38	2.66
13	103	40	4.12	8	75	29	2.17
12	100	41	4.10	9	85	12	1.20
11	95	39	3.71	10	92	46	4.23
10	95	26	2.47	11	94	35	3.29
9	80	30	2.40	12	80	26	2.08
8	95	49	7.66	13	105	36	3.78
7	103	35	8.61	14	92	18	1.66
6	80	41	3.28	15	94	29	2.73
5	89	24	2.14	16	130	46	5.98
4	100	26	2.60	17	87	25	2.67
3	124	22	2.73	18	95	38	3.61
2	78	33	2.67	19	110	60	6.60
1	95	24	2.28	20	98	34	3.32

EFFECT OF LAPAROTOMY ON GASTRIC ACID SECRETION.

DOG No. 8.

BEFORE LAPAROTOMY				AFTER LAPAROTOMY			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	Output MEq.
17	35	99	3.47	1	84	88	7.39
16	42	113	4.85	2	84	88	7.39
15	66	86	5.68	3	126	108	13.61
14	65	93	6.05	4	92	96	8.83
13	39	97	3.78	5	97	91	8.83
12	50	88	4.40	6	70	56	3.92
11	36	56	2.02	7	102	97	9.89
10	42	94	3.95				
9	36	104	3.74				
8	49	107	4.95				
7	50	82	4.10				
6	33	67	2.21				
5	46	116	5.34				
4	38	67	2.55				
3	42	115	4.83				
2	23	48	1.10				
1	122	106	12.95				

EFFECT OF LAPAROTOMY ON GASTRIC ACID SECRETION.

DOG No. 9.

BEFORE LAPAROTOMY				AFTER LAPAROTOMY			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	MEq.
12	50	70	3.50	1	66	102	6.73
11	56	74	4.19	2	46	68	3.13
10	75	85	6.38	3	52	92	4.78
9	60	88	5.28	4	61	98	5.98
8	74	90	6.66	5	77	111	8.55
7	83	87	7.12	6	86	111	9.55
6	69	90	6.12	7	60	96	5.75
5	88	100	8.80				
4	59	85	5.02				
3	69	91	6.28				
2	66	63	5.48				
1	49	73	3.58				

EFFECT OF LAPAROTOMY ON GASTRIC ACID SECRETION.

DOG No. 10.

BEFORE LAPAROTOMY				AFTER LAPAROTOMY.			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	Output MEq.
26	24	69	1.66	1	22	97	2.73
25	20	44	0.88	2	25	98	2.45
24	22	68	1.50	3	29	87	2.52
23	20	65	1.30	4	38	106	4.03
22	24	50	1.20	5	19	64	1.22
21	44	85	3.74	6	74	124	9.18
20	34	52	1.77	7	27	85	2.30
19	40	80	3.20				
18	32	97	3.10				
17	28	90	2.52				
16	38	111	4.22				
15	40	60	2.40				
14	47	111	5.22				
13	37	110	4.07				
12	45	95	4.29				
11	43	82	3.52				
10	60	120	7.20				
9	47	98	4.61				
8	53	103	5.46				
7	40	100	4.00				
6	47	111	5.22				
5	38	111	4.22				
4	31	80	2.48				
3	27	66	1.78				
2	29	100	2.90				
1	28	100	2.80				

EFFECT OF LAPAROTOMY ON GASTRIC ACID SECRETION.

DOG No. 11.

BEFORE LAPAROTOMY				AFTER LAPAROTOMY			
Day	Vol.	C.U.	Output MEq.	Day	Vol.	C.U.	Output MEq.
19	84	103	8.65	1	70	123	8.51
18	55	112	6.16	2	73	108	7.88
17	46	100	4.60	3	85	100	8.50
16	60	122	7.32	4	84	103	8.65
15	47	98	4.61	5	156	131	20.44
14	50	100	5.00	6	180	130	23.40
13	106	123	13.04	7	69	102	7.04
12	70	102	7.14				
11	73	108	7.88				
10	61	100	6.10				
9	103	121	12.46				
8	67	100	6.70				
7	68	118	8.02				
6	85	105	8.93				
5	69	107	7.38				
4	40	67	2.68				
3	50	94	4.75				
2	87	123	10.70				
1	50	86	4.30				