STUDIES, BIOCHEMICAL AND CLINICAL, ON THE TOXAEMIAS OF PREGNANCY.

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C O N T E N T S.

I. INTRODUCTORY NOTE.

Sir Thomas Lewis (1933) in his Harveian Oration on "Clinical Science" emphasises the importance of the observation of transient phenomena.

The period of pregnancy offers a unique opportunity for the application of the methods of clinical science, and that mainly for three reasons. In the first place, the ordinary metabolism is completely altered for a certain length of time, during which various abnormal conditions may appear. Secondly, after the termination of pregnancy, the same individual can be studied: further observation will then determine whether the particular affection initiated in the pregnant state disappears entirely, whether it persists in the same form, or whether it modifies its character. Thirdly, it is a great advantage that the same individual can generally be studied in her response to repeated pregnancies, enabling comparisons to be made of her health in one gestation and another, as well as in the gravid and non-gravid states: the cumulative effect of numerous pregnancies can then be determined.

How frequently are transient phenomena encountered and how often are they missed, or, if noticed, dismissed as of no significance because the observer has eyes that see not and ears that hear not! The toxaemias of pregnancy constitute a problem almost as baffling as in the days of Hippocrates. How should the cause of these disturbances be investigated? There is none to say which line of research will lead to a solution of the mystery. Hence the writer has attempted to combine within himself the rôles of clinician and laboratory worker. During the past five years he has concentrated on the toxaemias peculiar to pregnancy: it has been his aim to make accurate observations of transient phenomena and to explore such avenues

of biochemical investigation as were suggested by the clinical manifestations, in the hope that some light might be shed on the aetiological basis of these obscure conditions.

The award of a Research Scholarship by the McCunn Trustees in 1929 enabled the writer to embark on the study of a branch of medicine which had attracted him from student days. The Scholarship was continued for two years, and this is the third year he has been in receipt of a part-time personal grant from the Medical Research Council. To these bodies sincere thanks are tendered.

The material has been obtained in the wards of the Glasgow Royal Maternity and Women's Hospital, to the visiting staff of which, especially Professor J.M. Munro Kerr and Professor James Hendry, the writer is indebted for access to suitable cases.

The laboratory work has been carried out in the Biochemical Laboratory of the Pathological Institute of the Royal Infirmary, Glasgow, under the kind direction of the late Professor J.H. Teacher, Professor John Shaw Dunn and Dr. D.P. Cuthbertson.

Unless where specifically stated otherwise, the work presented in the following pages has been carried out entirely by the writer. A large number of references has been consulted: many of these have been omitted, so that only those having a direct bearing on the various aspects of the subject under discussion find a place in the text and bibliography.

Each section is complete in itself in so far as case-numbering, table-numbering and bibliography are concerned.

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II. ON THE SERUM CALCIUM CONTENT IN NORMAL PREGNANCY, PRE-ECLAMPSIA AND ECLAMPSIA.

INTRODUCTORY NOTE.

It is generally agreed that during the eighth and ninth months of pregnancy the foetus requires increasingly greater quantities of calcium (Bar, 1907). De Wesselow (1922) found that during the last months of pregnancy there is a tendency to a fall in the calcium content of the blood-serum. Bogert and Plass (1923) made observations on 23 women at the time of labour, and found that the average calcium content of the blood-serum was 9·1 mgm. per 100 c.c., while for 12 normal non-pregnant women, the average figure was 10·2 mgm. per 100 c.c. The calcium content of the blood at different stages of pregnancy has also been studied by Widdows (1923). She has shown that, in almost all cases, there is a decrease of the calcium content towards the last months of gestation, and a general rise directly after confinement. As regards the serum calcium in cases of eclampsia, contradictory statements have been made. Stander and his co-workers (1925), while noting a tendency toward a slight lowering of the calcium in pregnancy, found no deviation from these values in nephritic toxaemia, pre-eclampsia or eclampsia. Nixon (1931) records two cases of eclampsia in which the serum calcium was respectively 8·5 and 11·3 mgm. per 100 c.c. He also gives results of serum calcium estimations in 8 cases of pre-eclampsia and 1 of hyperemesis gravidarum, and concludes that, in pregnancy toxaemia, there is little deviation from the normal value, while, in eclampsia, there may be fairly wide variations.

METHOD.

The method adopted was that of Kramer and Tisdall (1921), as modified by Clark and Collip (1925), by which the normal serum calcium is found to vary between 9·0 and 11·0 mgm. per 100 c.c. Stewart and Dunlop (1930) give the normal range of serum calcium as 9·5 - 10·5 mgm. per 100 c.c. Many of the estimations here recorded were done in dulpicate in order to test the accuracy of the method. Greville (1931) reported that the method gives an accurate measure of the blood-calcium. The results are shown in Tables I to IV. In Table V are given notes of the cases of eclampsia treated by injection of calcium gluconate.

A noteworthy feature was the great increase in viscosity of the blood in those cases associated with high blood pressure. According to Harris and McLoughlin (1930) there is no evidence that this increased viscosity is due to an increase in size or number of the erythrocytes. During starvation, viscosity is increased, and it is found to vary inversely with the urinary output. These are factors of essential importance in eclampsia. For some time before admission to hospital and afterwards the patient is more or less starving. Even after the commencement of treatment, if the patient be unable to swallow and resort must be made to rectal salines, the fluid intake is very low.

RESULTS.

TABLE I — Cases of Normal Pregnancy at Full Time, in Labour and Shortly after Delivery, Grouped according to Serum Calcium Value (mgm. per 100 c.c. Serum) (35 Cases).

Levels of serum Ca mgm. per 100 c.c. serum.	Number of cases.	Approximate percentage of total.	Remarks.
12·1 - 12·5	. .	. .	. .
11·6 - 12·0	1	2·9	. .
11·1 - 11·5	. .	. .	. .
10·6 - 11·0	1	2·9	. .
10·1 - 10·5	7	20·0	. .
9·6 - 10·0	7	20·0	. .
9·1 - 9·5	13	37·2	. .
8·6 - 9·0	5	14·3	. .
8·1 - 8·5	1	2·9	Post-partum haemorrhage.

Approximately 17 per cent. show values of 9 mgm. per 100 c.c. and under (taking 9 mgm. per 100 c.c. as the lower limit of normality)..

TABLE II — Cases of Nephritic and Pre-eclamptic Toxaemia Grouped according to Serum Calcium Value (17 Cases).

Levels of serum Ca mgm. per 100 c.c. serum.	Number of cases.	Approximate percentage of total.
12·1 - 12·5	1	5·9
11·6 - 12·0	. .	. .
11·1 - 11·5	. .	. .
10·6 - 11·0	. .	. .
10·1 - 10·5	. .	. .
9·6 - 10·0	2	11·8
9·1 - 9·5	4	23·6
8·6 - 9·0	2	11,8
8·1 - 8·5	3	17·7
7·6 - 8·0	2	11·8
7·1 - 7·5	3	17·7

Taking 9·0 mgm. per 100 c.c. as the lower limit of normality, approximately 59 per cent. of these cases show subnormal values.

TABLE III — Cases of Eclampsia Grouped according to Serum Calcium Value (44 Cases).

Levels of serum Ca mgm. per 100 c.c. serum.	Number of cases.	Approximate percentage of total.	Remarks.
11·1 - 11·5	1	2·3	3 minutes before sixteenth and last fit.
10·6 - 11·0	..	..	..
10·1 - 10·5	..	..	..
9·6 - 10·0	6	13·6	In 1 case 10 minutes after last fit.
9·1 - 9·5	1	2·3	After second and last fit.
8·6 - 9·0	5	11·3	..
8·1 - 8·5	12	27·2	..
7·6 - 8·0	13	29·5	In 1 case later estimation gave value of 5·7.
7·1 - 7·5	4	9·0	..
6·6 - 7·0	1	2·3	..
6·1 - 6·5	1	2·3	..

In approximately 82 per cent. of these cases of eclampsia the serum calcium value is subnormal.

TABLE IV — Average Value of Serum Calcium in Various Conditions not Previously Mentioned (31 Cases).

Average serum Ca mgm. per 100 c.c. serum.	Type of case.	Number of cases.
4·1	Toxic jaundice; foetus macerated; placenta 3¾ lb.; death.	1
8·2	Puerperal sepsis.	1
8·9	Repeated abortions.	1
9·0	Uraemia; polycystic kidneys.	1
9·1	Normal puerperium; second day.	1
9·2 lowest 9·0, highest 9·2	Pyelitis.	4
9·2 lowest 8·8, highest 9·6	Chorea gravidarum.	3
9·3 lower 9·1, higher 9·5	Hysteria.	2
9·4 lowest 8·1, highest 11·2	Hyperemesis gravidarum.	7
9·5	Jacksonian epilepsy.	1
9·6	Twin pregnancy shortly after delivery.	1
9·8 lowest 9·5, highest 10·1	Incomplete abortion.	3
10·0	Ante-partum haemorrhage.	2
10·0	Pyelitis in labour.	1
10·5	Rheumatoid arthritis.	1
12·5	Exophthalmic goitre.	1

TABLE V — Results of Treatment with Calcium Gluconate (10 c.c. 10 per cent. Solution) in Eclampsia.

Case number.	Method of administration.	Number of fits.	Remarks.
1 (3-gravida)	5 c.c. subcutaneously 5 c.c. intravenously	6	No obvious effect; died undelivered. Liver fatty, with much punctate subcapsular haemorrhage. Lungs oedematous, large recent infarctions. Myocardium fatty and very soft. Brain moderate oedema. Uterus showed retroplacental clot. Placenta very degenerate, with infarctions, both recent and of long standing.
2 (1-gravida)	10 c.c. subcutaneously	15	8 fits after injection before forceps delivery of dead child; 1 fit post-partum. Developed mental symptoms, but ultimately recovered.
3 (5-gravida)	10 c.c. intravenously	7	1 fit after injection. About 7 hours later spontaneous delivery. Slight mental symptoms. Blood-pressure remained high (over 200 mm. Hg.) for some days. 1 month after delivery B.P. 150 mm. Hg. Serum Ca before injection was 8·8 mgm. per 100 c.c.; 15 days later it was 10·2 mgm. per 100 c.c.
4 (1-gravida)	10 c.c. intravenously	10	4 fits before forceps delivery of mature live child, 6 thereafter. Injection given after sixth post-partum fit; no further fits. Uninterrupted recovery. Before injection, serum Ca was 7·9 mgm. per 100 c.c.; 22 days later it was 11·6 mgm. per 100 c.c.
5 (2-gravida)	10 c.c. intravenously	9	6 fits after injection. Os undilated. Death 12 hours after first fit. Undelivered.
6 (1-gravida)	10 c.c. intramuscularly	3	No further fits after injection. Premature live child delivered by Caesarean section. Uninterrupted recovery.
7 (1-gravida)	10 c.c. intramuscularly on 2 occasions	2	1 fit after first injection. Mature live child delivered by forceps. Recovery.
8 (1-gravida)	10 c.c. intramuscularly on 2 occasions	14	8 fits after first injection; none after second. 2 fits just before forceps delivery; 12 fits thereafter. Mental symptoms during puerperium, but complete recovery. Serum Ca when in labour before onset of fits = 9·9 mgm. per 100 c.c. On sixth day of puerperium serum Ca = 9·7 mgm. per 100 c.c.

DISCUSSION.

For the present, no account has been taken of the two forms — diffusible and non-diffusible calcium — as it was considered that the main object was to establish whether there was or was not a definite lowering of the serum calcium due to this toxaemia, eclampsia. Further, it was held that present methods are not sufficiently reliable to warrant the determination of the partition, although work has been attempted in this field by (among others) Bokelmann and Bock (1928) using the method of Rona, Haurowitz and Petow.

The very abrupt increase in calcium retention by the foetus, which was shown by Bar (1907) to occur in the last sixty days of pregnancy, must mean a sudden change in the demands made upon the maternal stores of calcium. The maternal blood contains about 0·5 gm. calcium, and the requirements of the foetus necessitate the supply of approximately 8 gm. calcium during the last month of pregnancy (Theobald, 1930). Unless the pregnant and lactating woman be provided with adequate supplies of calcium, the drain of calcium into the foetus directly and through the milk secretion is liable to be followed by untoward results.

In the present investigation, 82 per cent. of the cases of eclampsia had serum calcium values below 9 mgm. per 100 c.c. As will be seen from the other tables, the lowering of the serum calcium value is not peculiar to eclampsia, but, relative to pre-eclamptic and other toxaemic conditions, the proportion of cases showing a low value is much greater. In addition to the figures shown, twenty normal cases in labour were examined with respect to their serum calcium content: the average value was found to be 9·9 mgm. per 100 c.c. In another

group of twelve normal cases shortly after delivery, the average reading was 9·4 mgm. per 100 c.c.

Attention has already been drawn to the relationship of increased viscosity of the blood and starvation in cases of eclampsia. Various observations have been made in experimental vitamin B deficiency and inanition. The convulsions and, in the most typical cases, the head retraction of pigeons fed on a polished rice diet have been considered the most characteristic symptoms of the vitamin B deficiency, but this state is also obtained by prolonged fasting. Ungar (1926) working on pigeons, assumed a relationship between the convulsions and the blood calcium level, but, on determination of the serum calcium in beri-beri pigeons, there was found to be no alteration. Kon and Drummond (1927) observed a slight increase of the serum calcium in pigeons similarly affected. The opposite view was held by Smith (1927) who stated that "blood calcium determinations on dogs in spastic paralysis from vitamin B deficiency diets ranged from 7·25 to 7·45 mgm. per 100 c.c.: this is near the tetany level". Schelling (1930) investigated this problem on account of the divergence of opinion. Working on dogs deprived of vitamin B (whole complex) and on fasted dogs, he found that, with one exception, where the calcium dropped from 13·6 mgm. to 11·5 mgm. there was no remarkable decrease in the calcium during the vitamin B-free period. No noteworthy change was observed in the proteins or inorganic phosphorus.

Achard and Ornstein (1930) determined certain chemical constituents of the blood serum in twelve patients whose metabolic rate was low — myxoedematous patients, and, among other findings, they reported the serum proteins normal,

while calcium was noticeably diminished. However, the general consensus of opinion is that, during the latter half of pregnancy, there is a definite elevation of the basal metabolic rate, for which the slightly increased activity of the thyreoid gland is at least partially responsible. In those pregnant women in whom the thyreoid remains apparently unaltered in size and where the functional activity of the gland is consequently not increased, albuminuria frequently develops, and this in many instances has been found to disappear with the administration of thyreoid extract.

The parathyreoid glands are closely linked with calcium metabolism. It has been found that in dogs in which partial parathyreoidectomy had been performed, and which had recovered and were leading an apparently healthy life, pregnancy precipitated the development of tetany, the lesion characteristic of parathyreoid insufficiency. Vassale and Generali (1898) working with bitches, produced tetany in the early days of lactation, eighteen months after extirpation of the parathyreoid glands. They suggested that pregnancy and lactation placed an undue strain on the parathyreoid glands.

Adler and Thaler (1906) performed partial parathyreoidectomy in rats and produced tetany thereby during pregnancy. These workers also discovered (1908) that subsequent pregnancies caused the reappearance of tetany and that the symptoms subsided after the birth of the young. This is interesting in view of the fact that, in a large proportion of cases, eclamptic convulsions cease when the uterine contents have been evacuated.

Collip (1925) isolated a potent parathyreoid extract: a potent therapeutic agent was thus available by which the low

serum calcium prevailing in tetany could be raised to normal and all symptoms of tetany caused to disappear.

Lisser, Smith and Shepardson (1927) described a case of very severe tetany occurring immediately after labour: the marked hypocalcaemia which existed was probably produced by the loss of some 1,500 c.c. of blood during labour. The condition was promptly relieved by the administration of parathyreoid extract, and the blood serum calcium returned to normal without having to resort to calcium therapy.

Collip (1926) demonstrated that, in rabbits, death usually follows very rapidly after the production of tetany, and that injections of parathyreoid or even of calcium chloride may be of little avail in saving them. It was his experience that some animals such as dogs and cats are very sensitive to parathyreoid administration, whereas other animals such as rabbits, guinea-pigs and rats are comparatively resistant to the extract.

King (1930) describes a case of tetany complicating pregnancy toxaemia. Here the peculiar feature was the failure of parathyreoid extract to exert any influence on the level of the blood serum calcium. On admission, the mother's blood serum calcium was 6·2 mgm. per 100 c.c. and, immediately after delivery, it was 6·0 mgm. per 100 c.c. King suggests that tetany may be a rare complicating factor in pregnancy toxaemia and that, in such a case as that cited, parathyreoid extract may fail to have any effect in raising the blood serum calcium.

The milk fever of cows presents very similar symptoms to those found to be associated with the lowered calcium content of the blood of parathyreoidectomised animals, and it has been related to eclampsia in the human. Dryerre and Greig (1921)

suggested a possible relationship between milk fever and parathyreoid deficiency, and that, if such did exist, a lowered blood calcium content would probably be found in milk fever. Little and Wright (1925) investigated this suggestion, and showed that the onset of milk fever is accompanied by a greatly reduced concentration of calcium, the severity of the case being paralleled by a proportionately large decrease in calcium concentration. With mild symptoms, reductions of 20 to 30 per cent. were obtained, while with severe symptoms, the fall was as much as 60 per cent. of the normal. These workers suggest that dietetic factors may play an important part in the causation of milk fever. Dryerre and Greig suggested that milk fever was primarily due to relative parathyreoid deficiency, leading to guanidine intoxication of the tissues. However, parathyreoid deficiency is not an invariable accompaniment of tetany. Tetany can be produced by various means, and in such cases there is no evidence that it is primarily the result of guanidine intoxication; rather would it appear to be due to faulty salt balance in the blood or the reduction of the ionised calcium. It is still a moot point whether the tetany resulting from parathyreoid deficiency itself is due to guanidine intoxication or to calcium deficiency, or to some other factor of which these two are merely accompaniments. Little and Wright feel the same difficulty exists with regard to milk fever. They were unable to demonstrate any significant increase in the total acetone bodies of the blood or urine in these cases of milk fever. It is interesting to compare these findings with the observations mentioned on page 42, where it is noted that, in the pre-eclamptic state, there is an abnormally high content of acetone and diacetic acid in the

blood.

King, Bigelow and Pearce (1911) showed that calcium protects the organism against the toxicity of bile pigments, but, at the same time, there is a depletion of the reserve of calcium in the tissues and an increased elimination. An increased amount of guanidine, which is antagonistic to calcium, appears in the blood should liver function be upset by any toxin. They showed that, although relatively large doses of eclamptic blood can be given to pregnant bitches without apparent ill effect, the same dose of guanidine is made much more toxic to dogs if the blood calcium be previously lowered by an injection of sodium oxalate. Guanidine carbonate causes a rapid and prolonged rise in systolic blood pressure in dogs. This observation is suggestive, in as much as elevation of blood pressure is frequently the first indication of toxaemia in the human subject (page 219). These workers further demonstrated that, while sodium and potassium oxalate produce severe degeneration of the liver and kidneys in dogs, and cause them to die with convulsions, the animals may be saved by the intravenous administration of calcium.

Minot and Cutler (1928, 1929) discovered by accident that a low calcium diet rendered dogs more susceptible to carbon tetrachloride poisoning, and this finding led them to make an extensive investigation of the blood chemistry in acute necrosis of the liver. In dogs on a meat diet severe intoxication is caused by carbon tetrachloride, but the addition of calcium salts to such a diet produces a high degree of tolerance to the drug. The relief and protection afforded by calcium seem to depend upon its antagonistic effect on the retained guanidine. Similar results were obtained in a study

of chloroform poisoning in dogs. Their investigation was then carried to liver disease in the human subject, and more especially to eclampsia, where it was found that some cases showed hypoglycaemia and guanidine retention. In these cases prompt symptomatic relief was said to follow the intravenous injection of 10 c.c. of a 10 per cent. solution of calcium gluconate. These workers stated that, in the case of an eclamptic who was semi-conscious and blind, within fifteen minutes of the injection the vision was much improved; within forty minutes the sight was restored and the blood sugar raised towards normal.

In the treatment of milk fever, inflation of the mammary gland has been practised for many years: gaseous inflation or the injection of fluid is known as a specific for milk fever in cattle. Greig (1930) in a study of fifteen cases, found that this procedure brings about a rise in the blood calcium values, this rise being coincident with and bearing a direct relation to the disappearance of the symptoms of the disease. From a further study of such cases, in which he found milk fever invariably to be associated with a very low blood calcium content, Greig suggested acute calcium deficiency as the essential cause of milk fever, this being brought about by failure of the parathyreoid regulating mechanism to replace the calcium which is rapidly transferred to the milk at the onset of free lactation. It has been shown in the sheep that "lambing sickness" or "ewe distemper" is identical in its essential pathology with "milk fever" in the cow.

If this concept be true, it follows that milk fever should be prevented by ensuring a high concentration of calcium in the blood. Prophylaxis by inclusion of calcium in the diet

has been advocated, but, as Greig has pointed out, many cows with milk fever have received an abundance of calcium in their food. The injection of parathyreoid extract, with a view to converting the deposited calcium in bone into an ionised and readily assimilable form, is found in practice to be an inadequate method of treatment. A readily assimilable salt of calcium, such as the gluconate, was advocated by Greig as a practicable measure in the treatment of milk fever. Dairymen who employ the old practice of allowing the udder to remain distended with milk for the seventy-two hours succeeding calving owe the success of their treatment to the fact that it prevents the sudden transference of large quantities of calcium from the blood to the milk.

In cattle, milk fever occurs in a heavy milker and after parturition. In the human subject, on the contrary, eclampsia appears, in the majority of cases, weeks or months before the expected date of delivery. According to Sherman and his co-workers (1920) the daily calcium requirement of an adult is between 0·4 and 1·0 gm. Eclampsia is characterised by a deficiency of calcium in the blood in the majority of cases, but that calcium deficiency may not be due to an absence of calcium from the body. Havoc may be wrought on the teeth by pregnancy due to the demand by the growing foetus for calcium. Hunter (1930) in his Goulstonian Lectures states that certain experimental, radiological and pathological evidence suggests that the spongiosa of bone acts as the store-house of readily available calcium, and that the corticalis is at first spared in the process of calcium mobilisation. Calcium deficiency in the pre-eclamptic and eclamptic states, therefore, is probably due not to an absence of calcium from

the body, but to the incapacity to utilise the calcium which is present and available.

With regard to the treatment of eclampsia by administration of calcium, it is clear from the few cases recorded in this series that a single injection of 10 c.c. of a 10 per cent. solution of calcium gluconate is not sufficient to cause the immediate cessation of fits, even if given intravenously. The persistence of fits after injection might be accounted for by the fact that a certain amount of time must elapse before maximal elevation of the serum calcium can occur. Lieberman (1931) states that the blood calcium figure attains its maximal elevation within an hour after the subcutaneous or intramuscular administration of calcium: he further declares that intravenous calcium therapy is dangerous on account of the risk of sudden intravascular clotting and death. In any case, the production of hypercalcaemia must be guarded against, and caution is necessary in repeating the dose, especially if given by the intravenous route.

In the treatment of pre-eclampsia, Cameron (1932) has reported success with the intravenous administration of calcium and alkali. Equally beneficial results have been secured by the writer, without discomfort to the patient, by means of dietary measures. Milk may be given with advantage. Not only does it provide protein, but it conveys to the body supplies of calcium and other mineral elements of which there is a deficiency in the maternal blood in many instances. As there is no noteworthy increase in the blood urea or non-protein nitrogen in eclampsia or pre-eclamptic toxaemia (pp.36, 50, 244, 245), such easily assimilable protein is of advantage in preventing or ameliorating oedema. Cowell (1932)

showed that the outermost leaves of cabbage are richer sources of calcium than any other common food with the possible exception of cheese, their calcium content in summer being from 20 - 30 times as great as that of the inner leaves. However, these outermost leaves, while preferred by the rabbit, are usually discarded by the human subject. Such green food should figure prominently in the diet of the patient suffering from pre-eclamptic toxaemia. Since the activity of the mammary gland is responsible for a concentration of calcium averaging 42 mgm. per 100 c.c. in human milk and 120 mgm. per 100 c.c. in cow's milk (Bogert and Plass, 1923), it is essential that pregnant and lactating women be provided with a high calcium diet of adequate vitamin content, in order to allow for the drain of calcium into the foetus and especially through the mother's milk.

SUMMARY.

(a) 82 per cent. of the 44 cases of eclampsia investigated showed subnormal serum calcium values — that is, 9 mgm. per 100 c.c. and under.

(b) 59 per cent. of the 17 cases of nephritic and pre-eclamptic toxaemia were associated with a subnormal serum calcium.

(c) 17 per cent. of the 35 cases of normal pregnancy at term, in labour, and shortly after delivery had serum calcium values lower than normal.

(d) 31 other cases, mainly of complicated pregnancy, were examined in respect of their serum calcium level for comparative purposes.

(e) From the cases observed, it is clear that in the doses

given — 10 c.c. of a 10 per cent. solution — calcium gluconate has no abrupt effect on the frequency of the eclamptic fits.

CONCLUSION.

The lowering of the serum calcium in such a large percentage of cases of eclampsia and pre-eclampsia is suggestive. With a lessened concentration, as occurs towards the end of pregnancy, any sudden change or demand on the reserves may prove too much for the maternal organism.

It is not indicated that lowered calcium concentration is necessarily the aetiological factor in eclampsia, but is a sign, just as is the raised serum inorganic sulphur (p. 36). Calcium deficiency is probably not due to an absence of calcium from the body, but to the incapacity to utilise the available supplies. Symptoms which appear in normal pregnancy, due to the increased activity of the organs of internal secretion, may reach a degree which is definitely pathological in an organism less capable of adaptation to the changing demands of the foetal organism. It seems to be a question of supply and demand, of adaptability or failure.

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III. ON THE CALCIUM CONTENT OF THE CEREBRO-SPINAL FLUID IN NORMAL PREGNANCY, ECLAMPSIA AND INFANTILE CONVULSIONS.

INTRODUCTORY NOTE.

It is known that in the central nervous system are generated the stimuli necessary for the various functions and also sundry restraining influences. Loeb (1901) indicated that the stimuli shown in the rhythmic contractions of muscles and glands are dependent on sodium, calcium, potassium and magnesium ions. Calcium ions, which are indispensable for every living thing, have a restraining influence on the activity of the muscles, wherefore, according to Loeb, we owe it to the normal calcium content of the blood that our muscles are not subjected continually to rhythmic contractions.

Meltzer and Auer (1908) found that calcium antagonises abnormal activity in the body, be this abnormal activity exaggerated inhibition or exaggerated excitation.

In view of the fact that calcium ions are believed to play an important part in allaying the irritability of the tissues in which they are contained, and following on the observation that a very large percentage of the cases of eclampsia already investigated showed a subnormal serum calcium value, it was decided to estimate the calcium content of the cerebro-spinal fluid in the hope that variations in concentration might throw some light on the occurrence of convulsions.

Merritt and Bauer (1931) considered the cerebro-spinal fluid calcium content to be a more accurate physiological representation of the diffusible calcium of the serum than the values obtained by the various filtration methods used to determine diffusible calcium. McCance and Watchorn (1931), while mentioning that the cerebro-spinal fluid is generally considered to contain about 5 mgm. of calcium per 100 c.c., quote authorities to the effect that variations are normally from 4·4 - 6·6 mgm. per 100 c.c. They estimated the calcium in the

cerebro-spinal fluid to be, on the average, 54.7 per cent. of that of the serum. These workers (Watchorn and McCance, 1932) state that opinion is still divided as to whether ultra-filtration will wholly explain the calcium in the cerebro-spinal fluid, but, they add, there is no doubt that, when a series is averaged, the cerebro-spinal fluid calcium and the ultra-filtrable calcium lie very close together, and that both tend to rise and fall with the total serum value. They only studied one case of eclampsia, and found it presented no abnormalities. Peters and Van Slyke (1931) state that the cerebro-spinal fluid contains about 5·0 mgm. of calcium per 100 c.c., and that the decrease in calcium of exudates and spinal fluid as compared with serum appears to parallel the protein content. These estimates are borne out by the investigations of Salvesen and Linder (1923), Gollwitzer-Meier (1925), and Schade and his co-workers (1926). Hunter (1931) places the cerebro-spinal fluid calcium level at 5 - 6 mgm. per 100 c.c., and states that it is evident that the calcium in the ultra-filtrates considered as a percentage of the serum calcium is about equal to the cerebro-spinal fluid calcium expressed on the same basis.

METHOD AND SOURCE OF MATERIAL.

The method employed was that of Kramer and Tisdall (1921) as modified by Clark and Collip (1925).

The cerebro-spinal fluids were obtained by lumbar puncture performed in the routine investigation of the cases of eclampsia. Other specimens were secured in a similar manner for diagnostic purposes, or, as in the cases of physiologically uncomplicated pregnancy requiring intervention (Caesarean section, forceps delivery, etc.), opportunity was taken to

carry out the operative procedure under spinal anaesthesia.

RESULTS.

Table I shows the findings in 20 cases of eclampsia. The values obtained in 30 cases of normal pregnancy appear in Table II.

Table III gives the results obtained in various conditions (18 cases), all except one associated with pregnancy.

In Table IV are recorded the figures obtained for the calcium content of the cerebro-spinal fluid in 12 infants having convulsions.

TABLE I — Calcium Content of Cerebro-spinal Fluid in Eclampsia. (20 Cases.)

Case No.	Age.	Gravida.	Type of Eclampsia.	Number of fits.	Mode of delivery.	Child (M.=male. F.=female).	C.S.F. calcium mgm. per 100 c.c.	Result to mother
1	20	1	Post-partum	5	Spontaneous	M., alive, 6 lb.	4·1	Recovery
2	37	2	Ante-partum	6	Instrumental	F., alive, 8 lb.	5·0	"
3	40	6	"	5	Induction, spontaneous	M., dead, 4½ lb.	5·1	"
4	26	1	"	5	Ditto	M., alive, 3 lb.	5·1	"
5	21	3	"	23	Instrumental	F., dead, 5 lb.	5·1	Death
6	15	1	"	4	Spontaneous	F., alive, 7 lb.	5·1	Recovery
7	32	3	"	7	Induction of abortion		5·1	"
8	28	1	"	5	Hydatidiform mole		5·2	"
9	17	1	"	5	Spontaneous	Anencephalic, spina bifida. M., 2 lb.	5·2	"
10	26	1	"	3	Instrumental	M., alive, 4½ lb.	5·3	Death
11	39	5	Post-partum	4	Spontaneous	M., alive.	5·5	Recovery
12	34	4	"	16	"	Alive	5·5	"
13	27	1	Intra-partum	4	Instrumental	F., alive, 7 lb.	5·5	Death
14	27	1	Post-partum	3	Spontaneous	M., alive, 5½ lb.	5·6	Recovery
15	26	1	Ante-partum	10	Instrumental	F., dead, 3 lb.	5·8	Death
16	26	1	Intra-partum	14	"	M., dead, 8 lb.	5·9	"
17	24	1	Ante-partum	None	Undelivered	Dead. Mature.	5·9	"
18	18	1	"	2	Spontaneous	F., dead, 3½ lb.	5·9	Recovery
19	23	1	"	4	Spontaneous	F., alive, 4⅛ lb.	6·0	"
20	22	3	"	2	Abdominal hysterotomy	Foetus 5 months	6·3	"

Average value = 5·4 mgm. per 100 c.c.

TABLE II — Calcium Content of Cerebro-spinal Fluid in Cases of Pregnancy Requiring Instrumental or Other Interference on Account of Disproportion, but otherwise Normal in All Respects (30 Cases).

Number of cases.	Cerebro-spinal fluid calcium mgm. per 100 c.c.
1	4·3
2	4·7
1	4·8
3	4·9
8	5·0
4	5·1
2	5·2
1	5·4
1	5·5
1	5·6
3	5·7
1	5·9
1	6·1
1	6·2
Total 30	Average value = 5·2 mgm. per 100 c.c.

TABLE III — Calcium Content of Cerebro-Spinal Fluid in Various Conditions, All Except One (Case 10) Associated with Pregnancy (18 Cases).

Case Number.	Type of Case.	C.S.F. Calcium mgm. per 100 c.c.
1.	Diagnostic lumbar puncture 7 days after spontaneous delivery.	4·6
2.	Retroverted gravid uterus (2½ months) and ovarian cyst.	4·8
3.	Nephritic toxaemia.	5·0
4.	Nephritic toxaemia.	5·0
5.	Cerebral symptoms 3 days after instrumental delivery.	5·0
6.	Pre-eclamptic toxaemia.	5·0
7.	Normal pregnancy complicated by carcinoma cervicis.	5·1
8.	Pre-eclamptic toxaemia (after delivery).	5·1
9.	Twin pregnancy.	5·1
10.	Uraemic convulsions. (Female, not pregnant.)	5·2
11.	Pre-eclamptic toxaemia.	5·2
12.	Mitral stenosis. 3½ months' pregnancy.	5·2
13.	Pontine haemorrhage.	5·3
14.	Placenta praevia.	5·3
15.	Meningococcal meningitis. (Sent to hospital as post-partum eclampsia.)	5·4
16.	Mycotic aneurism.	5·7
17.	Hydrocephalus.	5·7
18.	Fulminating pneumococcal meningitis. (Sent to hospital as ante-partum eclampsia.)	6·7

Average value = 5·2 mgm. per 100 c.c.

TABLE IV — Calcium Content of Cerebro-spinal Fluid in Infants Not More Than a Few Days Old Having Convulsions (12 Cases). Table Also Shows Immediate Foetal Mortality of 33⅓ per cent.

Case No.	Child.	Mode of delivery.	Age of mother.	Gravida.	Duration of labour.	C.S.F. Calcium mgm. per 100 c.c.	Result.
1.	Male. 8 lb.	Breech. Spontaneous.	49	4	12½ hours	6·0	Dismissed well.
2.	Male. 6¾ lb.	Instrumental.	28	1	61½ hours	6·1	Dismissed well.
3.	Female. 9 lb.	Instrumental.	29	1	28 hours	6·1	Died 3½ days after birth.
4.	Male. 6½ lb.	Instrumental.	24	1	16¼ hours	6·2	Dismissed well.
5.	Male. 8 lb.	Failed forceps before admission. Spontaneous.	33	2	43 hours	6·2	Child died when 8 days old.
6.	Female. 3¾ lb.	Spontaneous.	24	2	28 hours	6·3	Dismissed well.
7.	Male. 4½ lb.	Breech. Spontaneous.	34	3	3¼ hours	6·5	Died 3¼ days after birth.
8.	Male. 6½ lb.	Instrumental.	21	1	72¼ hours	6·8	Dismissed well.
9.	Female. 6¾ lb.	Spontaneous.	31	2	13 hours	6·9	Dismissed well.
10.	Female. 9 lb. Encephalocele.	Caesarean Section (Repeat).	32	3	—	7·0	Dismissed well.
11.	Male. 6½ lb.	Instrumental.	31	1	32¾ hours	7·8	Dismissed well.
12.	Male. 5½ lb.	Twin II. Breech. Spontaneous.	38	8	5 hours	8·7	Died 4 days after birth.

Average value = 6·7 mgm. per 100c.c.

DISCUSSION.

In 20 cases of eclampsia, the lowest recorded value for the cerebro-spinal fluid calcium was 4·1 mgm. per 100 c.c. in a case of the post-partum variety with five fits, while the highest value was 6·3 mgm. per 100 c.c. in a case of the ante-partum variety in which pregnancy had only advanced to the stage of five months. The average figure for the 20 cases was 5·4 mgm. per 100 c.c.

Incidentally, in this group of 20 unselected cases, there were 6 maternal deaths (30 per cent.), while a live child was born in 10 instances (50 per cent.). Furthermore, it is seen that of these 20 cases, taken at random, 14 (70 per cent.) were of the ante-partum variety.

The cerebro-spinal fluid calcium in 30 cases of normal pregnancy ranged from 4·3 to 6·2 mgm. per 100 c.c., giving an average of 5·2 mgm. per 100 c.c.

In a group of 17 cases taken at random, comprising various conditions such as nephritic and pre-eclamptic toxaemia, twin pregnancy, and including a case of uraemia in a non-pregnant woman, the calcium of the cerebro-spinal fluid ranged from 4·6 to 5·7 mgm. per 100 c.c., giving an average of 5·15 mgm. per 100 c.c. This average becomes 5·2 mgm. per 100 c.c. if the eighteenth case, which was an example of fulminating pneumococcal meningitis in association with pregnancy, is included: in this case, the calcium content was abnormally high.

The results in normal and toxaemic pregnancy fall within the physiological limits indicated. Watchorn and McCance (1932), who examined 12 cases of pregnancy, found the ultrafiltrable portion of calcium increased and suggest that,

during pregnancy, a larger amount of calcium is ultra-filtrable than in normal conditions.

As already indicated (p. 8), Bokelmann and Bock (1928) attempted determination of the diffusible calcium. They found that, only at the end of pregnancy is there a noteworthy increase in the concentration of diffusible calcium, whereas a fairly uniform relative increase of the diffusible calcium is noticed during pregnancy and right up to the time of birth. Lower values are found during delivery, while, in the puerperium, there is again an increase to be noted, according to these workers. In a further communication dealing with the calcium concentration in the blood-serum of the umbilical cord, they showed that the total calcium content, as also the absolute concentration of the dialysable portion, is always higher than in the maternal serum, while the relative value of the dialysable part is low. The total calcium and the diffusible calcium in the serum of the umbilical vein as compared with that of the umbilical arteries were found constantly increased: furthermore, the absolute calcium content and the absolute concentration of the diffusible calcium were noted by them to be higher in the umbilical vein than in the blood of the respective mother.

In Table IV are shown the results of estimation of the calcium content of the cerebro-spinal fluid in a dozen infants, a few days old, having convulsions. The maximal and minimal values are 8·7 and 6·0 mgm. per 100 c.c. respectively, with an average of 6·7 mgm. per 100 c.c.

Price (1926), referring to children, gives the calcium of circulating lymph, pleuritic, ascitic and spinal fluid as approximately 40 - 60 per cent. of the blood calcium.

Levinson (1928), in connection with the cerebro-spinal fluid in infants and in children, mentions 4·0 mgm. per cent. as a low cerebro-spinal fluid calcium, 6·3 mgm. per cent. as a high cerebro-spinal fluid calcium, and the normal value as 5·2 mgm. per 100 c.c.

The figures shown in Table IV indicate, therefore, that in these infants having convulsions within a few days after birth, there is a decided elevation of the cerebro-spinal fluid calcium. These results form an interesting comparison with the convulsive state in the adult, viz. eclampsia, in which physiological values are not exceeded.

SUMMARY.

(a) The cerebro-spinal fluid calcium content in 30 cases of normal pregnancy was found to be within physiological limits, the average being 5·2 mgm. per 100 c.c.

(b) 5·2 mgm. per 100 c.c. was the average reading in a group of conditions, all except one associated with pregnancy (18 cases).

(c) Abnormally high values were obtained in a group of 12 infants only a few days old, suffering from convulsions, the average being 6·7 mgm. per 100 c.c.

(d) In 20 cases of eclampsia, physiological limits were not exceeded, the average being 5·4 mgm. per 100 c.c.

(e) The original hypothesis was not substantiated. There was no abnormal variation in the level of the cerebro-spinal fluid in eclampsia which could be connected with the occurrence of convulsions.

CONCLUSION.

It is interesting to contrast the practically identical figures for cerebro-spinal fluid calcium in normal pregnancy and in eclampsia with the subnormal serum calcium in 17 per cent. of cases of normal pregnancy and in 82 per cent. of cases of eclampsia (p. 17).

The constancy of the cerebro-spinal fluid calcium in association with variable diminutions in the calcium content of the serum is noteworthy as indicating that the diminution in the serum calcium level in toxaemic cases is due to a reduction in the non-diffusible calcium.

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IV. ON THE INORGANIC SULPHATE CONTENT OF THE BLOOD IN NORMAL PREGNANCY AND IN ECLAMPSIA.

RARITY OF OBSERVATIONS.

Comparatively few observations have been made on the inorganic sulphate content of human blood, and, from a perusal of the literature, this would appear to be mainly due to the difficulties experienced in the determination of the low concentrations present in the blood. In a multiplicity of investigations on the more common constituents of the blood in eclampsia, inorganic sulphate seems to have been neglected. Hence the writer determined to estimate the inorganic sulphate content of the blood in eclampsia, and, in this part of the work, he had S.L. Tompsett as collaborator.

METHOD.

Reed and Denis (1927) consider that inorganic sulphate is present only in blood-serum, none being contained in the corpuscles. In this investigation the blood-serum has been examined, the method employed being that described by Cuthbertson and Tompsett (1931) in which the normal values vary between 0·8 and 1·6 mgm. S per 100 c.c.

In the cases of eclampsia selected at random, blood-pressure estimations and Esbach readings corresponding to the days on which the tests were made showed wide variations. The highest systolic blood-pressure recorded was 214 mm. Hg. and the lowest 120 mm. Hg., while the Esbach level ranged between 34 and ½ gm. per 1,000 c.c. urine.

Table I shows the inorganic sulphate and non-protein nitrogen values in normal and toxaemic pregnancy, while similar estimations in eclamptic patients appear in Table II.

RESULTS.

TABLE I — Inorganic Sulphur and Non-protein-nitrogen in Control Cases.

Case No.	Age.	Gravida.	Non-protein nitrogen mgm. per 100 c.c. serum.	Inorganic sulphur mgm. S per 100 c.c. serum.	Remarks.
1	26	4	..	0·6	Hyperemesis.
2	38	1	25	0·6	"
3	22	4	..	0·6	"
4	22	5	..	0·3	"
5	28	5	..	0·3	Lactosuria.
6	34	4	25	0·5	Pyelitis.
7	29	1	31	1·3	Normal pregnancy. In labour.
8	20	1	22	1·5	" " " "
9	20	1	18	1·4	" " " "
10	23	1	25	1·3	" " " "
11	19	1	26	1·2	" " " "
12	30	7	22	1·2	" " " "
13	24	2	18	1·2	" " " "
14	38	2	26	1·0	Pyelitis. In labour.
15	26	1	18	0·9	Normal pregnancy. After delivery.
16	21	1	22	1·1	" " " "
17	27	2	28	1·4	" " " "
18	38	10	32	1·3	" " " "
19	18	1	27	1·3	" " " "
20	29	2	24	1·2	Ante-partum haemorrhage.
21	26	1	32	1·8	Pre-eclampsia. Esbach 2%. B.P. 145/100.
22	21	1	28	1·8	Pre-eclampsia. Esbach 2%. B.P. 130/85.
23	21	1	23	1·8	Twin pregnancy. Trace of albumin. Oedema. B.P. 130/85.
24	30	1	26	0·5	Nephritic toxaemia. B.P. 148/100.

TABLE II — Inorganic Sulphur and Non-protein-nitrogen in Eclampsia.

Case No.	Age.	Gravida.	Non-protein nitrogen mgm. per 100 c.c. serum.	Inorganic sulphur mgm. S per 100 c.c. serum.	Remarks.
1	41	5	23	2·2	Ante- and intra-partum. 7 fits.
2	19	1	24	2·0	Post-partum. 1 fit. Twin pregnancy.
3	22	1	30	2·6	Intra-partum. 5 fits. Post-partum, 1 fit.
4	32	2	60	2·9	Intra-partum. 1 fit. Previous eclampsia. Death.
5	19	2	30	2·3	Post-partum. 6 fits. Twin pregnancy.
6	29	3	37	2·8	Ante- and intra-partum. 5 fits.
7	17	1	25	2·8	" " " " 2 fits.
8	30	5	18	2·6	Ante-partum. 5 fits.
9	19	2	48	2·7	" " 6 fits.
10	36	3	46	2·5	" " " " Death.
11	19	1	30	2·3	Post-partum. 1 fit.
12	19	1	18	2·1	Ante-partum. 2 fits.
13	22	1	38	2·5	Ante- and intra-partum. 12 fits. Diabetic.
14	22	1	30	2·1	Ante-partum and intra-partum. 4 fits.
15	21	1	28 32	1·1 3·6	In labour, before onset of fits. Intra-partum. 2 fits. Post-partum, 12. 6th. day puerperium.
16	39	5	50 32	3·6 3·2	Ante-partum. 2 fits. Fourth day of puerperium.

SUMMARY OF FINDINGS.

Previous investigations into the sulphur content of the serum or plasma in disease have been particularly directed towards cases of nephritis with nitrogen retention. It has been shown by Loeb and Benedict (1927), Reed and Denis (1927) and Cuthbertson and Tompsett (1931) that, in cases of nephritis and cardio-renal disease, there is an increased retention of inorganic sulphate coincident with the increased retention of non-protein nitrogen, inorganic sulphate being retained in proportionately greater amount than nitrogen, and this particularly in the lower grades of nitrogen retention.

Although little variation in the non-protein nitrogen was noted in this study of cases of eclampsia, the striking feature was the considerable elevation above the normal of the inorganic sulphate content. This marked elevation was not observed in toxaemias of pregnancy other than eclampsia, although in the pre-eclamptic state, values greater than normal were obtained. In normal pregnancy, the inorganic sulphate level of the blood was within physiological limits.

It is difficult to appreciate why the inorganic sulphate content of the plasma or serum should be raised while the non-protein nitrogen is within normal limits unless it be assumed that, relative to nitrogen, inorganic sulphate is a more difficult substance to excrete. If that assumption be correct, it follows that the retention of inorganic sulphate may be an earlier indication of renal impairment than is afforded by the study of non-protein nitrogen or urea content of the blood. In this connection the kidney is brought prominently before us in the case of eclampsia. Probably the finding of blood non-protein nitrogen within physiological

limits in eclampsia, in conjunction with raised inorganic sulphate, can be explained by the sudden action, of relatively short duration, of some toxin on the renal epithelium.

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V. ON THE KETONE CONTENT OF THE BLOOD IN LABOUR AND PRE-ECLAMPTIC TOXAEMIA.

INTRODUCTORY NOTE.

In the course of an ordinary labour, with the patient on the usual restricted diet, it is frequently noticed that the intensity of the reaction for ketonuria becomes progressively more marked as the time of delivery approaches. Signs of maternal and foetal distress are apparently coincident with an increased ketone content of the urine.

With a view to arriving at a more accurate estimate of the degree of ketosis, the blood of patients in labour was examined with regard to its acetone and diacetic acid content. At the same time, a similar analysis was carried out in a few cases of pre-eclamptic toxaemia, in which a more or less restricted diet, corresponding to that in vogue in the labour ward, is the usual routine method of treatment. These pre-eclamptic cases were women in whom no trace of previous renal damage could be detected, and who were normal prior to the development of the toxaemic manifestations, which were, therefore, primarily due to the pregnant state.

METHOD.

The colorimetric method described by Behre and Benedict (1926) was adopted for the determination of acetone and diacetic acid in the blood. Under normal conditions these seldom exceed 1 mg. per 100 c.c. The results are shown in Tables I and II.

RESULTS.

TABLE I — Non-toxaemic Cases in Labour.

The term "normal" is applied to the cases in which the position was normal and no disproportion existed. Instrumental interference in such a case was determined by maternal or foetal distress. In none of these seven cases was there any sign or symptom of toxaemia.

Case No.	Type	Type of delivery	Blood withdrawn before or after delivery	Acetone and diacetic acid content of blood (mgm. per 100 c.c.)	Duration of 1st and 2nd stages of labour		Child
					hrs.	mins.	
1	Normal	Forceps	8 hrs. before	1·7	31	40	Alive, 8 lb.
2	Occipito-posterior	Spontaneous	35 mins. after	3·2	11	5	Alive, 6½ lb.
3	Occipito-posterior	Spontaneous	Immediately after	2·6	17	30	Alive, 7¼ lb.
4	Normal	Spontaneous	Immediately after	1·7	28	0	Alive, 8½ lb.
5	Normal	Forceps	Immediately after	3·1	21	20	Alive, 6 lb.
6	Twin pregnancy	(a) Spontaneous (b) Forceps	Immediately after	1·1	12	5	Alive, (a) 5¼ lb. (b) 3½ lb.
7	Normal	Forceps	Immediately after	1·7	55	0	Alive, 6¾ lb.

TABLE II — Cases of Pre-eclamptic Toxaemia (Not in Labour).

Case No.	Acetone and diacetic acid content of blood (mgm. per 100 c.c.)	Remarks
1	5·8	Blood withdrawn 45 mins. before Caesarean section. Child: female, alive, 6½ lb.
2	1·6	Blood withdrawn 9½ hrs. prior to spontaneous delivery. Child, male, alive, 6¾ lb. Brisk post-partum haemorrhage.
3	3·7	7 months' pregnancy.
4	1·1	4 months' pregnancy. Abdominal hysterotomy performed.
5	1·6	Almost at term.

DISCUSSION.

Bokelmann and Bock (1926-28) find that during pregnancy the concentration of ketone acids in the blood rises. Schmidt (1928) makes the same claim.

In the present series of cases in labour, all showed an acetone and diacetic acid content of the blood above normal level. With one exception, labour had not been unduly prolonged. The values obtained did not appear to bear a definite relation to the duration of labour, yet it is probable that the more protracted the labour the greater is the tendency for ketosis to occur.

There appears to be an intimate relation between the condition of obstetric shock and the state of ketosis.

Almroth Wright and Colebrook (1918), following up the pioneer work of Crile and Cannon on surgical shock, directed attention to the large output of acid waste products from the body and the provisions by which, despite that, the alkalinity of the blood is maintained. In their discussion of the acidosis of anaesthesia, they laid stress on Cannon's observation that there is risk in inducing upon a "wound-shock acidosis" an "anaesthesia acidosis". Phillips (1931), in a paper on obstetric shock, mentions the following conditions as predisposing to its occurrence: Bodily fatigue from prolonged muscular exertion, cold from exposure, deprivation of food and water, sweating, haemorrhage, anaesthetics, toxaemia of pregnancy, infection, emotion.

Omitting toxaemia and haemorrhage, these factors are present in varying degree in every protracted labour. With the more prolonged labour and its implication of a greater tendency to ketosis, there is the greater likelihood of the occurrence of

obstetric shock. One might reasonably expect that the absorption of histamine is greatest in the protracted labour. As it is in precisely this type of case that instrumental interference under anaesthesia is necessary, the choice of anaesthetic is of great moment. Chloroform and ether, administered for even a short time, are liable to render the degree of acidosis more pronounced and the supervention of obstetric shock more imminent.

McDowall, in the Arris and Gale Lecture (1933), discussing the relation of anaesthetics to deferred shock, states that here the shock is apparently produced chemically by the action of histamine and similar bodies: it seems certain from experimental evidence that ether, and probably other anaesthetics, sometimes make recovery from the histamine bodies impossible when it might have taken place in the absence of the anaesthetic. Ether is believed to produce its depressing effect by dilating blood-vessels and rendering them more permeable: its action is masked at the time of operation by the stimulating nature of the drug. McDowall further points out that spinal anaesthesia does not meet the case, because it interferes with the nerve-control of the vessels and also causes vasodilatation. Nitrous oxide has been shown by Dale not to increase the susceptibility of an animal to histamine shock in the way that ether does.

It is, therefore, obvious that nitrous oxide administered with oxygen is the safest anaesthetic to employ in a woman exhausted after a long labour, as a result of which ketosis of more or less marked degree exists. Local anaesthesia might be employed with advantage in selected cases.

Lévy-Solal (1932) states that, during parturition,

the blood-sugar which gradually rises during the ninth month increases still more rapidly, but after delivery it quickly drops and that, if this fall is unduly rapid, symptoms of shock are produced. He emphasises the importance of prophylaxis by giving sugar to women during labour. Garofalo (1933) observes that a moderate degree of hyperketosis is to be noted during the last three months of pregnancy and during labour; that, during gestation, β-oxybutyric acid in the blood is augmented, but acetone and diacetic acid are maintained at a low level, the latter showing an increase during labour.

Observations such as the foregoing lead one to plead for the more generous treatment of women in labour as regards diet. Man undergoing severe muscular exertion requires and receives adequate nourishment. Woman, at the time of her greatest muscular effort, is denied a bare sufficiency. It is recognised that ordinary meals during labour are impossible, but starvation acidosis should be guarded against by the administration of carbohydrate. This is best done by giving the woman barley sugar to suck.

The five patients suffering from pre-eclamptic toxaemia all had an abnormally high acetone and diacetic acid content of their blood. The extremely limited diet on which such patients are so frequently put does not tend to diminish the ketosis, and still further restrictions may be enforced if the toxaemia, instead of clearing up, becomes more pronounced. Should operative intervention then become necessary, the choice of anaesthetic is of the greatest importance, and, for the reasons already mentioned, nitrous oxide administered with oxygen is undoubtedly the safest.

Garofalo states that the increase of β-oxybutyric

acid was especially well marked in the cases of pregnancy albuminuria and eclampsia examined by him, although he found it impossible to trace a parallelism between the amount present in the blood and the clinical severity of the disease.

With regard to the treatment of pre-eclamptic toxaemia, a plea may be made for more generous diet, particularly in respect of carbohydrate and minerals. Milk may be given with advantage: not only does it provide protein, but it conveys to the body supplies of calcium and other mineral elements of which there is a deficiency in the maternal blood in many instances. This decrease in calcium in the blood towards the end of pregnancy is probably related to the slight decrease in protein which usually occurs. Hence the administration of protein might be of especial value in those cases of pre-eclamptic toxaemia in which oedema is a prominent feature, since the presence of oedema and of albuminuria (frequently massive) with no noteworthy increase in the urea and non-protein nitrogen of the blood is, in non-pregnant cases, generally an indication that protein should be given in adequate amount, as is the régime in the nephrotic types of Bright's Disease. The problem is, however, not so simple, as the blood-pressure in the latter condition is not raised. It has still to be determined what factor or factors are concerned in the raising of the blood-pressure in the pre-eclamptic state, although the work of Anselmino, Hoffmann and Kennedy (1932) would ascribe this and the accompanying phenomena to premature and excessive activity of the posterior lobe of the pituitary gland.

Harding and van Wyck (1930) feel that protein <u>per se</u> could not play a part in the production of eclampsia. Their

words may be quoted. "That a dietary factor exists appears certain. That the dietary factor is protein or even fat is uncertain despite the popularity of the former supposition". In the treatment of pre-eclampsia they accordingly advocated ordinary mixed diets of protein, carbohydrate and fat, provided they were salt-free or salt-poor, since their observations have shown a connection between sodium chloride and convulsions, albuminuria, high blood-pressure, oedema, epigastric pain and vomiting in the toxaemic subject.

Recognising, therefore, the tendency to ketosis in the pre-eclamptic state, carbohydrate especially ought to bulk more largely in the diet than is frequently the case. A useful addition would appear to be milk, not only for the protein it supplies, but on account of its mineral content, particularly calcium. A plea is put forward for the supply of adequate nourishment for the woman suffering from this toxaemia of pregnancy, whether the symptoms be many or few.

It is of interest to note that Anselmino and Hoffmann (1931) have reported the presence of the so-called fat metabolism hormone in extracts of the anterior lobe of the hypophysis. When such an extract was injected into rats or human beings, there occurred an increase in ketosis, which was presumably due to a rise in the metabolism of fat.

Butts, Cutler and Deuel Jr. (1934) have pointed out that the injection of a neutralised alkaline extract of the anterior lobe of the pituitary gland into fasting rats receiving aceto-acetate daily increased the excretion of total acetone bodies. The response obtained was as marked with males as with females and with castrated animals as with normal ones. The injection of similar extracts into fasting rats which were

receiving sodium chloride solution resulted in a marked augmentation of ketonuria. With the extract made from steers, the response was practically quantitative. The daily injection for four days was followed by a continued gradual rise in level of acetonuria, which indicates, according to these workers, that the effect is not due to a flushing out of ketogenic material. They further found that the administration of small amounts of sugar to rats receiving pituitary extracts resulted in a complete suppression of the acetone body excretion. In one experiment they confirmed the high ketonuria of fasting during pregnancy.

Such findings are of supreme interest, indicating as they do the intimate relationship between the anterior lobe of the pituitary and the state of ketosis. During pregnancy pronounced hypertrophy of the anterior lobe occurs, and the increased activity resulting therefrom would, in the light of these experimental findings, account for the development of ketosis, especially if the diet be deficient. Diet, as a rule, tends to be most severely curtailed at the time of labour and in pre-eclamptic toxaemia.

CONCLUSIONS.

1. There does not seem to be any necessity for resorting to routine estimation of the acetone and diacetic acid in the blood of patients in labour, but such an analysis may yield valuable information if the labour be unduly prolonged. It is of importance to recognise the severe muscular effort taking place at this time, and to take measures to prevent the development of acidosis by ensuring that the patient receives adequate although necessarily limited nourishment. Barley sugar sucked regularly throughout the duration of labour is an efficient prophylactic.

2. The information afforded by estimation of the blood-acetone and diacetic acid in cases of toxaemia of pregnancy does not justify its adoption as a routine. The high values obtained, however, would focus attention on the inadequacy of the diet prescribed in many cases of albuminuric toxaemia — so often "fluids only". Even if protein be restricted, a sufficient supply of carbohydrate ought to be ensured. The plea is put forward that, since a noteworthy increase of the blood-urea or non-protein nitrogen levels is not noted in these cases of pre-eclamptic toxaemia, oedema should be prevented or ameliorated by adequate intake of easily assimilable protein, e.g. milk.

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VI. ON THE PLASMA PROTEINS IN NORMAL AND COMPLICATED PREGNANCY.

INTRODUCTORY NOTE.

In the vast number of observations which have been made on the blood in pregnancy, probably few have exhibited such discrepancies as those dealing with the plasma proteins. Plass and Matthew (1926) emphasised this and, while they reported no figures for the toxaemias of pregnancy, they found a definite decrease in the albumin and a slight relative increase in the globulin of the blood in normal pregnancy.

Eufinger (1928) found that, during pregnancy, there was a marked decrease in the stability of the plasma colloids, as tested by the Gerloczy reaction (1922). With his co-worker, Spiegler (1928), he studied the protein composition of the blood during pregnancy, and found that the total protein content of the serum in the same individual is subject to considerable variation, but that, in the last months of pregnancy, a decrease is evident. They further noted a progressive increase in fibrinogen, globulin and euglobulin, while there was a marked decrease in albumin. These observers state that the appearance of a pregnancy albuminuria is not evidence of a renal lesion, but must be understood as the elimination from the blood, by the healthy kidney, of albuminous bodies which have become useless. In another communication (1928) they found the albumin:globulin ratio at term to be $\frac{0{\cdot}81}{1}$, while in eclampsia the ratio is still further reduced. Their view is that the predominating involvement of the liver and kidneys is a secondary manifestation of oedema, brought about by the change in their cell colloids which take up and eliminate the inflow of harmful products.

Prompted especially by the work of Eufinger, the writer set out to determine whether any constant change in the plasma proteins was associated with the various toxaemic

conditions in pregnancy, and particularly to note whether a certain albumin:globulin ratio could be considered as characteristic of a specific toxaemia.

METHOD.

For non-protein nitrogen the method of Folin and Wu (1919) was employed, while for protein nitrogen the methods adopted were those described by Howe (1921) and Wu (1922). By these methods, the following variations are normally found:-

Total nitrogen = 1,000 - 1,300 mgm. per 100 c.c.

Non-protein nitrogen = 20 - 40 mgm. per 100 c.c.

Fibrinogen nitrogen = 50 - 100 mgm. per 100 c.c.

Albumin:Globulin ratio = $\frac{2}{1} - \frac{3}{1}$.

RESULTS.

The analytical findings appear in Tables I - VI. Table I shows the results obtained in cases of normal pregnancy near term, in labour and after delivery. In 17 cases, the non-protein nitrogen varied between 15 and 34 mgm. per 100 c.c., giving an average of 28 mgm. per 100 c.c.

In 16 cases, other findings were noted. The total nitrogen varied between 831 and 1,543 mgm. per 100 c.c., giving an average of 1,094 mgm. per 100 c.c. The fibrinogen nitrogen varied between 27 and 231 mgm. per 100 c.c., giving an average of 122 mgm. per 100 c.c. The combined albumin and globulin nitrogen varied between 744 and 1,496 mgm. per 100 c.c., giving an average of 944 mgm. per 100 c.c.

In these normal cases, wide variations in the albumin:globulin ratio were observed, the lowest noted being

$\frac{1 \cdot 33}{1}$ and the highest $\frac{3 \cdot 28}{1}$.

Table II shows the results obtained in 12 cases of hyperemesis gravidarum.

The total nitrogen varied between 923 and 1,250 mgm. per 100 c.c., the average being 1,142 mgm. per 100 c.c.

The non-protein nitrogen varied between 18 and 49 mgm. per 100 c.c., the average being 32 mgm. per 100 c.c.

The fibrinogen nitrogen ranged between 52 and 338 mgm. per 100 c.c., the average being 154 mgm. per 100 c.c.

The combined albumin and globulin nitrogen varied between 740 and 1,113 mgm. per 100 c.c., the average being 957 mgm. per 100 c.c.

The albumin:globulin ratio varied between $\frac{1 \cdot 23}{1}$ and $\frac{3 \cdot 30}{1}$.

Table III shows the values obtained in 13 cases of pyelitis of pregnancy.

The non-protein nitrogen in this group varied between 20 and 71 mgm. per 100 c.c., the average being 30 mgm. per 100 c.c.

In 12 cases, additional findings were as follows:- The total nitrogen ranged between 890 and 1,276 mgm. per 100 c.c., the average being 1,052 mgm. per 100 c.c.

The fibrinogen nitrogen varied between 63 and 289 mgm. per 100 c.c., giving an average of 170 mgm. per 100 c.c.

The combined albumin and globulin nitrogen varied between 728 and 1,048 mgm. per 100 c.c., giving an average of 884 mgm. per 100 c.c.

The lowest albumin:globulin ratio recorded in this series was $\frac{2 \cdot 26}{1}$ and the highest $\frac{3 \cdot 40}{1}$.

Table IV shows the results in 3 cases of haemorrhage associated with pregnancy. The lowest value for non-protein nitrogen was 18 and the highest 30 mgm. per 100 c.c., the average being 23 mgm. per 100 c.c.

In 2 cases of haemorrhage in the earlier stages of pregnancy, the following observations were made:-

The average total nitrogen was 1,395 mgm. per 100 c.c., the average fibrinogen nitrogen, 227 mgm. per 100 c.c. and the average albumin plus globulin, 1,143 mgm. per 100 c.c.

In a case of threatened abortion at the stage of 8 weeks, the albumin:globulin ratio was $\frac{0 \cdot 61}{1}$, while in a case of threatened miscarriage at the stage of 5 months, the ratio was $\frac{3 \cdot 04}{1}$.

Table V shows the results obtained in 18 cases of albuminuric toxaemia — 6 of the nephritic type and 12 of the primary or pre-eclamptic variety.

In the 6 cases of nephritic toxaemia, the following observations were made:-

The non-protein nitrogen ranged from 28 to 76 mgm. per 100 c.c., giving an average of 43 mgm. per 100 c.c.

The total nitrogen varied between 962 and 1,337 mgm. per 100 c.c., giving an average of 1,080 mgm. per 100 c.c.

The fibrinogen nitrogen varied between 90 and 219 mgm. per 100 c.c., the average being 149 mgm. per 100 c.c.

The combined albumin and globulin nitrogen varied between 822 and 1,105 mgm. per 100 c.c., giving an average of 888 mgm. per 100 c.c.

The lowest albumin:globulin ratio was $\frac{1 \cdot 18}{1}$ and the highest $\frac{3 \cdot 38}{1}$.

In the 12 cases of pre-eclamptic toxaemia, the following were the findings:-

The non-protein nitrogen varied between 26 and 39 mgm. per 100 c.c., the average being 31 mgm. per 100 c.c.

In 10 of the cases, additional results were noted.

The total nitrogen varied between 756 and 1,163 mgm. per 100 c.c., the average being 956 mgm. per 100 c.c.

The fibrinogen nitrogen ranged between 20 and 343 mgm. per 100 c.c., the average being 148 mgm. per 100 c.c.

The combined albumin and globulin nitrogen varied between 637 and 1,068 mgm. per 100 c.c., giving an average of 777 mgm. per 100 c.c.

The lowest albumin:globulin ratio was $\frac{0{\cdot}60}{1}$ and the highest $\frac{3{\cdot}51}{1}$.

Table VI shows the findings in eclampsia.

In 16, the non-protein nitrogen varied between 18 and 69 mgm. per 100 c.c., the average being 36 mgm. per 100 c.c.

Further results were recorded in 3 cases:-

The total nitrogen averaged 1,092 mgm. per 100 c.c., the fibrinogen nitrogen 110 mgm. per 100 c.c. and the combined albumin and globulin 935 mgm. per 100 c.c.

The albumin:globulin ratio in 1 case was $\frac{2{\cdot}38}{1}$, in another $\frac{2{\cdot}10}{1}$ and in another $\frac{1{\cdot}83}{1}$.

Another series of findings in eclampsia is tabulated on page 244.

TABLE I — Cases of Normal Pregnancy near Term, in Labour and after Delivery. (17).

Case No.	Age.	Para.	Non-protein nitrogen. mgm. per 100 c.c.	Total nitrogen. mgm. per 100 c.c.	Fibrinogen nitrogen. mgm. per 100 c.c.	Albumin + Globulin nitrogen. mgm. per 100 c.c.	Albumin / Globulin Ratio.	Remarks.
1	18	1	30	1220	220	970	--	Near term.
2	25	3	19	1543	28	1496	854/642 = 1·33	Near term.
3	29	5	30	969	73	866	--	Near term.
4	29	2	30	1059	35	994	--	Near term.
5	25	3	30	831	57	744	--	Near term.
6	28	1	31	1004	187	786	602/184 = 3·28	Near term.
7	31	3	25	1078	123	930	--	Near term.
8	35	5	29	1012	79	904	--	Near term.
9	36	4	30	1004	118	856	--	Near term.
10	19	2	29	1220	35	1156	--	Near term.
11	30	4	26	1101	105	970	--	Near term.
12	30	4	32	877	27	818	--	Near term.
13	26	1	29	1101	218	854	--	In labour.
14	29	7	30	1121	199	892	--	In labour.
15	20	1	15	1163	216	932	708/224 = 3·16	In labour.
16	21	1	34	1196	231	931	677/254 = 2·67	1½ hours after delivery.
17	30	7	22	--	--	--	--	55 hours after delivery.

TABLE II — Cases of Hyperemesis Gravidarum. (12).

In 13th. case, vomiting was due to the association of gallstones and pregnancy.

Case No.	Age.	Para.	Non-protein nitrogen. mgm. per 100 c.c.	Total nitrogen. mgm. per 100 c.c.	Fibrinogen nitrogen. mgm. per 100 c.c.	Albumin + Globulin nitrogen. mgm. per 100 c.c.	Albumin / Globulin Ratio.	Remarks.
1	32	7	33	1250	338	879	485/394 = 1·23	--
2	28	3	29	1068	197	842	616/226 = 2·72	Chorea gravidarum.
3	28	3	18	1142	161	963	738/224 = 3·30	Abdominal hysterotomy. Death.
4	25	3	42	1152	119	991	681/310 = 2·19	--
5	29	1	35	1116	207	874	614/260 = 2·36	--
6	25	1	49	1163	52	1062	--	Uterus emptied. Death.
7	23	2	30	1226	107	1089	769/320 = 2·40	--
8	25	2	28	1020	128	864	--	Uterus emptied. Recovery.
9	34	3	34	1244	97	1113	781/332 = 2·35	--
10	32	4	30	1179	115	1034	--	Uterus emptied. Recovery.
11	28	5	31	1226	162	1033	736/297 = 2·48	--
12	28	1	28	923	160	740	559/181 = 3·08	--
13	34	11	52	992	136	804	--	Gallstones in association with pregnancy.

TABLE III — Cases of Pyelitis Gravidarum. (13).

Case No.	Age.	Para.	Non-protein nitrogen. mgm. per 100 c.c.	Total nitrogen. mgm. per 100 c.c.	Fibrinogen nitrogen. mgm. per 100 c.c.	Albumin + Globulin nitrogen. mgm. per 100 c.c.	Albumin / Globulin Ratio.	Remarks.
1	24	1	25	- -	- -	- -	- -	- -
2	24	6	32	1000	120	848	- -	- -
3	21	1	25	909	156	728	523/205 = 2·60	General toxaemia. Death.
4	28	3	20	890	125	745	- -	- -
5	24	3	24	1097	210	863	- -	- -
6	38	7	22	1111	289	800	555/245 = 2·26	- -
7	23	1	26	1082	146	910	- -	- -
8	24	4	30	1262	255	977	755/222 = 3·40	- -
9	19	1	32	1196	200	944	- -	- -
10	20	1	20	1073	130	923	- -	- -
11	33	5	29	1276	198	1048	- -	- -
12	28	5	71	954	63	820	- -	Surgical induction of labour. Death.
13	37	3	31	1179	146	1002	- -	Surgical induction of labour. Child still-born. Recovery.

TABLE IV — Cases of Haemorrhage in Pregnancy. (3).

Case No.	Age.	Para.	Non-protein nitrogen. mgm. per 100 c.c.	Total nitrogen. mgm. per 100 c.c.	Fibrinogen nitrogen. mgm. per 100 c.c.	Albumin + Globulin nitrogen. mgm. per 100 c.c.	Albumin / Globulin Ratio.	Remarks.
1	46	8	30	1786	315	1441	546/895 = 0·61	Threatened abortion at stage of 8 weeks.
2	33	10	21	1004	139	844	635/209 = 3·04	Threatened miscarriage at stage of 5 months.
3	24	2	18	- -	- -	- -	- -	Post-partum haemorrhage severe, before expulsion of placenta.

TABLE V — Cases of Nephritic and Pre-eclamptic Toxaemia. (18).

Case No.	Age.	Para.	Non-protein nitrogen. mgm. per 100 c.c.	Total nitrogen. mgm. per 100 c.c.	Fibrinogen nitrogen mgm. per 100 c.c.	Albumin + Globulin nitrogen. mgm. per 100 c.c.	Albumin / Globulin Ratio.	Remarks.
1	26	1	53	1020	111	856	651/205 = 3·17	Nephritic toxaemia.
2	38	13	42	1337	190	1105	788/317 = 2·48	Nephritic toxaemia. Death.
3	38	7	76	1121	219	826	447/379 = 1·18	Nephritic toxaemia.
4	26	3	29	1029	173	827	- -	Nephritic toxaemia.
5	40	4	29	962	111	822	- -	Nephritic toxaemia.
6	29	6	28	1012	90	894	690/204 = 3·38	Nephritic toxaemia.
7	30	4	31	756	86	639	- -	Pre-eclamptic toxaemia.
8	38	9	35	1004	20	949	673/276 = 2·44	Pre-eclamptic toxaemia, 3rd. day of puerperium.
9	21	1	29	865	109	727	- -	Pre-eclamptic toxaemia.
10	31	1	31	988	320	637	496/141 = 3·51	Pre-eclamptic toxaemia.
11	20	1	34	1050	232	784	509/275 = 1·85	Pre-eclamptic toxaemia.
12	21	1	39	760	75	646	444/202 = 2·19	Pre-eclamptic toxaemia.
13	21	1	28	- -	- -	- -	- -	Pre-eclamptic toxaemia.
14	25	1	26	1163	343	794	293/500 = 0·60	Pre-eclamptic toxaemia.
15	24	1	26	996	157	813	612/201 = 3·04	Pre-eclamptic toxaemia.
16	19	1	28	1131	35	1068	- -	Pre-eclamptic toxaemia.
17	18	1	39	850	102	709	497/212 = 2·34	Pre-eclamptic toxaemia.
18	30	1	26	- -	- -	- -	- -	Pre-eclamptic toxaemia.

TABLE VI — Cases of Eclampsia. (16).

Case No.	Age.	Para.	Non-protein nitrogen. mgm. per 100 c.c.	Total nitrogen. mgm. per 100 c.c.	Fibrinogen nitrogen. mgm. per 100 c.c.	Albumin + Globulin nitrogen. mgm. per 100 c.c.	Albumin / Globulin Ratio.	Remarks.
1	27	2	39	1066	150	877	594/283 = 2·10	Ante-partum. 7 fits.
2	34	3	69	1152	51	1032	727/305 = 2·38	Chronic nephritis. Ante-partum. 10 fits.
3	19	1	32	1059	130	897	580/317 = 1·83	Ante-partum. 4 fits.
4	22	1	30	- -	- -	- -	- -	Ante-partum. 5 fits. Post-partum. 1 fit.
5	32	2	60	- -	- -	- -	- -	Chronic nephritis. Previous eclampsia. Ante-partum. 1 fit.
6	19	1	24	- -	- -	- -	- -	Post-partum. 1 fit.
7	29	3	37	- -	- -	- -	- -	Ante-partum. 5 fits.
8	19	2	30	- -	- -	- -	- -	Post-partum. 6 fits. Twins, 2nd. being anencephalic.
9	17	1	25	- -	- -	- -	- -	Ante-partum. 2 fits.
10	30	5	18	- -	- -	- -	- -	Ante-partum. 5 fits.
11	19	2	48	- -	- -	- -	- -	Eclampsia again 2 years later. Death. Post-mortem showed subacute nephritis with recent acute change.
12	36	3	46	- -	- -	- -	- -	Ante-partum. 6 fits. Death.
13	19	1	18	- -	- -	- -	- -	Ante-partum. 1 fit. Post-partum. 1 fit.
14	19	1	30	- -	- -	- -	- -	Post-partum. 1 fit.
15	22	1	38	- -	- -	- -	- -	Ante-partum. 12 fits.
16	22	1	30	- -	- -	- -	- -	Ante-partum. 4 fits.

DISCUSSION.

In their monograph de Wesselow and Wyatt (1924) emphasise that any marked retention of nitrogenous waste-products is exceptional in the eclamptic condition, although the non-protein nitrogen of the blood frequently attains a level corresponding to the upper limit of the normal in the non-gravid.

Lloyd (1926) mentions that the animal globulins exist in two forms — euglobulin, which is insoluble in water, and pseudoglobulin, which is soluble in water. She points out that the biological importance of albumins and globulins in cells appears to lie in their extreme sensitiveness to physical conditions.

Hewitt (1929) contradicts the view that in albuminuria the first stage is liver damage caused by circulation of toxins, followed by the passage of liver proteins into the blood stream and their subsequent leakage through the kidney into the urine. His results suggested that no abnormal liver albumin occurs in the urine of nephrosis, albuminuria of pregnancy and eclampsia, and that the globulin fraction, where liver proteins might occur, is generally very small. In addition, he showed that the passage of some foreign proteins through the kidney for long periods does not appear to cause leakage of serum albumin. Within the limits of experimental error he found the optical rotatory powers of the urinary albumins in nephrosis, albuminuria of pregnancy and eclampsia, identical with that of serum albumin. His view is that, in these diseases, kidney damage occurs, and serum albumin leaks through unchanged: the consequent reduction in serum albumin and the lowering of the osmotic pressure of the blood account for the oedema.

Stander, Eastman, Harrison Jr. and Cadden (1929) observed that normal pregnancy is associated with a reduction in total serum base, which is accompanied by a decrease in serum protein, while severe eclampsia is associated with a true acidosis due to an uncompensated alkali deficit.

With regard to the vomiting of pregnancy, Harding and van Wyck (1929) found that, as the result of partial or complete abstention from food, coupled with the loss of fluid by vomiting, acute anhydraemia is produced with consequent increase in the concentration of serum protein. However, they also found subnormal values for serum protein in such cases, and it must be remembered that varying results may be obtained according to the stage of dehydration at which observations are made.

Eastman (1930), in an investigation of the albumin: globulin ratio of the blood, found the average to be 1·8 for normal non-pregnant women, 1·5 for normal gravidae and 1·2 for eclamptic patients. He noted that the general direction of the changes undergone by the serum proteins during gestation and in toxaemias of pregnancy is toward a decrease in total protein, with a very slight relative increase in the globulin in normal pregnancy and a more marked absolute increase in pre-eclampsia and eclampsia. However, he concludes that a causative rôle in the production of eclampsia cannot be assigned to alterations in the serum proteins.

Regarding the increase of fibrinogen in the blood in normal and toxaemic pregnancy, it is interesting to note that, as Howe (1925) has pointed out, the site of formation of this protein is almost exclusively the liver.

Wiener and Wiener (1930) indicate that, while variations in the plasma protein concentrations of the same

subject are slight, they tend to be greater in the female. In 20 normal adults they found the average total serum protein to be 1,016 mgm. per 100 c.c., the average albumin:globulin ratio 2·7, and the average fibrinogen 280 mgm. per 100 c.c.

Arnold and Fay (1932) believe that eclampsia can be prevented and controlled by properly balancing the water metabolism of the patient. In their opinion, eclampsia is probably a syndrome rather than a disease, and takes its origin from a variety of disturbances which produce a common cerebral action, indicating that no specific aetiological cause can be expected to be responsible for the various clinical manifestations of this condition.

Muntwyler, Way, Binns and Myers (1933) state that the oedema of nephritis is generally accompanied by a lowering of both the plasma protein and the plasma colloid osmotic pressure: with return to normal of the plasma protein, there is a parallel increase in the plasma colloid osmotic pressure.

In severe diabetic acidosis, Peters, Kydd and Eisenman (1933) found that the serum proteins are usually within or above the normal limits, but fall, during recovery, below the normal level.

Rennie (1933) states that there is evidence to show that rise in blood pressure and fall in serum osmotic pressure may be jointly responsible for the development of oedema, and that the level of the serum proteins offers a valuable prognostic index, because, in cases where the fall in serum osmotic pressure is not marked, oedema is a very transient feature. He suggests that defective synthesis of serum protein is the important immediate factor in the reduction of serum osmotic pressure.

SUMMARY.

The average values obtained in this investigation of the plasma proteins are summarised in the following table.

Type of case.	Non-protein nitrogen. mgm. per 100 c.c.	Total nitrogen. mgm. per 100 c.c.	Fibrinogen nitrogen. mgm. per 100 c.c.	Albumin + Globulin nitrogen. mgm. per 100 c.c.	Albumin / Globulin Ratio.
Normal pregnancy	28	1094	122	944	2·61
Hyperemesis	32	1142	154	957	2·46
Pyelitis	30	1052	170	884	2·75
Ante-partum haemorrhage	23	1395	227	1143	1·83
Nephritic toxaemia	43	1080	149	888	2·55
Pre-eclamptic toxaemia	31	956	148	777	2·28
Eclampsia	36	1092	110	935	2·10

CONCLUSIONS.

Wide variations are found in the plasma proteins in both normal and toxaemic pregnancy.

Two noteworthy features are these:-

(a) The average non-protein nitrogen is within normal limits save in the group designated "Nephritic Toxaemia".

(b) In pregnancy, whether physiological or pathological, there is, on the average, a decided elevation of the fibrinogen content of the blood.

However, apart from these observations, in no group of cases is there any constant change which could be associated with any one condition, nor is the albumin:globulin ratio characteristic. It would appear impossible, therefore, to assign a particular albumin:globulin ratio to any specific toxaemia, as has been done by some workers, notably Eufinger

(1928). Such variations as occur should be regarded as secondary phenomena, and not primarily responsible for the development of toxaemic manifestations.

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VII. ON THE CHLORIDE CONTENT OF THE CEREBRO-SPINAL FLUID IN PHYSIOLOGICAL AND PATHOLOGICAL PREGNANCY, AND IN INFANTILE CONVULSIONS.

INTRODUCTORY NOTE.

In view of the intimate relationship of the cerebro-spinal fluid and the cerebral matter, and because oedema of the brain is such a frequent finding in fatal cases of eclampsia, it was thought that estimation of the chloride content of the cerebro-spinal fluid in physiological and pathological pregnancy might yield some helpful information.

METHOD.

The cerebro-spinal fluid was obtained by lumbar puncture, and the chloride content estimated by the method of Van Slyke (1923). The normal range in adults is from 720 - 750 mgm. per 100 c.c., and, according to Stewart and Dunlop (1930), any reading above or below these amounts must be regarded with suspicion.

RESULTS.

The results obtained in physiological and pathological pregnancy appear in Tables I - IV.

Table I shows that, in 28 cases of normal pregnancy, the chloride content varies between 644 and 796 mgm. per 100 c.c., the average being 710 mgm. per 100 c.c. According to the standard set for normal non-pregnant subjects, 75 per cent. of these cases show subnormal values and approximately 21 per cent. are above normal level.

In Table II are shown the results in 14 cases of complicated pregnancy including examples of accidental haemorrhage, placenta praevia, hydramnios, etc. The readings vary between 655 and 865 mgm. per 100 c.c., the average being 728 mgm. per 100 c.c. Thus, in this group, approximately

64 per cent. show subnormal values, while 21 per cent. are above normal level.

The findings in 8 cases of nephritic and pre-eclamptic toxaemia are shown in Table III, in which it is noted that the values range from 690 to 772 mgm. per 100 c.c. with an average of 727 mgm. per 100 c.c. 50 per cent. of these cases show subnormal values, while 25 per cent. are above normal level.

The main clinical facts in 14 cases of eclampsia are correlated with the cerebro-spinal fluid chloride content in Table IV. Here the range is from 632 to 827 mgm. per 100 c.c., the average being 719 mgm. per 100 c.c. Approximately 64 per cent. of these cases show subnormal values, and 21 per cent. are above normal level. It is seen that four of the five deaths in this series occurred in cases with subnormal readings.

TABLE I — Chloride Content of Cerebro-spinal Fluid in Cases of Pregnancy requiring Instrumental or Other Interference on Account of Disproportion, but Otherwise Normal in All Respects. (28 Cases.)

Taking 720 - 750 mgm. per 100 c.c. as the normal range, 75 per cent. of these cases show subnormal values and approximately 21 per cent. are above normal level.

Case No.	Age.	Gravida.	Mode of delivery.	Child. M = Male. F = Female.	NaCl Content of C.S.F. mgm. per 100 c.c.	Remarks.
1	31	5	Caesarean section.	F. Alive. 7 lb.	644	- -
2	40	9	Caesarean section.	F. Alive. 7½ lb.	661	- -
3	33	1	Caesarean section.	M. Alive. 6¼ lb.	661	- -
4	23	1	Breech. Manual.	F. Alive. 8½ lb.	667	- -
5	26	1	Forceps.	F. Alive. 9 lb.	667	- -
6	23	1	Forceps.	M. Alive. 6¼ lb.	679	- -
7	27	1	Forceps.	M. Alive. 7⅞ lb.	679	Forceps applied unsuccessfully thrice before admission.
8	27	1	Forceps.	M. Alive. 7⅛ lb.	690	- -
9	26	3	Caesarean section.	M. Alive. 6½ lb.	690	- -
10	25	3	Caesarean section.	M. Alive. 9 lb.	690	- -
11	19	1	Caesarean section.	F. Alive. 6 lb.	702	- -
12	21	4	Forceps.	M. Alive. 9 lb.	702	- -
13	34	8	Caesarean section.	M. Alive. 5⅞ lb.	702	- -
14	28	2	Caesarean section.	M. Alive. 7 lb.	714	- -
15	28	2	Caesarean section.	M. Alive. 6¾ lb.	714	- -
16	28	1	Forceps.	M. Alive. 7½ lb.	714	- -
17	22	1	Forceps.	F. Alive. 8¾ lb.	714	- -
18	18	1	Forceps.	M. Alive. 7⅛ lb.	714	- -
19	26	2	Caesarean section.	M. Alive. 5¾ lb.	714	- -
20	31	3	Caesarean section.	M. Alive. 9½ lb.	714	- -
21	25	1	Forceps.	F. Alive. 7½ lb.	714	- -
22	45	18	Craniotomy.	F. 11¾ lb.	725	Forceps applied unsuccessfully before admission.
23	27	2	Caesarean section.	F. Alive. 7 lb.	761	- -
24	27	4	Caesarean section.	F. Alive. 7 lb.	761	- -
25	42	1	Caesarean section.	F. Alive. 6½ lb.	761	- -
26	32	2	Forceps.	F. Alive. 7 lb.	766	- -
27	20	1	Forceps.	F. Alive. 7¾ lb.	775	- -
28	25	2	Caesarean section.	M. Alive. 6 lb.	796	- -

Average value = 710 mgm. per 100 c.c.

TABLE II — Chloride Content of Cerebro-spinal Fluid in a Variety of Complications of Pregnancy Necessitating Interference. (14 Cases.)

Taking the normal range as 720 - 750 mgm. per 100 c.c., approximately 64 per cent. of these cases show subnormal values, while 21 per cent. are above normal level.

Case No.	Age.	Gravida.	Type of Complication.	Operative Procedure.	Child. M = Male. F = Female.	NaCl Content of C.S.F. mgm. per 100 c.c.	Remarks.
1	24	2	Flaccid paralysis with loss of reflexes.	Diagnostic lumbar puncture.	-	655	20 weeks' pregnancy. Tests for protein and colloidal gold - negative. Cells normal.
2	34	11	Phthisis.	Caesarean section.	F. Alive. 5¾ lb.	655	- -
3	25	1	Phthisis.	Abdominal hysterotomy.	-	661	22 weeks' pregnancy.
4	28	4	Mitral stenosis.	Abdominal hysterotomy.	-	679	16 weeks' pregnancy.
5	29	1	Phthisis.	Caesarean section.	M. Alive. 8 lb.	690	- -
6	42	11	Accidental haemorrhage.	Abdominal hysterotomy.	Dead.	702	32 weeks' pregnancy. Child dead for some time.
7	27	6	Mitral stenosis.	Abdominal hysterotomy.	-	702	14 weeks' pregnancy.
8	35	5	Accidental haemorrhage. Hydramnios.	(1) Forceps. (2) Breech. Manual.	F. Alive. (1) 7⅛ lb. (2) 6½ lb.	714	Twin pregnancy. Post-partum haemorrhage.
9	38	2	Central placenta praevia.	Caesarean section.	M. Alive. 5¾ lb.	714	- -
10	34	8	Central placenta praevia.	Caesarean section.	F. Alive. 10 lb.	725	- -
11	38	1	Twin pregnancy.	(1) Forceps. (2) Breech. Manual.	(1) 5⅛ lb. (2) 5¼ lb.	737	- -
12	36	7	Mitral stenosis.	Caesarean section.	Alive. 5⅝ lb.	823	- -
13	33	8	Myocarditis. Hysteria.	Abdominal hysterotomy.	-	865	18 weeks' pregnancy.
14	19	1	Disproportion. Hydramnios.	Caesarean section.	F. Alive. 10 lb.	865	- -

Average value = 728 mgm. per 100 c.c.

TABLE III — Chloride Content of Cerebro-spinal Fluid in Nephritic and Pre-eclamptic Toxaemia. (8 Cases.)

Taking 720 - 750 mgm. per 100 c.c. as the normal range, 50 per cent. of these cases show subnormal values, while 25 per cent. are above normal level.

Case No.	Age.	Gravida.	Type of Toxaemia.	Mode of Delivery.	Child. M = Male. F = Female.	NaCl Content of C.S.F. mgm. per 100 c.c.	Remarks.
1	18	1	Pre-eclamptic	Forceps.	F. Alive. 6 5/16 lb.	690	- -
2	24	1	Pre-eclamptic	Forceps.	M. Alive. 9 1/8 lb.	702	- -
3	23	3	Nephritic	Abdominal Hysterotomy.	—	702	Post-partum eclampsia with 1st. pregnancy. 2nd. pregnancy terminated at 7 months with still-birth.
4	34	7	Nephritic	Abdominal Hysterotomy.	F. Alive. 1 5/8 lb. Lived 2 days.	714	Mixed accidental haemorrhage in 5th. pregnancy.
5	25	1	Pre-eclamptic	Caesarean Section.	M. Alive. 7½ lb.	737	Caesarean section (lower segment operation) on account of disproportion. Circumvallate placenta.
6	35	1	Pre-eclamptic	Forceps.	M. Alive. 7 3/4 lb.	737	- -
7	29	2	Nephritic	Forceps.	F. Alive. 6 3/4 lb.	760	Eclampsia in 1st. pregnancy at stage of 8 months.
8	35	1	Nephritic	Complete Miscarriage. Foetus 2 3/4 lb.		772	Arcus senilis in both eyes. On admission, blood pressure 218/130 mm. Hg., and Esbach 11 parts.

Average value = 727 mgm. per 100 c.c.

TABLE IV — Chloride Content of Cerebro-spinal Fluid in Eclampsia. (14 Cases.)

Taking 720 - 750 mgm. per 100 c.c. as the normal range, approximately 64 per cent. of these cases show subnormal values and 21 per cent. are above normal level.

Case No.	Age.	Gravida.	Type of Eclampsia.	Number of Fits.	Mode of Delivery.	Child. M.= Male. F.= Female.	NaCl Content of C.S.F. mgm. per 100 c.c.	Result to Mother.	Remarks.
1	23	2	Intra- and post-partum.	15	Spontaneous.	M. Dead. 5 lb.	632	Recovery.	Previous eclampsia.
2	32	1	Intra-partum.	2	Instrumental.	F. Dead. 6¼ lb.	667	Recovery.	Blood pressure 190/130 mm. Hg. Esbach 15 parts.
3	23	1	Intra- and post-partum.	2	Instrumental.	F. Dead. 7 lb.	679	Death.	Blood prexsure 200/110 mm. Hg. Esbach 26 parts.
4	21	1	Intra-partum.	7	Spontaneous.	M. Alive. 5½ lb.	690	Death.	Blood pressure 194/126 mm. Hg. Esbach 1·5 parts.
5	23	1	Ante-partum.	5	Spontaneous.	F. Alive. 4⅛ lb.	702	Recovery.	Blood pressure 200/165 mm Hg. Esbach 10 parts.
6	38	3	Ante-partum.	5	Spontaneous.	M. Dead. 4½ lb.	702	Recovery.	Blood pressure 220/130 mm. Hg.
7	17	1	Ante-partum.	23	Undelivered. (7 months' pregnant.)		702	Death.	No oedema. Death 12 hours after onset of convulsions.
8	22	1	Ante-partum.	3	Spontaneous.	M. Alive. 3⅛ lb.	702	Recovery.	Blood pressure 196/112 mm. Hg. Esbach 10 parts.
9	25	5	Post-partum.	23	Spontaneous.	M. Alive.	714	Death.	4 previous normal pregnancies.
10	26	1	Ante-partum.	8	Spontaneous.	M. Dead. 4½ lb.	725	Recovery.	Blood pressure 230/168 mm. Hg. Esbach 2 parts.
11	22	3	Ante-partum.	5	Abdominal hysterotomy.		737	Recovery.	4½ months' pregnant.
12	18	1	Ante-partum.	2	Spontaneous.	F. Alive. 5⅛ lb.	786	Recovery.	Blood pressure 150/108 mm. Hg. Esbach Tr.
13	36	6	Ante-partum.	8	Undelivered. (7 months' pregnant.)		796	Death.	Blood pressure 162/104 mm. Hg. Esbach 28 parts.
14	18	1	Ante-partum.	2	Spontaneous.	F. Dead. 3½ lb.	827	Recovery.	Blood pressure 170/115 mm. Hg. Esbach 6 parts.

Average value = 719 mgm. per 100 c.c.

CONCLUSION.

There is no appreciable difference in the cerebro-spinal fluid chloride level in eclampsia and normal pregnancy, but, in both normal and pathological pregnancy, there is a reduction of the chloride percentage in a substantial proportion of cases as compared with the standard in normal non-pregnant subjects. It would appear that the upper and lower limits are extended in pregnancy. It may be that the tendency to sub-normal values in the majority of cases means that there is a larger quantity of chloride in the cerebral matter, and that consequently a very slight upset may suffice to produce oedema of the brain. However, in the cases investigated, the same percentage, viz. 21, was found above normal level in both normal pregnancy and the examples of eclampsia. Hence it would seem permissible to deduce that in the pregnant state, there is a widening of the range of the cerebro-spinal fluid chloride content, the tendency to lower values being emphasised in the majority of cases.

NOTE ON THE CEREBRO-SPINAL FLUID CHLORIDE CONTENT IN INFANTILE CONVULSIONS.

According to Stewart and Dunlop (1930), a somewhat greater physiological variation of the cerebro-spinal fluid chloride may be observed in young children, so that readings between 700 and 760 mgm. per 100 c.c. may be consistent with health. It was thought that it might be interesting to contrast the findings in the eclamptic state with those in the infantile convulsive state.

TABLE V — Chloride Content of Cerebro-spinal Fluid in Infants Not More Than A Few Days Old Having Convulsions. (18 Cases.)

Taking 700 mgm. per 100 c.c. as the lower limit of normality, approximately 78 per cent. of these show subnormal values. None exceeds the upper limit of normality.

Immediate Infant Mortality = 39 per cent.

Case No.	Child. M = Male. F = Female.	Mode of Delivery.	Age of Mother.	Gravida.	Duration of Labour.	NaCl Content of C.S.F. mgm. per 100 c.c.	Remarks.
1	M. 6 lb.	Caesarean section.	23	1	12 hours.	562	Child dismissed well.
2	M. 7¼ lb.	Spontaneous.	30	1	43 hours.	585	Child dismissed well.
3	F. 7¼ lb.	Breech. Manual.	23	1	35⅓ hours.	607	Child died 30 hours after birth.
4	M. 8 lb.	Spontaneous.	32	2	43 hours.	620	Failed forceps before admission. Child lived 8 days.
5	F. 6 lb.	Forceps.	21	1	12¾ hours.	620	Child dismissed well.
6	M. 7¾ lb.	Spontaneous.	27	2	12½ hours.	620	Child dismissed well.
7	M. 8 9/16 lb.	Forceps.	24	1	23½ hours.	632	Forceps applied unsuccessfully before admission. Child dismissed well.
8	M. 7⅛ lb.	Forceps.	24	2	35 hours.	632	Convulsions severe and frequent. Child died 3½ days after birth.
9	F. 6¼ lb.	Spontaneous.	19	2	7¼ hours.	632	Child lived 4 days.
10	F. 6 lb.	Spontaneous.	21	1	6¾ hours.	655	Child dismissed well.
11	M. 7¼ lb.	Breech. Manual.	24	1	11½ hours.	655	Child died 3 days after birth.
12	M. 6¾ lb.	Spontaneous.	24	1	18 hours.	667	Child dismissed well.
13	M. 7½ lb.	Forceps.	23	1	20¾ hours.	679	Child dismissed well.
14	M. 6¾ lb.	Breech. Manual.	26	1	11 hours.	690	Child dismissed well.
15	M. 7⅝ lb.	Spontaneous.	35	3	17½ hours.	702	Child dismissed well.
16	F. 6½ lb.	Breech. Spontaneous.	27	6	20 hours.	714	Child lived 34 hours.
17	M. 8 lb.	Forceps.	24	3	24¾ hours.	725	Child dismissed well.
18	M. 7 lb.	Spontaneous.	20	1	20½ hours.	725	Child lived 6 hours.

Average value = 651 mgm. per 100 c.c.

In Table V there is shown the chloride content of the cerebro-spinal fluid in 18 infants, none of them more than a few days old, having convulsions. Approximately 78 per cent. of these show subnormal values according to the standard laid down, and none exceeds the upper limit of normality. Incidentally, the immediate foetal mortality in this series is 39 per cent.

There is a resemblance between the infantile convulsive state and pregnancy in that both show a reduction in the cerebro-spinal fluid chloride level in a large proportion of cases.

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VIII. ON THE RESULTS OF AN INVESTIGATION OF THE LIQUOR AMNII IN PHYSIOLOGICAL AND PATHOLOGICAL PREGNANCY.

INTRODUCTORY NOTE.

Having examined the calcium content of the blood and cerebro-spinal fluid in cases of normal and toxaemic pregnancy, and decided that, in eclampsia, there is a diminution in the non-diffusible portion in the serum of the majority of cases, attention was next directed to the fluid which is in such intimate contact with the foetus throughout its development *in utero*, namely, the liquor amnii, with the idea that, in the later toxaemias of pregnancy, there might be an abnormal drain of calcium into the liquor amnii.

On consultation of the literature, detailed information regarding the chemical composition of normal liquor amnii was found to be scanty. Williams (1930) mentions the findings of Hoppe-Seiler, published in 1877, which are as follows:-

Water	= 98·48 per cent.
Albuminoid material	= 0·19 per cent.
Soluble inorganic salts	= 0·556 per cent.
Extractives	= 0·8 per cent.
Insoluble organic salts	= 0·024 per cent.

According to Merritt and Bauer (1931) the calcium content of amniotic fluid varies between 5·4 and 8·8 mgm. per 100 c.c., the average being 6·6.

De Lee (1933) states that the chemical analyses of liquor amnii vary considerably. He quotes the figures of one worker (Prochownik) for albumin, fats, inorganic matter, urea and water, and of another (Sandmeyer) for albumin. The latter found 0·22 per cent. of albumin present, comprising serum albumin, globulin and an ovo-vitelline-like substance.

Cantarow, Stuckert and Davis (1933) carried out a comparative study of human amniotic fluid and maternal blood in 36 women during the 7th. - 9th. months of normal pregnancy.

Among other findings, they state that the calcium of the amniotic fluid varied from 3·26 to 7·84 mgm. per 100 c.c., averaging 5·46 mgm. The conclusion of these workers was that amniotic fluid cannot be regarded as a dialysate of maternal blood plasma.

Liquor amnii has recently been studied from other aspects. Dieckmann and Davis (1933) applied the colorimetric dye method (using Congo red) employed in blood volume investigations, to the problem of the quantitative determination of the liquor amnii in the uterus. The dye was found to disappear slowly from the amniotic cavity, there being no appreciable loss in twenty-four hours.

An interesting finding is reported by Castagna (1933) who obtained a positive Zondek-Aschheim reaction after the injection of 3 c.c. of amniotic fluid into immature rats.

In the absence of more detailed information regarding normal liquor amnii, it was not surprising to find only one paper dealing with the chemistry of the fluid in the presence of maternal disease, the author of this communication (Shrewsbury, 1933) lamenting that he had been unable to discover any such reference. Shrewsbury analysed the liquor amnii in 9 cases — 3 of phthisis, 1 of renal insufficiency, 1 of albuminuria of pregnancy, 1 of epilepsy, 1 of puerperal insanity, 1 of mitral stenosis and 1 of pneumonia. In the case of pneumonia, he obtained the liquor amnii from the gravid uterus at autopsy, and in the remaining 8, a subtotal hysterectomy was performed on each of the patients and the fluid withdrawn from the intact uterus as soon as possible after the removal of that organ from the body. In these nine cases, the total protein showed much variation, the chloride

content did not vary much from the normal content of the blood, while the calcium readings were fairly constant at a slightly lower level than the readings for the normal serum calcium.

While the original plan was to study the calcium content of the liquor amnii, the scope of the investigation was extended to include the albumin:globulin ratio, and, finally, attention was concentrated on the calcium and chloride content of the fluid in normal and abnormal pregnancy.

METHOD OF PROCEDURE.

The liquor amnii was obtained in three ways:-

(a) by the usual method for induction of labour, viz. artificial rupture of the membranes by means of a male silver catheter;

(b) in a few cases by the withdrawal of the fluid through the abdominal wall by means of a long needle and syringe;

(c) at Caesarean section or abdominal hysterotomy by withdrawal of the fluid from the amniotic sac, using a syringe and needle.

In all cases, of course, every aseptic precaution was adopted, the amniotic fluid was received into a sterile bottle, and the analysis was proceeded with as soon as possible thereafter.

The analytical methods employed were:-

for calcium, the method of Kramer and Tisdall (1921);

for chloride, the method of Van Slyke (1923);

for albumin and globulin, the method of Hewitt (1927).

ANALYSIS OF RESULTS.

The findings are shown in Tables I - XI.

Table I shows the calcium content of the liquor amnii in various conditions, including toxaemia, accidental haemorrhage and hydramnios. The average for the group was 8·9, the lower and upper limits being respectively 6·3 and 11·3 mgm. per 100 c.c. The lowest values in this series of 8 cases occurred in the examples of nephritic and pre-eclamptic toxaemia, while the highest reading was noted in a case of hydramnios. The suggestion that a low calcium content of the liquor amnii was associated with the later toxaemic manifestations in pregnancy made it desirable that this aspect of the problem should be pursued and that a more detailed investigation should be undertaken.

Table II shows an analysis of the liquor amnii in a group of conditions with respect to its calcium, chloride, albumin and globulin content. The series comprised 10 cases — 2 of normal pregnancy, 2 of accidental haemorrhage, 1 of acute pyelitis, 1 of hydramnios, 2 of nephritic toxaemia, 1 of pre-eclamptic toxaemia and 1 of ante-partum eclampsia. The calcium ranged between 4·3 and 10·4 mgm., giving an average of 7·4 mgm. per 100 c.c. The lowest values occurred in the two cases of nephritic toxaemia and the case of eclampsia. The chloride did not vary much from the normal blood range, the average being 620 mgm. per 100 c.c.; and the lower and upper limits were 550 and 685 mgm. per 100 c.c. respectively. The total protein varied between 0·102 and 0·211 gm. per 100 c.c., the lowest value being obtained in a case of pre-eclamptic toxaemia and the highest in a case of mixed accidental

haemorrhage. The albumin:globulin ratio ranged between 0·20 in a case of hydramnios and 1·15 in a case of mixed accidental haemorrhage, the average ratio being 0·67. It is noteworthy that there was little difference between the total protein and albumin:globulin ratio of Case 1 (normal pregnancy) and Case 10 (eclampsia). In the succeeding tables, only the calcium and chloride findings are charted.

Table III shows the calcium and chloride content of the liquor amnii in 18 cases of normal pregnancy. The calcium value ranged between 6·0 and 11·7 mgm. per 100 c.c., giving an average of 8·3, while the lowest chloride reading was 515 and the highest 673 mgm. per 100 c.c., giving an average of 583.

Table IV gives the calcium and chloride values in the liquor amnii from 3 cases of uncomplicated twin pregnancy — 1 uniovular and 2 binovular. The calcium varied between 8·0 and 9·5 mgm. per 100 c.c., and the chloride between 468 and 597 mgm. per 100 c.c. The average calcium value was 8·7 and the average chloride value 531 mgm. per 100 c.c.

In Table V appear the results of an analysis of the liquor amnii in 7 cases of hydramnios. The calcium ranged between 6·4 and 11·0 mgm. per 100 c.c. and the chloride between 550 and 632 mgm. per 100 c.c. The average calcium content was 8·8 and the average chloride content 588 mgm. per 100 c.c.

Table VI shows the calcium and chloride content of the liquor amnii in 2 cases of pyelitis. The average calcium value was 8·1 and the average chloride value 521 mgm. per 100 c.c.

Table VII gives the values obtained for calcium and chloride in the liquor amnii from 9 cases of ante-partum

haemorrhage. The lowest calcium value was 5·5 and the highest 10·8 mgm. per 100 c.c., giving an average of 9·4. The chloride varied between 445 and 655 mgm. per 100 c.c., giving an average of 610.

Table VIII shows the results of an analysis of the liquor amnii in 7 cases of nephritic toxaemia with respect to its calcium and chloride content. The calcium varied between 5·2 and 9·7 mgm. per 100 c.c., giving an average of 7·3, while the chloride varied between 468 and 597 mgm. per 100 c.c., giving an average of 518.

Table IX gives the calcium and chloride content of the liquor amnii in 17 cases of pre-eclamptic toxaemia. The lowest calcium value recorded was 4·6 and the highest 10·5, giving an average of 7·8 mgm. per 100 c.c. The chloride ranged between 456 and 655, giving an average of 546 mgm. per 100 c.c.

In Table X appear the calcium and chloride values in the liquor amnii from 5 cases of eclampsia. The calcium varied between 7·2 and 10·3 mgm. per 100 c.c., giving an average of 8·8. The chloride varied between 527 and 632 mgm. per 100 c.c., giving an average of 580.

Table XI shows the calcium and chloride content of the liquor amnii obtained at abdominal hysterotomy in 2 cases of hyperemesis gravidarum in which the pregnancy had to be terminated at the 12th. and 16th. week respectively. The average calcium content was 9·0 mgm. per 100 c.c. and the average chloride content 638 mgm. per 100 c.c.

CONCLUSION.

Two facts of note emerge from a study of these findings:-

(a) On the whole, the chloride level remains remarkably constant, within limits not unlike those of the blood chloride.

(b) A glance at Tables III - XI shows that the lowest average calcium occurred in the cases of nephritic and pre-eclamptic toxaemia. In this respect the liquor amnii reflects the blood picture, for, as already emphasised (p. 17) the serum calcium in a large proportion of cases of nephritic and pre-eclamptic toxaemia is subnormal.

TABLE I — Calcium Content of Liquor Amnii in Various Conditions. (8 Cases.)

Case No.	Age.	Gravida.	Condition of Patient.	Child. M = Male F = Female.	Calcium Content of Liquor Amnii, mgm. per 100 c.c.	Remarks.
1	38	7	Nephritic toxaemia.	M. Alive. 4¾ lb.	6·3	- -
2	23	1	Pre-eclamptic toxaemia.	M. Alive. 6 lb.	7·7	- -
3	32	4	Mitral stenosis.	M. Alive. 7 lb.	8·0	- -
4	37	7	Apparent accidental haemorrhage.	M. Alive. 7¾ lb.	8·6	- -
5	22	2	Hydramnios.	M. Alive. 9½ lb.	8·6	90 ounces of liquor amnii drawn off when membranes were ruptured.
6	31	7	Apparent accidental haemorrhage.	F. Dead. 1¾ lb.	10·3	Chronic nephritis.
7	32	8	Apparent accidental haemorrhage.	F. Dead. 3½ lb.	10·3	- -
8	41	4	Hydramnios.	M. Alive. 10 lb.	11·3	- -

Average value = 8·9 mgm. per 100 c.c.

TABLE II — Analysis of the Liquor Amnii in a Group of Conditions with Respect to its Calcium, Chloride, Albumin and Globulin Content. (10 Cases.)

Case No.	Age.	Gravida.	Condition of Patient.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Total Protein. gm. per 100 c.c.	Albumin. gm. per 100 c.c.	Globulin. gm. per 100 c.c.	Albumin: Globulin Ratio.	Remarks.
1	40	5	Normal pregnancy. (36 weeks)	-	10·4	620	0·178	0·065	0·113	0·58	Fluid removed through abdominal wall.
2	28	2	Normal pregnancy.	F. Alive. 6 5/16 lb.	7·6	685	0·122	0·052	0·070	0·74	- -
3	30	5	Mixed accidental haemorrhage.	F. Dead. 6¼ lb.	7·5	608	0·158	0·029	0·129	0·22	- -
4	27	4	Mixed accidental haemorrhage.	M. Dead. 3½ lb.	7·9	643	0·211	0·113	0·098	1·15	- -
5	18	1	Acute pyelitis. (20 weeks)	-	8·6	550	0·178	0·039	0·139	0·28	Abdominal hysterotomy.
6	29	2	Hydramnios.	Twin miscarriage.	8·2	620	0·178	0·030	0·148	0·20	Over 7 pints of fluid collected.
7	47	9	Nephritic toxaemia.	M. Alive. 6 lb.	4·3	649	0·163	0·083	0·080	1·04	Patient very anaemic.
8	27	2	Nephritic toxaemia.	M. Alive. 5 5/8 lb.	5·8	620	0·149	0·076	0·073	1·04	- -
9	19	1	Pre-eclamptic toxaemia.	M. Alive. 7 1/16 lb.	8·0	585	0·102	0·052	0·050	1·04	- -
10	23	1	Ante-partum eclampsia.	M. Alive. 4½ lb.	5·8	620	0·153	0·047	0·106	0·44	Nephritis at age of 14 yrs.

Average calcium value = 7·4 mgm. per 100 c.c.

Average chloride value = 620 mgm. per 100 c.c.

Average albumin: globulin ratio = 0·67.

TABLE III -- Calcium and Chloride Content of Liquor Amnii in Normal Pregnancy. (18 Cases.)

Case No.	Age.	Gravida.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	27	4	F. Alive. 6 13/16 lb.	6·0	515	--
2	37	10	M. Alive. 9 3/4 lb.	6·3	585	--
3	24	1	M. Alive. 6 1/2 lb.	6·6	608	--
4	37	7	M. Alive. 8 lb.	6·6	550	--
5	21	1	F. Alive. 7 1/2 lb.	6·7	597	--
6	23	1	M. Alive. 6 lb.	7·0	550	--
7	25	1	M. Alive. 6 1/2 lb.	7·1	562	--
8	24	1	F. Alive. 7 1/2 lb.	7·3	550	--
9	42	11	F. Alive. 8 lb.	7·8	620	--
10	23	2	M. Alive. 9 lb.	7·9	562	--
11	22	1	F. Dead. 7 3/4 lb.	8·0	550	Meningocele: Anencephalic foetus.
12	32	2	M. Alive. 7 1/2 lb.	8·5	562	--
13	27	6	--	8·8	644	Abdominal hysterotomy on account of mitral stenosis at stage of 14 weeks.
14	30	3	M. Alive. 7 1/4 lb.	9·5	644	--
15	36	2	F. Alive. 7 3/4 lb.	10·8	573	--
16	21	1	F. Alive. 7 5/8 lb.	10·8	503	Caesarean section on account of congenital heart disease. Child showed spinal meningocele.
17	34	2	M. Alive. 8 lb.	11·3	644	--
18	31	2	F. Alive. 7 5/8 lb.	11·7	673	--

Average calcium value = 8·3 } mgm. per 100 c.c.
Average NaCl value = 583 }

TABLE IV — Calcium and Chloride Content of Liquor Amnii in Uncomplicated Twin Pregnancy. (3 Cases.)

Case No.	Age.	Gravida.	Children. M = Male F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	27	1	F. Alive. (1) 5 lb. (2) 5½ lb.	8.0	527	Uniovular Twins. Liquor amnii from 2nd. sac.
2	38	9	Alive. (1) F. 6½ lb. (2) M. 6¾ lb.	8·6	468	Binovular Twins. Liquor amnii from 1st. sac.
3	24	1	F. Alive. (1) 4¾ lb. (2) 5⅛ lb.	9·5	597	Binovular Twins. Liquor amnii from 1st. sac.

Average calcium value = 8·7
Average NaCl value = 531
} mgm. per 100 c.c.

TABLE V — Calcium and Chloride Content of Liquor Amnii in Hydramnios. (7 Cases.)

Case No.	Age.	Gravida.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	43	4	M. 6 lb. Macerated.	6·4	597	Gross oedema of legs.
2	22	1	F. 3¼ lb. Anencephalic.	7·8	632	- -
3	35	1	F. Alive. 8⅛ lb.	8·1	573	Pre-eclamptic toxaemia.
4	28	2	Complete miscarriage. (25 weeks).	8·5	550	2nd. foetus anencephalic with meningocele. 1st. normal. Liquor amnii from 1st. sac.
5	35	5	F. Alive. (1) 7⅞ lb. (2) 6½ lb.	9·5	562	Liquor amnii from 1st. sac.
6	16	2	F. Alive. 8 lb.	10·3	585	- -
7	45	15	M. Dead. 9½ lb.	11·0	620	- -

Average calcium value = 8·8
Average NaCl value = 588
} mgm. per 100 c.c.

TABLE VI — Calcium and Chloride Content of Liquor Amnii in Pyelitis. (2 Cases.)

Case No.	Age.	Gravida.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl mgm. per 100 c.c.	Remarks.
1	27	1	F. Alive. 4½ lb.	7.0	491	Patient emaciated and toxic.
2	27	4	M. Alive. 7 lb.	9.2	550	Post-partum haemorrhage.

Average calcium value = 8.1
Average NaCl value = 521
} mgm. per 100 c.c.

TABLE VII — Calcium and Chloride Content of Liquor Amnii in Ante-partum Haemorrhage. (9 Cases).

Case No.	Age.	Gravida.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	37	9	F. Dead. $2\frac{3}{4}$ lb.	5·5	608	Apparent accidental haemorrhage.
2	28	3	M. Twin miscarriage.	8·1	655	Central placenta praevia. Bin-ovular twins. Liquor amnii from 1st. sac.
3	34	3	F. 5 lb. Macerated.	9·2	632	Velamentous insertion of cord.
4	40	9	F. Dead. $2\frac{1}{2}$ lb.	9·6	655	Mixed accidental haemorrhage.
5	27	4	M. Dead. 5 lb.	10·0	445	Marginal placenta praevia.
6	36	3	M. Alive. 9 lb.	10·2	597	Lateral placenta praevia.
7	34	3	M. Dead. $5\frac{1}{2}$ lb.	10·3	620	Mixed accidental haemorrhage.
8	38	4	F. Dead. $4\frac{1}{4}$ lb.	10·7	644	Mixed accidental haemorrhage.
9	38	10	M. Alive. $8\frac{3}{4}$ lb.	10·8	632	Apparent accidental haemorrhage.

Average calcium value = 9·4 } mgm. per 100 c.c.
Average NaCl value = 610 }

TABLE VIII — Calcium and Chloride Content of Liquor Amnii in Nephritic Toxaemia. (7 Cases.)

Case No.	Age.	Gravida.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	27	4	F. Alive. 5½ lb.	5·2	468	Previous diphtheria. (37 weeks).
2	23	3	—	5·7	515	Abdominal hysterotomy. (22 weeks). Previous diphtheria.
3	39	5	Alive.	6·7	433	- - (36 weeks).
4	35	1	Miscarriage. 2¾ lb.	7·1	597	Previous diphtheria. (24 weeks).
5	37	3	F. Alive. 6¼ lb.	8·0	456	Previous diphtheria. (37 weeks).
6	39	6	M. Alive. 6⅞ lb.	9·0	597	Previous diphtheria. (38 weeks).
7	34	3	F. Alive. 9¼ lb.	9·7	562	Post-maturity.

Average calcium value = 7·3
Average NaCl value = 518
} mgm. per 100 c.c.

TABLE IX -- Calcium and Chloride Content of Liquor Amnii in Pre-eclamptic Toxaemia. (17 Cases.)

Case No.	Age.	Gravida.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	19	1	M. Alive. 6¾ lb.	4·6	515	--
2	15	1	F. Alive. 6¾ lb.	5·1	468	--
3	26	1	F. Alive. 4⅞ lb.	5·4	491	--
4	20	1	M. Alive. (1) 4¾ lb. (2) 5 1/16 lb.	6·4	527	Uniovular twins. Fluid from 1st. sac.
5	23	1	F. Alive. 1½ lb.	6·5	474	Foetus (22 weeks) died later.
6	41	5	F. Alive. 7½ lb.	6·7	503	--
7	34	1	M. Alive. 7 lb.	7·4	597	--
8	34	4	F. Alive. 6⅝ lb.	7·5	608	--
9	34	5	F. Alive. 7⅜ lb.	8·0	550	--
10	37	4	M. Alive. 8¾ lb.	8·1	608	--
11	23	1	F. Alive. 3 15/16 lb.	8·6	597	--
12	41	2	M. Alive. 7 lb.	8·8	607	--
13	36	3	F. Alive. 3⅞ lb.	9·2	550	--
14	39	3	F. Alive. 5½ lb.	9·4	527	--
15	19	1	F. Alive. 6⅛ lb.	10·0	550	--
16	37	1	F. Alive. 9 lb.	10·2	456	--
17	29	2	F. Alive. 8½ lb.	10·5	655	--

Average calcium value = 7·8
Average NaCl value = 546
} mgm. per 100 c.c.

TABLE X — Calcium and Chloride Content of Liquor Amnii in Eclampsia. (5 Cases.)

Case No.	Age.	Gravida.	Type of Eclampsia.	Child. M = Male. F = Female.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	38	3	Ante-partum. (36 weeks.)	M. Dead. 4½ lb.	7·2	527	5 fits. Recovery.
2	34	1	Ante-partum. (20 weeks.)	Macerated foetus.	7·5	573	3 fits. Recovery.
3	28	1	Ante-partum. (36 weeks.)	M. Dead. 4½ lb.	9·3	608	8 fits. Recovery.
4	18	1	Ante-partum. (37 weeks.)	F. Alive. 5⅛ lb.	9·5	562	2 fits. Recovery.
5	22	1	Ante-partum. (28 weeks.)	M. Alive. 3 lb.	10·3	632	3 fits. Recovery.

Average calcium value = 8·8
Average NaCl value = 580
} mgm. per 100 c.c.

TABLE XI — Calcium and Chloride Content of Liquor Amnii in Hyperemesis Gravidarum. (2 Cases.)

Case No.	Age.	Gravida.	Stage of Pregnancy.	Calcium. mgm. per 100 c.c.	NaCl. mgm. per 100 c.c.	Remarks.
1	21	1	16 weeks.	8·4	632	Every possible measure tried for 8½ weeks without success. Steady improvement after abdominal hysterotomy. Liquor amnii yellowish-green, clear — almost like urine.
2	31	1	12 weeks.	9·6	644	Emaciated, jaundiced and practically comatose prior to operation. Steady improvement after abdominal hysterotomy. Liquor amnii yellow, clear — suggestive of urine.

Average calcium value = 9·0
Average NaCl value = 638
} mgm. per 100 c.c.

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IX. ON GESTATION AS THE INITIATOR OF MORBID PROCESSES.

Bronchial Asthma
associated with Pregnancy.

Catalepsy
associated with Pregnancy.

Toxic Neuritis
associated with Pregnancy.

Bibliography.

James (1931) recorded a case of asthma in which the attacks were in abeyance during pregnancy only to recur shortly after delivery. Later in a personal communication to the writer, he stated that in the six most marked cases of asthma in his practice, he had noted the following "associations".

Case.	Association.
1. Male, aet. 31.	Father has paroxysmal tachycardia. Mother had goitre ? toxic adenoma.
2. Female, aet. 31.	The above case in which attacks were in abeyance during pregnancy and recurred shortly after delivery.
3. Male, aet. 30.	Sister had amenorrhoea which responded to the administration of thyreoid extract.
4. Female, aet. 58.	Sister has paroxysmal tachycardia.
5. Female, aet. 6.	A cretin who showed improvement with thyreoid extract.
6. Female, aet. 63.	Daughter had toxic adenoma removed two years ago.

One cannot fail to be impressed by the association of such a complaint as asthma with

(1) paroxysmal tachycardia

and (2) thyreoid conditions.

The most interesting of these six cases is undoubtedly the second, in association with pregnancy, a state in which there is increased activity of all the endocrines.

No disease is benefitted by the pregnant state. Undoubtedly, many women of indifferent health feel better during pregnancy than at any other time, largely due, probably, to the fillip given to their sluggish metabolism by the increased endocrine activity resulting therein, and partly to the satisfaction of the procreative instinct with the

achievement of the gravid state. The phthisical woman, while she experiences an increased sense of well-being during pregnancy, is ultimately in a worse plight than before. Morbid processes in the kidney, for example, are aggravated by the advent of the pregnant state, and the damage tends to become more apparent and to develop at an earlier stage in each successive gestation. Nervous troubles are liable to show exacerbation during pregnancy, while respiratory disturbances, such as bronchitis and asthma, are well known to become more pronounced when the patient is in the gravid condition. What havoc is wrought by pregnancy in the victims of cardio-vascular disease! Anaemia may become progressively more severe with each successive pregnancy, and may ultimately present the characteristic features of the true pernicious type.

Not only may pregnancy be the means of aggravating abnormalities already in existence, but it may frequently initiate morbid processes in the body which ultimately, in a fairly large proportion of cases, lead to chronic lesions. A woman who has emerged apparently scathless from her first three or four pregnancies is often found to present symptoms in succeeding pregnancies as the result of damage to some organ such as the kidney: thus a chronic renal lesion is instituted and this becomes progressively worse with successive gestations. Even normal pregnancies do not seem to be without baneful effect. It would appear as if in the healthy woman, the "limit of tolerance" is reached at the fourth or fifth pregnancy, and that thereafter the cumulative results of the slight damage done by the previous pregnancies become obvious. If this be true of normal pregnancies, it is still more apparent in connection with

toxaemic pregnancy. There is a high incidence of recurrence of toxaemia in succeeding pregnancies shown by the woman who has been the victim of pre-eclampsia or eclampsia. Thus Young (1932) found a recurrence rate of 55·8 per cent. in a series of such cases investigated, while Evans (1933) in a follow-up of 76 albuminuric patients discovered after-effects in two-thirds. Other investigations of this nature have yielded similar results.

The following three cases, recently under observation, are illustrative of gestation as the initiator of morbid processes.

BRONCHIAL ASTHMA ASSOCIATED WITH PREGNANCY.

A woman, aged 32 years, pregnant for the third time, was admitted to the Glasgow Royal Maternity and Women's Hospital on 16th. October 1933, suffering from bronchial asthma. Her only previous illness was measles as a child, and she volunteered the information that she had never been troubled with a cough except when pregnant. The following obstetric history was elicited:-

About midway in the course of her first pregnancy, which terminated spontaneously on 7th. April 1932, the patient began to be troubled with a cough and breathlessness. Three or four days after the birth of the child, these symptoms disappeared.

In November 1932, there occurred an abortion at the stage of two months: during this pregnancy she had a slight cough, but may have caught cold.

However, there was no further complaint of cough until she again became pregnant, the last menstrual period

occurring on 1st. March 1933. The cough and associated dyspnoea appeared one month previous to the date of admission, i.e. when gestation had advanced to the stage of six months. On admission, when the uterus was about seven months' size, it was found that the patient suffered from a dry, hacking cough without sputum. Albuminuria was absent, while the blood-pressure was 136/74 mm. Hg. The respiratory murmur was harsh and its expiratory phase prolonged. Rhonchi were audible throughout the chest. The cardiac sounds were pure and of fair quality. Oedema has never been present. Apart from pregnancy, the patient has had no complaint. Only while in the gravid state has she been troubled with bronchitis and breathlessness.

COMMENTARY.

1. A somewhat unusual complication has here presented itself towards the end of what one might term "the quiescent phase", which usually intervenes between the typical toxaemic manifestations of the early months and those of the latter part of pregnancy.

2. Typical toxaemic manifestations have neither accompanied this complication, nor have they preceded its development.

3. In the intervals between pregnancies, the patient has been perfectly well.

4. Pregnancy is seen as the initiator of these attacks of bronchial asthma.

CATALEPSY ASSOCIATED WITH PREGNANCY.

A woman, aged 25 years, pregnant for the third time, was admitted in labour to the Glasgow Royal Maternity and Women's Hospital on 9th. October 1933. Labour was only of two and three-quarter hours' duration, a healthy, female child, weighing 7¼ lb. being delivered spontaneously. Apart from the fact that the patient's skin and mucous membranes were of rather poor colour, there was nothing of note on physical examination. There was no history of previous illness.

On the second day of the puerperium, while a sample of blood was being withdrawn for examination, it was noticed that the patient had taken a cataleptic seizure. The eyelids were flickering, the pupils dilated, the pulse steady and of good volume, yet she was quite unconscious. Respiration was scarcely perceptible. The limbs could be placed in any position and remained there. At the expiration of about five minutes, she heaved a big sigh, the eyes opened, the pupils contracted, and she sat up in bed, looking about her in a dazed manner. Very soon she was quite rational and could tell that she had had similar "attacks" on previous occasions.

Inquiry elicited the following story:-

The patient's first pregnancy in 1929 ended as an abortion at the stage of six weeks. When three months' pregnant on the second occasion, she began to suffer from attacks similar to that described: these had no relationship to missed-period times: two or three seizures occurred daily thereafter throughout pregnancy. Spontaneous delivery of a healthy, female child, weighing 9½ lb., occurred on 29th. May 1930, after a short labour, and the puerperium was uneventful. The woman did not nurse the child, and, a month after delivery, had her first

menstrual period accompanied by a seizure. From that time onwards, it was a regular occurrence to have two or three seizures daily for the few days preceding the period and during the days of menstruation: only a few seizures took place during the remainder of the month.

Not a month passed without a period and its associated seizures until she again became pregnant (the last menstrual period occurring on 15th. February 1933). During this gestation, while the attacks were not more frequent, their duration was increased, and once more there did not appear to be any relationship to missed-period times.

The patient has never had any warning of an impending seizure beyond a feeling of sickness immediately prior to the sensation of sinking down. There is never time to sit or lie down — she simply falls away — and she has hurt her head on several occasions. On recovery, she experiences a feeling of weakness, and in that way surmises that she has had a seizure. At no time has she bitten her tongue, and there has been no incontinence of urine or of faeces.

COMMENTARY.

1. An unusual complication of the pregnant state presented itself at the commencement of "the quiescent phase".

2. Typical toxaemic manifestations were absent in all the patient's pregnancies.

3. Pregnancy is seen as the instigator of these cataleptic seizures, yet the condition persisted after the expulsion of the uterine contents and became aggravated by the subsequent gestation.

4. The pregnancy initially responsible for the condition resulted in the delivery of a female child.

5. The association of this cataleptic state with the gravid state would have passed unrecorded had not the writer chanced to witness a seizure, whereupon the history was elicited. It is sad to reflect on the knowledge which is unpossessed on account of the faulty and imperfect history vouchsafed by so many patients. Pregnant women are notoriously prone to consider unusual developments as natural accompaniments of their condition, and as such do not even mention them.

TOXIC NEURITIS ASSOCIATED WITH PREGNANCY.

A woman, aged 26 years, pregnant for the fourth time, first came to the ante-natal clinic of the Glasgow Royal Maternity and Women's Hospital on 31st. July 1933, when she was six months' pregnant, complaining of loss of power of the right arm of a week's duration. The loss of power was of sudden onset and, although shooting pains were experienced in the affected limb from time to time, the entire forearm and hand seemed to be useless. The patient was deprived of the normal use of the right arm for exactly one month, that is, from the stage of six to seven months of gestation: from that time, power was restored to the affected limb.

She remained well until she was eight months' pregnant, when she began to be troubled with frontal headaches. A fortnight later, albuminuria was noted (Esbach 1·5 per 1,000), although the blood-pressure was 120/84 mm. Hg. and there was no oedema. At this stage, the muscles of both arms — and of the body generally — were flabby. The radial pulse could

not be detected on the right, nor was there any indication of the presence of an abnormal radial artery: the left radial showed normal pulsation. Rather sluggish supinator and biceps reflexes were obtained on both sides, but the triceps reflex could not be elicited in either arm. There was evidence of an excellent grip with the right hand, and no diminution in power was apparent.

A week after the appearance of albuminuria (which vanished on the second day after admission to hospital) the blood-pressure rose to 140/96 mm. Hg., the left arm always being employed for this purpose. Five days thereafter, spontaneous delivery occurred after a labour of a little over six hours. The child was a healthy male, weighing 9 lb. and the puerperium was uneventful.

This woman would not admit any previous ill health. Throughout the three preceding gestations, she was perfectly well. In none of the four pregnancies had she experienced sickness: even nausea had been conspicuous by its absence. Constipation had not been troublesome, and aperients were not required. A functional murmur was audible at the pulmonic area, but no other abnormality was revealed on examination. There was no enlargement of the thyreoid gland.

COMMENTARY.

1. In the absence of any other aetiological factor, one is constrained to regard the loss of power of the right upper limb as a toxaemic manifestation of pregnancy, and label the case accordingly as toxic neuritis of pregnancy.

2. Toxic neuritis is a rare toxaemic manifestation of the pregnant state; in this instance it occurred towards the end of

"the quiescent phase" in a woman who had previously, in this or in the three preceding gestations, exhibited no toxaemic disturbance.

3. There is added interest in the fact that this rare toxaemic manifestation was succeeded by the more common toxaemic syndrome in the latter part of pregnancy, viz. headache, albuminuria and raised blood pressure, in that order of development.

4. In this case there is the suggestion that three apparently normal pregnancies proved to be the limit of tolerance for the patient, and that these toxaemic manifestations in the fourth constituted the proof thereof, in as much as they represented the cumulative damage of three gestations on which had been superimposed the strain of a fourth.

Munro Kerr (1933) quotes a table showing that, in pregnancies subsequent to the fourth, there is apparent a higher rate of maternal mortality which increases steadily with increasing number of pregnancies thereafter. Observations such as these furnish a very strong argument against permitting women to have an indefinite number of pregnancies.

Berkwitz and Lufkin (1932), in a paper on peripheral neuritis as it occurs in pregnancy, give a review of forty-eight cases from the literature and cite four additional cases.

Alteri (1932), who reviews the condition of toxic neuronitis in gestation and its pathological aspects, comments on its serious nature. He states that, although the complication is rare it is ultimately responsible for a mortality of 25 per cent.; its occurrence in the state of hyperemesis gravidarum calls for the greatest vigilance.

Strauss and McDonald (1933) present evidence which

favours the view that the polyneuritis of pregnancy is a deficiency disease, and may be satisfactorily treated as such. They consider it to be a dietary deficiency disorder similar to beri-beri, and suggest that rational therapy should aim to supply the deficiency which may be especially some portion of the vitamin B complex.

It was Whitfield (1889) who first noted the association of peripheral neuritis with persistent vomiting of pregnancy. In the case just described, the noteworthy feature was the absence of sickness. However, as will be pointed out later (p. 150), there are profound changes in gastric secretion even in normal pregnancy: hence dietary deficiency disorders are not unlikely.

Cravings or longings for unusual articles of diet are well recognised features of some pregnancies, and it is possible that these represent an attempt on the part of the maternal organism to remedy some deficiency in the dietary.

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X. ON THE ASSOCIATION OF PAROXYSMAL TACHYCARDIA WITH PREGNANCY.

Case 1, with commentary and photograph of tracings. (Personal).

Case 2, with commentary and photograph of tracings. (Personal).

Case 3, with commentary. (Personal).

Case 4, personally communicated by B.W.F. Bishop.

Case 5, reported by C. Davis.

Case 6, personally communicated by D.H. Fraser.

Case 7, reported by J.M. Whyte.

Case 8, reported by A. Dumas and H. Pigeaud.

Cases 9 and 10, reported by J. Meyer, J.E. Lackner and S.S. Schochet.

Case 11, reported by D.A. Mitchell and P.W. McKeag.

Concluding Remarks.

Bibliography.

In view of the toll (terrible in many instances) exacted by pregnancy, there is peculiar pleasure in recording cases in which the beneficial effect exercised by the pregnant state is manifested. The category is small, such cases being extremely rare. Those which have come under the notice of the writer are examples of paroxysmal tachycardia. Other cases of paroxysmal tachycardia have been encountered in which the attacks were initiated during pregnancy: these are recorded by way of comparison in as much as scant reference is made in the literature to the association of paroxysmal tachycardia and the gravid condition.

Sir Thomas Lewis (1933), in emphasising the importance of the observation of transient phenomena, singles out the paroxysm of tachycardia as "a very notable example of this kind".

Case 1.

A woman, aged 22 years, pregnant for the first time, was admitted in labour to the Glasgow Royal Maternity and Women's Hospital on the evening of October 30th. 1931. On general examination the only points of note were that the skin was very pale, although the mucous membranes were of fairly good colour, and that there was a supernumerary breast on the left side. The heart sounds were pure and of good quality: there was no oedema. The patient had been a regular attender at the ante-natal dispensary, and, during these months, the progress was uneventful. She would not admit any ill-health, and the only item of interest gleaned from the family history was that her father was classed C3 during the war on account of a weak heart.

At 1.40 a.m. on October 31st. a healthy female mature

child was delivered spontaneously. The puerperium was uneventful until 5 a.m. on November 6th., when the heart suddenly began to beat rapidly. It was impossible to count the pulse at the wrist. The apical rate was ascertained to be 220 per minute. The heart continued beating at this rate until about 5.45 p.m. on November 11th., when the patient saw everything suddenly becoming black; she had a feeling as if the heart stopped for a couple of seconds, and as if something in the praecordial region snapped, whereupon the heart commenced to beat at about half its previous rate. The pulse and apical rate were then found to be 104 per minute. Breast-feeding was discontinued at the onset of the paroxysm.

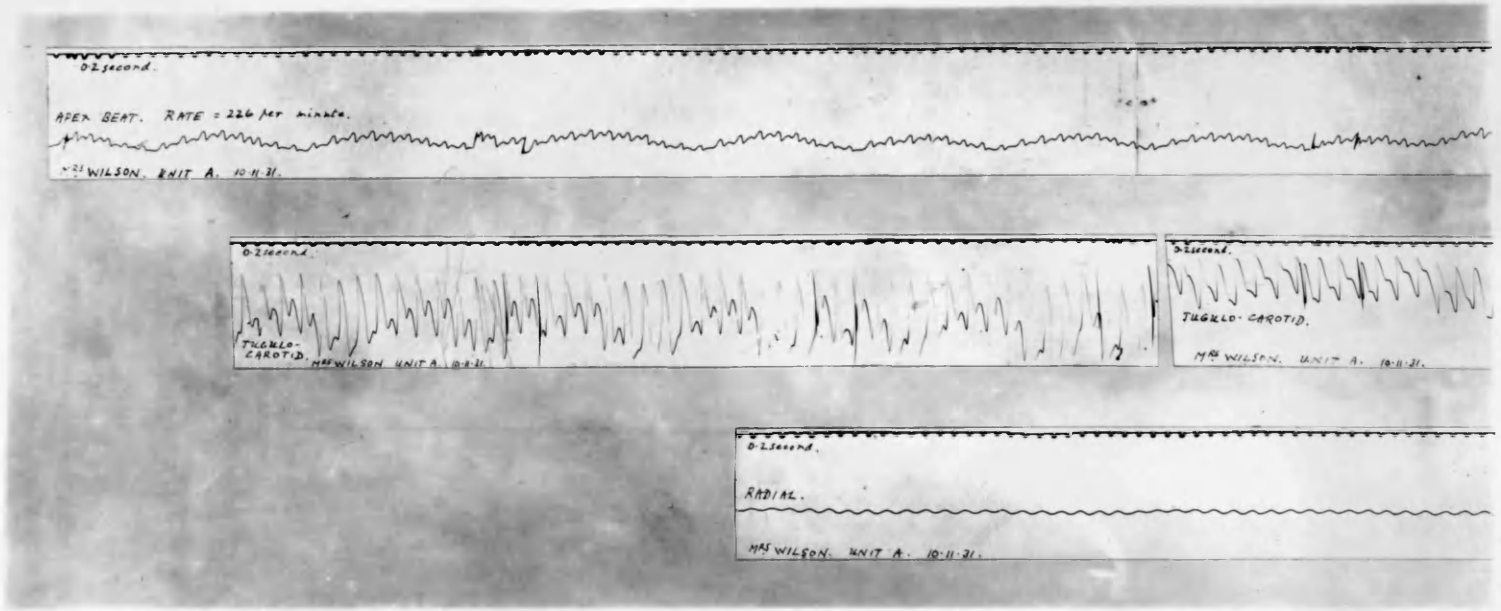
Throughout this attack, lasting just over five and a half days, the cardiac rhythm was perfectly regular; this was confirmed, as was also the rate, by polygraphic tracings. The blood pressure did not exceed 106/78 mm. Hg, and the patient did not suffer from breathlessness. She ate her food normally. In fact, her sole complaint was of the rapid beating of her heart and of drowsiness. The medicinal measures adopted during the attack consisted in the administration of different preparations of digitalis, but mainly the tincture: the importance of the part played by the drug is difficult to assess. Venous thrombosis (without pyrexia) developed in the right leg, necessitating a prolongation of the period of her confinement to bed, but this cleared up satisfactorily. During the interval November 11th. to December 11th. there was no further tachycardia, the pulse being regular in rhythm, and varying in rate between 80 and 90 per minute. The thyreoid appeared to be slightly enlarged. On dismissal exactly six weeks after delivery the pulse rate was running at about 60 per minute, the cardiac dulness was within normal limits, and the

heart sounds were pure and of good quality. The pallor of the patient's skin still remained a noticeable feature, although the mucous membranes were fairly well coloured.

The following history was elicited from the patient. The first bout of "palpitation" occurred when she was six years of age, a few months after an attack of measles. Every two or three months thereafter there was a recurrence of these bouts, during which she was sick, and vomited; while the attack lasted, she would neither eat nor drink, and was very drowsy. Menstruation commenced when she was 10½ years old; the periods have never been regular, occurring as a rule every two to six weeks, and the flow lasting seven to ten days. Quite frequently, but not invariably, a bout of palpitation was associated with the period — often on the third or fourth day of the period. She was married in April 1930, and the date of the last menstrual period was 7th. February, 1931.

There has never been any warning of an impending attack; at no time has she suffered from breathlessness or oedema, and she has never fainted. She has had an occasional frontal headache.

On December 24th. 1931, the fourth day of the first period which occurred after delivery, the patient had a paroxysm which lasted about ten hours. Again she felt drowsy, and, after vomiting, the heart suddenly began beating at its normal rate. When seen on January 10th. 1932, the thyreoid was definitely enlarged, the pallor of the skin was striking, but otherwise physical examination proved negative.



CASE 1. Polygraphic tracings taken during paroxysm lasting over five and a half days.

The patient has been kept under close supervision since dismissal from hospital. A few descriptive notes at intervals are appended.

16th. April 1932. She looks much better generally. The thyreoid is still slightly enlarged. Cardiac dulness is within normal limits, there is no abnormality of rate or rhythm, while the heart sounds are pure and of good quality. Menstruation is reported to have been much more regular than previously, practically four weeks intervening between periods. Slight tachycardial attacks, not lasting for more than fifteen minutes, have occurred, but these have not been associated with menstruation in January, February, March or April.

27th. April 1932. Last night she had facial neuralgia, which is accounted for by a large cavity in a molar tooth. At 3.45 a.m. today the patient was awakened with palpitation, which continued without interruption until 4 p.m. when it suddenly disappeared as she shook hands with the doctor.

14th. May 1932. Today the patient, seen during a period, exhibits slight fulness of the neck. The pulse is running at about 100 per minute, the rhythm being regular. The skin is remarkably pale, but the mucous membranes are of good colour.

30th. July 1932. Three paroxysms of tachycardia have occurred since the patient was seen in May. The June attack took place during menstruation, but the other two were unrelated to periods. The paroxysms lasted for twelve or thirteen hours: none developed during sleep. The last attack passed off without vomiting after she had partaken of a meal. There has been no sickness or breathlessness, although she has felt as if she would like bigger breaths during the attacks. During an

attack she has been unable to raise her arms, not on account of pain, but because of a feeling of heaviness. Headache has only been occasional. Examination shows the cardiac dulness to be within normal limits. The pulse rate is 90 per minute and the rhythm regular. The heart sounds are pure and of good quality. There is no oedema. The mucous membranes are well coloured, but the skin is extremely pale. No enlargement of the thyreoid is detected today. The baby is found to have a left supernumerary nipple like that of the mother. This mark was noticed at birth, and, while suspiciously like a nipple, was not large enough to warrant the diagnosis. Today there is no doubt.

2nd. February 1933. The patient is considerably stouter than formerly. The thyreoid is noticeably enlarged, but there are no evidences of exophthalmic goitre. The skin is still deathly white. No abnormality of cardiac rhythm or rate is detected, while the heart sounds are pure and of good quality. Tachycardial paroxysms have been of frequent occurrence.

12th. October 1933. There has been no attack of tachycardia since April 1933, in spite of the fact that the patient has had more work to do in connection with removal to another house. She volunteers the information that she has felt better with the greater expenditure of energy. Menstruation has occurred every four weeks, the flow lasting for three or four days and some discomfort being experienced on the first and second days. She complains of being more irritable than formerly. Headache in the frontal and occipital regions has been experienced, but astigmatism probably accounts for this, and a change of glasses is indicated. Oedema has not been present. The cardiac rhythm is regular, the rate about 88 per minute, and the sounds pure and of good quality with the exception of the pulmonic area

where a soft, blowing, systolic murmur is audible. The patient has not been sleeping well but blames domestic troubles for this. The skin is somewhat less pale and the mucous membranes are well coloured. She is much stouter, old clothes do not fit, and she is told in shops, to her disgust, that an outsize will be necessary. She has heard people remark on her plumpness. The same size of shoe is still worn, and there is no suggestion of abnormal bony growth. Slight enlargement of the thyreoid is obvious. Apart from pregnancy, the patient has never been free from paroxysms for such a lengthy period, and feels in better health generally than for some years.

The child looks pale but the mucous membranes are of good colour. The left supernumerary nipple is well marked. The cardiac rhythm is regular, while the sounds are pure and of good quality. The mother states that the child has always had cold hands and feet.

14th. October 1933. While asleep in the afternoon, she was awakened by a paroxysm which lasted for half an hour, during which she felt her arms and legs powerless, and had a sensation as if her heart were about to burst. The attack passed off abruptly after she had made herself sick. She was menstruating at the time.

27th. October 1933. The X-ray examination of the sella turcica by Dr. A. Bruce MacLean is reported on as follows:- 'There is no material alteration in the sella turcica, but the sella is bridged over with bone.'

6th. September 1934. There has been no attack of tachycardia save one since 14th. October 1933, although the patient has frequently experienced an indescribable "fluttering" or

"whirring" sensation as if a paroxysm were about to commence. Last Christmas, when sitting on the edge of the bath, she suddenly found everything before her eyes become black and fell back into the bath: this is the only occasion on which she has lost control of herself. The periods are regular, but associated with pain. Headaches are less frequent and severe.

The patient is very much more obese than formerly. Whereas her weight just before the birth of the child never exceeded 9½ stones, it is now 13½ stones. Slight oedema is detected in the right tibial region: this leg is more easily tired than the other — although last week she went for a walk of fourteen miles, probably with the idea that some reduction in weight might be secured thereby. The thyreoid is enlarged and the patient states that she notices increased swelling in this region from time to time.

The cardiac rate is 86 per minute, the rhythm is regular and the sounds are pure and of good quality. The colour of her skin is better than it has ever been, the cheeks being quite pink.

She has never felt in better health than at present, and seems to possess more energy than formerly. All that worries her is that bigger shoes and an outsize in clothes are necessary on account of her obesity.

Commentary.

1. The outstanding feature of this case of paroxysmal tachycardia is that, throughout the entire period of pregnancy, not a single attack occurred, whereas on the seventh day of the puerperium a severe paroxysm manifested itself. The last menstrual period and the first after delivery were each

associated with a paroxysm.

One cannot fail to be impressed with the absence of attacks during pregnancy, when many organs are over-taxed. Endocrine activity, known to be so pronounced in pregnancy, must be concerned with the abeyance of these paroxysms throughout gestation, and it is suggested that, with the waning of this activity shortly after delivery, the control over the paroxysms was lost.

2. Labour was not prolonged, the patient was not distressed in any way and delivery was spontaneous. The child was a female.

3. Both mother and child presented a left supernumerary breast. The child has suffered from coldness of the extremities.

4. The attack described, which commenced on the seventh day of the puerperium and lasted for more than five and a half days, far surpassed in duration her previous record which was thirty-six hours.

5. The cardiac rate over that period of over five and a half days was consistently sustained at 220 per minute.

6. No cardiac lesion was noted, but there was definite enlargement of the thyreoid gland.

7. The abrupt onset and termination of the paroxysm were significant.

8. The medicinal measures adopted during the paroxysm were apparently valueless.

9. Venous thrombosis developed in the right leg.

10. The patient was a primipara. It would be interesting to observe whether a subsequent pregnancy would exert a similar influence in abolishing the tachycardial paroxysms during the period of gestation. However, the lady concerned has decided views on this subject, and refuses to entertain the idea of an addition to the family.

11. Had not the patient chanced to have a paroxysm before the tenth day of the puerperium (ten days being the usual period of residence in hospital for normal cases) the history would not have been elicited, and the opportunity of making an interesting record would have been lost.

Case 2.

The following are the particulars of a case of paroxysmal tachycardia presenting a direct contrast to that first mentioned:-

The patient, aged 30 years, pregnant for the seventh time, was admitted to the ante-natal wards of the Glasgow Royal Maternity and Women's Hospital on October 1st. 1932, having been sent from the outdoor department on account of her anaemic condition. The skin was pale, the mucous membranes of poor colour, and examination of the blood confirmed the diagnosis of secondary anaemia. Of previous illnesses she had had none, with the exception of measles and whooping-cough in childhood. The Wassermann reaction was negative and the blood pressure within normal limits. Percussion of superficial cardiac dulness revealed the right border at mid-sternum. The first sound at the apex was almost entirely replaced by a soft, blowing murmur,

conducted to the axilla, while a short systolic murmur was audible at the other areas. There was no oedema, and no thyreoid enlargement could be detected.

The following is the patient's obstetric history:- First Pregnancy, 1921: uneventful, spontaneous delivery at term. Second Pregnancy, 1924: uneventful, spontaneous delivery at term. Third Pregnancy, 1926: uneventful, spontaneous delivery at term. Fourth Pregnancy, 1927: one day, when six months' pregnant, she dealt with a big wash in a public wash-house. On finishing she came home, climbed two flights of stairs without difficulty, and sat down. Just at that moment she experienced a tight feeling across her chest. This lasted for two or three seconds, and was immediately relieved with the onset of a bout of palpitation. This initial attack lasted for about half an hour. Similar attacks occurred on two occasions before the birth of the child. The delivery was spontaneous, following an easy labour of two hours' duration (June 16th. 1927).

No further attacks were experienced until she was once more eight months' pregnant (fifth pregnancy). During a stormy passage from Uist she had the tight sensation across the chest, followed by a bout of palpitation, which lasted for an hour and relieved her discomfort at its onset. No other attack occurred during this pregnancy, which at term ended in spontaneous delivery after an easy labour lasting two hours (October 17th. 1929). There were no attacks thereafter until she became pregnant again (sixth pregnancy). She aborted at three months, having had in that period three or four bouts of palpitation, each lasting for about an hour (October 15th. 1931).

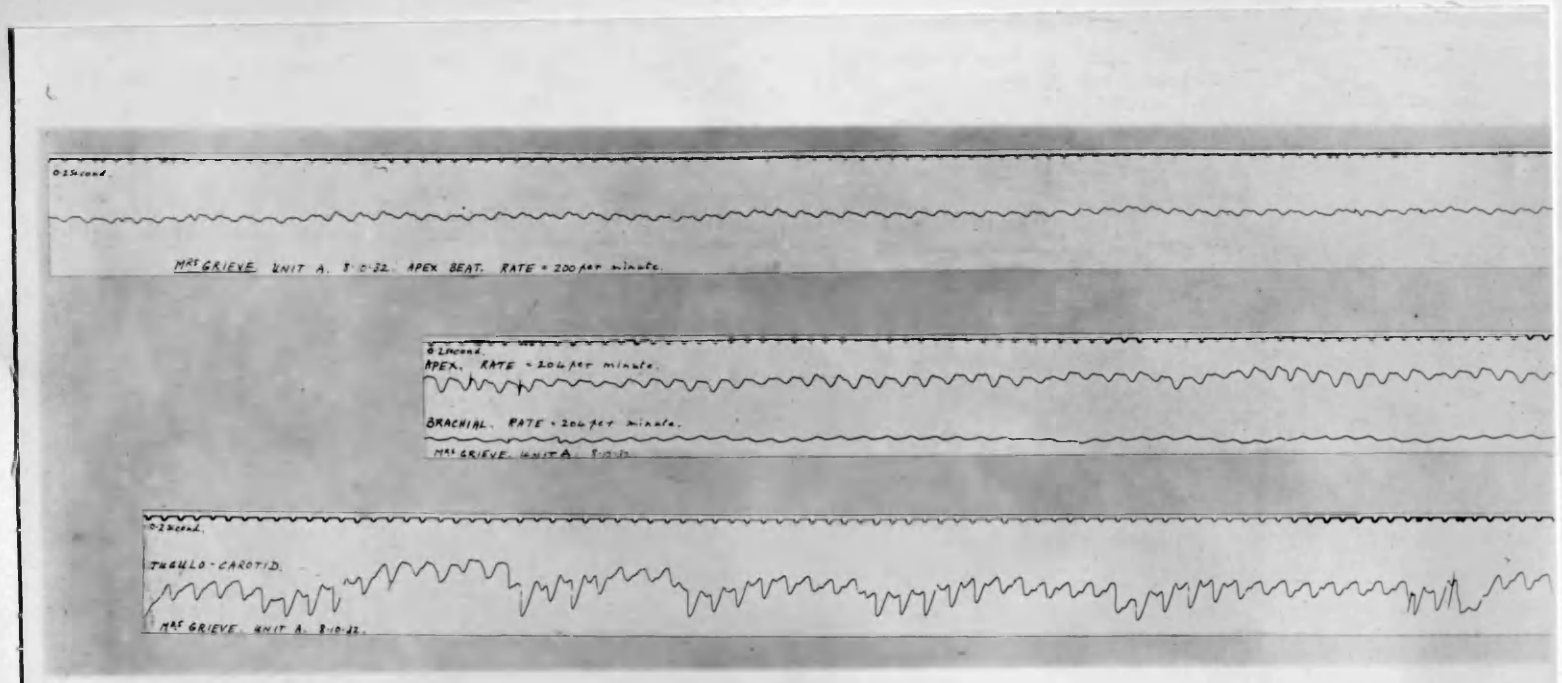
During the seventh pregnancy she had several attacks. They began when she was five months' pregnant. A fortnight

before admission she had the longest attack in her experience, lasting for twelve hours. A week after admission (October 8th. 1932), at 7.45 a.m. she suddenly complained of palpitation. The pulse at the wrist was uncountable, but the apical rate was ascertained to be 200 per minute. This rate remained practically constant throughout the attack, which was of about thirteen hours' duration and more protracted than any hitherto. During this time the rhythm was perfectly regular, and the patient, apart from slight breathlessness, was undisturbed, eating her food normally. Polygraphic tracings confirmed the regularity of the rhythm and the rate (200 - 204 per minute), records being taken of the apical, jugulo-carotid and brachial pulsations: typical portions of these are shown. Fifty minutes after the administration hypodermically of 1/10 of a grain of digitalone the radial pulse was running at 96 per minute. On October 21st. 1932, a bout of tachycardia occurred while the patient was in the act of settling down for the afternoon rest. The apical rate was determined to be 200 per minute. Twenty minutes after the hypodermic injection of 1/10 of a grain of digitalone the tachycardia ceased and the normal rate was restored. With the usual preliminary tight sensation in the chest there was another bout of tachycardia on November 1st. 1932. The attack ceased as suddenly as it had begun, without the administration of any drug, the duration being thirty-five minutes. Spontaneous delivery occurred on November 4th. The child weighed $8\frac{3}{4}$ lb. During the labour, which lasted for four hours, the patient was not distressed in any way, and had no tachycardia. The puerperium was uneventful, and she was dismissed on November 13th.

During all her attacks the patient has felt a little

breathless, but has never vomited. She usually lay down at the beginning of an attack, then got up and walked about. She used to drink cold water, but the attack finished as suddenly as it had begun. There has never been oedema, and at no time has anything suggesting thyreoid enlargement been noticed. The onset and termination of an attack have always been heralded by the sensation of constriction in the chest.

The patient was advised to have sterilisation performed, but declined.



CASE 2. Polygraphic tracings taken during paroxysm of about thirteen hours' duration.

Later Notes.

13th. October 1933. Today she feels well and looks better. The skin is not so pale and the mucous membranes are of fair colour. The pulse rate is 72 per minute and the rhythm regular. There is no evidence of thyreoid enlargement.

Menstruation occurred normally in January, February, March, April and May 1933. Five weeks after delivery, she began to have paroxysms of tachycardia lasting for one or two hours. Never before has she had attacks apart from pregnancy. Furthermore, these have had no relationship to menstrual periods. The most lengthy paroxysm of her career occurred about the end of March 1933: it began at midnight and continued without interruption until 3 o'clock on the following afternoon, when it passed off as suddenly as it had commenced.

The last menstrual period was on 26th. May 1933, and, when about three months' pregnant, she aborted, as the result, she thinks, of falling off steps.

The lengthy paroxysm in March was the last. On the third day after its cessation she journeyed to Carfin, drank the water there, and ascribes her cure to the local H_2O.

Commentary.

The outstanding features of this case of paroxysmal tachycardia are these:-

1. Three uneventful pregnancies prove to have been the limit of tolerance for the patient. The fourth pregnancy, at the end of the sixth month, that is, towards the end of the "quiescent phase" was marked by the initiation of tachycardial paroxysms.

2. It is especially noteworthy that, during the fifth, sixth and seventh pregnancies, paroxysms of tachycardia recurred, and that in the intervals between these (fourth - fifth, fifth - sixth, sixth - seventh) there were no attacks.

3. After the seventh pregnancy a further limit seems to have been reached, and paroxysms now occur apart from gestation. Unlike Case I, these paroxysms are entirely unrelated to menstrual periods.

4. The most severe paroxysm has been of fifteen hours' duration: this occurred in the non-pregnant state.

5. The cardiac rate during the paroxysms observed in hospital was consistently sustained at 200 per minute.

6. Spontaneous delivery has occurred in all the pregnancies. Labour has been short, and has apparently caused little or no distress to the patient. A paroxysm of tachycardia has never taken place during labour.

7. The pregnancy responsible for the initiation of these tachycardial paroxysms resulted in the delivery of a female child.

8. An obvious cardiac lesion is present in this patient.

9. No enlargement of the thyreoid has ever been detected.

10. The abrupt onset and termination of the paroxysms are noteworthy.

11. Digitalis on two occasions seemed to be efficacious in terminating the attack; however, on another occasion, without the exhibition of this or any remedy, the paroxysm ceased as

suddenly as it had begun. In this there is an illustration of the difficulty of assessing the value of a drug in such a condition.

12. Briefly, the case would be regarded as one in which the heart, although slightly damaged, was equal to the demands made upon it in the course of the woman's daily life — and even to the increased demands of three pregnancies. However, the strain of pregnancy on each occasion since the fourth gestation has proved too much for an already over-taxed organ. With regard to the endocrine system, there are two possibilities:-

(a) Either endocrine activity, although increased during gestation, has proved inadequate;

or (b) a disturbed balance in the endocrine system may have been responsible for the occurrence of attacks during pregnancy. Successive pregnancies, associated with tachycardial paroxysms, have so upset the endocrine balance that attacks have occurred since the seventh apart from the gravid state.

13. This is yet another case which might easily have passed unnoticed, since the history was only elicited following observation of a paroxysm.

Case 3.

A woman, aged 29 years, pregnant for the fifth time, was admitted in labour to the Glasgow Royal Maternity and Women's Hospital on 4th. February 1934. Spontaneous delivery of a healthy, female child weighing 8 lb. occurred on that date. During the puerperium she was observed to have paroxysms of tachycardia, which never lasted for more than ten minutes and

were frequently of shorter duration. Graphic registration was, unfortunately, not possible. The apical rate during the attack was usually 200 per minute, and the rhythm invariably regular. The heart sounds were pure and of good quality, there was no oedema, while the skin and mucous membranes were of good colour. She looked well nourished, and no thyreoid enlargement was obvious.

Although on admission no mention was made of these attacks, observation of the paroxysms led to further questioning of the patient and the elicitation of the following history:-

The first three gestations were uneventful until during the third labour, when these "turns" first made their appearance. They continued thereafter, and persisted during the fourth pregnancy without exhibiting increased frequency. There were attacks during the fourth labour, which occurred exactly two years after the third: the puerperium which followed was marked by the development of thrombo-phlebitis of the right leg which necessitated hospitalisation for six weeks. During the fifth pregnancy, paroxysms were more frequent, but none occurred during labour.

The patient mentioned that heavy work seemed to precipitate an attack, and many of her paroxysms were associated with the wash-tub. The attacks commenced suddenly without warning, lasted as a rule for about ten minutes, and then terminated equally abruptly. She stated that, in an attack, she suddenly felt her heart beating rapidly, and, while the increased rate persisted, she experienced breathlessness. She was never sick, and, while sometimes dizzy, never fainted. At the end of the paroxysm, the heart seemed to beat forcibly thrice, pain was felt in the back of the neck and in the lumbar

region for a second or two, then the normal rate was restored, and she felt perfectly well. All her attacks have been similar. Nothing was ever done in an attempt to terminate the paroxysm: she simply sat down and waited until the tachycardia ceased.

During her residence in hospital, an attack was heralded by seeing the patient's face screwed up as if in pain. She then began to weep and whimper, following which the tachycardia commenced abruptly, while the veins in the neck showed forcible pulsation. The apical rate was practically always 200 per minute and the rhythm invariably regular during the paroxysm, which was frequently of three minutes' duration. The normal rate was thereupon abruptly restored, but the pulse for some minutes showed an abnormal rhythm suggestive of pulsus alternans.

On one occasion, immediately following an attack and again four hours later, the patient was given Tinct. digitalis m.V, but, as the pulse rate fell to 50 per minute, the drug was discontinued and was not thereafter administered in subsequent paroxysms.

Commentary.

1. Three uneventful pregnancies prove to have been the limit of tolerance for the patient, as evidenced by the development of paroxysmal tachycardia during the third labour.

2. The paroxysms persisted thereafter in the interval between the third and fourth pregnancy as well as during the fourth gestation and labour without exhibiting increased frequency.

3. Paroxysms occurred in the interval between the fourth

and fifth pregnancies and with increasing frequency during the fifth gestation. No attack took place during the fifth labour.

4. Spontaneous delivery has occurred in all the pregnancies, and paroxysms have been experienced in labour in two instances, viz. the third and fourth.

5. The pregnancy responsible for the initiation of these tachycardial paroxysms resulted in the delivery of a male child, the two previous children being females.

6. No abnormality was detected on physical examination: the cardiac sounds were pure and of good quality, and the patient was of healthy appearance.

7. There was no obvious enlargement of the thyreoid gland.

8. The abrupt onset and termination of the attacks is noteworthy. The paroxysms ended as suddenly as they had begun without the adoption of remedial measures.

9. Venous thrombosis developed in the right leg after the delivery of the fourth child.

10. The duration of a paroxysm has never exceeded ten minutes, and many of those observed in hospital only lasted for three to six minutes.

11. The cardiac rate during the attacks witnessed in hospital was usually 200 per minute.

12. Serious cardiac exhaustion must have been produced by these paroxysms of relatively short duration, as evidenced by the pulsus alternans detected immediately following an attack.

13. This is a case which might have passed unnoticed had not the patient been in hospital. No complaint was made, and the history was only elicited following observation of the paroxysms during the puerperium.

Case 4.

From Kimberley, South Africa, through the kindness of B.W. Franklin Bishop in a personal communication, come the details of a case of paroxysmal tachycardia associated with pregnancy.

A young married woman of about 24 years of age, alleged to have had left-sided pleurisy some six or seven years ago, has suffered since then from praecordial pain and breathlessness on the day preceding each menstrual period and throughout its duration, the condition clearing up automatically with the cessation of the flow. Considerable distress was caused, and her work was interfered with: between periods, however, she was perfectly fit and able to go about without discomfort of any kind. About the end of the year 1930, the woman married, and the condition described continued with each menstrual period. A specialist diagnosed paroxysmal tachycardia.

During an attack at the commencement of a period, she was described as being dyspnoeic, complaining of severe pain over the sternum which seemed to penetrate to the back: the heart rate was 140 per minute. This state of affairs was wont to continue during the period and to cease immediately at its termination: every period was associated with similar symptoms. Septic tonsils were enucleated and various drugs, including digitalis, were administered, but no apparent effect was produced.

In February 1932, she became pregnant. This case first came to the writer's notice when three menstrual epochs had passed without the occurrence of an attack: the report then was that the patient was feeling better than she had ever been previously. The cardiac rate was 72 per minute, the rhythm showed no irregularity, there was no enlargement of cardiac dulness, but there was slight accentuation of the second aortic sound which had been noted previously. At no time did she have oedema, and no other abnormal features were discovered.

A subsequent report stated that, throughout pregnancy not a single attack occurred. Emphasis was laid on the remarkable relief of symptoms and improvement in the general condition of the patient from the very commencement of pregnancy.

The child was delivered with forceps in November 1932, after a rather tedious labour. No attacks occurred during labour: even the administration of an anaesthetic failed to precipitate an attack.

The first period after delivery was accompanied by sternal pain and tachycardia, but the symptoms were apparently less severe than before pregnancy. Similar symptoms appeared with the second and third periods, but were much less pronounced. In April 1933, the patient was said to enjoy remarkably good health. The condition of the heart, on physical examination, was good, the only finding of note being accentuation of the second aortic sound.

Case 5.

Clyde Davis, Australia, having read of Case I, was prompted to place on record his case of paroxysmal tachycardia. His report is as follows:-

"Mrs. R., aged 39 years, engaged me on January 10th. 1930 for her confinement. It was her fourth pregnancy, there being three healthy children. She had a faint cloud of albumin in the urine which cleared up in the next fortnight. Examination on that date disclosed nothing abnormal with her heart, and she did not volunteer any information as to 'attacks' during pregnancy.

"She was admitted to a private maternity hospital at 7 a.m. on February 28th., pain having started at 5 a.m. At 9.30 a.m. there was dilatation of the os of less than a two-shilling piece; the membranes ruptured at 2 p.m. and the pains were severe. 0·5 c.c. of pitocin (Parke Davis and Co.) was administered at 2.15 p.m. as the head was almost on the perineum. A healthy, normal male child, weighing 9¾ lb. was born at 2.35 p.m. There was some delay in the passage of the head over the perineum, but no laceration occurred. The placenta and membranes were delivered complete at 3 p.m. when a further dose of 0·5 c.c. of pitocin was injected. Within two minutes of the second dose, paroxysmal tachycardia developed. The heart rate became 184 per minute, the pulse being uncountable at the wrist. At 4.15 p.m. the rate was 208; at 5.30 p.m. 180; at 6 p.m., 146; at 7 p.m., 120, and at 8 p.m., 100 per minute: the paroxysm lasted for nearly five hours. There was a moderate amount of post-partum haemorrhage, but not sufficient to cause much rise in the pulse rate.

"The following therapeutic measures were adopted:- morphine gr. ¼ and atropin gr. 1/100 were injected, and, as this had very little effect, digitalin gr. 1/100 was given. 1 c.c. of aseptic ergot (Parke Davis and Co.) was administered intramuscularly to control the haemorrhage. Unfortunately, it was

not possible to register the heart beat graphically, but, as far as the stethoscope could be trusted, the beats were regular. The treatment carried out seemed to have no effect on the condition. The next morning the heart returned to normal, the patient feeling quite well. The puerperium was uneventful.

"It was only on questioning the patient later that she disclosed the fact that she had had numerous similar 'turns' during the last three months of pregnancy. Her description of a 'turn' was that 'all the blood seemed to rush to the groins, the heart seemed to stop beating, then the blood rushed back to the heart which commenced beating again'. Each 'turn' lasted for about fifteen minutes. There had been no attacks prior to this pregnancy. She had no warning of the onset of the attack at the end of labour, nor of any which occurred during the latter months of pregnancy."

Case 6.

D.H. Fraser, London, after reading the account of Case I, kindly related in a personal communication the details of a case of paroxysmal tachycardia associated with pregnancy.

The daughter of a medical man commenced her menstrual life at the age of 13½ - 14 years. She was at a boarding-school in Yorkshire at this date. During one of her periods, the school went for a very long walk: towards the end of this walk, she noticed for the first time that her heart "was thumping and beating very fast". The girl was too shy to mention the occurrence to her teachers, and, by the following morning, the pulse rate had fallen to normal.

For many years there were frequent attacks of tachycardia: these always seemed to occur just before the

periods were due or shortly afterwards. Although living in her father's house, nothing seems to have been done except rest until the cessation of the attack.

On 2nd. April 1908, when 28 years of age, she married, and, the following August, was two months' pregnant. At this stage, an attack of tachycardia was apparently responsible for the onset of uterine haemorrhage, and the uterus had to be emptied of its contents.

Pregnancy did not again take place until the spring of 1909, and, in order to obviate the risk of abortion — there being definite "shows" at what would have been "period" times — she stayed in bed for ten days every month until the seventh month. About the middle or end of September, there commenced an extremely severe attack of tachycardia which lasted for nine days. The woman was seen by many physicians who evidently came, saw and went away. At one stage of this attack, the pulse was uncountable. The thyreoid was never enlarged, the urine was albumin-free and the blood pressure was not elevated. The attack ceased as abruptly as it had commenced.

On 28th. October, there was another attack of tachycardia which continued until the evening of the 31st. when the baby was born. Labour began early in the morning of the 31st. Between pains, the pulse rate was 180 per minute: while pains were present, none of those in attendance could count the pulse beats. The patient was much distressed with praecordial pain which developed just prior to the onset of a labour pain. When the cervix was fully dilated, the membranes were ruptured artificially: at this point, there was sickness and violent retching. As the woman herself described the occurrence, "the heart gave a jump or turned over", and normal rhythm was restored.

The babe was mature, turning the scale at 8½ lb. However, both arms and legs were absolutely white and, for some considerable time, the limbs had to be massaged in order to secure adequate circulation. (It is of interest to note that, at the time of writing, he was 23 years of age and that he had suffered as a child from chilblains which were very troublesome about the age of 14.)

The puerperium was uneventful but, five weeks later, at the first period following the confinement, there was a slight attack of tachycardia. During the succeeding few years, several slight attacks occurred; these were never so severe as the attacks during the previous pregnancy.

The year 1914 saw the birth of another boy. On this occasion, labour lasted only two and a half hours, and there was no tachycardia.

In the year 1918, a twin miscarriage occurred during a tachycardial attack.

At the age of 52, the menstrual periods had not ceased, but the attacks were much less frequent, only lasting for a few hours.

Every likely drug has been tried in this case. Digitalis was without effect. The woman found that sitting up suddenly and retching would often stop the attack. There is no foundation for the suggestion that there might be a neurotic basis for these bouts: they have frequently occurred during the night, causing the patient to awake with the thumping in her head: the act of coitus has precipitated an attack.

Case 7.

In the South African Medical Record (1926) there is an account by Whyte of delivery during an attack of paroxysmal tachycardia. The record is as follows:-

"For eighteen years, a woman, now aged 35 years, has suffered from attacks of paroxysmal tachycardia. There is also a slight mitral stenosis present. During the last six years, the attacks have been increasing in frequency and duration. At various times during the last two years she has had courses of quinidine sulphate stretching over some months at a time; during attacks also, she has been given this drug in 3-grain doses. Neither during the attacks nor in the intervals does this drug appear to have the least effect on her condition.

"At 1 a.m. on the 22nd. of March, an attack of average severity began. At 11.30 a.m. labour set in, and at 2 p.m. a normal healthy child was born. The delivery was normal and easy, although dyspnoea in the mother was marked. The child did not show the least sign of asphyxia and cried readily. The placenta was expelled at 2.15 p.m. without any trace of haemorrhage, but immediately afterwards, the mother showed signs of collapse. She rallied, however, with the administration of a little brandy. The pulse rate was 240 per minute and the respirations were rapid. Digitalis and bromides were given without effect.

"On the morning of the 23rd., her general condition was bad. Dyspnoea was marked: the face was grey, alternating every few minutes with a deep cyanosed appearance. She had had no sleep and was unable to take nourishment. The liver extended to four finger-breadths below the costal margin and was very tender to the touch. A quarter of a grain of morphine

sulphate was given hypodermically. After some hours' sleep, there was an improvement in her general condition: the distress was not so marked, but the cardiac condition was the same.

"On the 24th. the pulse was about 280, the blood pressure by the pulse being 80. Harsh bronchial breathing, accompanied by fine crepitations, was present over the whole area of the lung between the base of the heart and the left clavicle. A purgative, which under normal conditions works well and quickly, was given with practically no result. By evening, the condition of the patient was grave. Her face appeared to have shrunk considerably, and she was cyanosed. One and a half grains of quinidine sulphate were given orally, followed in twenty minutes by a quarter of a grain of morphine sulphate hypodermically. She slept practically right through the night.

"On the morning of the 25th., the pulse had dropped to 120. She ran a temperature of 101°. The breasts were greatly distended with milk. The harsh bronchial breathing had disappeared, but the crepitations were still present. The breasts were relieved and a purgative given. By evening the pulse had dropped to 108 and the temperature to 100·4°. She had an intense headache at the vertex.

"On the 26th., the temperature was normal and the pulse 72. The systolic blood pressure (by auscultation) was 94, the diastolic being 70. The liver was two inches below the costal margin. All crepitations of the lung had disappeared. No oedema of the extremities occurred at any time during the attack. She got out of bed on the tenth day, and thereafter carried out her household duties in the usual way.

"The obvious question arises, 'Why was quinidine sulphate not tried sooner?' This drug had been tried on so many previous occasions without causing any obvious improvement

that one had grown sceptical of its value in this case. Whether it had any real effect in cutting short this attack, one is not prepared to say."

Dr. Whyte communicated with the writer in March 1933, stating that the woman is now dead.

Case 8.

Dumas and Pigeaud (1932) report a case of paroxysmal tachycardia in association with pregnancy.

The patient, aged 24 years, was admitted to hospital towards the end of her second pregnancy for premature rupture of the membranes. For the three days which preceded confinement, the patient had several bouts of paroxysmal tachycardia with the pulse running at 180 and accompanied by slight distress. One of these bouts, particularly violent, was witnessed in the course of labour. Confinement was normal, spontaneous delivery occurring a little before term: the child was alive and weighed 2,950 grammes. During the puerperium, several further attacks were observed, but these were less characteristic and of shorter duration. This quietening down can be attributed to the emptying of the uterus and also to the treatment by quinidine which was administered immediately after delivery.

Interrogation of this patient showed that the bouts of tachycardia started at the age of 12. The frequency of these bouts appears to have increased in the course of her two pregnancies which, however, continued to term.

These authors make the comment that a tachycardia at the rate of 200 in the course of a confinement may be for the medical attendant, if not forewarned, a serious cause of anxiety: he will be tempted to attribute it to an obstetrical

complication — haemorrhage, rupture of the uterus, etc. They state that these bouts of paroxysmal tachycardia are not particularly serious from the fact of the physiological - obstetrical circumstances in the course of which they appear. With regard to the treatment by quinidine, these authors are of opinion that in the majority of cases there will be grounds, if not for abstaining, at least for not using except with prudence, quinidine medication.

Cases 9 and 10.

Meyer, Lackner and Schochet (1930) state that, in a critical review of the literature, only four or five case reports were found of true paroxysmal tachycardia associated with pregnancy. These authors give details of two cases which came under their notice.

Their first case, Mrs. A.Z., aged 28 years, a primigravida, six months' pregnant, was admitted to the service of Schochet with a history of extreme weakness, marked irritability and loss of weight. The patient was definitely neuropathic and had had several 'nervous break-downs', so that the clinical impression of hyperthyreoidism might have been given. On 20th. February the patient was examined and was apparently comfortable except for indisposition and irritability due to a cold. Thirty minutes later the patient suddenly felt her heart 'pounding', was faint and complained of a sense of constriction about the chest.

The patient was hospitalised. The pulse on admission was 138. Physical examination revealed extreme nervousness and moderate dyspnoea, with the pulse at the apex and at the wrist 180. A moderate exophthalmos and an enlarged right lobe of the

thyreoid gland were noted. The heart was 10 cm. to the left of the mid-sternal line, and the right border was about 4·5 cm. from the mid-sternal line. The heart tones were rapid and regular; a faint systolic (?) murmur was heard at times, and the second pulmonic was accentuated. There were no abnormalities in the lung. The patient was fairly comfortable. The clinical impression was that of paroxysmal tachycardia. The electrocardiogram confirmed this impression.

The following morning the condition continued without any marked change. Vagus pressure, change in position and other remedies, including tincture of digitalis, were tried without effect. On the third day of the attack, an irregularity of the radial pulse was noted. Cyanosis of the lips was marked and numerous râles appeared in the base of the lungs. Tincture of digitalis was increased to 30 minims (2 c.c.) every four hours. The heart extended 4·5 cm. to the right and 12 cm. to the left of the mid-sternal line. On the fourth day of the attack, the heart rate at the apex was 200 and dyspnoea was marked. Râles were heard at the right lower lobe and the liver was tender and enlarged. The condition of the patient did not look favourable. At 5.25 p.m. of this day the pulse rate was 200. It is a matter of common knowledge that these attacks may be abruptly ended by reflex inhibition produced by pressure on the vagus or sudden sneezing or coughing. It occurred to one of the authors to try snuff.

The patient coughed rather severely when the snuff was given, pressure being exerted on the vagus at the same time, and suddenly the pulse dropped to 90. The general condition of the patient improved; there were no recurrent attacks and she was discharged on the tenth day. The diagnosis was twin pregnancy, paroxysmal tachycardia and possible mitral stenosis with an

early myocardial insufficiency due to this severe attack of paroxysmal tachycardia. She was advised as to her condition and told to report any attacks. She was observed by the obstetrician and internist during the succeeding months of pregnancy.

In the thirty-sixth week of pregnancy, the patient was hospitalised in order that labour might be terminated. The heart at this time was 10.5 cm. to the left of the mid-sternal line and 4.5 cm. to the right. A presystolic murmur was heard and the pulmonic second sound was sharply accentuated. There was no pulmonary congestion or enlargement of the liver. The pulse was 90.

In view of the previous severe attack of paroxysmal tachycardia, with definite evidence of early decompensation and of symptoms pointing to mitral stenosis and the associated twin pregnancy in a neuropathic type of patient, it was deemed inadvisable to submit her to the test of labour. A low cervical Caesarean section was performed under local anaesthesia. There was no severe haemorrhage and two normal female infants were delivered. The uterus was closed in the routine manner (interrupted sutures). The patient was sterilised by excision of the cornua of the tubes and the pelvic toilet was completed. The abdominal wall was closed. The patient left the operating room in good condition. Her post-operative progress was uneventful. At the time she was discharged from the hospital, the heart condition was improved and there were no recurrent attacks of tachycardia.

The second case reported by these authors concerned a woman, aged 31 years, who was admitted to the medical service of Dr. Solomon Strouse in April 1927 because of recurring 'heart

attacks'. The patient dated her attacks from a severe attack of scarlet fever followed by 'rheumatism'. These 'heart attacks were often associated with severe pain in the praecordium simulating angina. During the time the patient was observed in hospital, attacks of paroxysmal tachycardia occurred, varying in duration from three hours to two days. The pulse rate was 200, and the electro-cardiograms showed tachycardia of nodal or auricular origin. The heart measured 10 cm. to the left of the mid-sternal line and 4 cm. to the right. The second pulmonic sound was accentuated: there were no murmurs. Roentgen examination of the heart showed a mitral configuration.

In August 1927 the patient was readmitted to Michael Reese Hospital with a similar complaint. In the interval she had had several attacks of paroxysmal tachycardia and was admitted on the fourth day of a similar attack. Physical examination showed a moderate increase in the transverse diameter of the heart. The right border was 5 cm. from the mid-sternal line and the left border 13·5 cm. The electro-cardiogram revealed paroxysmal tachycardia.

On 17th. June 1928, approximately ten months later, the patient, in her third pregnancy, was admitted to the service of Dr. Lackner. A normal delivery occurred two hours after admission to hospital. Two days later, 19th. June 1928, the patient complained of severe pain in the epigastrium, radiating to the praecordium and then down to the left arm. The patient recognised the nature of the attack. The pulse at this time was 180. The next morning she was seen by Dr. Sidney Strauss, who confirmed the diagnosis. This attack continued for six days, with a remission for only eight hours. The pulse rate was 200. The heart borders measured 4·5 cm. to the right of the

mid-sternal line and 12 cm. to the left. The liver was enlarged and tender: the pulsations in the neck were visible. The electro-cardiogram showed paroxysmal tachycardia. It was difficult to say whether it was nodal or auricular in origin. She was discharged to the cardiac clinic on 7th. July 1929.

In November 1929 the patient was readmitted to the service of Dr. W.W. Hamburger because of recurring attacks and increased shortness of breath. The patient believed that the attacks were more severe. Examination showed cyanosis of the lips, oedema of the extremities and an enlarged liver. The heart was 3·5 cm. to the right of the mid-sternal line and 11·5 cm. to the left. The clinical diagnosis was organic heart disease, cardiac enlargement with recurring attacks of paroxysmal tachycardia and moderate cardiac failure.

Case 11.

Mitchell and McKeag (1933), in a communication entitled "Paroxysmal Tachycardia and Pregnancy", give the following particulars:-

"A primipara, aged 27 years, was first seen on May 1st. 1932. Labour had been induced (stomach tube) on April 28th. Pains were said to have been good on April 29th. and 30th. and it was not until the morning of May 1st. that there was any cause for anxiety. Examination about noon showed a small child, head well down, perineum bulging with the pains, half-crown dilatation membranes ruptured. The pulse was 140, regular and of good volume. General condition excellent.

"The patient gave a history of several similar attacks of 'palpitation' during the previous twelve months. A provisional diagnosis of paroxysmal tachycardia was made, and an

injection was given of morphine sulphate, grain ¼. At 6 p.m. the patient presented a typical picture of acute heart failure. The pulse was 160 and barely countable at the wrist. Dyspnoea was severe, and moist crepitations could be heard over the greater part of both lungs. There had been no further dilatation of the os.

"The hypodermic injection of morphine was repeated, followed by 1/100 grain strophanthin intravenously, and under spinal (stovaine) anaesthesia, with gas and oxygen, the os was dilated manually. Delivery of a still-born child was completed by forceps extraction. The pulse was then 204, very irregular, and countable only by auscultation. Convalescence, except for a few days' pyrexia, was uneventful."

CONCLUDING REMARKS.

Sir James Mackenzie, discussing paroxysmal tachycardia in pregnancy (1921), states, "I have had no experience of this abnormal rhythm as a complication of pregnancy".

De Lee, in the latest edition of his text-book (1933), makes but a brief reference to the condition. "Paroxysmal tachycardia, a cardiac arrhythmia which needs better definition, occurring in parturition will have to be differentiated from abruptio placentae, obstetric shock, decompensation of a rheumatic heart, etc.". Previous editions did not even contain this statement.

In "Obstetrics and Gynaecology" edited by Curtis (1933) there occurs merely the statement that Meyer, Lackner and Schochet drew attention to paroxysmal tachycardia as a complication of pregnancy.

Standard text-books on obstetrics, with these exceptions, are silent as regards the association of paroxysmal tachycardia and pregnancy. The same can be said about all medical books and those dealing especially with cardiac disorder.

Sir Thomas Lewis in his book, "The Mechanism and Graphic Registration of the Heart Beat", 3rd. edition, 1925, (Shaw and Sons, London), makes no reference to the association of paroxysmal tachycardia and pregnancy, but mentions that a conspicuous and unexpected response of the heart, in the form of increased rate, to relatively slight disturbance is found where the body is invaded by organisms, locally or generally, in exophthalmic goitre and many other conditions. (P. 240).

He states (p. 244) that individual paroxysms in a given case are of fairly constant duration; from subject to subject the duration is very variable; it may continue for an hour, a day, a week or more without interruption. Paroxysms lasting for more than ten days are extremely rare, though a seeming duration of fifteen months has been recorded by F.N. Wilson and G.R. Herrmann, Arch. Int. Med., 1923, 31, 923.

Anselmino and Hoffmann (1932) mention that a physiological hyperfunction of the thyreoid gland occurs in pregnancy, and that there is justification for the assumption that the circulatory change in pregnancy is the result of this increased production of thyreoid hormone. "The increase in frequency of the pulse is a well known phenomenon in hyper-thyreoidism. The observation that in pregnant women there is frequently a slight tachycardia fits completely into the picture of the other changes in the circulation in pregnancy, and may readily be claimed as an effect of the physiological hyperfunction of the thyreoid gland in pregnancy."

Major and Wahl (1932) discuss the aetiology of paroxysmal tachycardia. Their cases, four in number, were carefully examined post mortem, and in all of them gross myocardial disease was discovered. The changes occurring were those usually found in myocarditis of varying degrees of acuteness and length of duration. As they state, the clinical diagnosis can be made on a clear description, even if the attack was not witnessed. The British Medical Journal (1933, I, 237), commenting on the findings of these authors, points out that it is as important to explain why the majority of cases in which pathological changes are present do not show disturbances of the nature of paroxysmal tachycardia as to associate the latter with the myocarditis described by Major and Wahl.

Wolff (1933) records four cases in support of his contention that angina pectoris and cardiac asthma may be induced by paroxysmal auricular fibrillation and paroxysmal tachycardia. He states that the cardio-vascular changes which take place during an attack of tachycardia are conducive to vascular thrombosis.

Much of the literature dealing with paroxysmal tachycardia has been consulted but, as no light is thrown on the relationship of the condition and pregnancy, it has been deemed inadvisable to include these references or to attempt to discuss the nature of paroxysmal tachycardia. Attention has been directed to the paucity of information in the literature with regard to the association of paroxysmal tachycardia and pregnancy. The submission is made that of outstanding importance and interest are the two cases (Case I, personally investigated, and Case 4, privately communicated) in which the patient, a sufferer from paroxysmal tachycardia, did not have a single paroxysm throughout gestation. In this we have a unique

and hitherto unrecorded illustration of the beneficial effect exerted by the pregnant state. Endocrine activity is known to be pronounced during pregnancy. Thus large quantities of a gonadotropic hormone are excreted in the urine during pregnancy, this being utilised as the basis of the well known Zondek-Aschheim test and the Friedman modification for pregnancy. The quantity of this gonadotropic hormone excreted in the urine increases progressively until the end of the fifth month, thereafter decreasing steadily to term and disappearing quickly from the urine after parturition. Throughout pregnancy, too, relatively large quantities of oestrin are produced and excreted in the urine: the elaboration of oestrin commences at the onset of pregnancy, increases steadily until the time of parturition and then rapidly subsides. Have we not here the suggestion that endocrine activity must be concerned in the abeyance of these tachycardial paroxysms during pregnancy, in as much as the return of the paroxysms coincided with the waning of this activity shortly after delivery?

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XI. ON THE EARLY TOXAEMIAS OF PREGNANCY, WITH SPECIAL REFERENCE TO GASTRIC ACIDITY IN EMESIS AND HYPEREMESIS GRAVIDARUM.

GENERAL REMARKS.

The toxaemias of pregnancy have constituted a baffling problem throughout the ages, and today the mystery remains obscure. For these disturbances, indeed, no common aetiological factor has been demonstrated save one — the fact of pregnancy.

Pregnancy is a physiological process characterised by its extreme liability to become pathological. Broadly speaking, in a healthy woman the period of gravidity may be divided into three phases or epochs, each of three months, viz. —

1. The first three months ending with the completion of the formation of the placenta. In even what may be regarded as a normal pregnancy, this is liable to be a period of disturbance.

2. The fourth, fifth and sixth months, during which the equilibrium appears to be restored. In the average case, this may be said to be a period of comparative well-being.

3. The seventh, eighth and ninth months of gestation duri which toxaemic manifestations are liable to develop.

During the first phase, three noteworthy features must be recognised:-

(a) Hormonal activity is pronounced, as evidenced by the positive Zondek-Aschheim test or the Friedman modification.

(b) The activity of the trophoblast is marked, and a proteolytic enzyme can be demonstrated in the villi.

(c) With the imbedding of the zygote, considerable destruction of maternal tissue must take place.

In the second phase, the fully formed placenta is exercising its physiological function. Through its agency, nutritive material is selected from the maternal circulation and suitably altered, is conveyed to the growing foetus. Similarly waste products from the foetal circulation are voided in the maternal blood.

The third phase is characterised by the degeneration

of the placenta: no longer are the villi active. Infarctions are frequent in the placenta, which has ceased to perform the physiological activity of the earlier phase. At this stage, waste products are probably more toxic and greater in amount.

Symptoms referable to the upper gastro-intestinal tract constitute probably the most frequent complications of the pregnant condition, and early in pregnancy, attention is focussed on gastric function. In most pregnancies, the first disturbance is morning sickness, which may manifest itself before amenorrhoea is noticed. There may be no actual vomiting, the woman experiencing simply a feeling of nausea: on the other hand, considerable quantities of vomitus may be ejected. Observation of a large number of cases indicates that, in the majority, sickness first occurs at the time of the first missed menstrual period. Recent work has shown that ovulation takes place between twelve and seventeen days from the onset of the preceding menstrual period, and it is generally believed that about seven days elapse between fertilisation and imbedding. It, therefore, follows that the occurrence of sickness corresponds in time to the process of imbedding of the zygote.

EXAMINATION OF THE VOMITUS IN HYPEREMESIS.

Emesis gravidarum cannot be regarded as a physiological phenomenon, occurring as it does in the morning when the stomach is empty. There is no seasonal variation in emesis or hyperemesis gravidarum as is apparently the case with the typical toxaemia of the later months, viz. eclampsia. Underlying the so-called "normal" morning sickness there is a basis of toxaemia, and such cases should not be dismissed lightly, airily attaching the label "neurotic vomiting". It must ever be borne

in mind that the most pernicious vomiting begins as emesis gravidarum. Even morning sickness is a toxaemic manifestation, primarily due to the presence of the fertilised ovum in the uterus, essentially connected with the process of imbedding and the consequent destruction of maternal tissue. The salutary effect of hospitalisation in many instances is remarkable, and has led to undue stress being laid upon the neurotic aspect of the condition. On the tendency to vomit there may be superimposed, in many cases, a neurotic element which results in aggravation of the sickness. The effect of the rigid dietetic régime in vogue in hospital is probably to check the development of the neurosis, which is to be regarded as a secondary factor. Hurst (1922) believes that such a condition as pernicious vomiting of pregnancy does not exist, and that it is typically hysterical, caused by suggestion and curable by psychotherapy. Hurst still holds this view, and believes that emptying of the uterus acts by suggestion and that, when vomiting continues and death occurs in spite of the operation, the suggestion has not proved sufficiently powerful, probably because the patient was not first made to believe with certainty that it would cure her. It may be that the cases of hyperemesis gravidarum occurring in Glasgow are more severe than those met with in the south, but certainly there are very many in whom no trace of a neurotic element can be detected.

Emesis gravidarum ceases normally about the end of the third or beginning of the fourth month of gestation, that is, its occurrence coincides with the presence in the villi of the proteolytic enzyme and with the consequent destruction of maternal tissue therefrom. There may be an undue amount of destruction of uterine tissue: a gross example is vesicular

mole in which there is over-production of the epithelial cells of the villi and enormous destruction of maternal tissue — so great in some instances that the uterine wall may actually be penetrated by the villi. This condition, in which the villous activity may be said to run riot, is in a very large proportion of cases associated with pronounced toxaemic manifestations. Between these two conditions, viz. normal villous activity with its associated destruction of maternal tissue, and the state of excessive destruction as in vesicular mole, it is not unreasonable to suppose

(a) that there are grades of villous activity and uterine destruction;

(b) that different individuals respond differently to such activity.

One should like to be able to gauge the potency of the proteolytic enzyme and to make an estimate of the degree of resistance of the maternal tissues.

The occurrence of sickness and vomiting would suggest that the stomach is attempting to get rid of some toxic body: its occurrence in the morning, very often as soon as the patient awakes, would appear to indicate that during the hours of sleep, there has been an accumulation of this toxic product. In hyperemesis gravidarum there is an aggravation of the toxaemia, and one would imagine that a larger amount of this toxic product might be found in the vomitus. It would appear that vomiting persists as long as the source of supply of this toxic product is maintained, or until it is inhibited. A fact which would lend still further support to this view is that, in the most pernicious varieties of the condition, the vomiting very often ceases, but the patient, instead of showing improvement, becomes progressively worse: in such instances, one would suppose that the toxic product, instead of being voided in the vomitus, is

retained and poisons the patient. It is also possible that patients who have little or no vomiting in the early months of pregnancy have relatively small quantities of this toxic product, but it is retained in the body in gradually increasing amount with the result that the cumulative effect is the production of eclampsia in the later months. Vomiting is a well recognised pre-eclamptic manifestation.

Analysis of the vomitus and of the gastric contents after test meals in both emesis and hyperemesis gravidarum has so far failed to demonstrate the presence of a toxic body. It is possible that only by the application of new analytical and biological methods will this toxic substance be recognised. Animals have been fed with the vomitus of acute cases, and no ill effects have been noted. Injection of the vomitus has apparently produced no harm. Extracts of the placenta, removed from patients who would undoubtedly have died without operative intervention, have been made with all aseptic precautions. These extracts might be presumed to be extremely toxic and to be capable of producing marked changes in an animal when injected. However, such injections have frequently been performed intra-peritoneally and intravenously without apparent harmful effect and without demonstrable histological change in any of the organs. Furthermore, attempts made to fortify pregnant women against toxaemia by injection of serum from highly toxic cases have been unsuccessful. Seldom is it necessary to terminate pregnancy on account of hyperemesis gravidarum, but on occasion this is essential. Proof of the toxaemic nature of the uterine contents in such a case is afforded by the uninterrupted recovery made by the patient on evacuation of the products of conception.

FRACTIONAL ANALYSIS OF GASTRIC CONTENTS IN EMESIS AND HYPEREMESIS GRAVIDARUM, IN PYELITIS, PRE-ECLAMPSIA AND ECLAMPSIA.

The writer embarked on his investigation of the vomiting associated with pregnancy by conducting a series of balance experiments of output and intake. For twenty-four hours all vomitus and urine were collected: during this time the patient was given a known fluid, and the amount taken was carefully measured. The vomitus was tested for free hydrochloric acid and total acidity, and the amount of chloride was estimated. In the urine, estimations were made of the total acidity, ammonia nitrogen and chloride. Thus it was possible to determine whether or not the chloride loss was greater than the intake, and whether or not the fluid loss was greater than the intake. In some of the cases the experiments were repeated thrice at intervals of six to eleven days. Experiments of this nature are far from ideal, but circumstances were such that little better could be attempted. When attempting to draw conclusions from such observations, there must be taken into account the shortness of the experimental period and the fact of loss of fluid in other ways. However, in these cases of hyperemesis, the skin as a rule was dry, and the amount of fluid lost by sweat must have been inconsiderable. In the most severe examples of hyperemesis gravidarum, as might be expected, the fluid and chloride loss was greater than the intake. However, the most striking fact which emerged was the frequency of achlorhydria in the vomitus of such women. At intervals of several days these observations were repeated and yielded identical results — achlorhydria in the majority and a very low concentration of free hydrochloric acid in the remainder. In order to concen-

trate on this aspect, only the findings with reference to free hydrochloric acid in the vomitus are here recorded. These are shown in Table I.

Table I — Results of Examination of Vomitus of Cases with Persistent Emesis during Pregnancy.

	No. of cases.	Achlorhydria.	Hypochlorhydria.
Emesis . . .	1	—	1
Hyperemesis	14	13	1
Pyelitis . .	5	2	3
Gallstones .	1	—	1

Thus it would appear that there is little or no acid lost from the body in this way and that there exists no sufficient ground for the belief that such cases suffer from a relative alkalosis. Incidentally, the highest figures for urinary ammonia were recorded in the achlorhydric group.

In consequence, the gastric acidity in cases of pregnancy associated with vomiting was investigated by means of fractional test meals. The findings have been grouped according to the percentage of free hydrochloric acid present, and, for the purpose of comparison, such free acid as appeared only during the $1\frac{3}{4}$ hours following the meal has been recognised.

Method.

The routine adopted was as follows:-

The pregnant woman to be examined received nothing by mouth after 8 p.m. on the night preceding the test. Next morning, shortly after 9 o'clock, a Ryle's stomach tube was passed: if the tube did not pass with ease, no force was used,

and the case was not included in the series. Many patients, however, had considerable practice in swallowing the tube before the actual experiment. Through the stomach tube, all the gastric contents were withdrawn. A test meal of oatmeal gruel was then given: this consisted of two tablespoonfuls of oatmeal to which had been added two pints of water, the whole having been boiled until the volume was approximately one pint. Samples withdrawn every fifteen minutes for two and a half hours were examined quantitatively for free hydrochloric acid by means of Toepfer's reagent, and for total acidity using phenolphthalein as indicator, the titration in each instance being made against $\frac{N}{10}$ NaOH. As a confirmatory test for the presence of free hydrochloric acid and to exclude the possibility of a positive reaction with Toepfer's reagent being due to lactic acid, Gunzberg's test was performed in all cases. In addition, the usual tests for starch, mucus, bile and blood were carried out.

Clinical Notes with reference to Hyperemesis Gravidarum.

Clinical histories were carefully taken to exclude the possibility of gastric trouble apart from pregnancy. Microscopic examination of the urine was carried out in all cases in order to exclude the presence of urinary infection, since it was found that many patients sent into hospital with the diagnosis of hyperemesis proved to be suffering from pyelitis associated with pregnancy.

Hyperemesis gravidarum seems to affect fair-haired subjects with a grey iris much more frequently than those possessing pigment in greater amount. This observation is recorded for what it is worth, and, at this point also, it may be mentioned that the association of the grey iris with eclampsia

was noted. It is well known that pigmented and non-pigmented individuals differ markedly in their tolerance to sunlight, those of fair complexion being much more susceptible to harmful effects.

Table II shows the comparison of 187 unselected and consecutive cases of pathological pregnancy with reference to the colour of the iris. From these figures it would appear that subjects with a grey or greyish iris are more susceptible to toxaemic manifestations during pregnancy.

TABLE II — Comparison of 187 Consecutive Cases of Pathological Pregnancy with reference to the Colour of the Patient's Iris.

Complication of pregnancy.	Number of cases.	Grey.	Blue.	Bluish-grey.	Brownish-grey.	Brown.	Remarks.
Hyperemesis Gravidarum	71	38	1	3	12	17	Approximately 76 per cent. had a blue, grey or greyish iris.
Eclampsia	66	40	-	2	17	7	Approximately 89 per cent. had a grey or greyish iris.
Pre-eclamptic Toxaemia	22	13	-	-	4	5	Approximately 77 per cent. had a grey or greyish iris.
Nephritic Toxaemia	9	5	-	-	2	2	Approximately 78 per cent. had a grey or greyish iris.
Pyelitis	19	10	-	-	1	8	Approximately 58 per cent. had a grey or greyish iris.
Total	187	106	1	5	36	39	Approximately 79 per cent. of the series of 187 cases had a blue, grey or greyish iris.

In the cases studied, oral sepsis and constipation occurred with notable frequency: the presence of these, naturally, cannot be stressed as being peculiar to hyperemesis

gravidarum. The constipation may be due to the fact that the patient is in a state of relative starvation, but such a condition of itself would render the patient's defences open to bacteriological attack. At any rate, in an already established toxaemia, oral sepsis and intestinal stasis are certain to contribute to its aggravation.

The only constant finding, so far as the nervous system was concerned, was an exaggeration of the knee-jerks, sometimes equally, sometimes unequally. In spite of the frequency of visual disturbances, the fundi were invariably normal on ophthalmoscopic examination, although in moribund patients retinal haemorrhages have been observed. Stander (1932) reports two patients who had haemorrhagic retinitis in the vomiting of pregnancy: in one, recovery took place, while the other died.

Fatal results have ensued only in those patients whose gastric secretion showed achlorhydria or hypochlorhydria.

In conjunction with R. Cruickshank, Bacteriologist to the Royal Infirmary, an examination for the presence of organisms was carried out in the vomitus and in the gastric contents removed for fractional analysis. Briefly, this showed that, in the presence of free hydrochloric acid, however low the concentration, there was a scanty flora, whereas achlorhydria was invariably accompanied by the appearance of abundant organisms. Gram-positive diplococci, streptococci and diphtheroid bacilli were the predominant organisms, both in the direct smear and on culture.

Results, showing Incidence of Achlorhydria.

In Table III are shown the results of fractional test meals grouped according to the maximal concentration of free hydrochloric acid (82 cases).

TABLE III — Results of Fractional Test Meals Grouped According to the Maximal Concentration of Free Hydrochloric Acid. (82 Cases).

	No. of cases.	Achlor-hydria.	10 per cent. and under.	11 to 20 per cent.	21 to 30 per cent.	31 to 45 per cent.	Above 45 per cent.
Emesis	30	6	3	7	9	5	-
Hyperemesis	23	11	2	5	1	1	3
Pyelitis	10	-	4	3	2	1	-
Pre-eclampsia	10	1	1	4	1	2	1
Eclampsia	9	2	-	1	4	1	1
Total	82	20	10	20	17	10	5

(a) Of 30 patients with emesis gravidarum, 6 showed achlorhydria, that is, 20 per cent.

(b) Of 23 patients suffering from hyperemesis gravidarum, 11 showed achlorhydria, that being an incidence of 48 per cent. In 3, hyperchlorhydria was present — cases in which, judging by the severity of the symptoms, achlorhydria or hypochlorhydria would have been expected.

(c) A group of 29 patients, comprising cases of pyelitis, pre-eclampsia and eclampsia (after the convulsive stage had passed) was examined in respect of gastric acidity. Patients with pyelitis associated with vomiting exhibited a tendency to hypochlorhydria, but none had achlorhydria. Achlorhydria occurred in 10 per cent. of the cases of pre-

eclampsia , and in 22 per cent. of the cases of eclampsia examined.

(d) The incidence of achlorhydria in the total series of 82 cases was 24 per cent. Grouping the cases of emesis and hyperemesis gravidarum (53), achlorhydria occurred in 32 per cent.

Relationship of Parity and Age.

TABLE IV.— Maximal Concentration of Free Hydrochloric Acid Related to Number of Pregnancies. (82 Cases).

Gravida.	Achlorhydria. 20 cases.	10 per cent. and under. 10 cases.	11 to 20 per cent. 20 cases.	21 to 30 per cent. 17 cases.	31 to 45 per cent. 10 cases.	Above 45 per cent. 5 cases.
1	9	4	7	10	5	2
2	5	2	4	1	-	3
3	4	-	3	3	1	-
4	1	1	1	3	1	-
5	-	-	-	-	-	-
6	-	1	1	-	-	-
7	-	-	-	-	2	-
8	1	-	2	-	1	-
9	-	-	1	-	-	-
10	-	1	1	-	-	-
11	-	1	-	-	-	-

In this series of 82 cases, 45 per cent. were primigravidae. Of the cases exhibiting achlorhydria, 45 per cent. were primigravidae. Strauss and Castle (1932), in a paper dealing with gastric secretion in pregnancy and the puerperium, state that they could obtain no correlation between reduction in gastric acidity and the age of the patients, nor did the number of previous pregnancies appear to be of significance.

TABLE V — Maximal Concentration of Free Hydrochloric Acid Related to Age Groups. (82 Cases).

Age group.	Achlorhydria. 20 cases.	10 per cent. and under. 10 cases.	11 to 20 per cent. 20 cases.	21 to 30 per cent. 17 cases.	31 to 45 per cent. 10 cases.	Above 45 per cent. 5 cases.
19 to 25	10	5	8	9	3	3
26 to 30	7	-	5	3	2	1
31 to 35	2	2	6	4	3	1
36 to 42	1	3	1	1	2	-

It must be remembered, of course, that there is great variability of the maximal acid concentration in a group of healthy individuals of similar age. High or low gastric acidity is considered to be a quality inherent in the individual even in very early life. Wright (1924), in an investigation of 250 normal children between the ages of six and fifteen years, found achlorhydria in 1·6 per cent. With advancing years there is known to be a greater frequency of achlorhydria. Thus Vanzant (1931), in an analysis of 3,746 records, showed that the incidence of achlorhydria increased from approximately 4 per cent. at the age of twenty years to approximately 26 per cent. at the age of sixty years. In that investigation it is further stated that the frequency of achlorhydria among women appears to be slightly more marked than among men, and that the decrease in the percentage which occurs in later years (after sixty) suggests the possibility that the mortality rate is a little higher in persons with achlorhydria than in those with free acid in the stomach. The suggestion is made that anacidity is an inherited peculiarity which tends to be uncovered as age progresses.

Hartfall (1932), in a series of 2,356 patients, found achlorhydria in 242 or 10·3 per cent. and noted the greater percentage of achlorhydria among females.

Bennett and Ryle (1921), in their investigation of healthy students, found 4 per cent. with achlorhydria, while 80 per cent. fell within normal limits.

A survey of 100 normal persons over the age of sixty by Davies and James (1930) showed the incidence of achlorhydria to be 32 per cent. These workers were able to demonstrate that the cases of achlorhydria could be divided into two groups:-

(a) those showing hydrochloric acid after the injection of histamine, a group which may be designated "apparent achlorhydria";

(b) those showing no hydrochloric acid after the injection of histamine, a group to which the term "true achlorhydria" may be given.

In the figures detailed, there would appear to be an indication of progressive decline in function of the gastric glands as age advances.

In the writer's series of 82 cases, achlorhydria is shown in 24 per cent., a figure which is greater than would fit into the scale of increased frequency with advancing years. It has been pointed out that, if senile changes bring anacidity, they should bring subacidity also, and they do not: hence the suggestion that anacidity is an inherited peculiarity which tends to be uncovered as age progresses. During the reproductive period, too, one would expect the gastric glands, in common with the other glands of the body, to be in their most active phase.

Grouping the cases of emesis and hyperemesis gravidarum (53), achlorhydria occurred in 32 per cent. 50 per cent. of the cases of achlorhydria were found in the age-group nineteen to twenty-five years, and 85 per cent. between the ages of nineteen and thirty years. The writer suggests that such

an incidence of achlorhydria at a time of life when strength and vigour are at their zenith must have some significance.

TREATMENT OF HYPEREMESIS GRAVIDARUM.

On the treatment of hyperemesis gravidarum it is not the intention of the writer to dwell, but the routine adopted may be outlined. For 24 - 48 hours after admission to hospital, as indicated by her response, the patient did not receive any nourishment orally. Salines and glucose per rectum were administered four-hourly, and frequent mouth washes were given. Usually at the end of the period indicated it was possible to revert to feeding by the ordinary channel: first, fluids in small quantities were given at short intervals, then oral feeding was gradually substituted. Barley sugar to suck was appreciated by the patient. An essential therapeutic measure in hyperemesis is the supply of nourishment, and particularly the exhibition of glucose, which may be given orally, rectally or intravenously as circumstances indicate. Shortly after the resumption of oral feeding, a start was made in some cases with treatment by means of liver extract. 75 grams were given thrice daily in soup or disguised in some other way, this being preceded by 15 minims of dilute hydrochloric acid in water on each occasion. The institution of this line of treatment by the writer was quite empirical, but, in most cases, the hydrochloric acid and liver extract taken in this manner seemed to be well borne by the patient, and apparently did not contribute to the already existing nausea. In this connection it is interesting to note that liver extract is now being employed to combat X-ray sickness. Aperients were avoided to begin with, daily colonic lavage being carried out.

TABLE VI — Comparison of Results of Fractional Analysis in Hyperemesis Gravidarum in the Active Stage and on Recovery. (Certain selected examples.)

	Type of free hydrochloric acid curve.	
Type of case.	In the active stage. (Noted in Table III.)	On recovery. (Not mentioned in Table III.)
Emesis gravidarum	31 per cent. to 40 per cent., free acid appearing at one hour.	31 per cent. to 40 per cent., free acid appearing at ½ hour.
Hyperemesis gravidarum	Achlorhydria.	11 per cent. to 20 per cent.
Hyperemesis gravidarum	Achlorhydria.	11 per cent. to 20 per cent.
Hyperemesis gravidarum	Achlorhydria.	Under 10 per cent.
Hyperemesis gravidarum	Under 10 per cent., only appearing at 1¾ hours.	Under 10 per cent., but appearing at ¾ hour.
Hyperemesis gravidarum	Achlorhydria.	Achlorhydria.
Hyperemesis gravidarum	11 per cent. to 20 per cent.	21 per cent. to 30 per cent.
Hyperemesis gravidarum	Above 45 per cent.	21 per cent. to 30 per cent.

Test meals on recovery showed that, in those patients who had previously been of the achlorhydric class, there was a return of free hydrochloric acid in low concentration, while in patients who had had hypochlorhydria there was noted an increase in the percentage of free acid. It must be said that, in those patients who recovered without treatment by dilute hydrochloric acid and liver extract, similar results were obtained. In a case of hyperemesis where hyperchlorhydria was in evidence, recovery was coincident with a fall in the percentage of free acid. It is important to emphasise, therefore, that with the disappearance of symptoms in the condition of hyperemesis gravidarum, no matter what aids may have been invoked to produce this result, there is a change in the gastric secretion. The most striking feature is the return of free hydrochloric acid to the gastric secretion in those cases in which it has previously been absent.

In the treatment of emesis and hyperemesis gravidarum practically every drug has at one time or another been

requisitioned. There is no evidence of specific effect in any, although the psychological value of the administration of a drug may be apparent in some instances. Much harm has doubtless been done by the giving of massive doses of alkali to such cases in the mistaken idea that hyperacidity was the cause of the condition. A plea might be made for prophylactic treatment. Great efforts, sometimes unavailing, are frequently made to combat the far advanced toxaemia, while the condition of mild sickness and vomiting from which it originates is looked upon as natural. In view of the results here presented, showing the tendency to achlorhydria and hypochlorhydria in the early months of pregnancy, is there not the suggestion that a small daily ration of dilute hydrochloric acid might prove beneficial in all cases in the initial stages as a preventive measure? It is possible that the injection of histamine might be beneficial in cases of hyperemesis gravidarum by making free hydrochloric acid available.

THE ALKALINE TIDE IN URINE.

Why should sickness during the early months of pregnancy occur in the morning, as soon as the woman awakes from sleep, while the stomach is still empty? This ever recurring and perplexing question prompts one to investigate any phenomenon that is peculiarly associated with the morning hours.

Hubbard (1930) found that the concentration of chlorine in the urine was high in the first hour after awakening and low in the hour after the morning meal. These observations were made in twenty-four subjects with achlorhydria, and were found to be independent of the variation in the amount of water excreted.

It has long been recognised that the reaction of the urine may alter as the result of the ingestion of food. This phenomenon is known as the alkaline tide, the increase in alkalinity being ascribed to the secretion of hydrochloric acid in the gastric juice.

Leathes (1919) states that alkaline tides after meals other than the first in the day are not the rule. It was shown by Hubbard, Munford and Allen (1924) that only cases which exhibited free hydrochloric acid in the stomach gave the alkaline tide, although the amount of free hydrochloric acid present had no effect on the depth or duration of the tide: if no breakfast was taken, no alkaline tide was observed.

According to Dodds (1923), the first meal of the day is followed by a decrease in the output of acid and ammonia in the urine, this alkaline tide, lasting for about two hours, being followed by a period of the same duration, during which there is an increased output of acid and alkali. Small (1928) found a rise in the percentage of dibasic phosphate excreted at the third and fourth hours after the ingestion of food, and showed that it is the actual ingestion of food which is responsible for the alteration in the composition of the urine. She confirmed the observation of other workers, namely, that when no solids are ingested, there is no alkaline tide, the reaction of the urine remaining approximately constant throughout the morning.

A similar investigation was carried out by the writer in a few cases of vomiting in the early stages of pregnancy. The method adopted was that of Leathes (1919) whereby dibasic phosphate (Na_2HPO_4) was estimated by titrating with $\frac{N}{10}$ H_2SO_4, using methyl orange as indicator, and acid phosphate (NaH_2PO_4) was estimated by titrating with $\frac{N}{10}$ NaOH, employing phenolphthalein

as indicator. A comparative figure in each specimen was obtained by dividing the number of cubic centimetres of $\frac{N}{10}$ H_2SO_4 by the sum of the number of cubic centimetres of $\frac{N}{10}$ H_2SO_4 and $\frac{N}{10}$ NaOH used. The percentage of alkali in the urine was thus estimated, and a graph of the results was plotted. The findings are shown in Charts I - VI.

The procedure adopted in these cases was as follows:-

The patient passed urine at 6 a.m., had a drink of water at 6.30 a.m., passed urine at 8 a.m., after which she ate a full, ordinary breakfast. Thereafter urine was passed every hour until 2 p.m., a drink of water being allowed hourly, but no solid food being given until after the completion of the test.

Chart I.

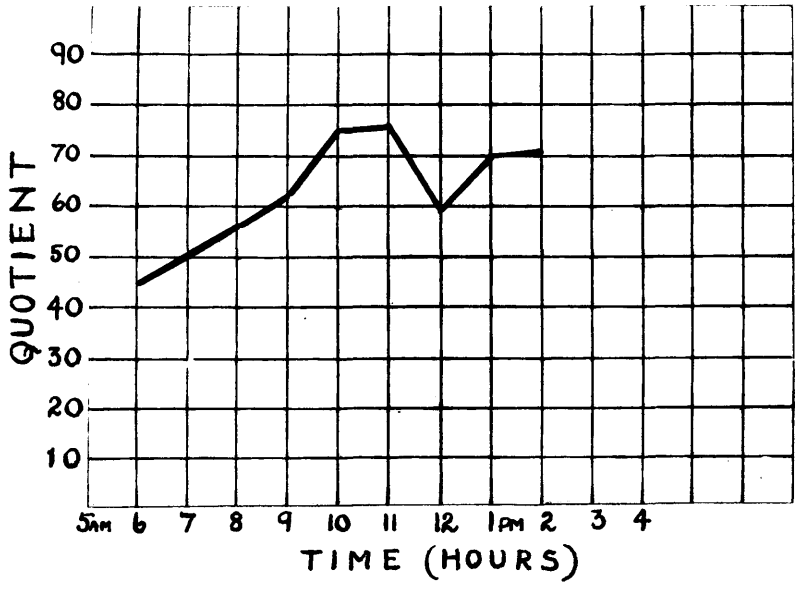


Chart I. Fractional test meal showed free HCl in 31-45 per cent. category.

Chart II.

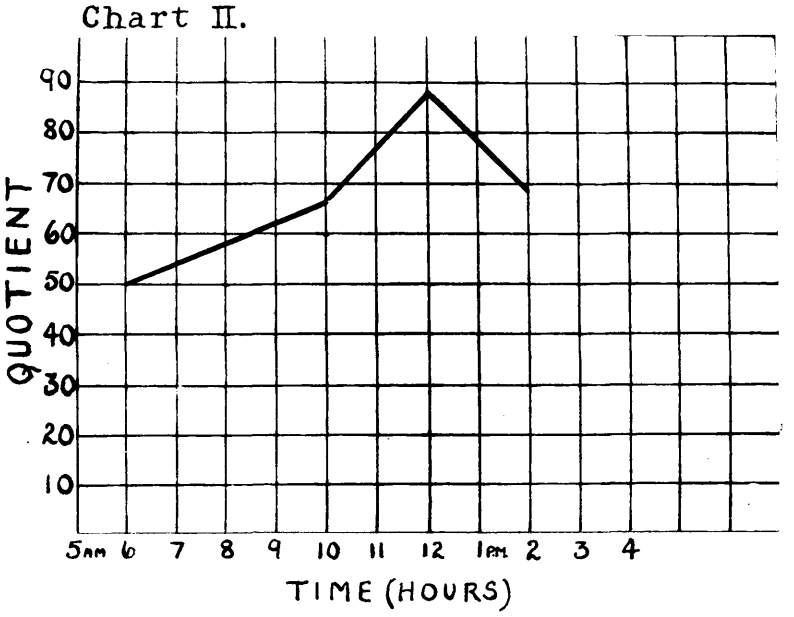


Chart II. Fractional test meal showed free HCl in 21-30 per cent. category.

Chart III.

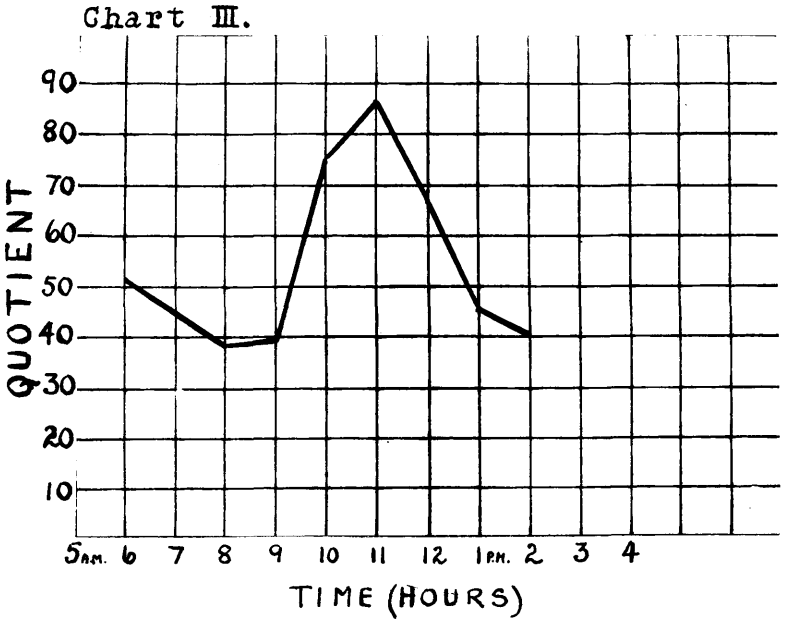


Chart III. Fractional test meal showed free HCl in 21-30 per cent. category.

Chart IV.

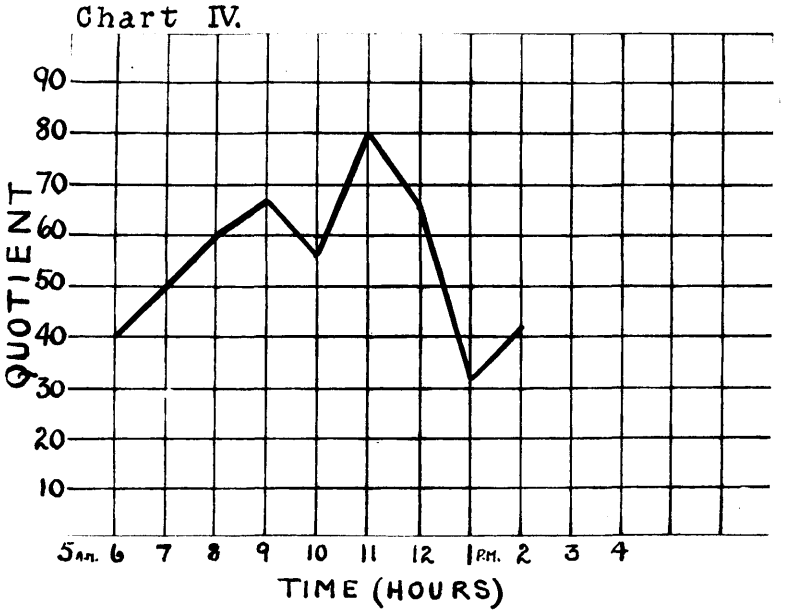


Chart IV. Fractional test meal showed free HCl under 10 per cent.

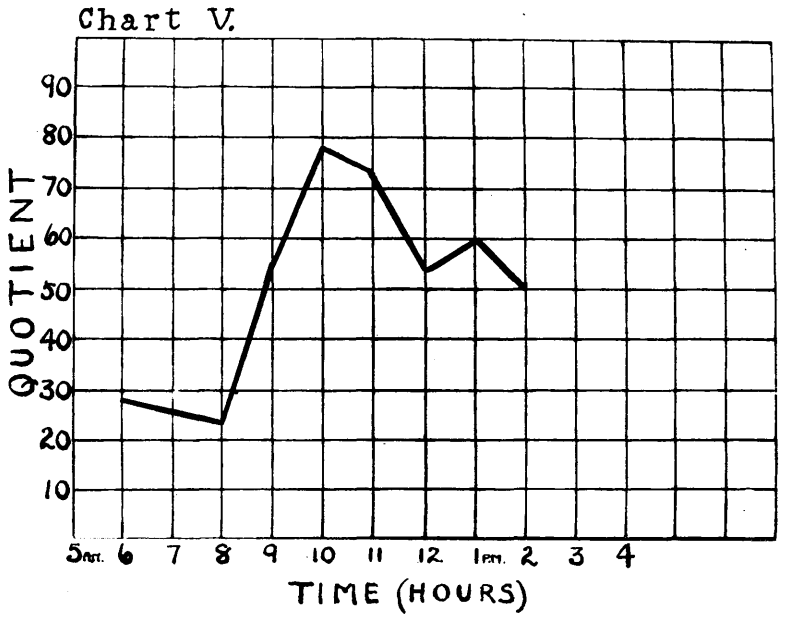


Chart V. Fractional test meal showed free HCl under 10 per cent.

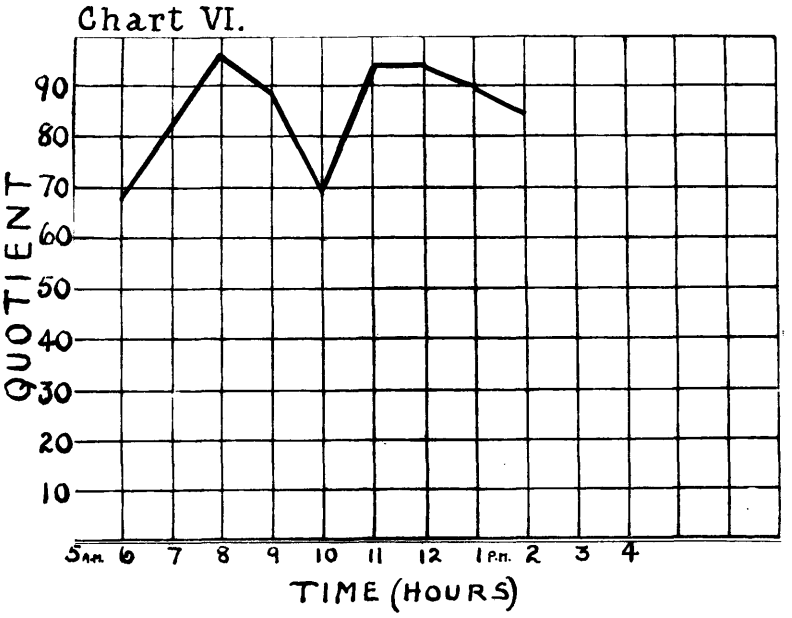


Chart VI. Fractional test meal showed achlorhydria.

The cases having free hydrochloric acid in the gastric secretion, independant of concentration, show a marked elevation in the graph after the ingestion of food, thus pointing to an increase in the percentage of dibasic phosphate excreted. In the patient with achlorhydria, on the other hand, there is an actual fall in the curve after the morning meal, and even the previous level is not regained in the subsequent rise: however, the important point is that the general level of the

graph is higher than in all the cases showing free hydrochloric acid in the stomach, irrespective of percentage. (Chart VI.) This is indicative of a sustained increase in the excretion of alkali in those cases in which there is achlorhydria — a factor contributing to the production of the state of acidosis. The examples are few, but they serve to emphasise the important part which must be played by achlorhydria in the development of toxaemic vomiting.

DISCUSSION.

It is remarkable that no previous investigation of gastric acidity in the vomiting associated with pregnancy has been carried out in this country. During the course of this study, certain other observations by Americans were noted. Kydd (1930) found free hydrochloric acid absent from the vomitus in two cases of vomiting of pregnancy. Arzt (1930) reported a series of 50 cases of pregnancy associated with nausea and vomiting. Of these, 29 (58 per cent.) in the first three months had a total absence of free hydrochloric acid, while the total acidity showed a corresponding decrease. The appearance of free hydrochloric acid in women who, earlier in pregnancy, had shown a total absence of free acid, was also demonstrated by him. The criticism to be advanced against Arzt is that he only examined specimens 45, 60 and 75 minutes after the commencement of the test meal. In the present series there were noted instances in which free hydrochloric acid did not appear until samples later than 75 minutes after the meal were examined, and which, according to Arzt's procedure would, therefore, have been classed as achlorhydria. Herein lies the explanation of the high incidence of achlorhydria in Arzt's series of cases (58 per

cent.) as compared with the writer's 32 per cent. Arzt, while observing a decrease in free hydrochloric acid in all his cases, found that the total chlorides in the fasting contents of the stomach were normal or even increased.

Mason (1931), in a study of six cases of vomiting of pregnancy during the second and third months, found a complete absence of free hydrochloric acid in four (66 per cent.) while, in the other two, the concentration was much decreased. Mason's series, of course, is too small for comparison.

With these exceptions, no reference to gastric acidity in the vomiting of pregnancy had been encountered in the literature until, when the work was well advanced, the papers of Strauss and Castle appeared.

Strauss and Castle (1932) carried out gastric analyses in twenty-four women during pregnancy and the puerperium, and their results showed that 75 per cent. of the patients did not secrete normal amounts of free hydrochloric acid or pepsin during more than half of the period of pregnancy. Excluding three patients who had persistent achlorhydria even after histamine injection, 80 per cent. of the patients secreted higher concentrations of hydrochloric acid in the gastric juice after delivery than during pregnancy, the secretion during the puerperium being approximately three times as great as that during the sixth month of gestation. In another paper (1932) in which they discussed the relationship of dietary deficiency and gastric secretion to blood formation during pregnancy, these workers concluded that anaemia in pregnancy occurs during the last trimester of pregnancy, when the foetus draws upon the maternal organism for blood-building, muscle-building and storage materials, and is found only in those patients who have

had for a considerable time a defective diet or dietary deficiences conditioned by gastric anacidity or related gastro-intestinal disturbances. Their observations suggest the importance of an optimal diet, and one especially rich in proteins and iron-containing foods for the prevention of anaemia in pregnancy. Cravings or longings for unusual and even repulsive articles of diet are not uncommon in pregnancy, and one wonders to what extent they represent an attempt on the part of the body to rectify dietary deficiences.

Strauss and Castle (1933) showed that the hypochromic anaemia of pregnancy is due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypo-acidity or associated defects, in the presence of the foetal demand for blood-building materials. It may be completely relieved, either during or after pregnancy, by the administration of iron in large doses. The macrocytic anaemia of pregnancy, they state, is presumably due to a temporary lack in the gastric juice of the specific intrinsic factor which has been shown to be absent from the gastric juice of patients with Addisonian pernicious anaemia in relapse. They make the hypothesis that there is an ultimate complete return of this factor after delivery. The macrocytic anaemia of pregnancy may ordinarily be completely relieved with liver extract, although iron is sometimes required in addition.

In an earlier paper (1930), Strauss recorded three cases of chlorotic anaemia of pregnancy in which there was complete absence of free hydrochloric acid on gastric analysis, including post-histamine specimens. The first of these cases was examined after delivery, so also was the second, while the third was investigated during the last month of pregnancy. All

three cases recovered on iron therapy alone, and it was felt that the diet furnished an adequate amount of iron, in spite of the possible faulty assimilation due to the achlorhydria, as long as there were no added demands upon the patients. Pregnancy, however, was just such an added demand, and, until more iron was therapeutically added to the diet, anaemia developed.

Wilkinson and Brockbank (1931), in an examination of a large number of patients with pernicious anaemia and their relatives, found that at least 24 per cent. had gastric impairment — achylia or achlorhydria. Wilkinson (1932) has shown that heredity is a very important factor in the aetiology of pernicious anaemia. He emphasises that the gastric impairment is of considerable significance, and indicates the advisability of periodical examinations of such relatives, especially females during the child-bearing period. It has been Wilkinson's custom to carry out regular investigations on as many as possible of the relatives of patients with pernicious anaemia. In consequence, it has been possible to keep under observation several women who are the subjects of gastric achylia with blood pictures of normal appearance, but who occasionally complained of varying symptoms such as vague dyspepsia: eventually pregnancy has occurred and, in two patients, typical pernicious anaemia has subsequently developed.

Achlorhydria has been detected in quite a variety of conditions. The apparently congenital type is present in only about 4 per cent. of all subjects, and some there are who assert that these people are liable to develop pernicious anaemia or subacute combined degeneration of the cord. The achlorhydria of hyperemesis gravidarum differs from that of pernicious anaemia

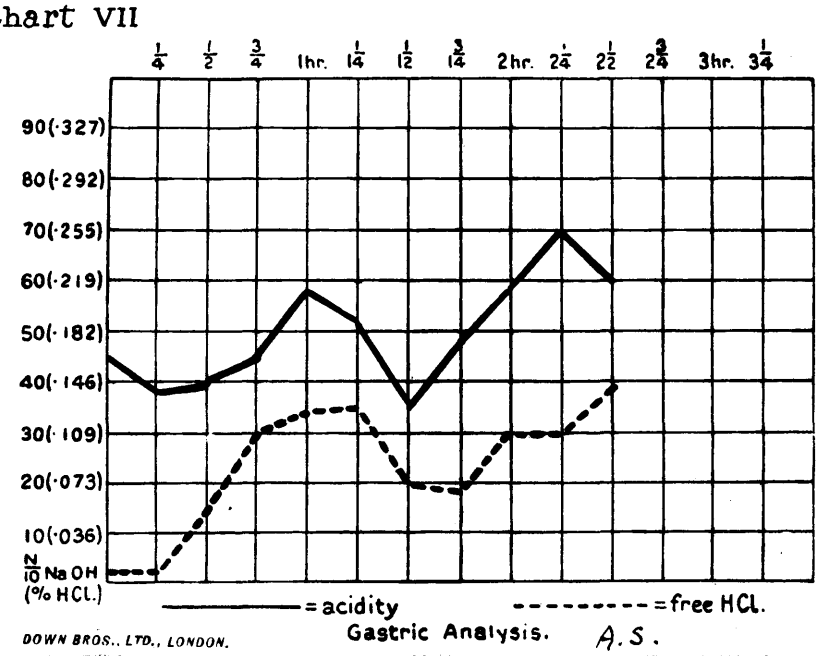
and gastric carcinoma in that it is not persistent: with treatment, free hydrochloric acid again appears in the stomach in a comparatively short time. Tertiary syphilis is associated with achlorhydria, but a positive Wassermann bears no relationship to the achlorhydria of the pernicious vomiting of pregnancy. Achlorhydria has been noted in allergic conditions such as asthma, and many investigators have observed its occurrence in a large number of infectious diseases. For example, typhoid, paratyphoid, typhus, pulmonary tuberculosis, malaria, influenza, pneumonia and enteritis show achlorhydria in a considerable proportion of cases, and hypochlorhydria in others. Conditions such as these are mentioned to emphasise the fact that the achlorhydria of emesis and hyperemesis gravidarum is in a category by itself. It is exhibited in a woman who does not suffer from any of these diseases, and who, prior to pregnancy, was normal in every way, having no gastric disturbance. Such achlorhydria, therefore, appears to be primarily due to the pregnant state.

In the present series, 15 of the specimens of vomitus from 21 patients suffering from more or less severe vomiting, showed achlorhydria, and of these, 13 belonged to the group of hyperemesis. The other 2 were cases of pyelitis, but these had suffered from excessive vomiting at an earlier period in their pregnancy. In the remaining 6 cases examined, only slight traces of free hydrochloric acid were found in the vomitus. There was, therefore, no reason for believing that free hydrochloric acid is lost in any considerable quantity in the vomitus.

Stewart and Dunlop (1930) state that the loss of water and hydrochloric acid in the vomitus has the effect of leading eventually to dehydration and depletion of the blood and tissue

chloride. They instance the very marked alkalosis which occurs in high intestinal obstruction, where there is a similar chloride loss with dehydration. In the cases under review, the absence of free hydrochloric acid in the vomitus, together with the small amount of chloride excreted would appear to indicate that the achlorhydria or hypochlorhydria of the vomiting of pregnancy cannot be accounted for in this way. This is in accordance with the fact that, although the blood chloride in severe cases of the vomiting of pregnancy may be as low as 250 mg. per 100 cubic centimetres, the carbon-dioxide combining power of the blood is low, if not within normal limits, thereby showing that there is rather a tendency to acidosis, which is probably of the starvation type.

Chart VII



Fractional analysis during menstruation in a case of pre-menstrual vomiting.

An interesting case for comparison was a girl who suffered from habitual pre-menstrual vomiting which disappeared immediately with the onset of the flow: this is by no means an uncommon occurrence. Here the vomitus did not contain free

hydrochloric acid, while a fractional test meal during menstruation disclosed normal acidity curves of the 31 per cent. to 45 per cent. type. Incidentally, such a case lends corroborative evidence to the view that sickness is associated with endometrial changes and hormonal variations (menstrual).

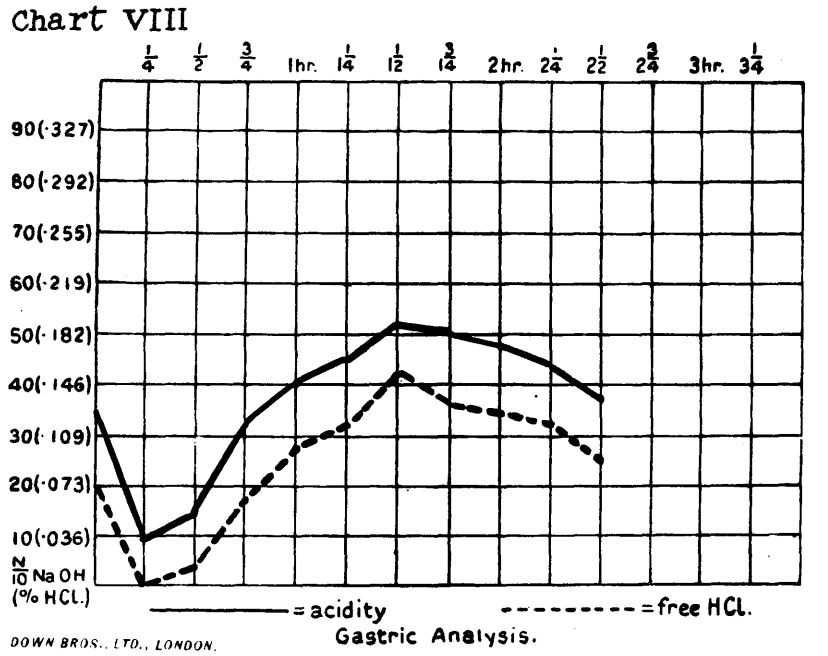
In the 82 cases in which fractional analysis of the gastric contents was carried out, there did not appear to be any necessity for determining the presence of a true achlorhydria in the toxic state, because in hyperemesis gravidarum, on which attention was mainly directed, with improvement in the condition of the patient there was a return of free hydrochloric acid in the gastric secretion. It is possible that this may have influenced the findings in the cases showing hypochlorhydria, and that examination at an earlier stage might have revealed achlorhydria. The achlorhydria of hyperemesis gravidarum is not, therefore, a congenital anomaly.

The suggestion has been made that the achlorhydria or hypochlorhydria is due to the regurgitation of alkaline duodenal contents into the stomach: were that the case, one would expect to find bile more constantly in evidence. Strauss and Castle (1932) have noted the absence of bile too, and have found peptic enzyme values fairly well correlated with acidity values, suggesting that neutralisation from duodenal contents has not been involved.

Neither mucus nor saliva has been present in excess in any of the cases save one. Brief notes of this case of hyperemesis, in which ptyalism was so distressing a feature, are appended. On the first occasion on which the vomitus was collected for twenty-four hours, it showed no free hydrochloric acid. In the belief that it might contain some specially toxic

product, the vomitus was fed to two rabbits. An hour thereafter one rabbit showed great lassitude: two hours afterwards the other exhibited similar symptoms. Twenty-four hours later both were in the same state, but recovery followed. Six days later the patient's vomitus collected for 24 hours contained no free hydrochloric acid. On the third occasion, nine days later, the stomach tube was passed, and the resting contents, even after some had been vomited up, amounted to 42 cubic centimetres. Free hydrochloric acid was absent. The stomach was washed out, and the fluid returned was found to contain free hydrochloric acid to the extent of five per cent., while the total acidity was seven per cent. An amount equivalent to two-thirds of the fluid returned in the gastric lavage was injected intravenously and intraperitoneally into a rabbit. No ill effects were noted. Steady improvement in the patient's condition followed a complete miscarriage. Just before dismissal a test meal showed the apex of the free hydrochloric acid curve as 42 per cent. at one and a half hours(Chart VIII).

Chart VIII



The absence of excessive mucus in the cases generally is significant, because it might exert a neutralising effect on account of its slightly alkaline reaction, and might further produce mechanical interference by blocking the minute openings of the ducts which convey the formed acid to the lumen of the stomach.

Fatty articles of diet are well known inhibitors of gastric secretion: fat, however, is the very type of food for which the patient having emesis or hyperemesis gravidarum has no desire — for which, indeed, she exhibits actual loathing.

In all save one of the cases associated with achlorhydria, the total acidity curve was low, and, in that instance, lactic acid was present in considerable amount. Consequently, combination of acid with protein cannot be advanced as the reason for the disappearance of free hydrochloric acid from the gastric secretion.

It is interesting to note that, during the second, third and fourth months of pregnancy — the period in which emesis and hyperemesis are likely to be most pronounced — a proteolytic ferment can be demonstrated in the trophoblastic villi, and a considerable amount of destruction of maternal tissue must result therefrom.

The psychic effect of the test meal has been quoted as accounting for the achlorhydria or hypochlorhydria in cases such as those under review. Apperly and Norris (1931) state that it has long been their view that temporary psychic disturbances have little appreciable effect on either the general form and magnitude of the acidity curve or on the emptying time of the stomach. Observations made in the present series certainly

support that conclusion: it was amazing to witness the apparent ease with which Ryle's tube was retained "in situ" even in severe examples of hyperemesis gravidarum.

It is important to note that, in the series investigated, there were three cases of hyperemesis gravidarum in which hyperchlorhydria was shown — cases in which, judging by the severity of the symptoms, one would have expected achlorhydria or hypochlorhydria. Wilkinson and Oliver (1931), examining cases in which the clinical condition suggested impairment of gastric secretion (but not associated with pregnancy) stress this fact, that occasionally one encounters a case presenting the typical clinical picture of the "achlorhydric syndrome" in which a test meal discloses a hyperacidic condition instead of the anticipated hypoacidity.

Numerous workers have shown that the state of hypochlorhydria and the degree of sensitivity of the tissues are closely related. Thus Hemingway (1926-27) from his experiments advances evidence of the exaggerated responses which result from sudden and repeated exposure of sensitised tissue to slight changes towards the alkaline side, of the exaggerated response to adrenalin, and of the reduction in the degree of this sensitiveness by the addition of hydrochloric acid to the perfusing fluid. In many cases, the first indication of sickness in pregnancy is at the time of the first missed menstrual period, which corresponds to the stage at which the process of imbedding of the zygote is taking place. It is not unreasonable to suppose that, with such an entirely new process occurring in the body, all the tissues (especially the endometrium) show increased sensitivity. Such a state of increased sensitivity is

in accordance with the well recognised capricious nature of hyperemesis gravidarum, and with the fact that an apparently trifling disturbance, mental or physical, may be sufficient to precipitate the patient into an irretrievable condition. It has been suggested that women having vomiting in pregnancy are sensitive to placental extract up to, but not after the fourth month of pregnancy. At any rate, the normal cessation of vomiting at the end of the third or the beginning of the fourth month of pregnancy, and its coincidence with the completion of the development of the placenta, points very definitely to the establishment of an equilibrium of some kind.

Endocrine activity, so marked in the early stages of pregnancy, must be concerned in the causation of emesis and hyperemesis gravidarum. Proof of this aetiological relationship of abnormal endocrine activity and the early toxaemias of pregnancy is not yet forthcoming, but it is certain to be demonstrated in due course. A common visible sign of increased activity of the endocrine glands in pregnancy is afforded by the enlargement of the thyreoid. In this connection, it is interesting to note the observation of Brown (1930), viz. that an increased thyreoid secretion, by increasing the sympathetic stimulation, produces a stimulation of the inhibitory acid-secreting fibres of the gastric mucosa, thereby causing a diminution or lack of secretion of acid.

The absence of free hydrochloric acid in the stomach, together with the presence of an abundant bacterial flora, suggests a feasible explanation of the occurrence of sickness in the morning. During the day, while food is being taken at regular intervals, the stomach is never really empty,

consequently bacterial toxins are diluted in the liquid and solid food ingested. During the night, the woman is asleep and no food is taken, with the natural result that, in the morning, the stomach is empty. Hence there is nothing to dilute the bacterial toxins which become more concentrated and are absorbed in pure undiluted form. This explanation is in accordance with the clinical observation that hot milk or tea with a biscuit taken as soon as the patient awakes in the morning is frequently efficacious in combatting the tendency to nausea and vomiting.

The writer has shown that, with increasing concentration of free hydrochloric acid, there is a decrease in the number of organisms present, and that, in cases of vomiting associated with achlorhydria or hypochlorhydria, recovery is coincident with a return or increase respectively of free hydrochloric acid. The administration of dilute hydrochloric acid to such patients is of two-fold benefit: not only does it serve a useful purpose in the digestion of the meal, but it is of the utmost value on account of its antiseptic qualities. Organisms are destroyed and their toxins neutralised: gradually a stop is put to the absorption of toxins. The activity of the gastric glands, previously inhibited by bacteriological activity, is restored by degrees, and eventually the natural secretion of free hydrochloric acid approaches normal limits. Roberts (1927) has noted the stimulating effect of caffeine on gastric secretion. The administration of caffeine citrate in cases of hyperemesis gravidarum, by increasing the secretion of free hydrochloric acid, has a similar beneficial result: bacteria and their toxins are overcome, and gradually improvement follows.

The patient showing achlorhydria, with the consequent abundant flora and generous absorption of toxins, is always in

a more serious condition than the patient having even a small percentage of free hydrochloric acid in the gastric secretion. Unfortunately, one cannot gauge the seriousness of the patient's condition with any degree of accuracy by the mere severity of the vomiting. There may be difficulty in appraising the importance to be attached to the neurotic element superimposed on the basis of toxaemia however slight it may have been originally. Frequently the mere knowledge of pregnancy seems to induce the woman to become apathetic and to exhibit neurotic or neurasthenic symptoms. The neurasthenic type of dyspepsia is well recognised and is frequently associated with achlorhydria. Organisms flourish in the absence of the normal acid germicidal barrier, and, unless the condition is recognised and treated, the whole gamut of symptoms associated with the fully developed toxaemia is soon apparent. Acidosis results from lack of nourishment, and the loss of fluid through continued vomiting eventually leads to dehydration. Fractional gastric analysis in these cases of vomiting of pregnancy enables a truer estimate to be made of the condition of the patient: her state, serious or otherwise, can be gauged more accurately than can be done by clinical observation alone. The writer, after some practice in correlating physical findings with the state of the gastric secretion in emesis and hyperemesis gravidarum, was in many instances able to forecast correctly the result of fractional analysis — as far as the absence or presence of free hydrochloric acid was concerned. Even in the absence of symptoms, the finding of achlorhydria early in pregnancy should lead one to regard that patient as more likely to develop toxaemia than the patient whose gastric secretion contains free hydrochloric acid, no matter how low the concentration.

In the state of hypochlorhydria, bacteria and their toxins have not been able to overcome completely the antagonising free hydrochloric acid. It is in precisely such a condition, when the fate of the free hydrochloric acid secretion is in the balance, that the administration of dilute hydrochloric acid or the stimulation of the gastric secretion by some agent such as caffeine may make all the difference in overcoming the activities of the bacteria and their toxins, and lead eventually to the restoration of the normal state in the stomach.

Of the cases investigated by the writer, there were three examples of hyperemesis gravidarum in which hyperchlorhydria was shown — cases in which the severity of the symptoms suggested achlorhydria. This observation clearly discountenances the routine administration of dilute hydrochloric acid to cases of hyperemesis gravidarum. In the cases cited, recovery was coincident with a fall to normal level of the free and total acid.

The inevitable conclusion is, therefore, that no case of hyperemesis gravidarum can be properly investigated and adequately treated without having fractional gastric analysis carried out.

CONCLUDING REMARKS ON EMESIS AND HYPEREMESIS GRAVIDARUM.

It would appear that variations in the composition of the blood are not characteristic of this toxaemia as contrasted with other toxaemias. Increase of this constituent or a slight decrease in that are not constant findings, and such changes would seem to be dependent upon the stage of the toxaemia at which the blood is examined. Instead of having any aetiological

relationship, these variations from the normal level of the different constituents of the blood must be regarded as being incidental findings and merely accompaniments of the condition. However, in addition to these normal constituents, variable quantities of the gonadotropic hormone emanating from the anterior lobe of the pituitary gland and of oestrin are present in the blood: the former is excreted in the urine in progressively increasing quantity until the end of the fifth month of pregnancy, thereafter decreasing steadily to term, and disappearing from the urine quickly after parturition: oestrin, on the other hand, is elaborated from the onset of pregnancy and increases steadily until the time of parturition, thereafter rapidly subsiding. In hyperemesis gravidarum, there is probably some error in the process of elaboration or excretion of these hormones, leading to endocrinal imbalance.

Achlorhydria and hypochlorhydria have been the outstanding features of the investigation of emesis and hyperemesis gravidarum. The recovery of the patient, coinciding as it does with the return of free hydrochloric acid to the gastric secretion in those cases in which it has been absent, or the increased concentration in those patients where hypochlorhydria has been in evidence, would appear to indicate that, so far as the immediate symptom of vomiting is concerned, achlorhydria or hypochlorhydria is the primary factor. Superimposed upon this is a bacteriological toxaemia; dehydration and emaciation follow as already described. It is probable that hyperemesis gravidarum has a very simple origin such as that stated, as far as the stomach is concerned, and that the complicated picture presented by the fully developed condition is simply the result of a continuous, unchecked, and, therefore, increasing absorption of bacterial toxins.

The initial metabolic process, which is responsible for the scanty secretion or lack of free hydrochloric acid in the gastric juice remains unknown. However, the normal cessation of vomiting at the end of the third or the beginning of the fourth month of pregnancy, by which time the placenta is fully formed, points to the relationship of sickness and placental development. At this stage, many factors are involved, but emphasis should be laid on the following:-

(a) Hormonal activity, initiated by the zygote.

(b) Imbedding of the zygote with destruction of endometrium.

(c) Metabolic disturbances resulting therefrom.

(d) Faulty adjustment between the maternal organism and the developing zygote.

These, individually or collectively, in the light of our present knowledge, are responsible for the early toxaemias of pregnancy.

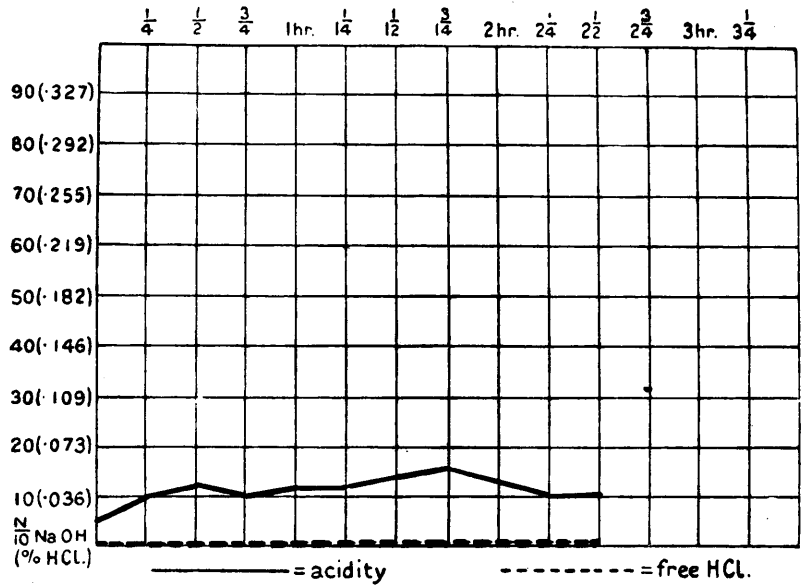
Alvarez and Hosoi (1930) have studied the intestinal tract of pregnant rabbits, and have found that the gradient of irritability is flattened in some and reversed in others, and that the rate of rhythmic contraction is generally slowed. Results such as those detailed would appear to indicate that, during pregnancy, there is a decreased secretory power of the gastric mucosa, but the nature of the mechanism responsible for this diminution is still unknown. The return of free hydrochloric acid to the stomach in those cases in which it has previously been absent suggests that the state of achlorhydria or hypochlorhydria is intimately related to the disturbance of gastric function, but the vicious circle may be more complicated than we imagine.

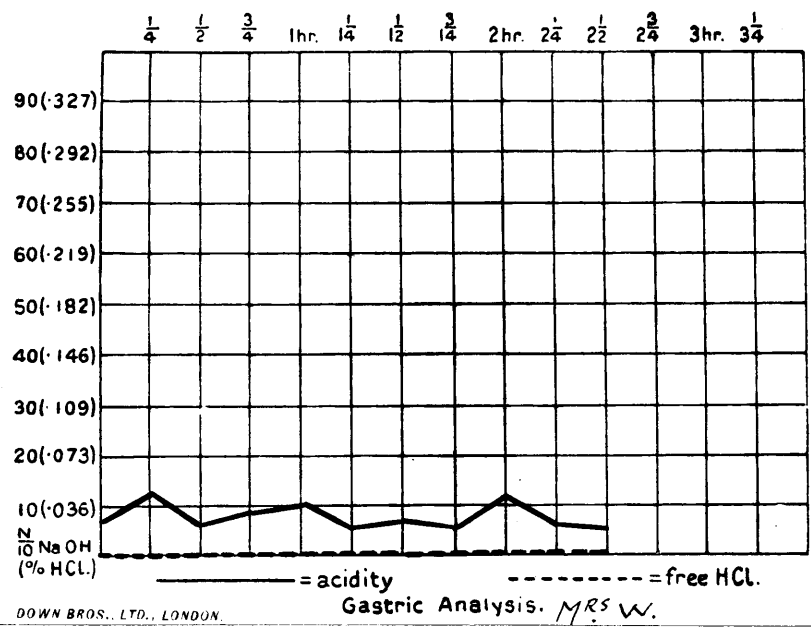
Strauss, in a personal communication (1933), said that

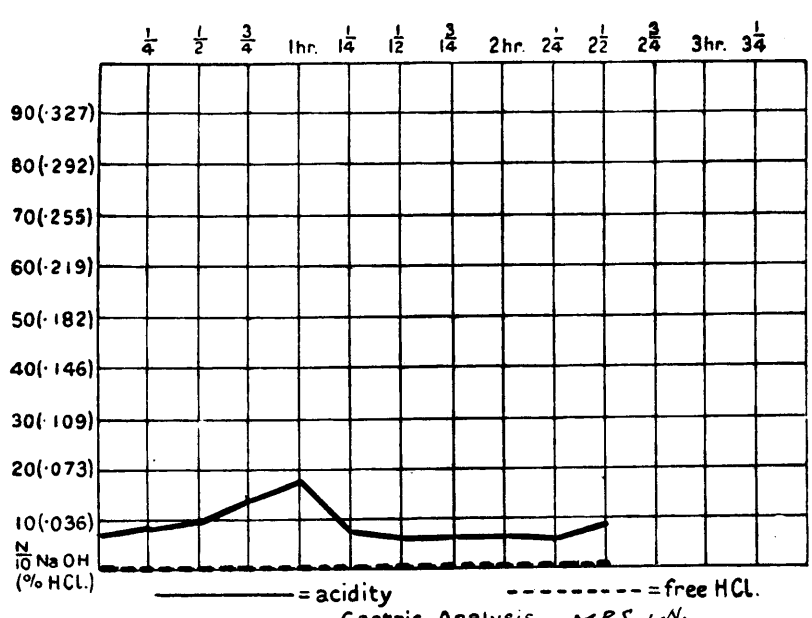
he was particularly impressed in his investigation with the entire lack of correlation between gastric secretory function and the vomiting of pregnancy. However, on the evidence presented, it seems feasible to believe that, in examples of emesis and hyperemesis gravidarum, a former power of secreting free hydrochloric acid has become lost or has disappeared because of the presence in the stomach of some toxic product of metabolism which the stomach attempts to eliminate in the process of vomiting. The discovery of this toxic substance would give the clue to the real nature of hyperemesis gravidarum and would possibly elucidate the mystery of eclampsia to a considerable degree.

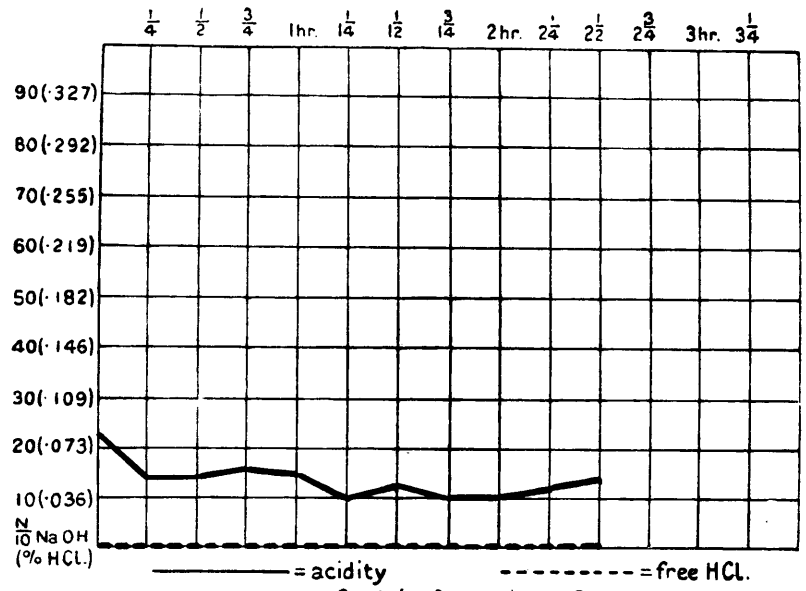
CASES OF EMESIS GRAVIDARUM (30).
(See Table III, p.150)

Achlorhydria (6).









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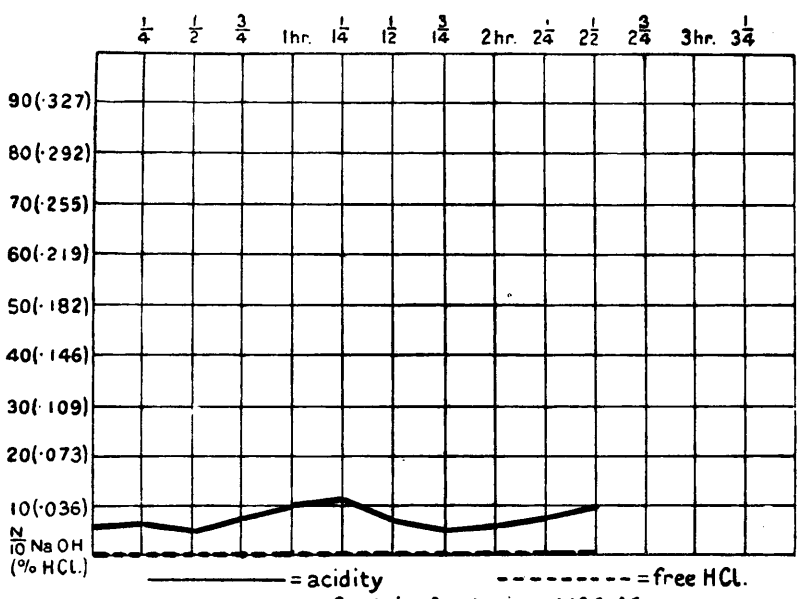
Gastric Analysis. MRS HON.



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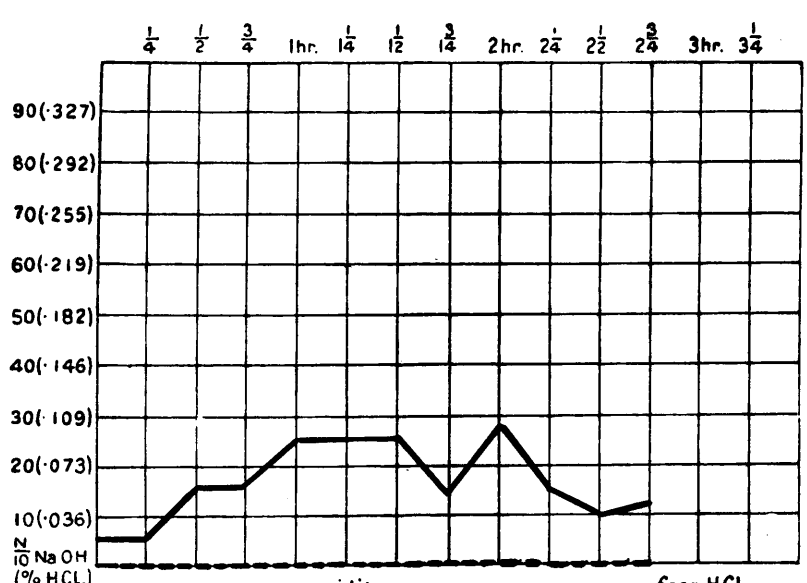

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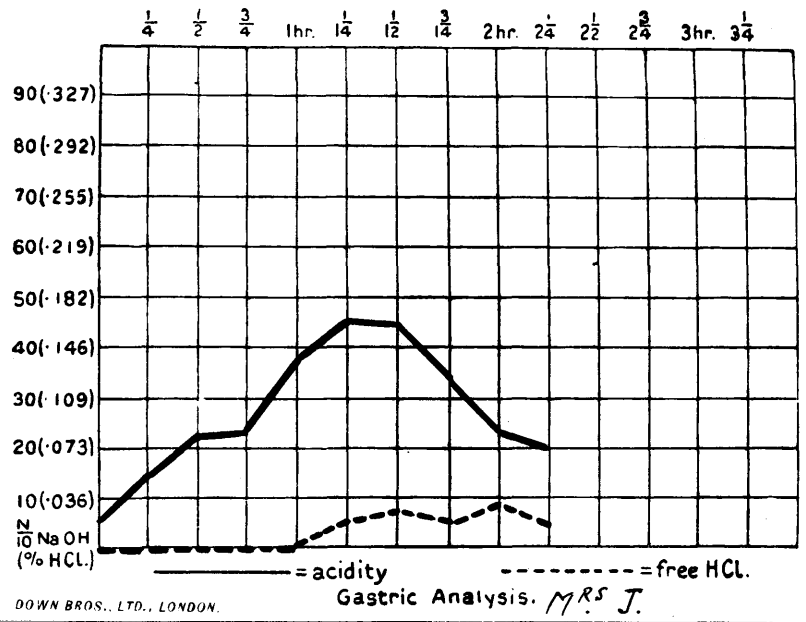
Gastric Analysis. MRS S.

Free Hydrochloric Acid.

10 per cent. and under (3).



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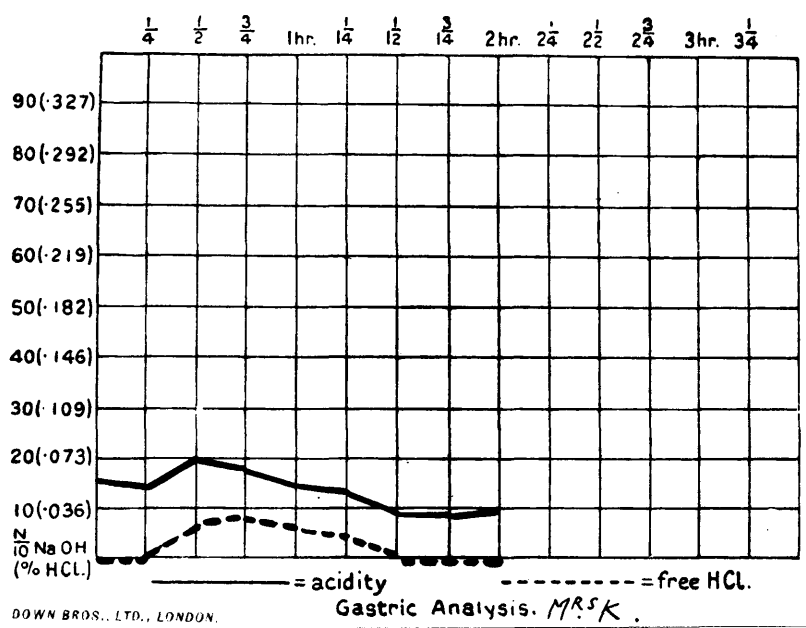

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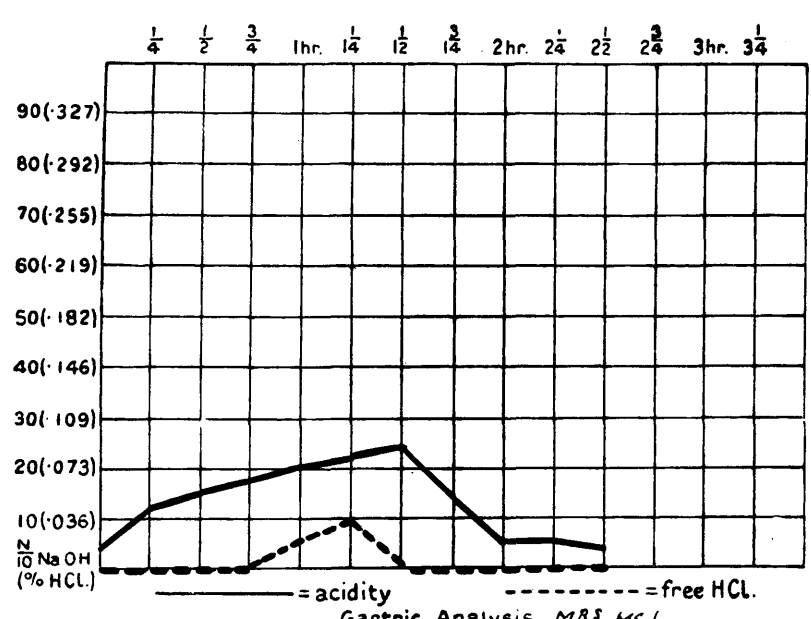
Gastric Analysis. MRS K.



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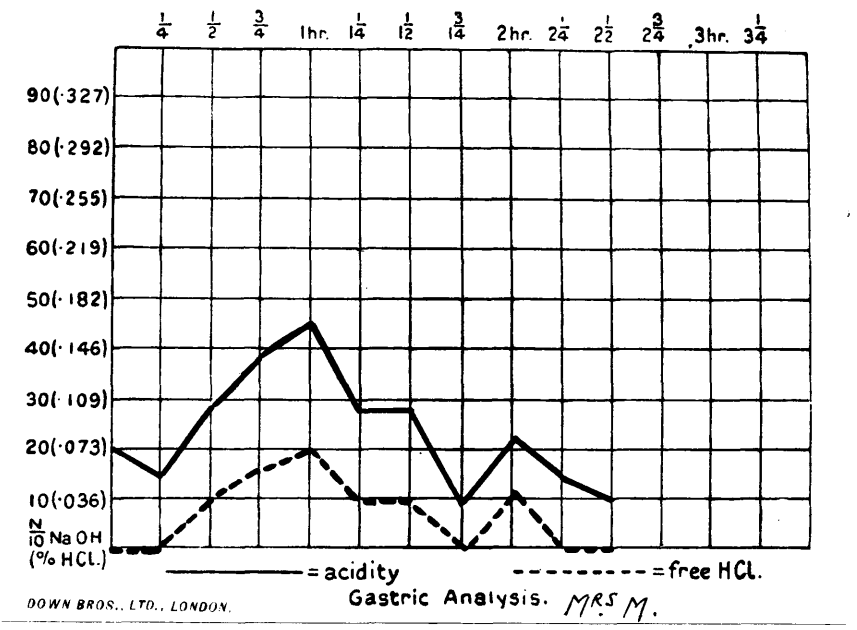
Gastric Analysis. MRS Mc I.

Free Hydrochloric Acid.

11 to 20 per cent. (7).



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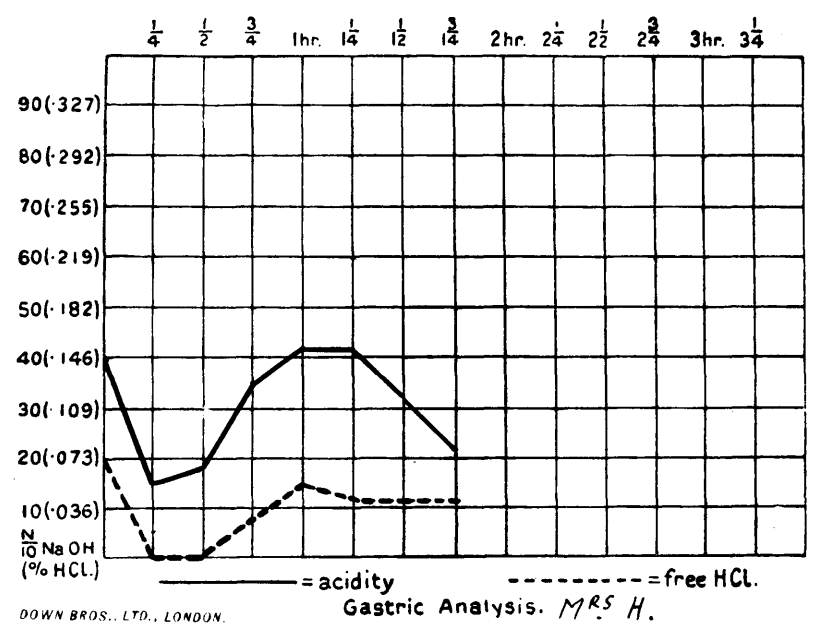
Gastric Analysis. MRS M.



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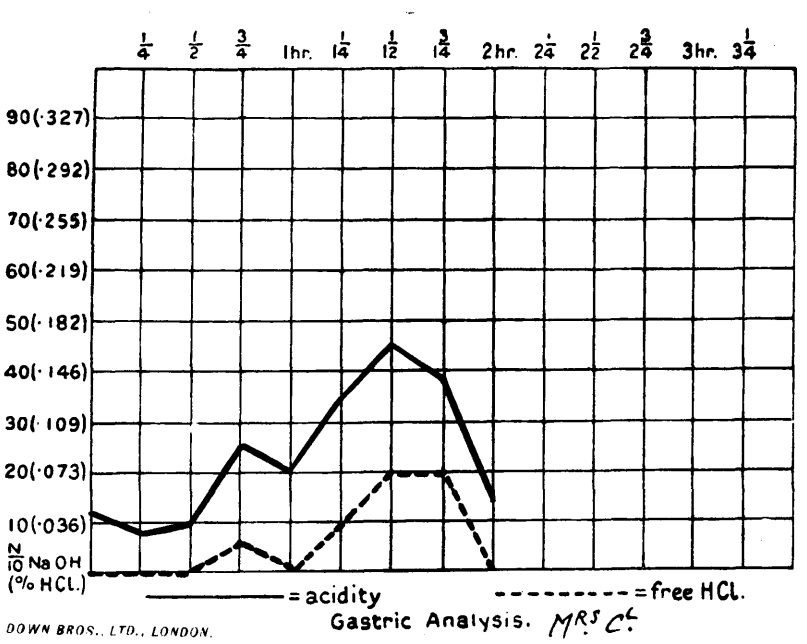

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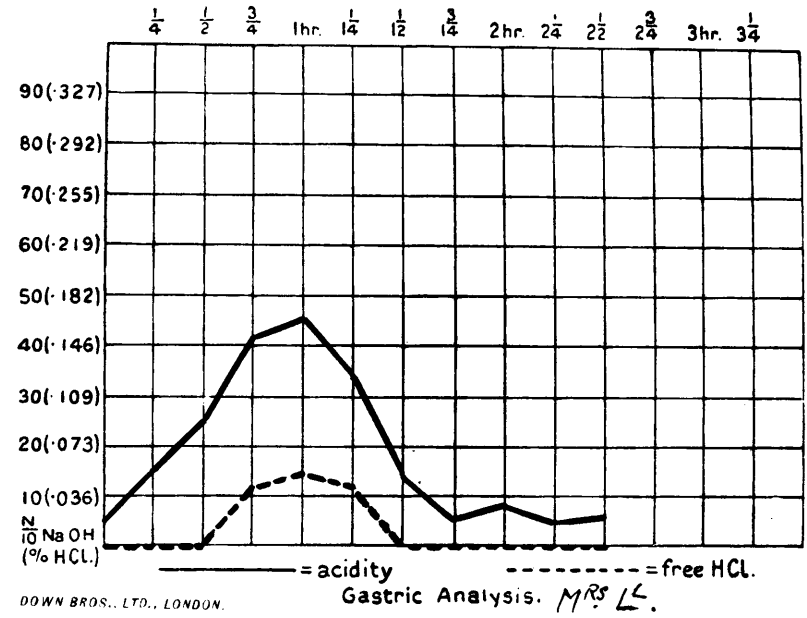
Gastric Analysis. MRS C.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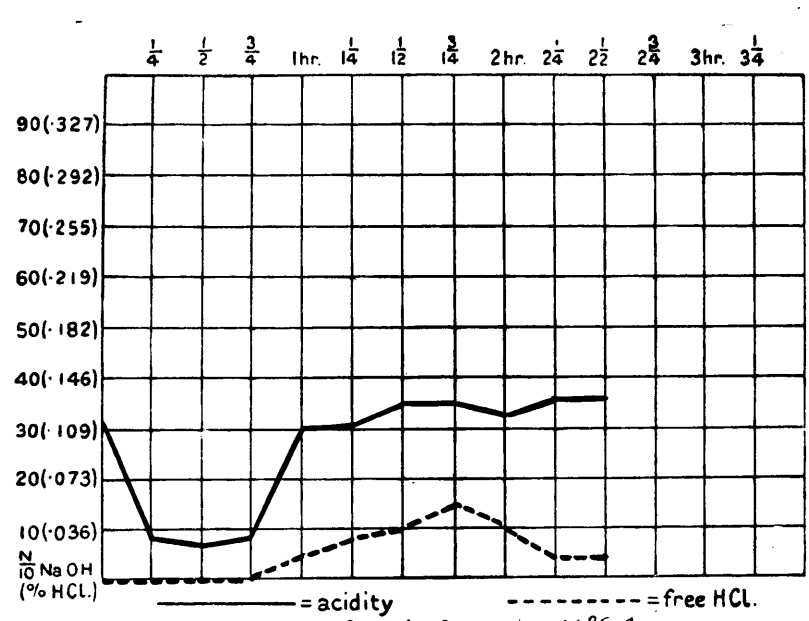
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 NaOH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS L.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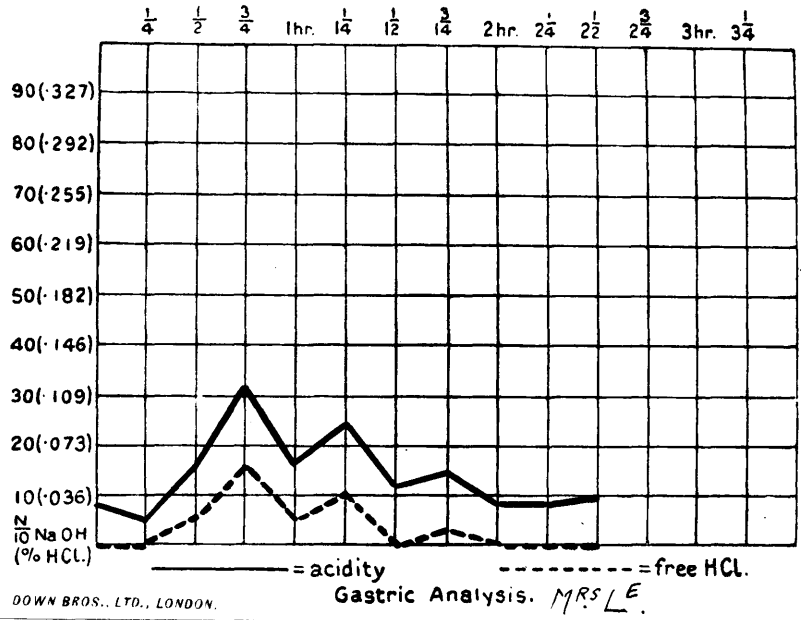
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 NaOH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS G.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40(·146)
30(·109)
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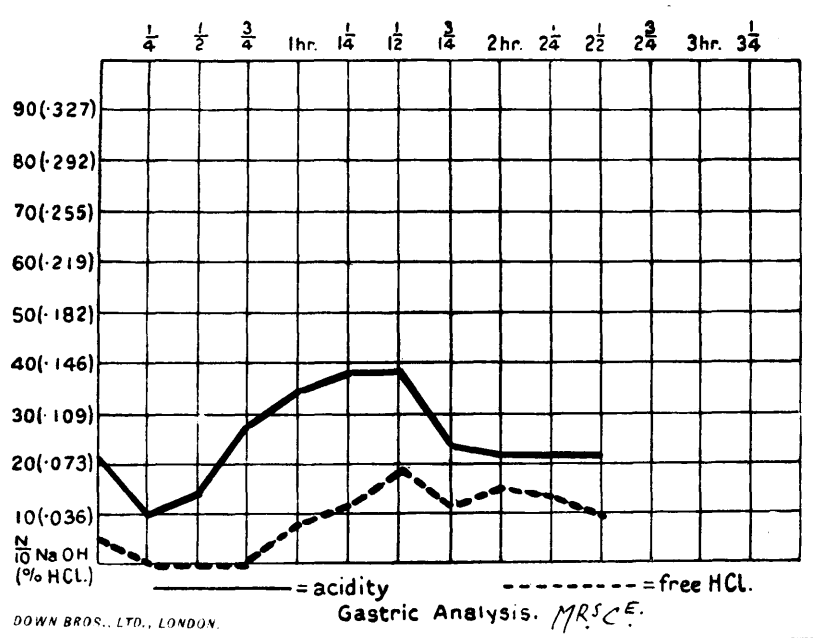
10(·036)
N/10 NaOH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS L E.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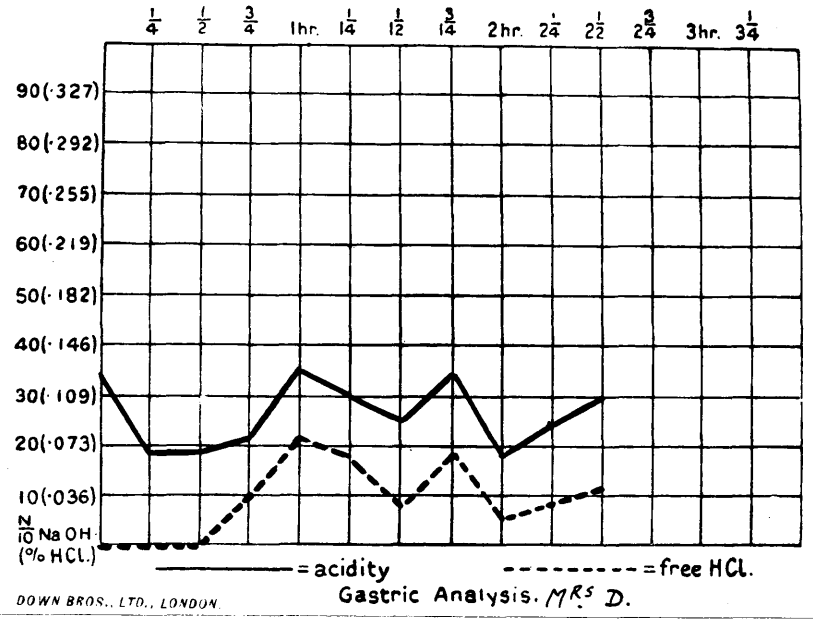
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 NaOH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS C E.

Free Hydrochloric Acid.

21 to 30 per cent. (9).



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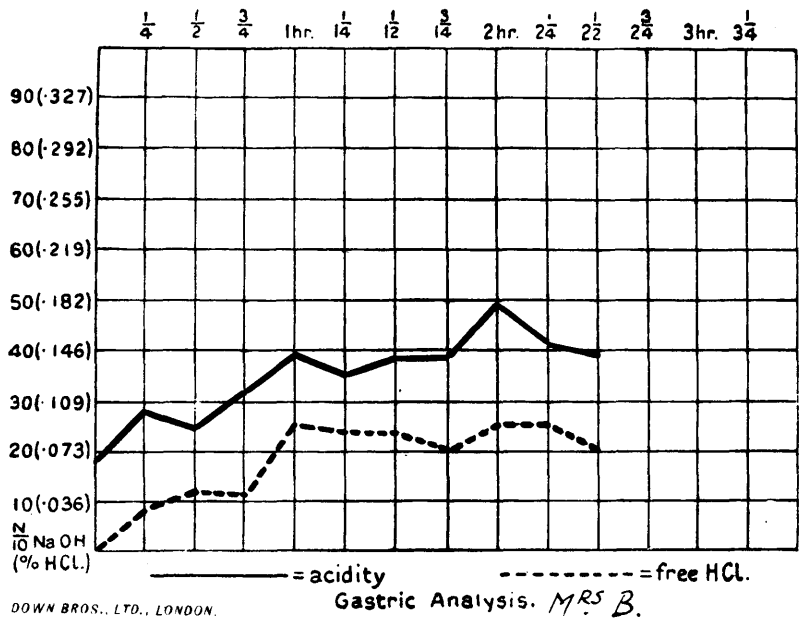
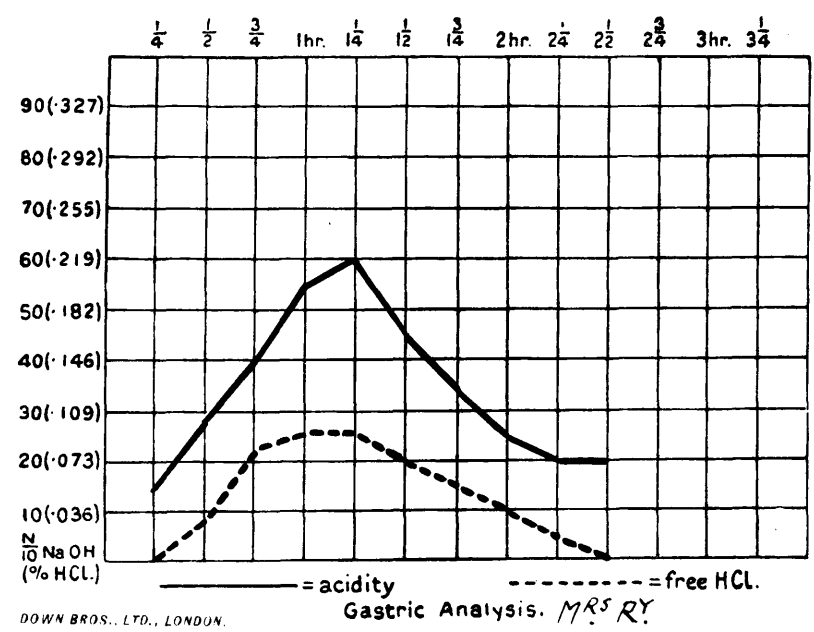
Gastric Analysis. MRS D.



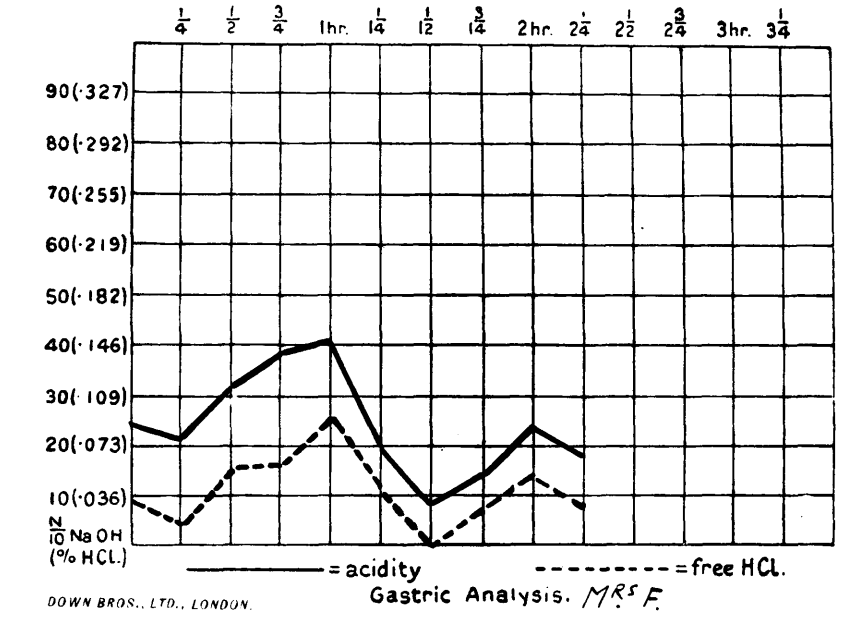
DOWN BROS., LTD., LONDON.

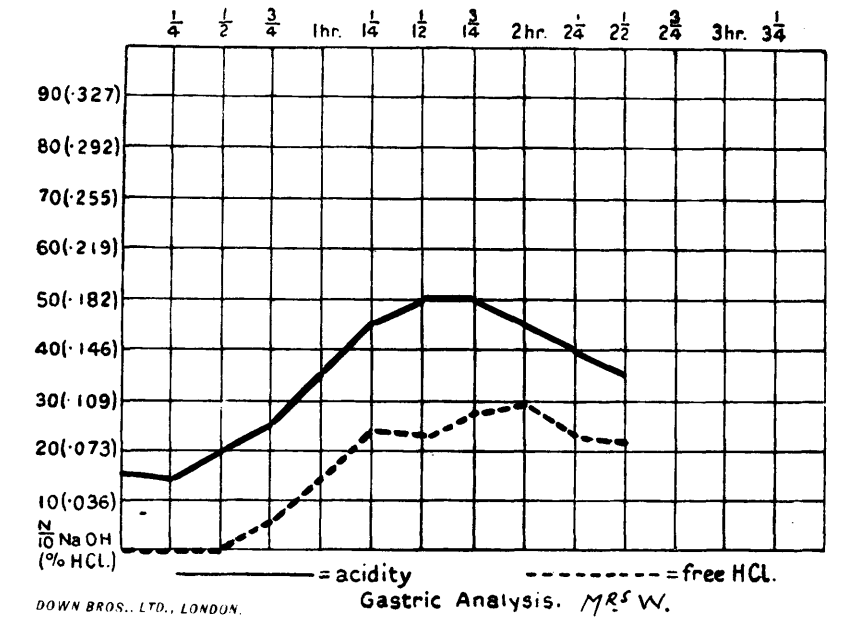
Gastric Analysis. MRS B.

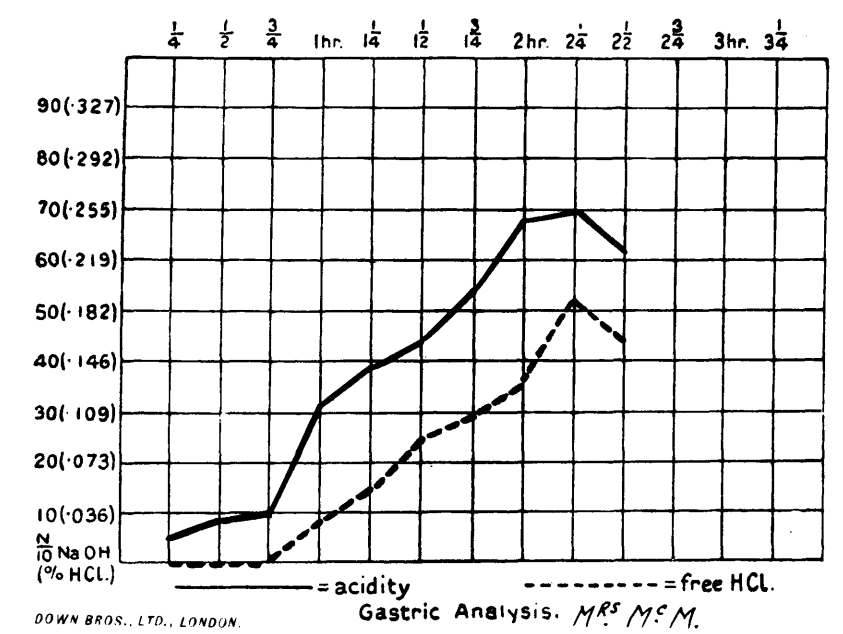


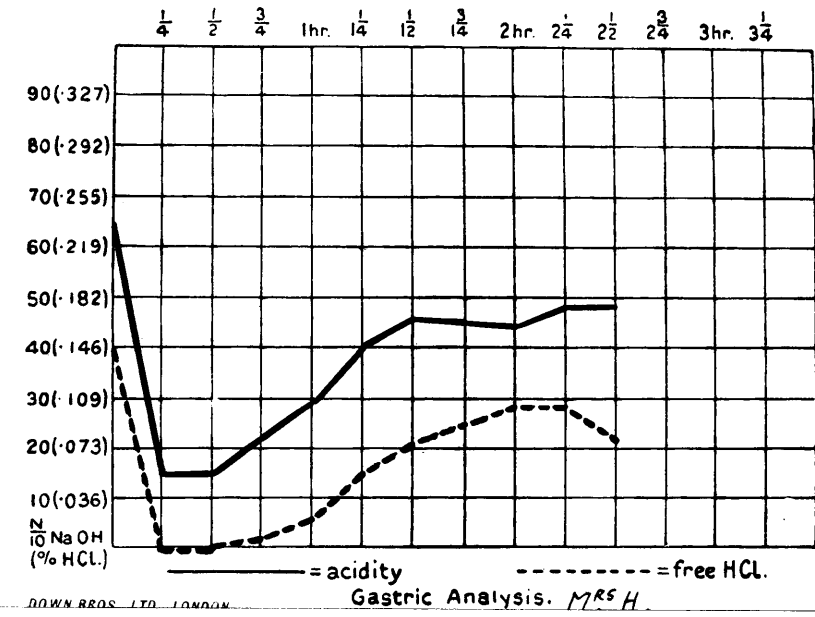
DOWN BROS., LTD., LONDON.

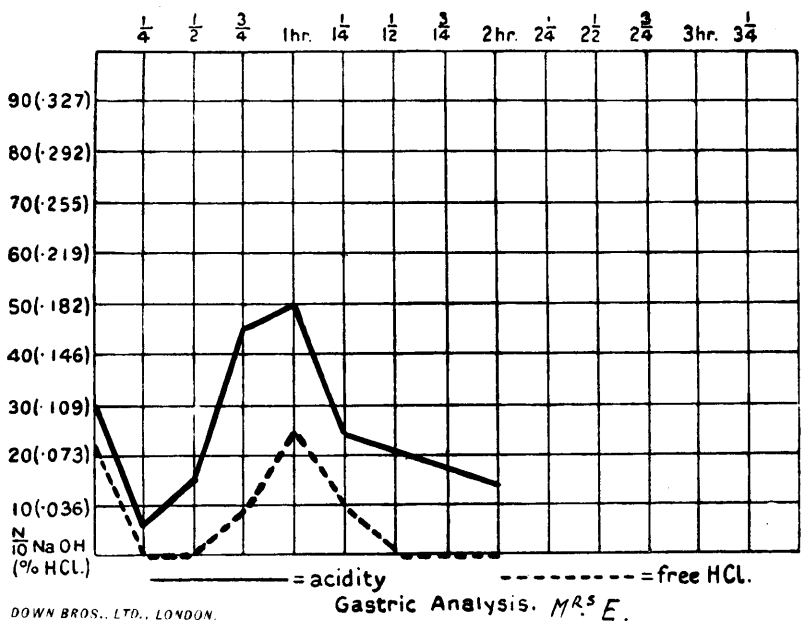
Gastric Analysis. MRS RY.

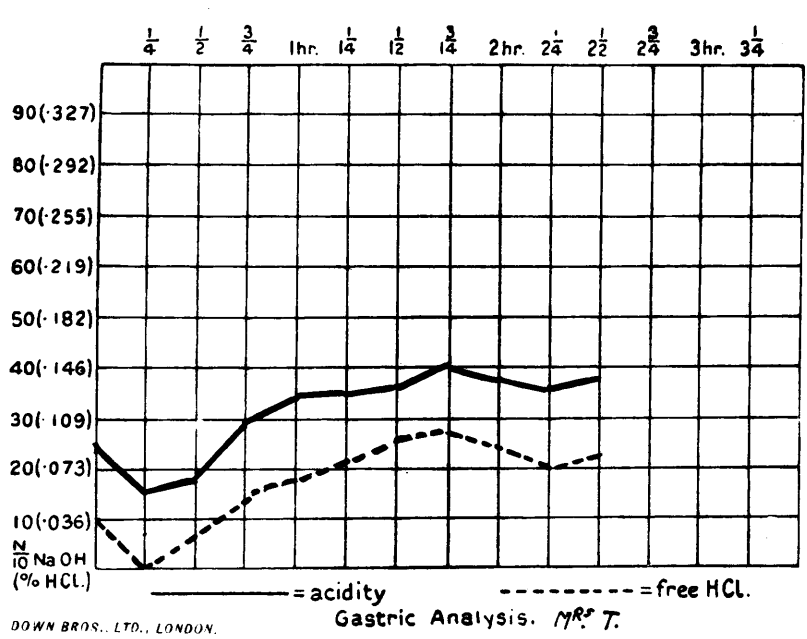

¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS F.


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS W.


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS McM.

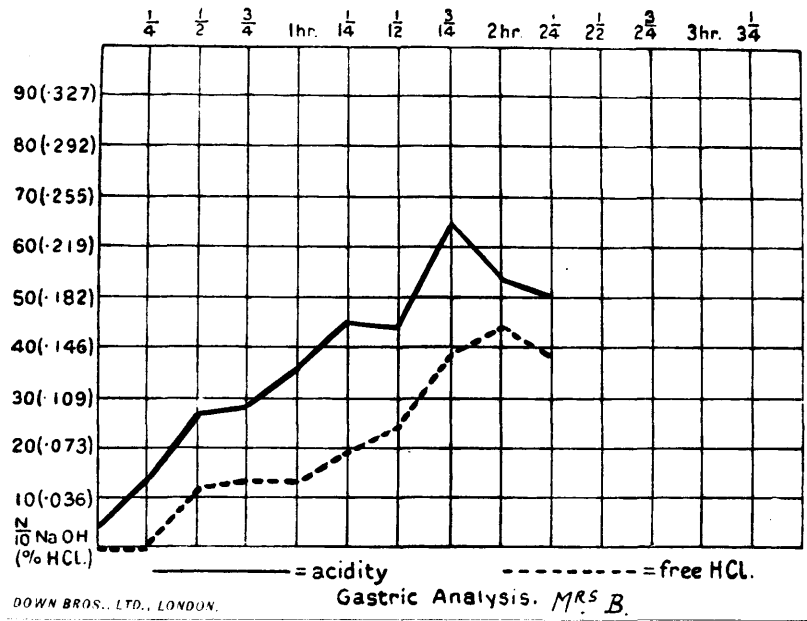

¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS. LTD. LONDON.
Gastric Analysis. MRS H.

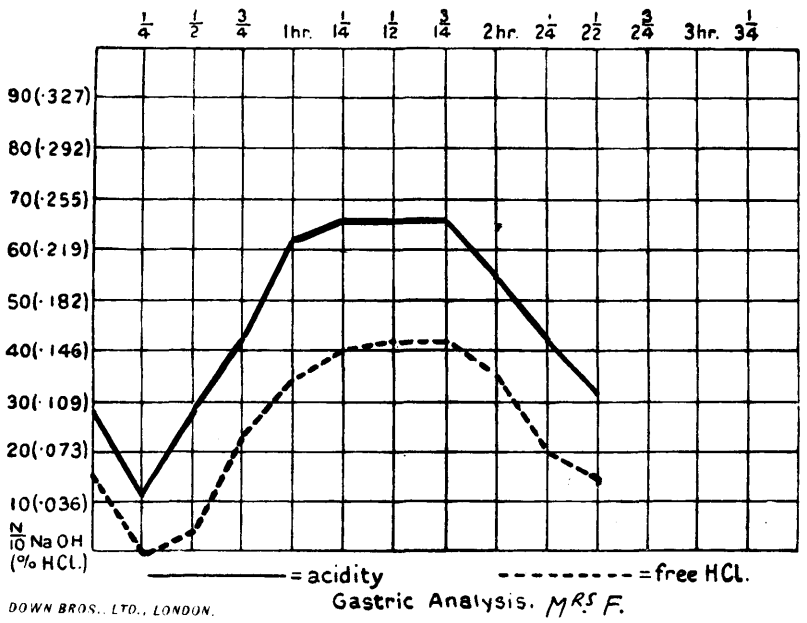

¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS E.

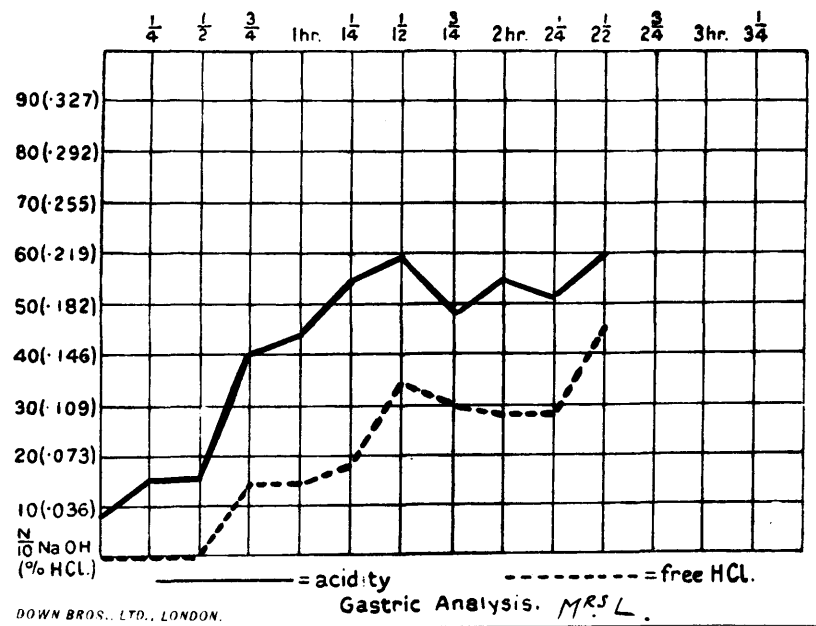

¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS T.

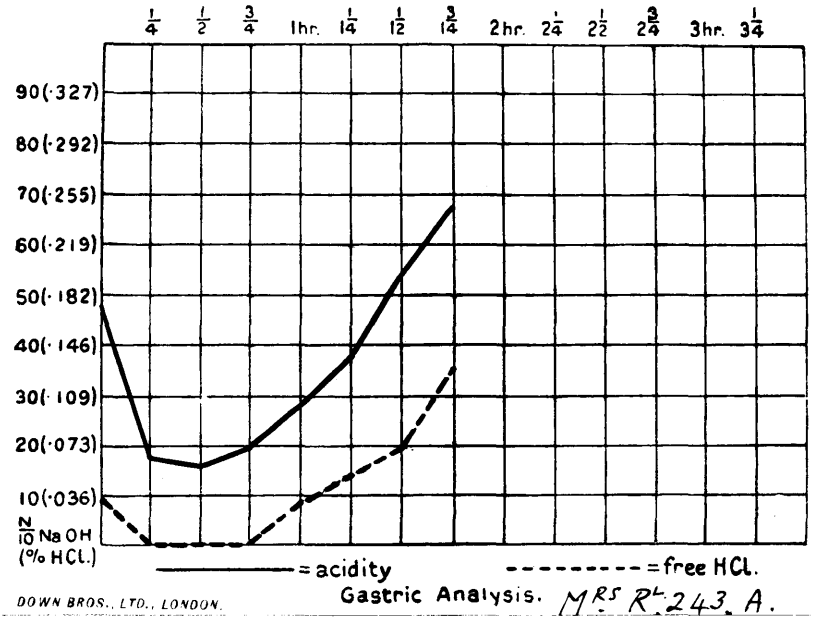
Free Hydrochloric Acid.

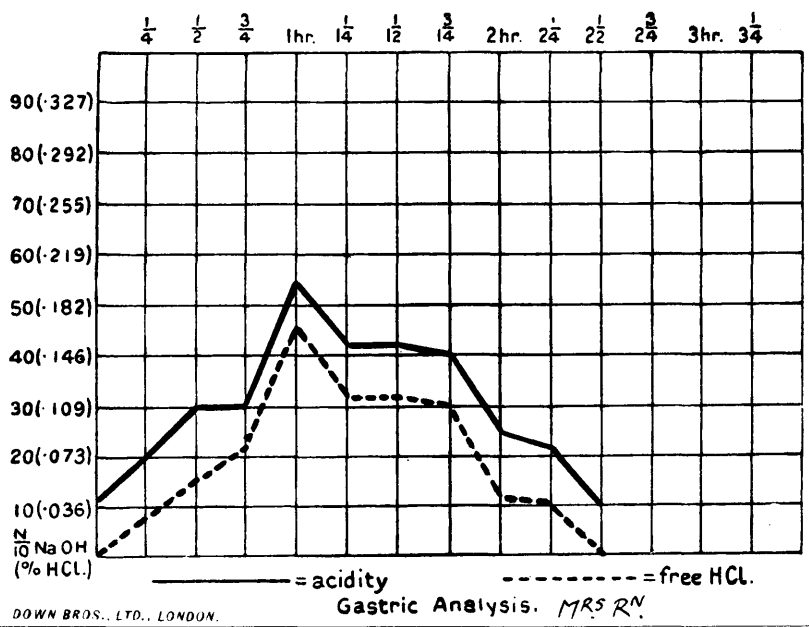
31 to 45 per cent. (5).







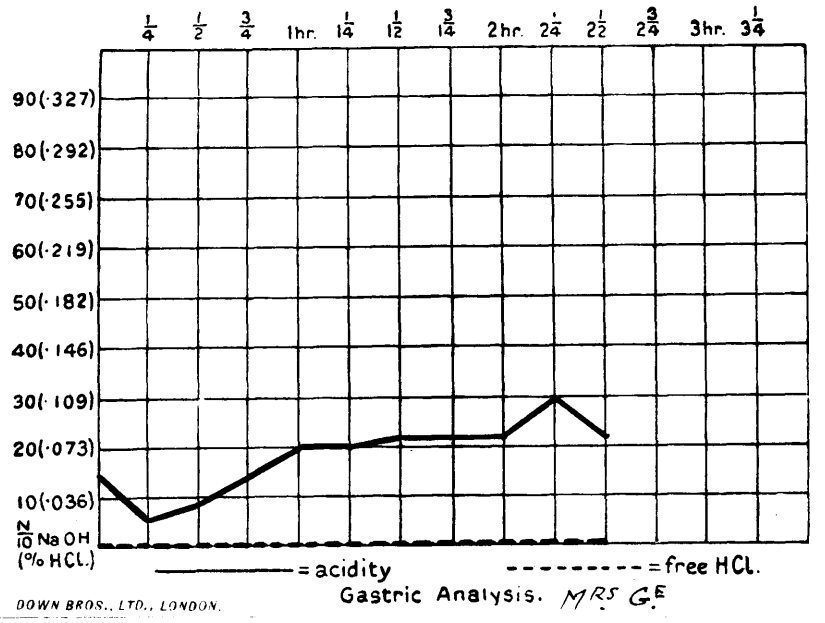

¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS RL. 243. A.

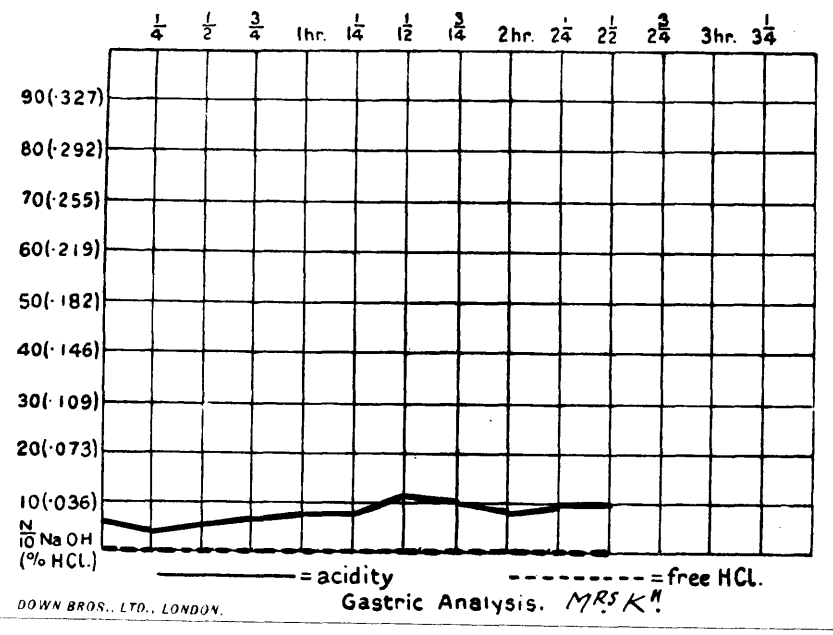

¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS RN.

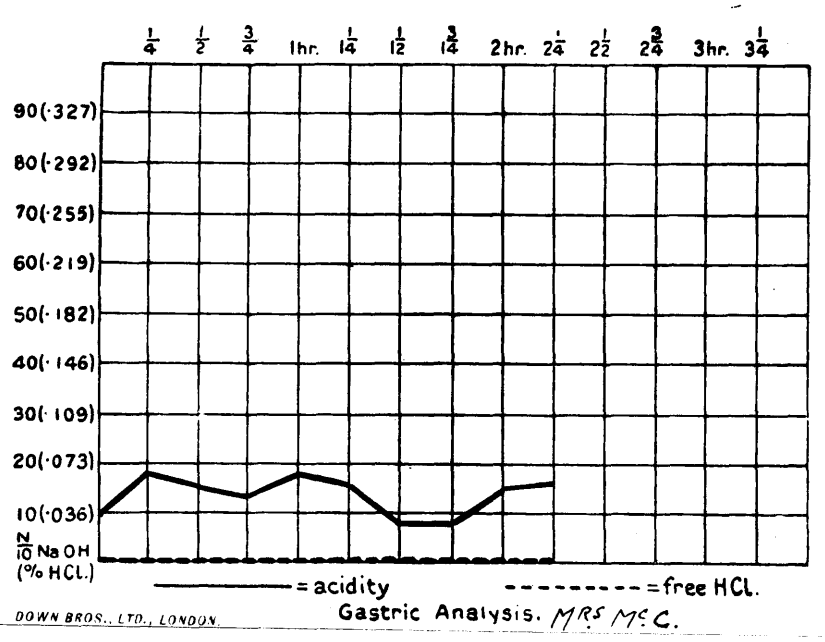
CASES OF HYPEREMESIS GRAVIDARUM (23).

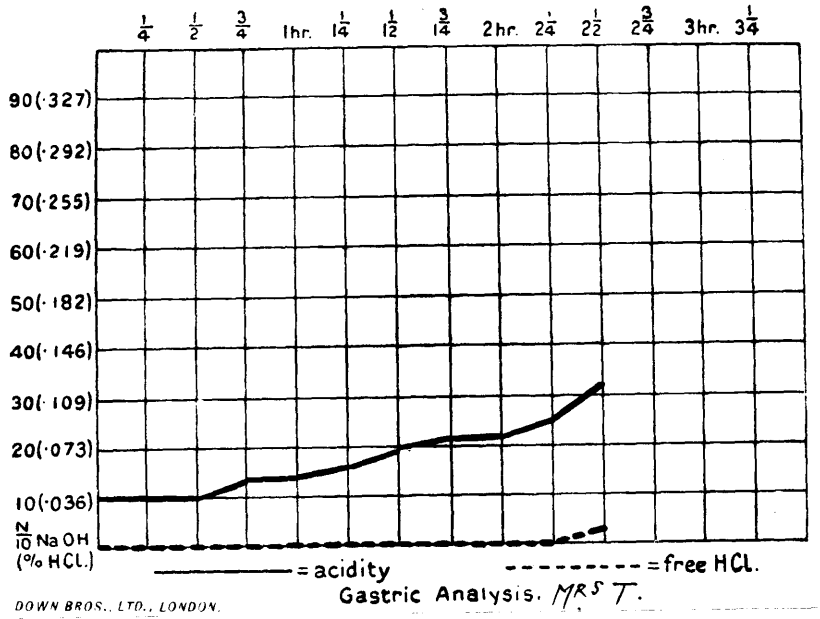
(See Table III, p.150)

Achlorhydria (11).



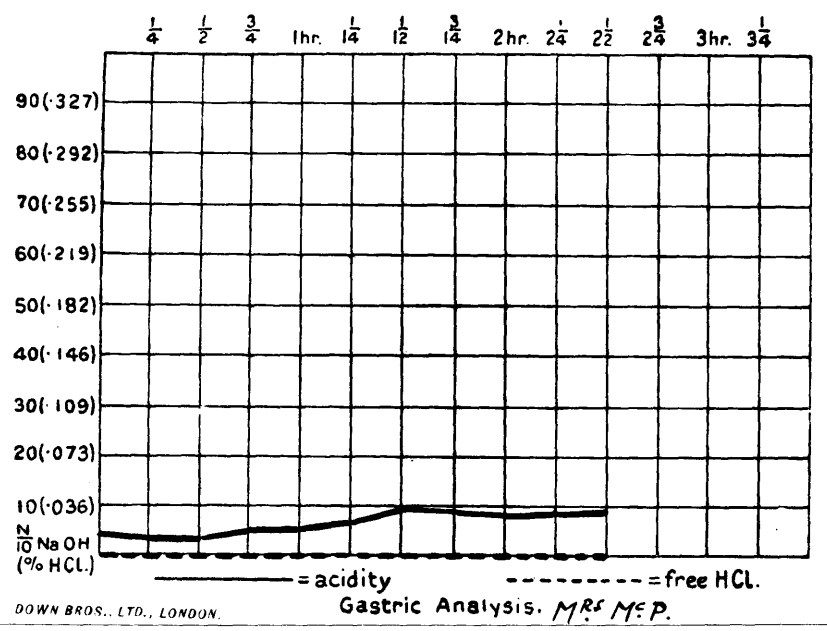






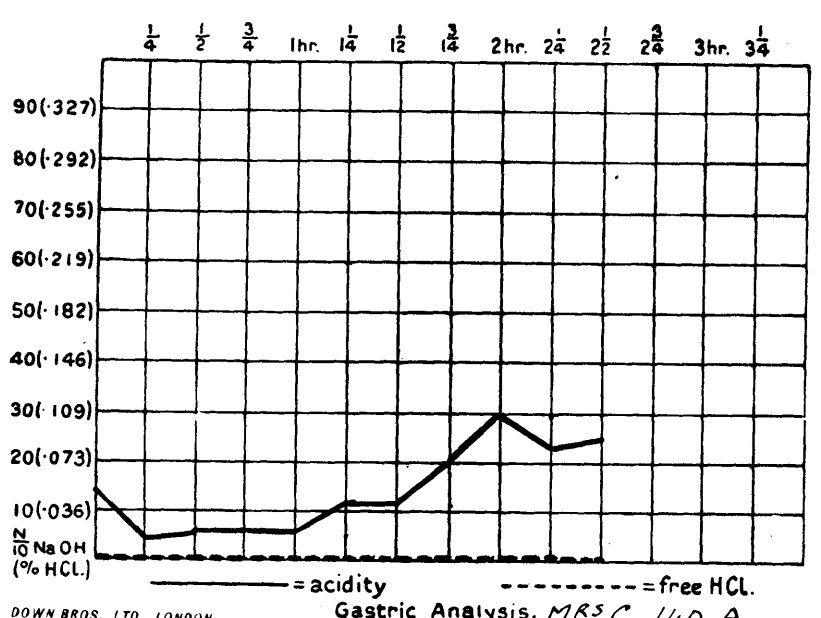
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS T.



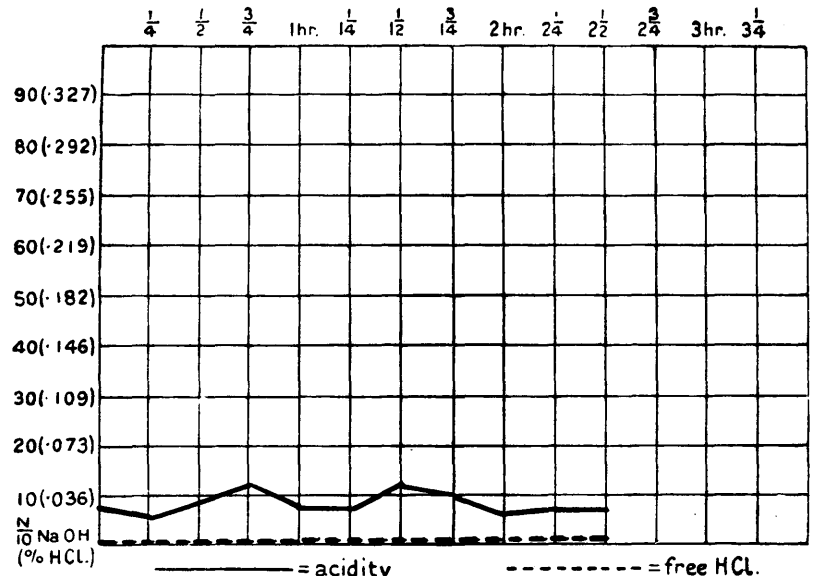
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS Mc P.



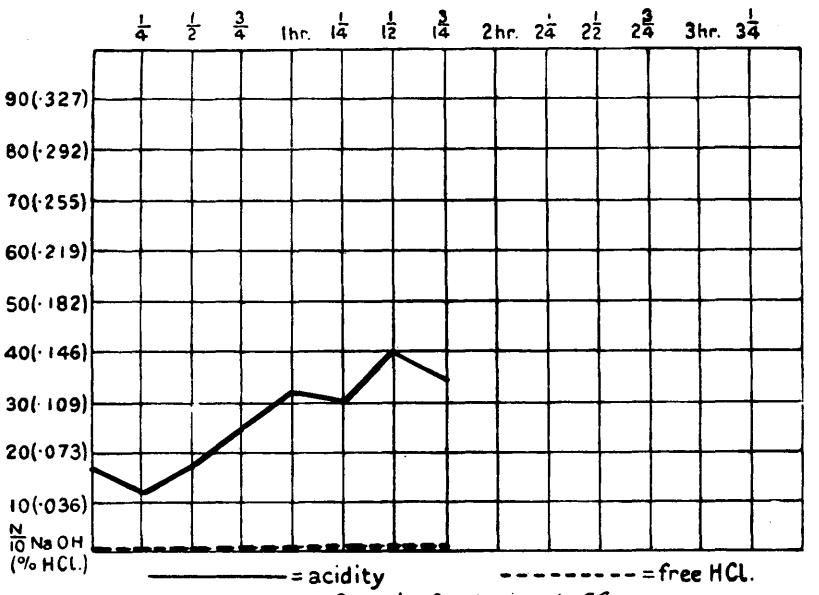
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS C. 140. A.



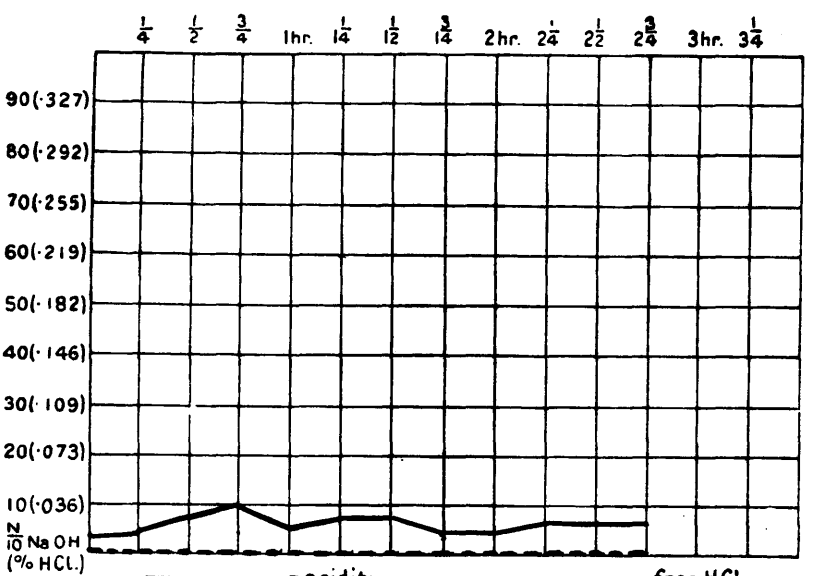
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS G.M. 164. A.



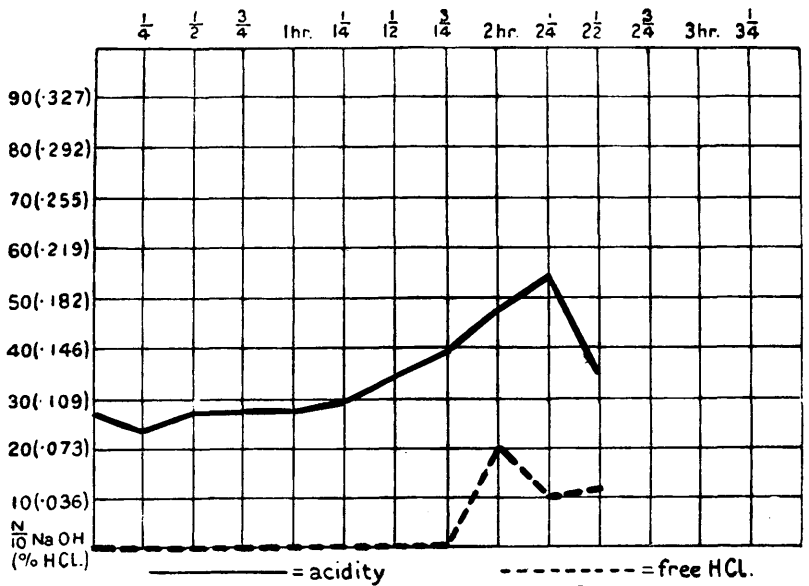
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS M. 245. A.

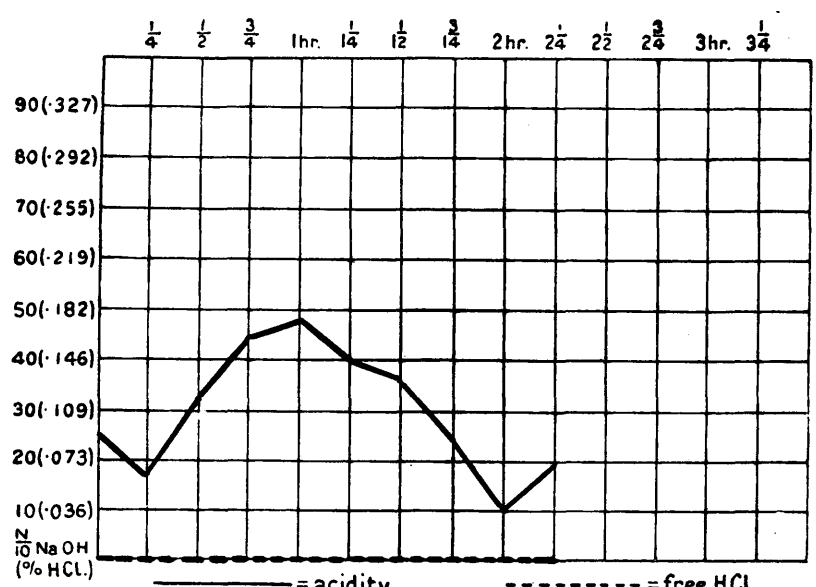


DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS B. 17. A.



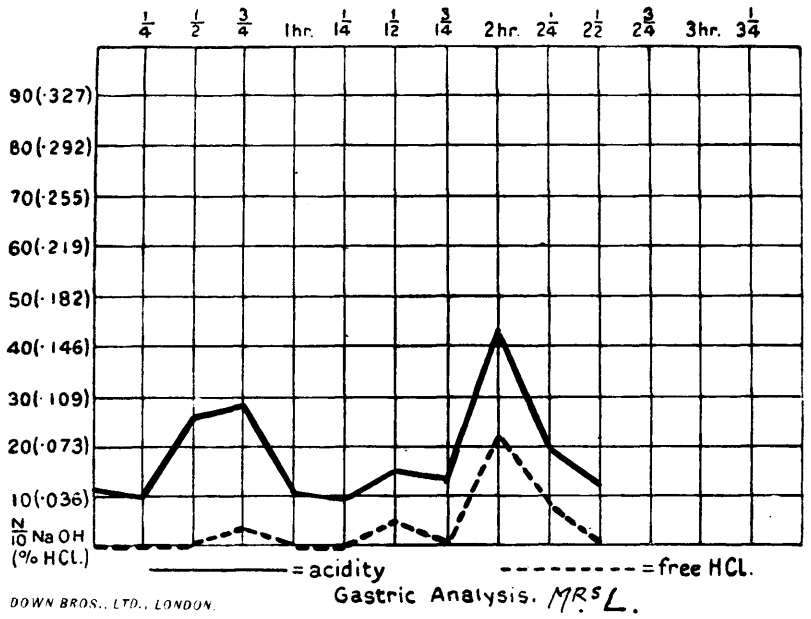
Gastric Analysis. MRS F.



Gastric Analysis. MRS C.

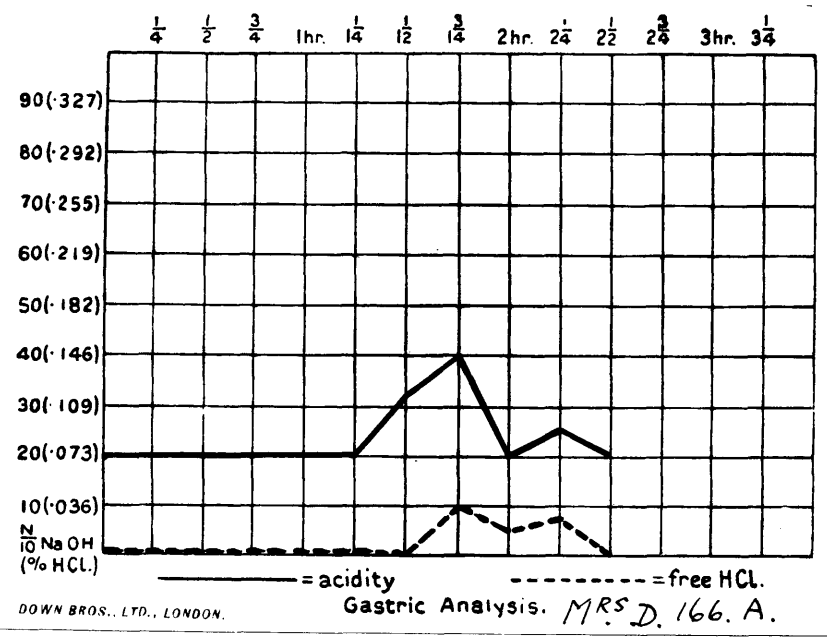
Free Hydrochloric Acid.

10 per cent. and under (2).



DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS L.

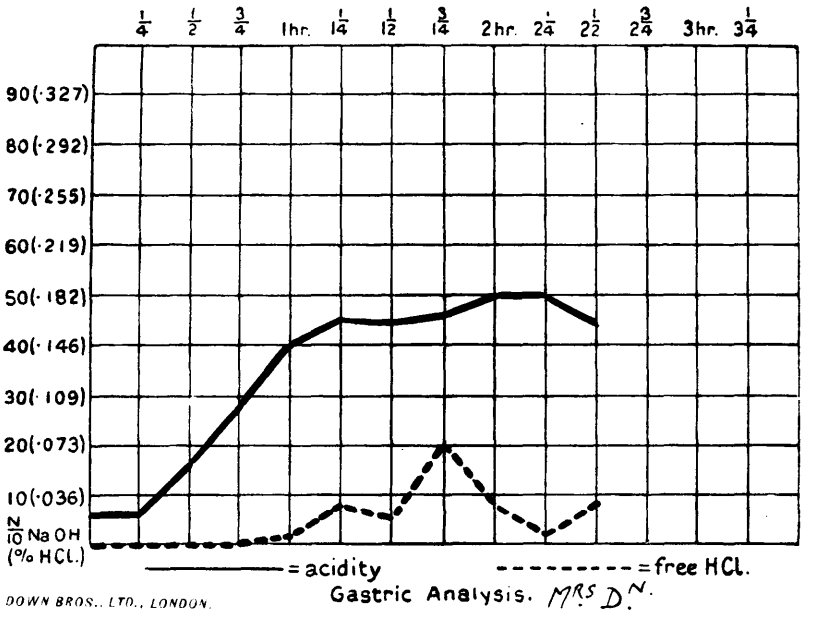


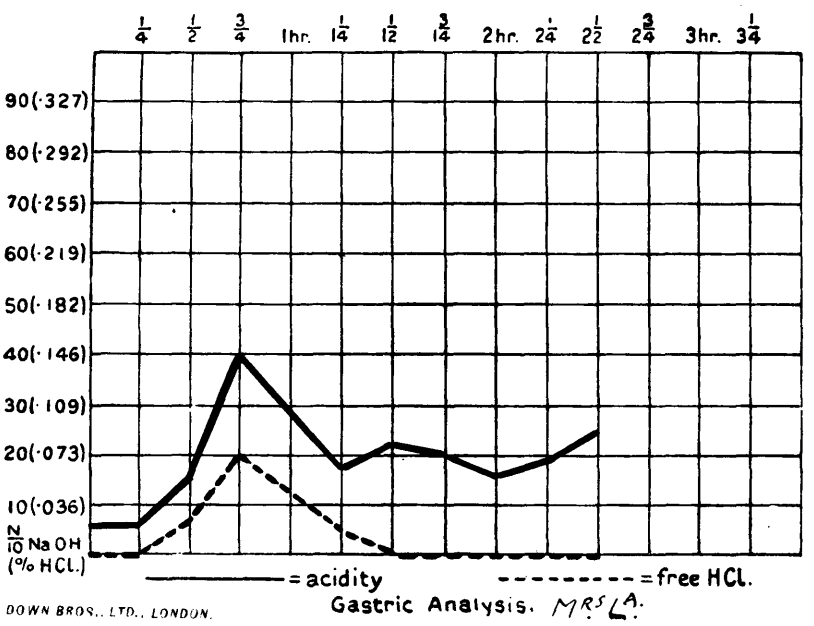
DOWN BROS., LTD., LONDON.

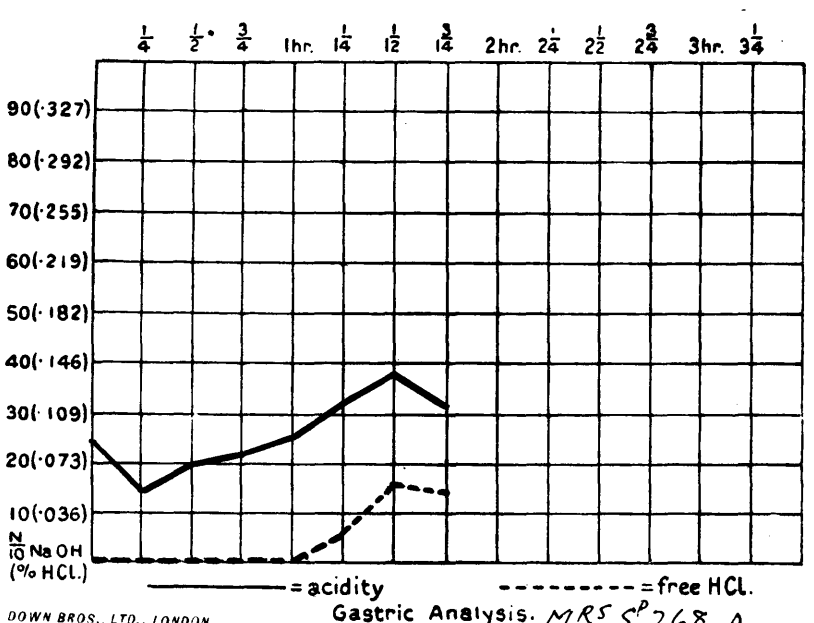
Gastric Analysis. MRS D. 166. A.

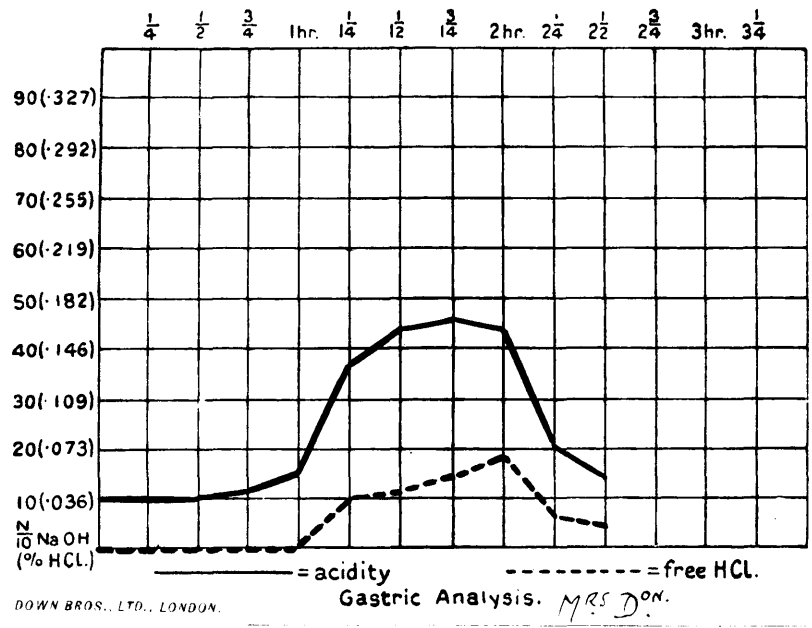
Free Hydrochloric Acid.

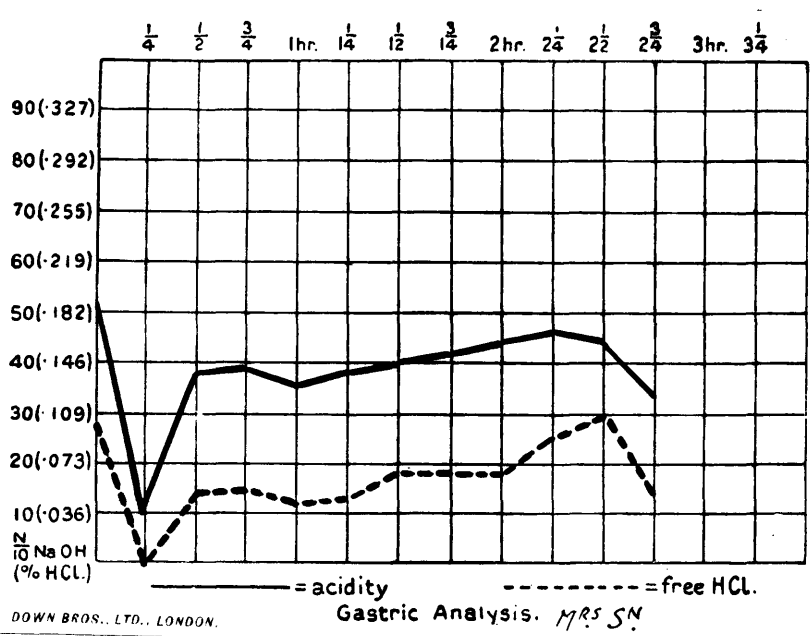
11 to 20 per cent. (5).





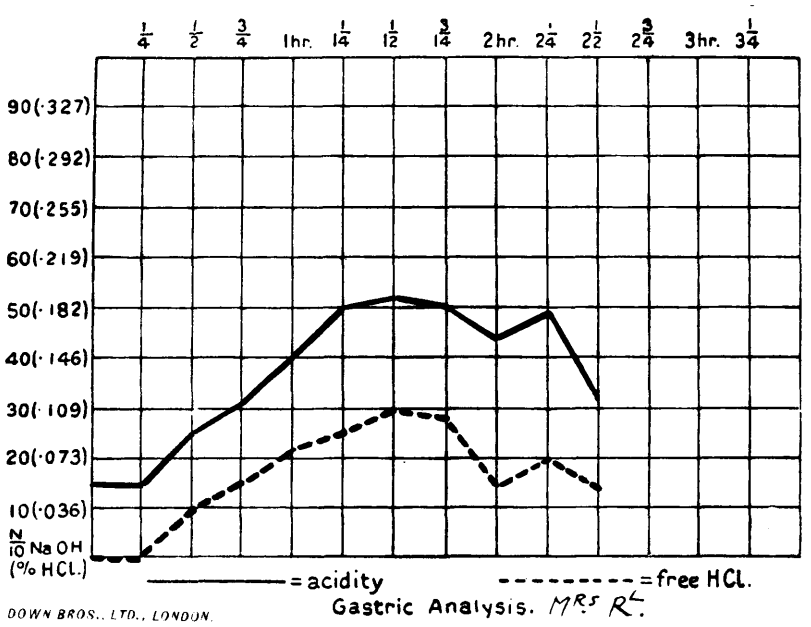



¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS DON.


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS SN.

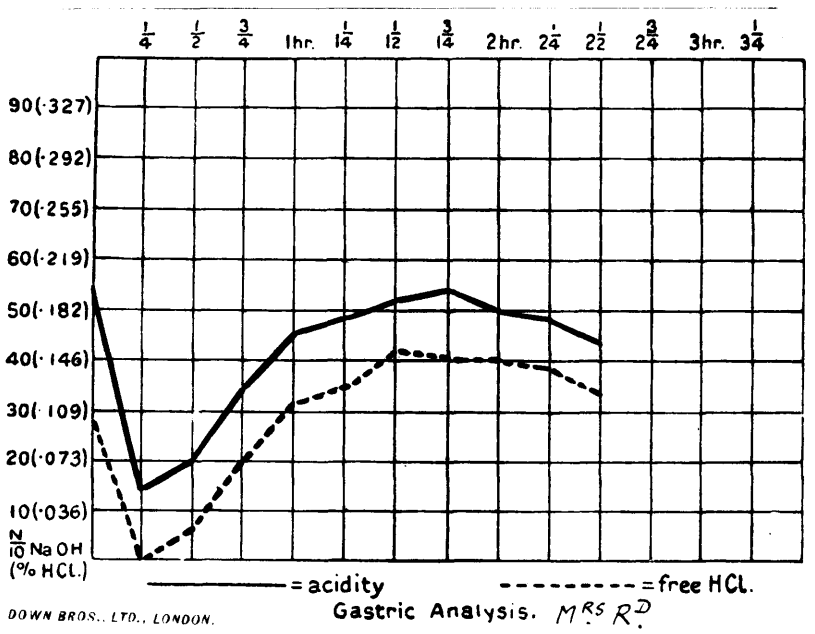
Free Hydrochloric Acid.

21 to 30 per cent. (1).



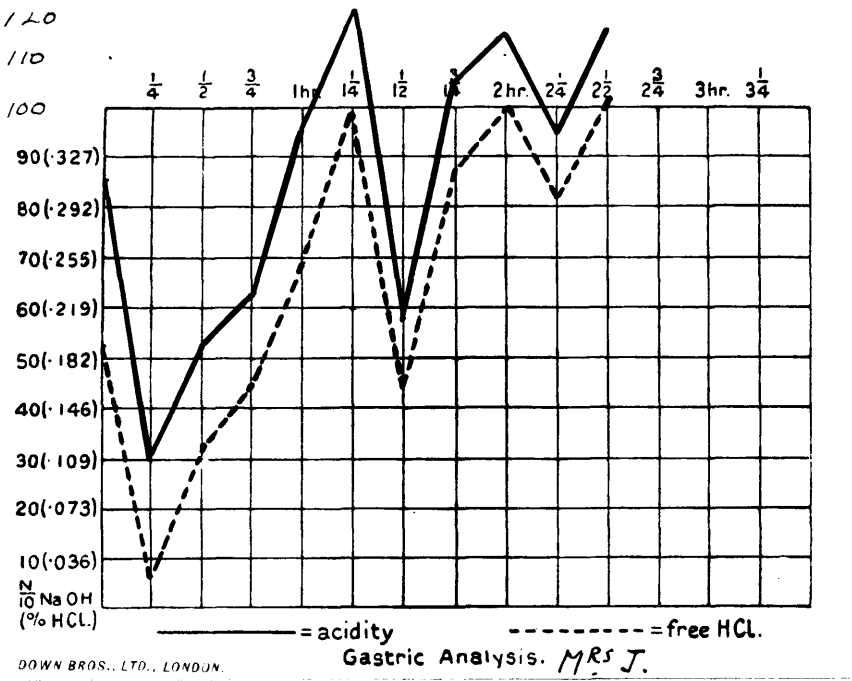
Free Hydrochloric Acid.

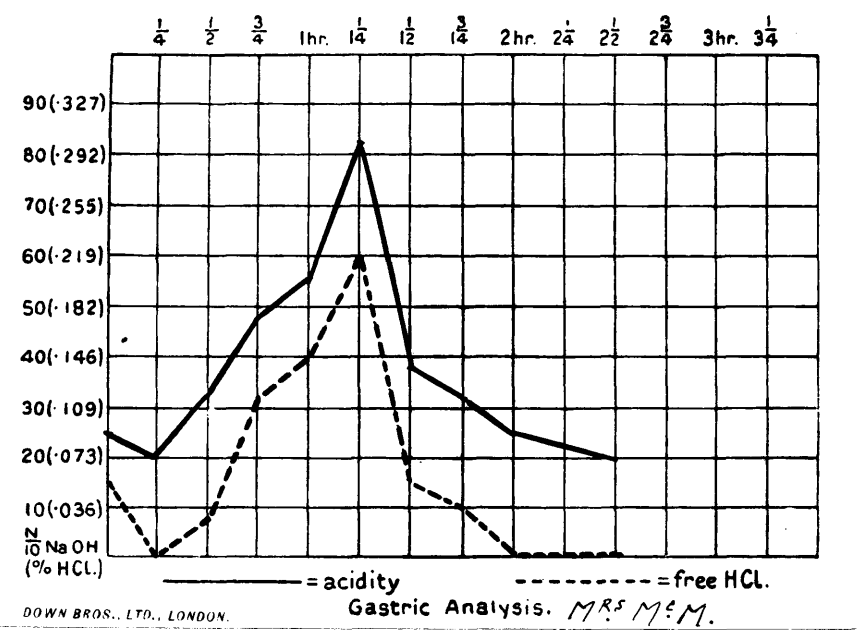
31 to 45 per cent. (1).

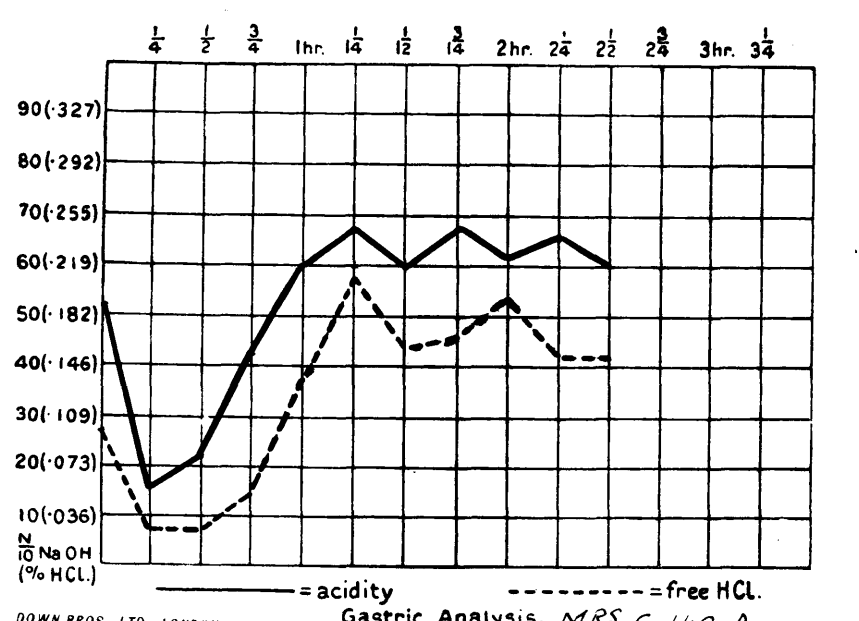


Free Hydrochloric Acid.

Above 45 per cent. (3).

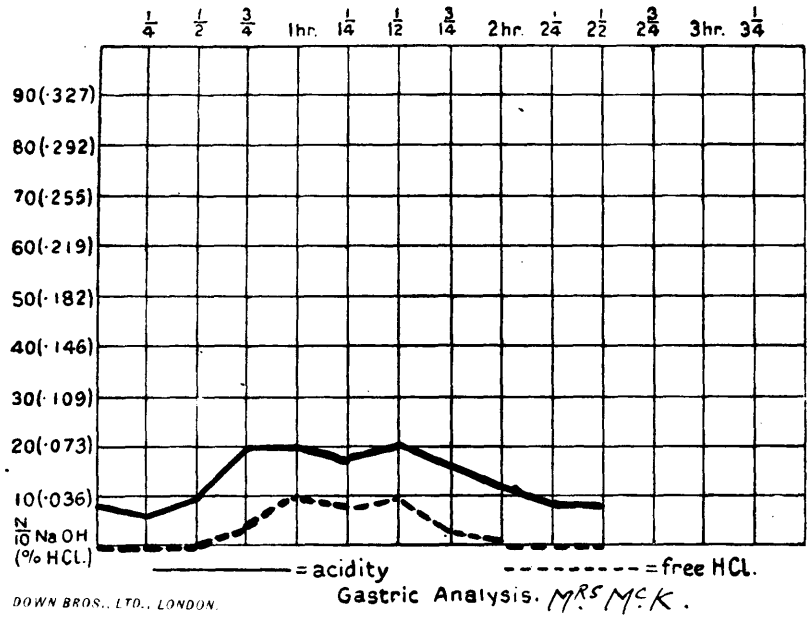


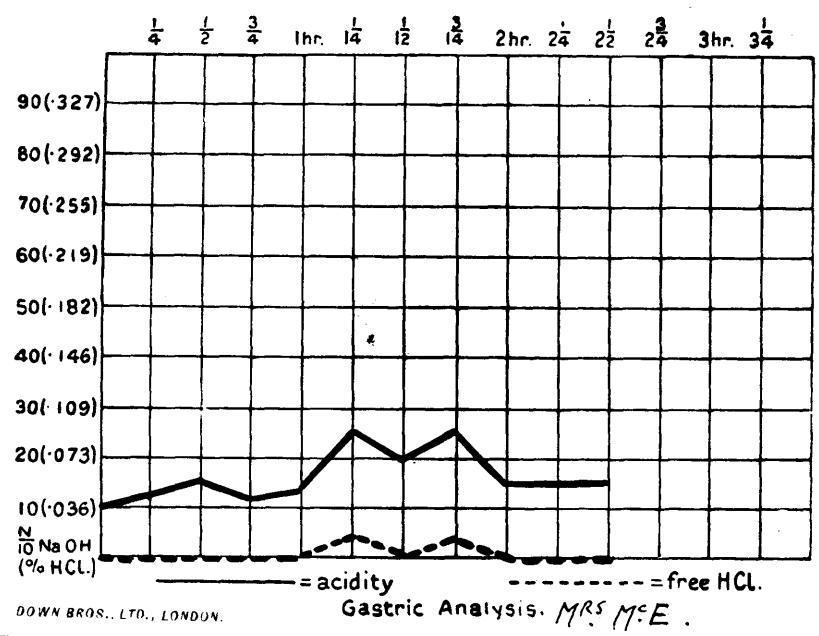


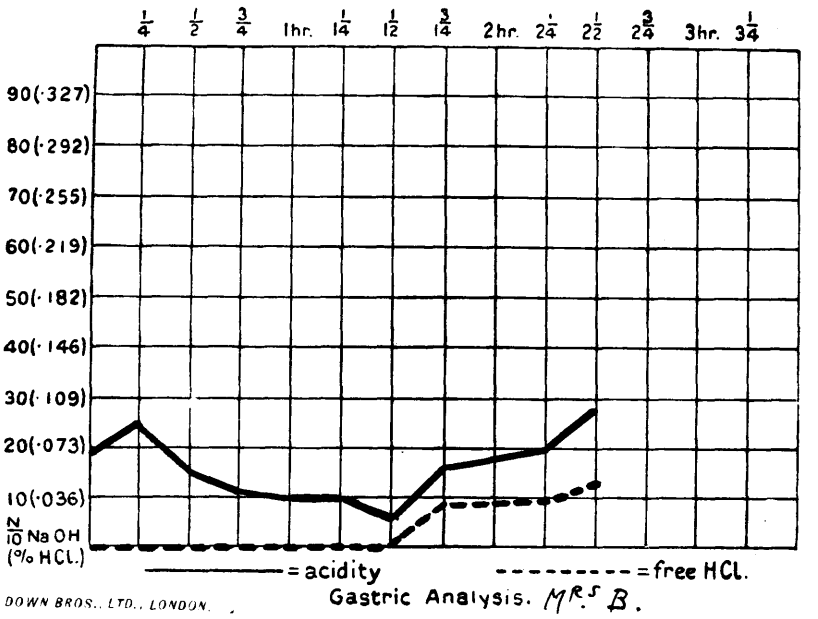


CASES OF PYELITIS (10).
(See Table III, p. 150).

Free Hydrochloric Acid.
10 per cent. and under (4).

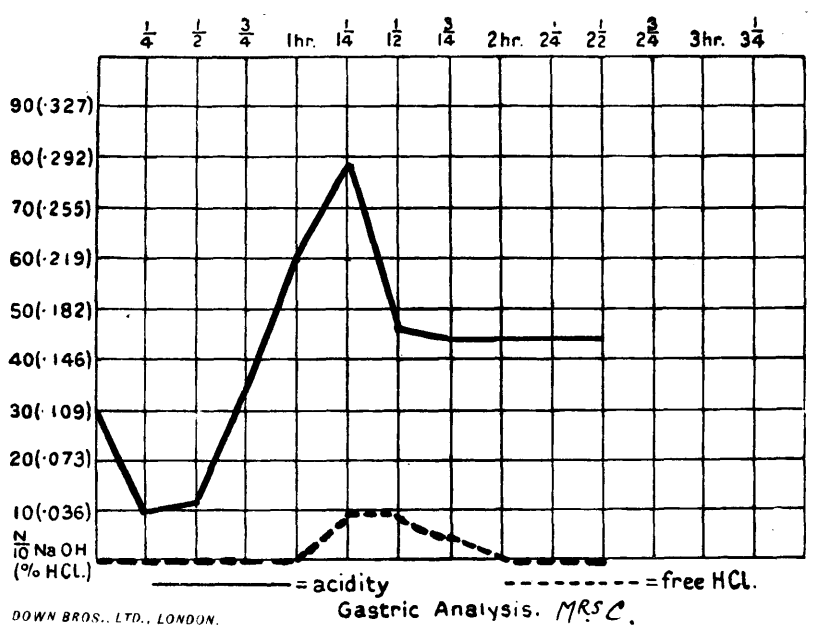






DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS B.

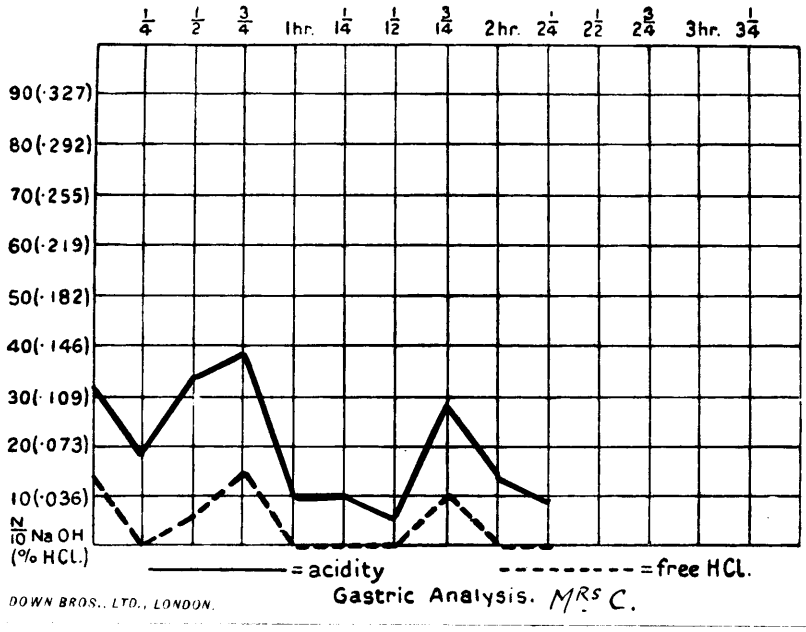


DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS C.

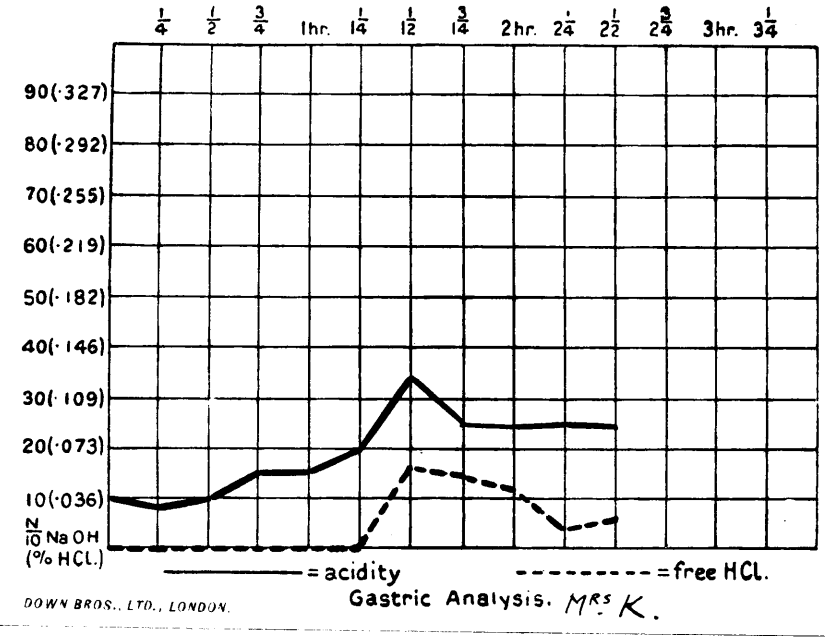
Free Hydrochloric Acid.

11 to 20 per cent. (3).



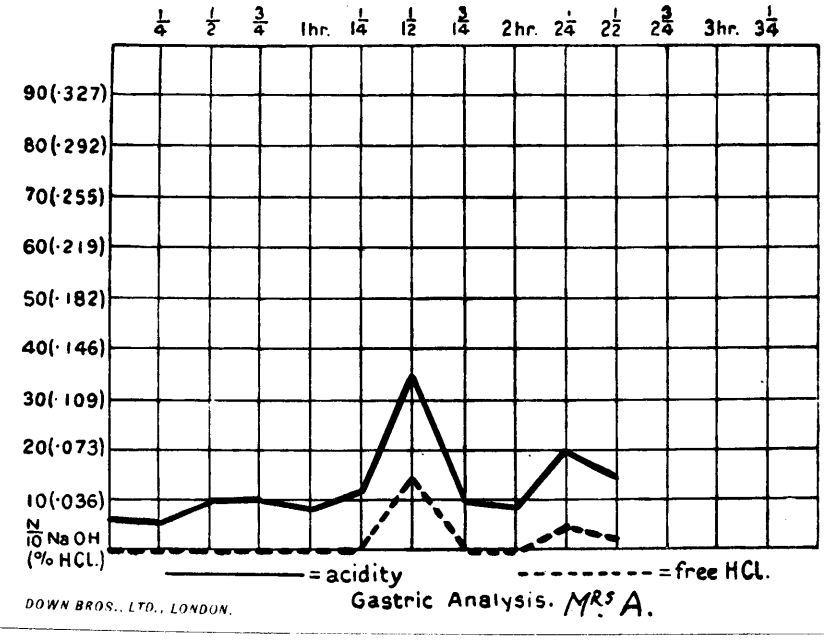
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS C.



DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS K.

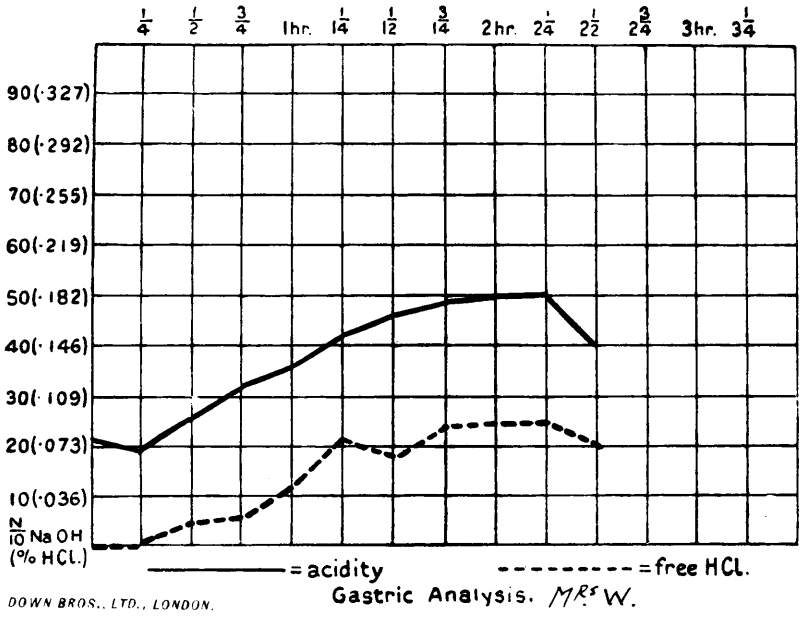


DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS A.

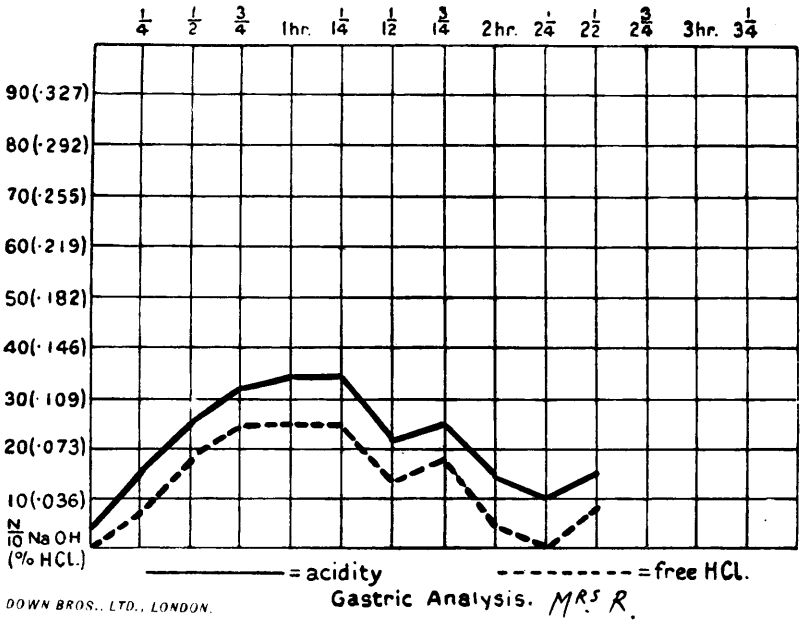
Free Hydrochloric Acid.

21 to 30 per cent. (2).



DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS W.

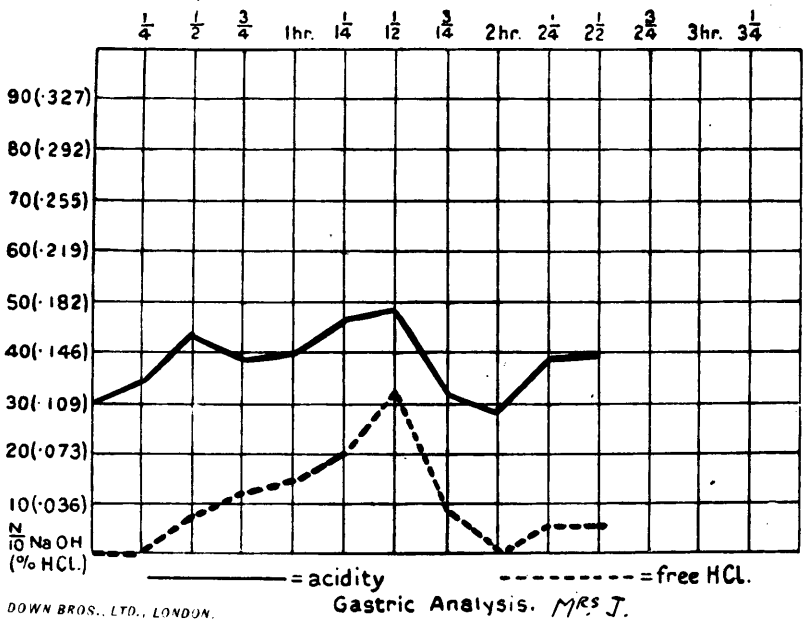


DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS R.

Free Hydrochloric Acid.

31 to 45 per cent. (1).

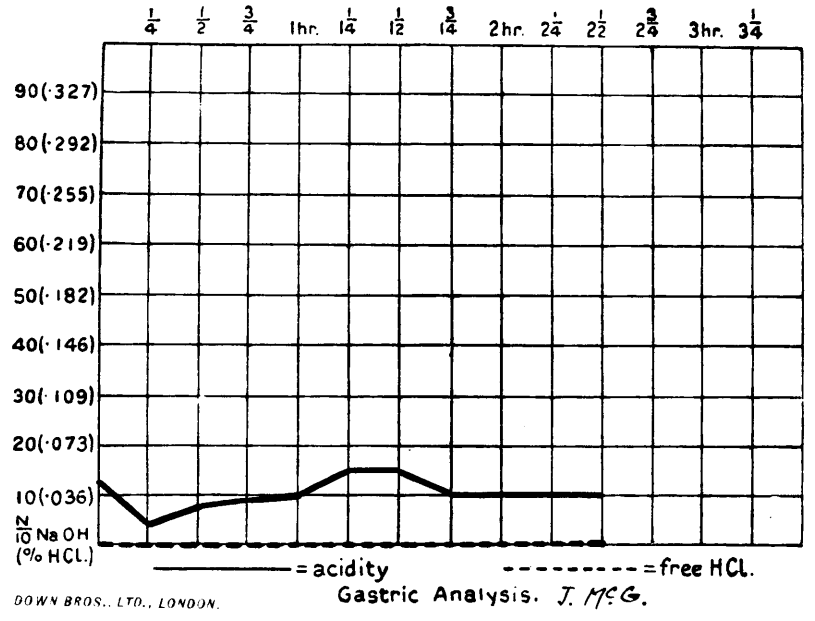


DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS J.

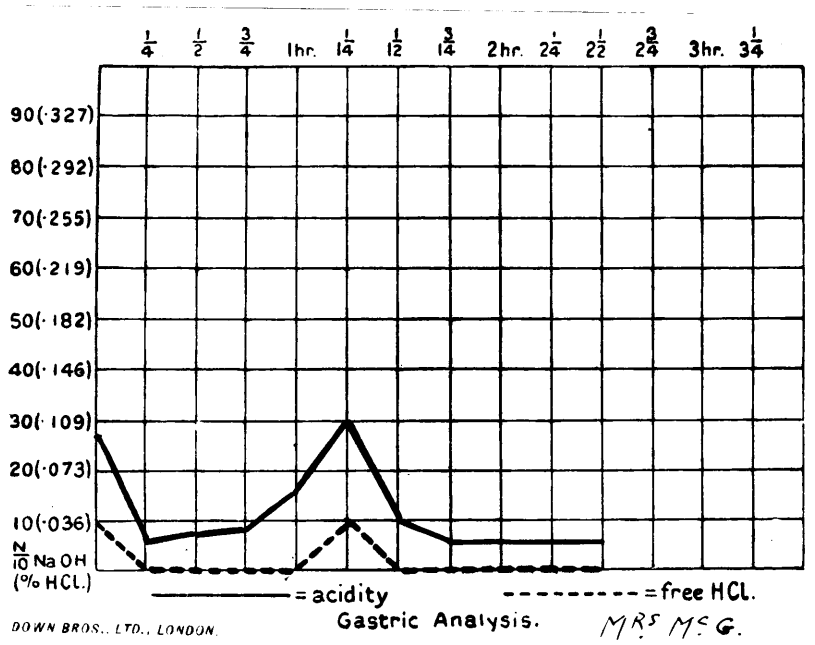
CASES OF PRE-ECLAMPSIA (10).
(See Table III, p.150).

Achlorhydria (1).



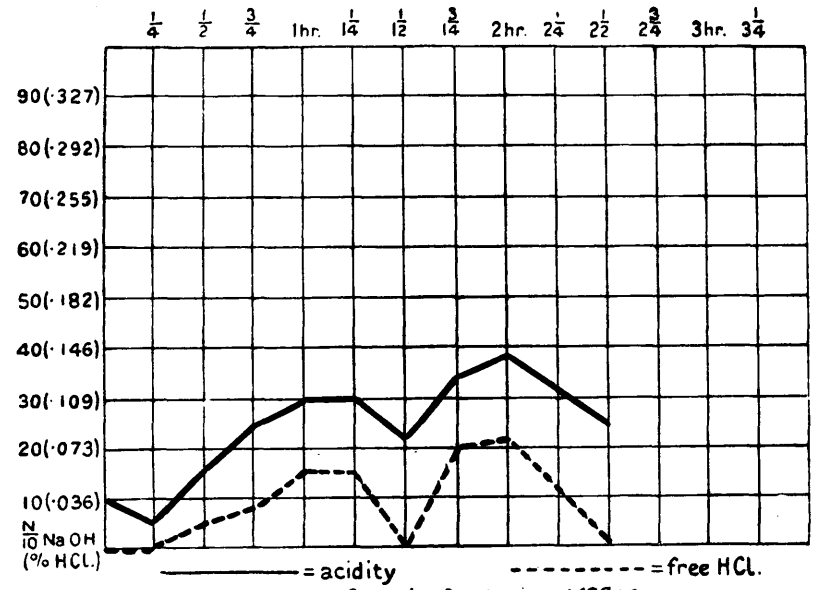
Free Hydrochloric Acid.

10 per cent. and under (1).



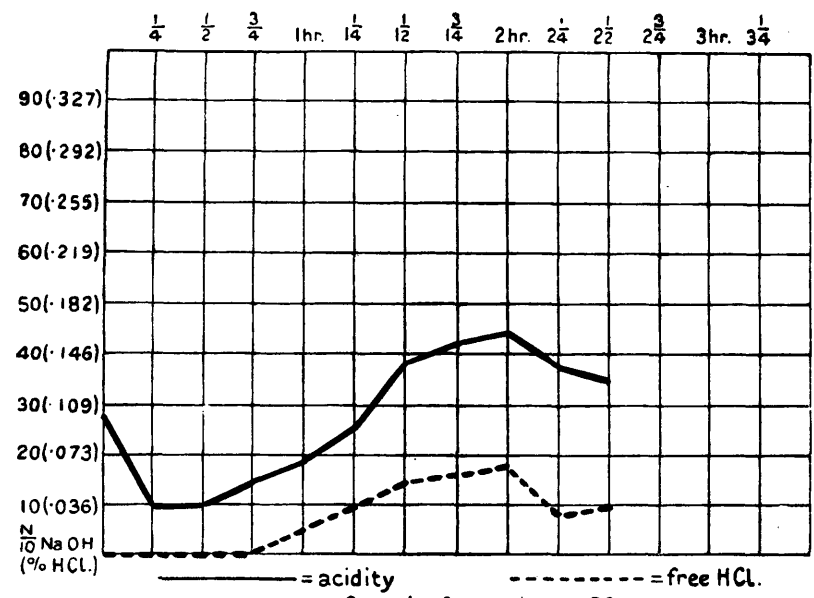
Free Hydrochloric Acid.

11 to 20 per cent. (4).



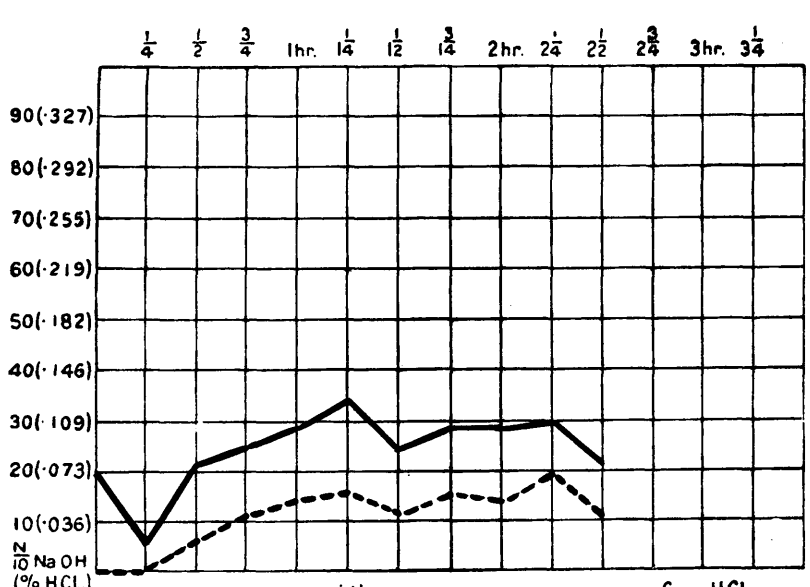
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS M.



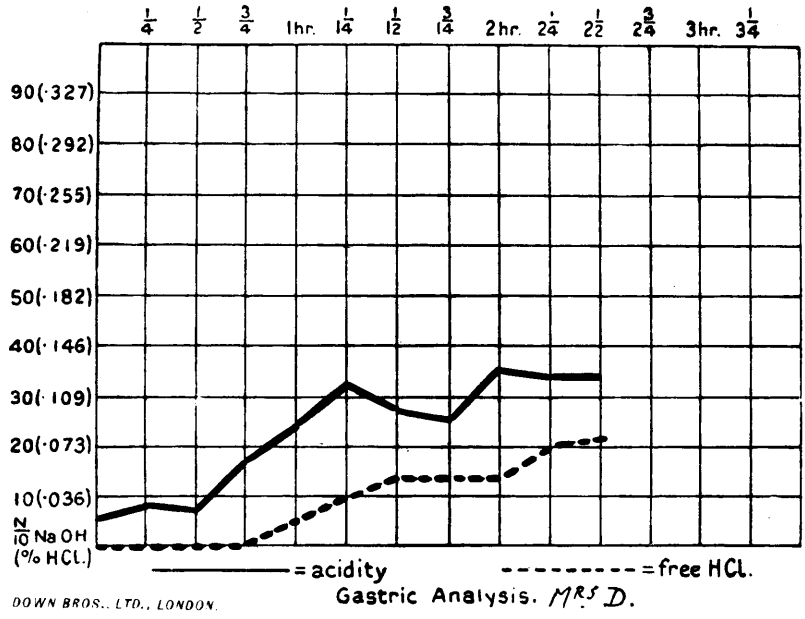
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS S.



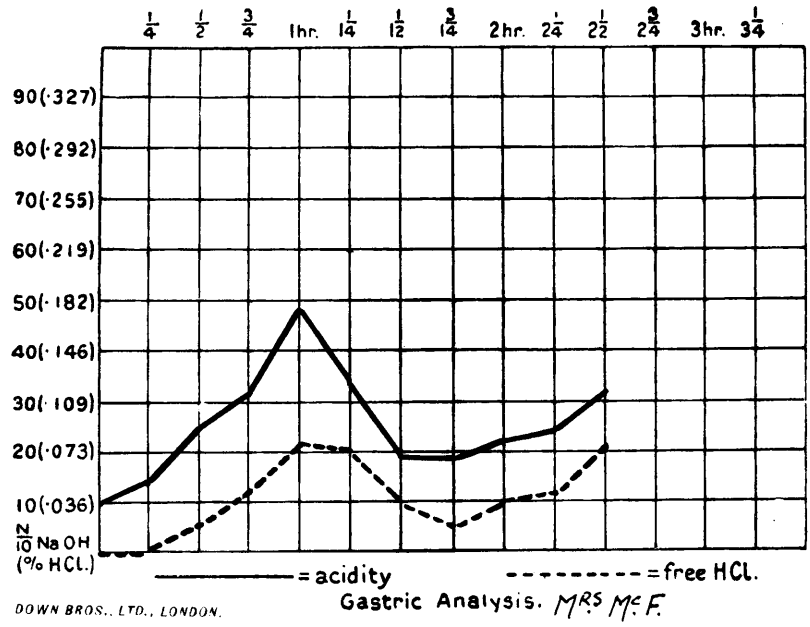
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS McP.



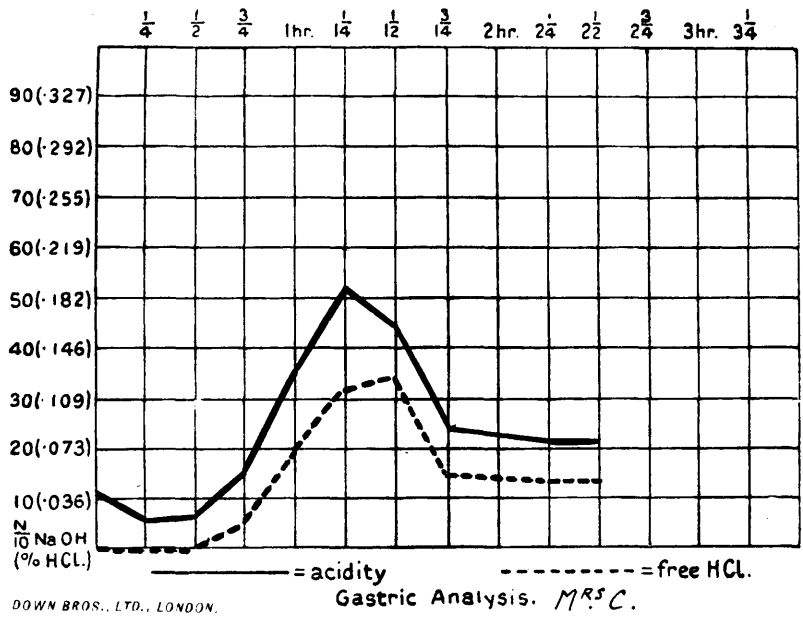
Free Hydrochloric Acid.

21 to 30 per cent. (1).



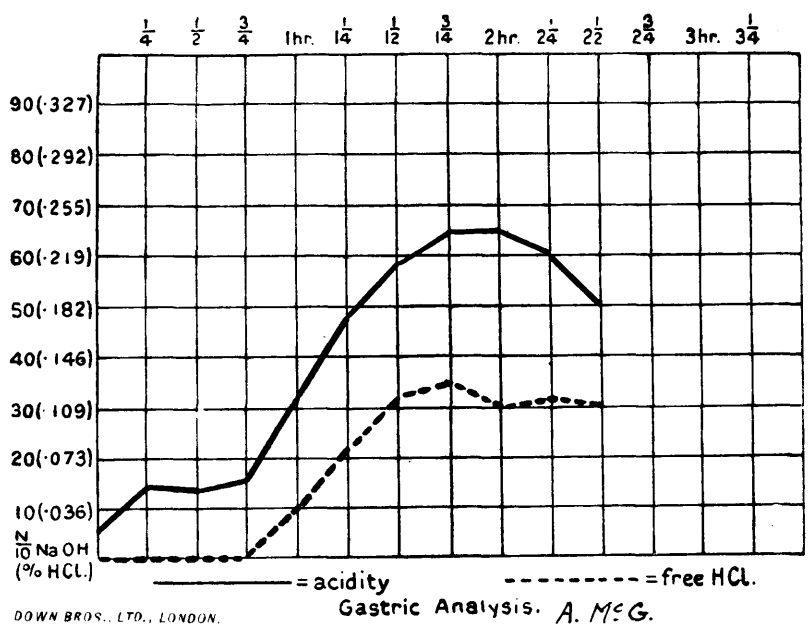
Free Hydrochloric Acid.

31 to 45 per cent. (2).



DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS C.

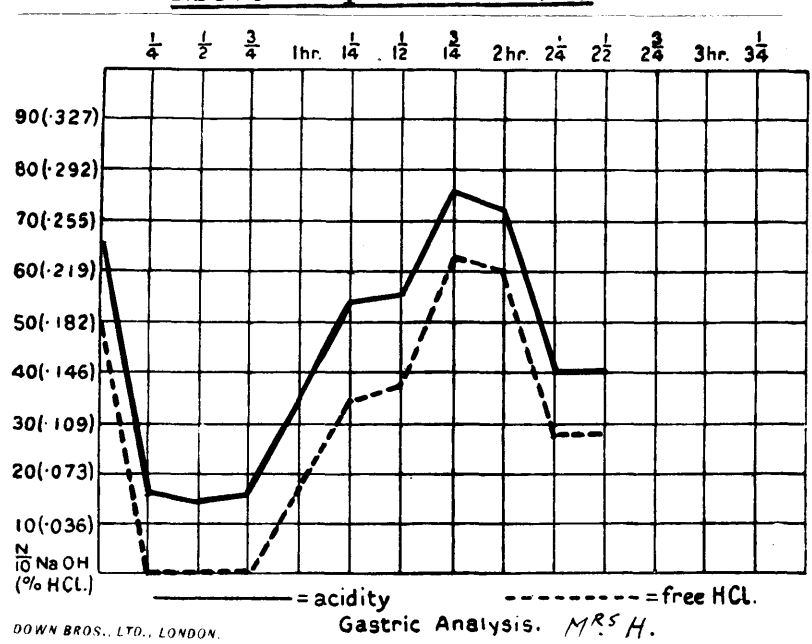


DOWN BROS., LTD., LONDON.

Gastric Analysis. A. McG.

Free Hydrochloric Acid.

Above 45 per cent. (1).

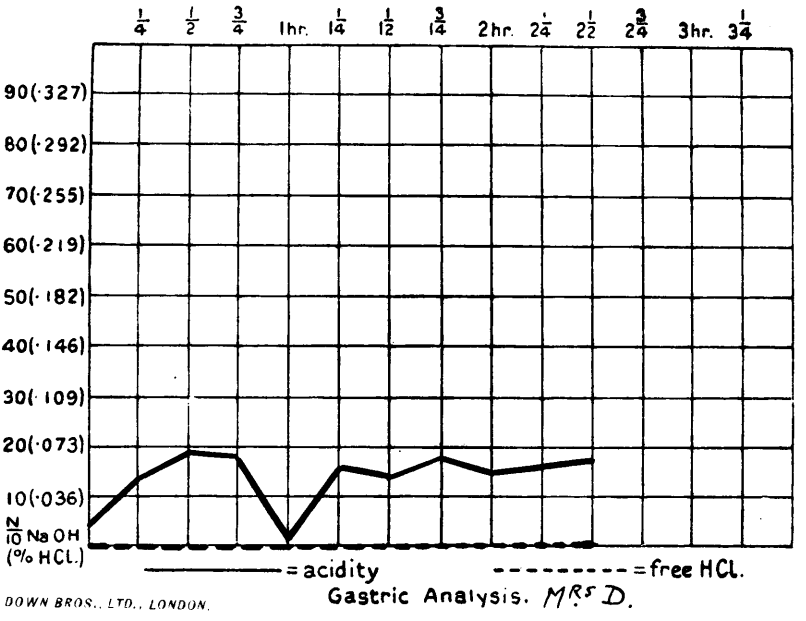


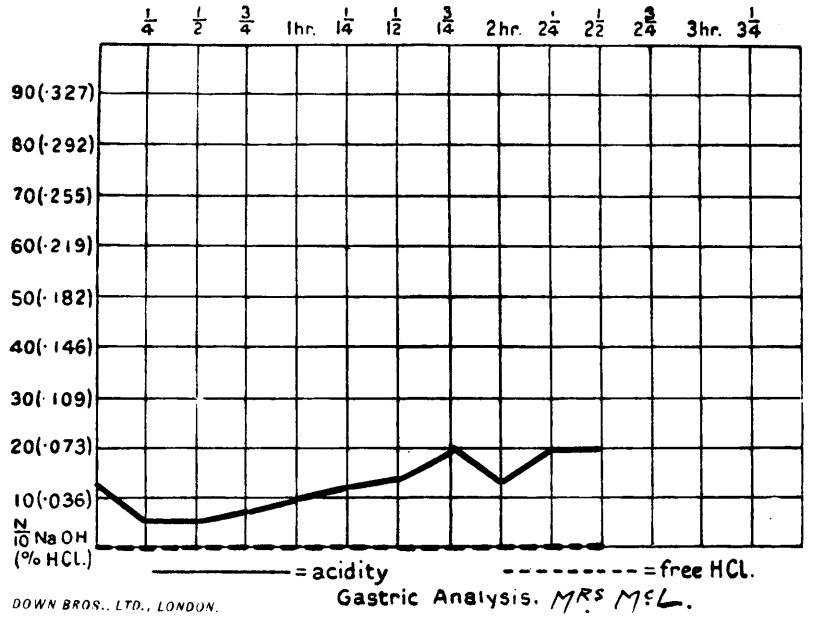
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS H.

CASES OF ECLAMPSIA (9).
(See Table III, p.150).

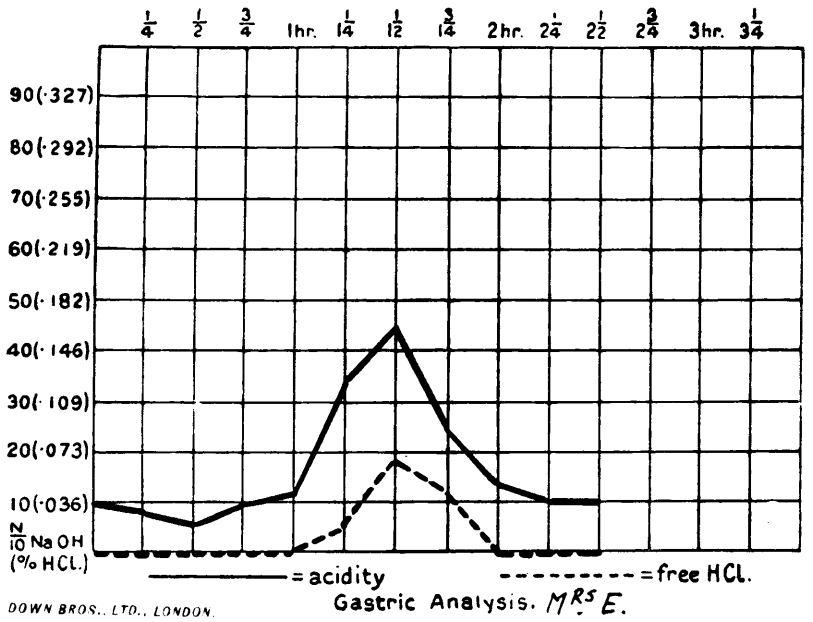
Achlorhydria (2).





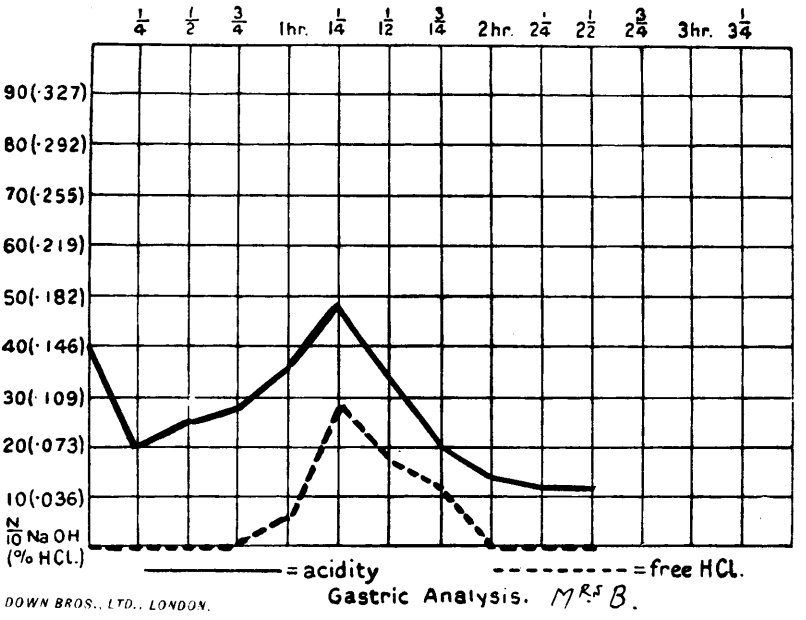
Free Hydrochloric Acid.

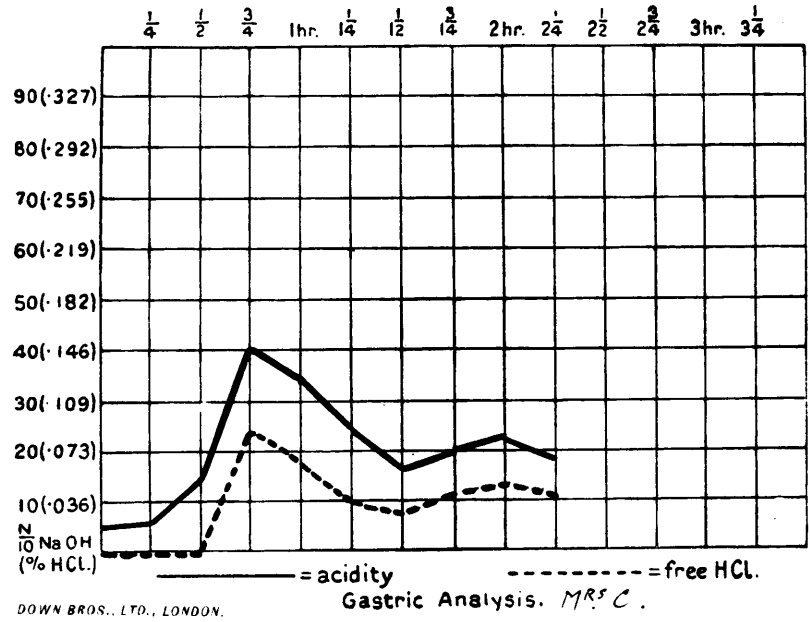
11 to 20 per cent. (1).

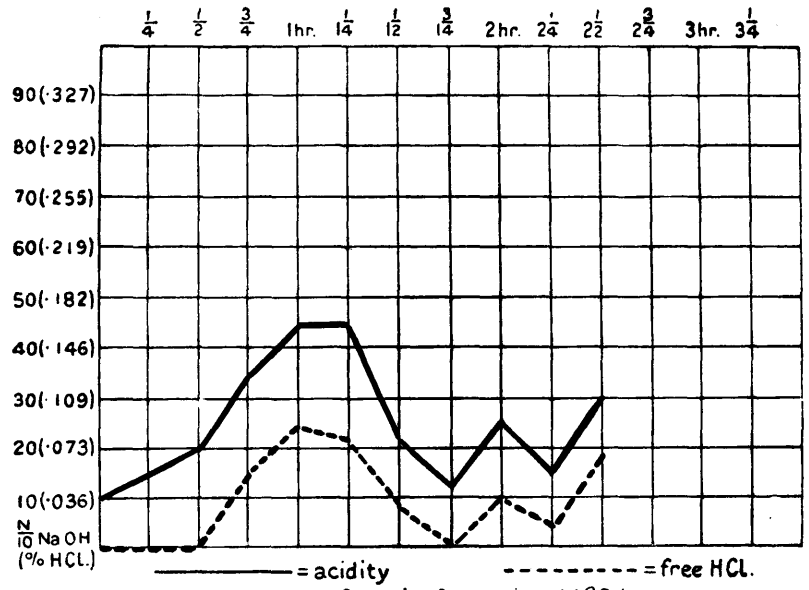


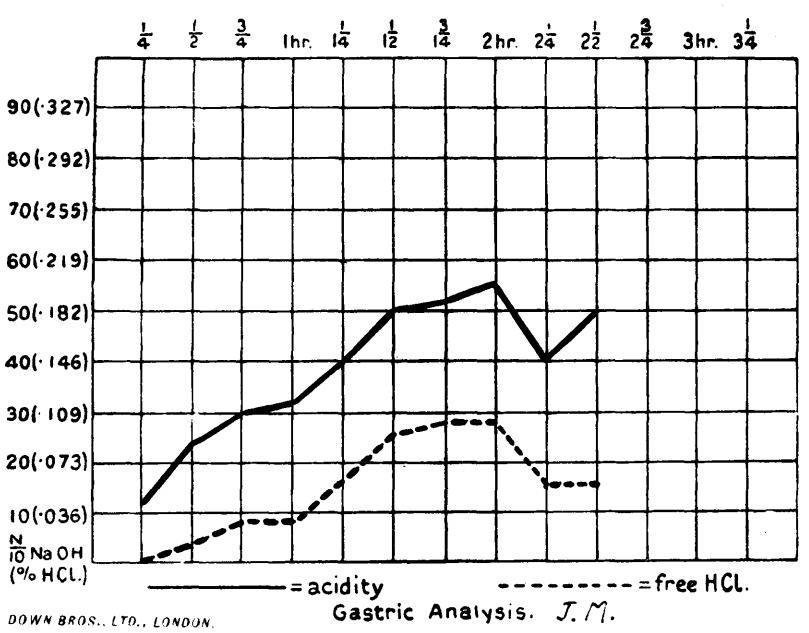
Free Hydrochloric Acid.

21 to 30 per cent. (4).



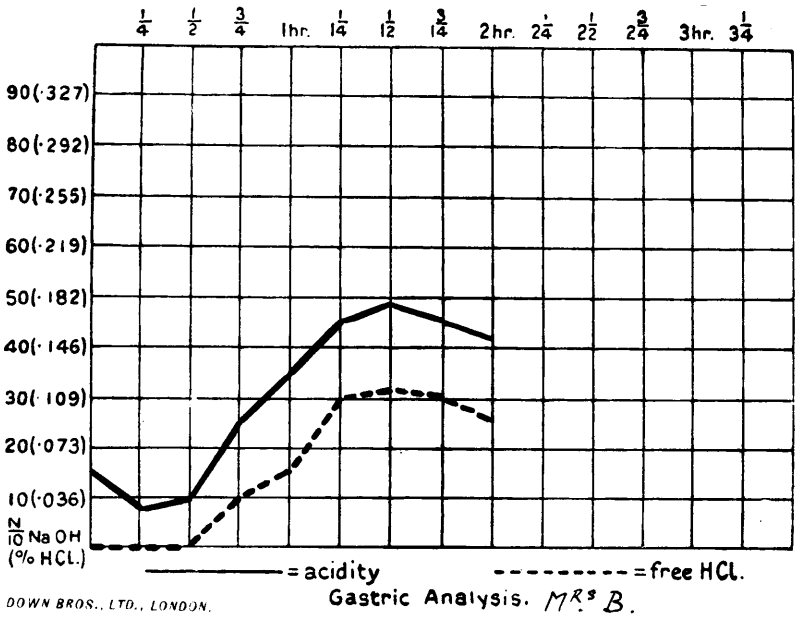



¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
———— = acidity
- - - - - - - - - = free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS L.


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
———— = acidity
- - - - - - - - - = free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. J. M.

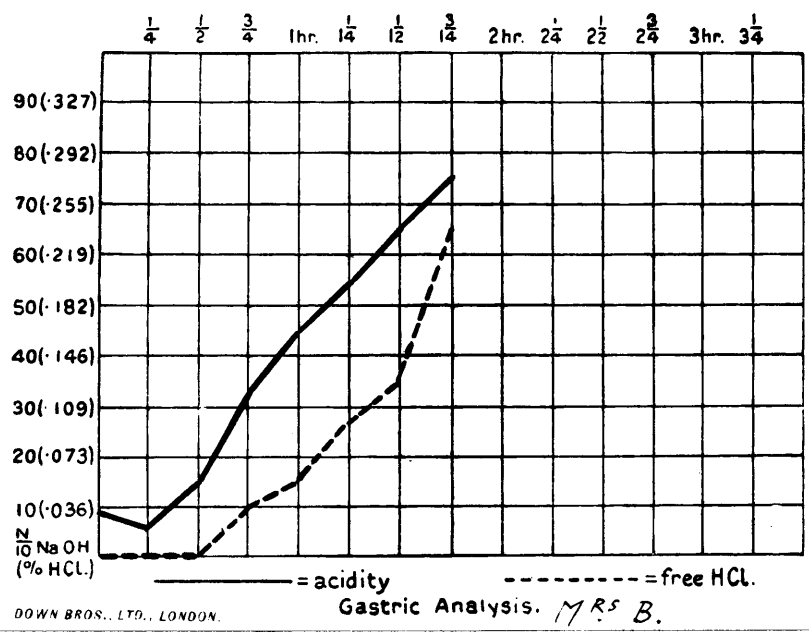
Free Hydrochloric Acid.

31 to 45 per cent. (1).



Free Hydrochloric Acid.

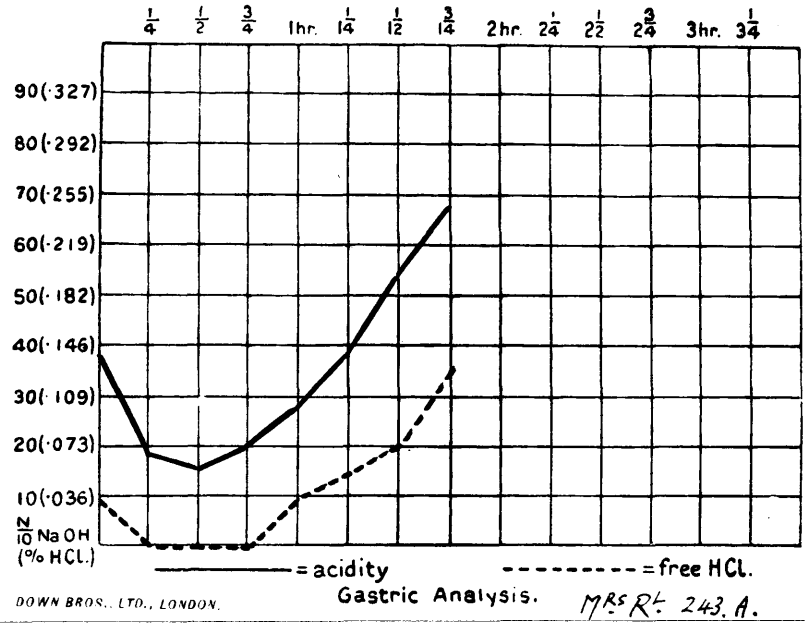
Above 45 per cent. (1).



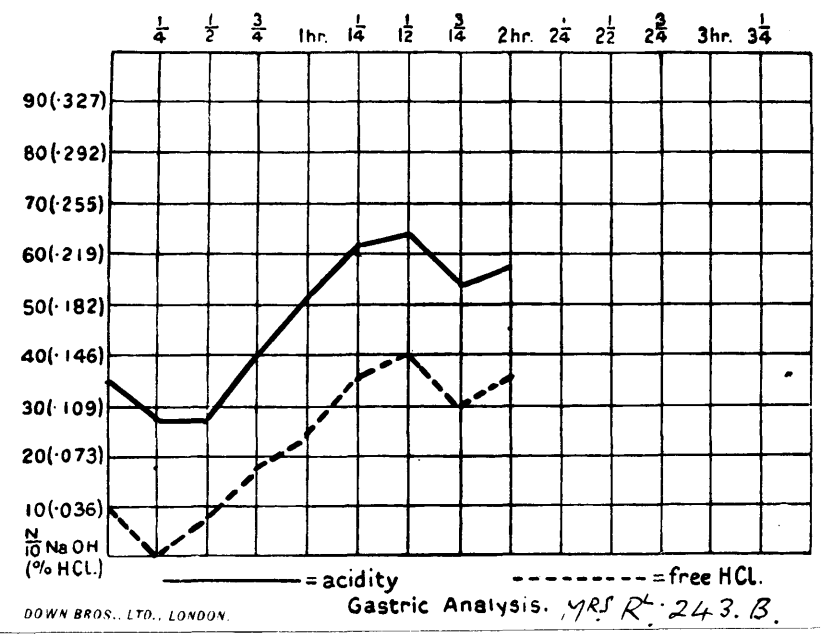
COMPARISON OF RESULTS OF FRACTIONAL ANALYSIS IN HYPEREMESIS GRAVIDARUM IN (A) THE ACTIVE STAGE, AND (B) ON RECOVERY.

(Arranged to correspond with Table VI, p.155)

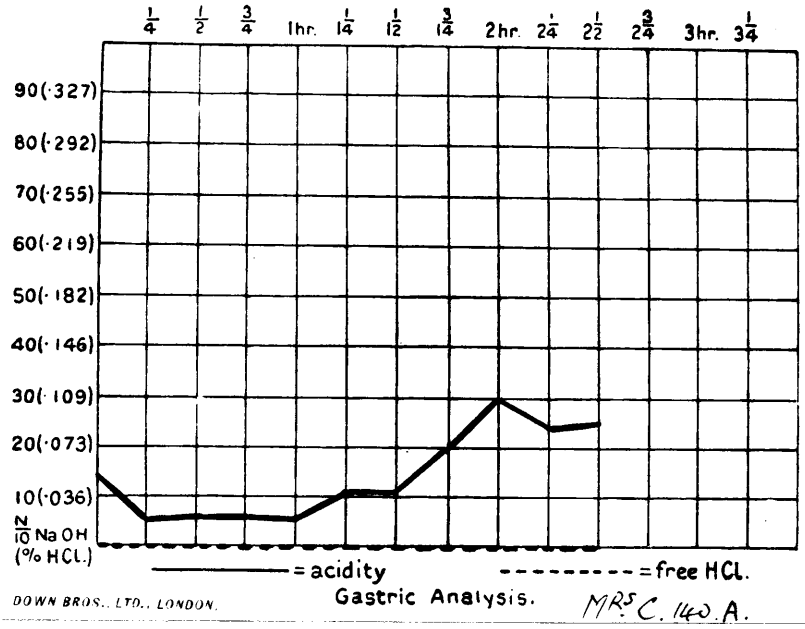
(A)



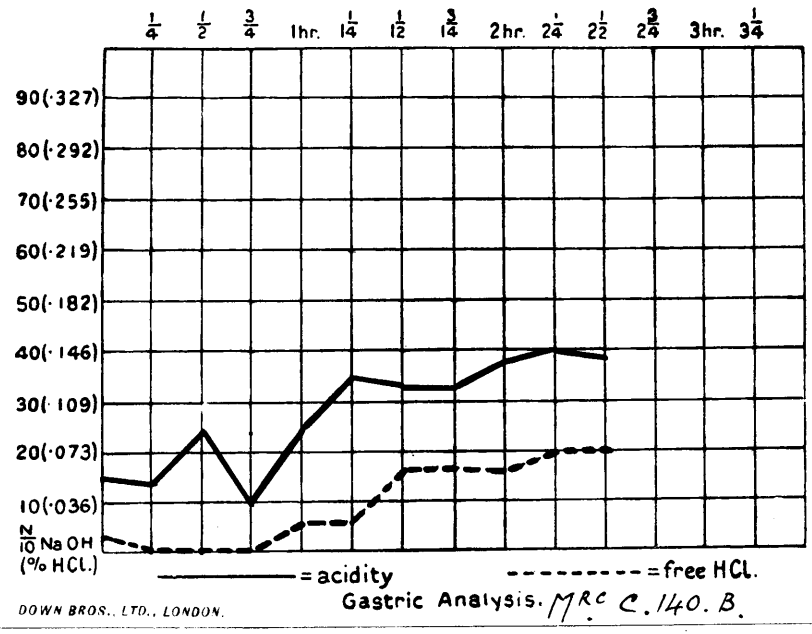
(B)



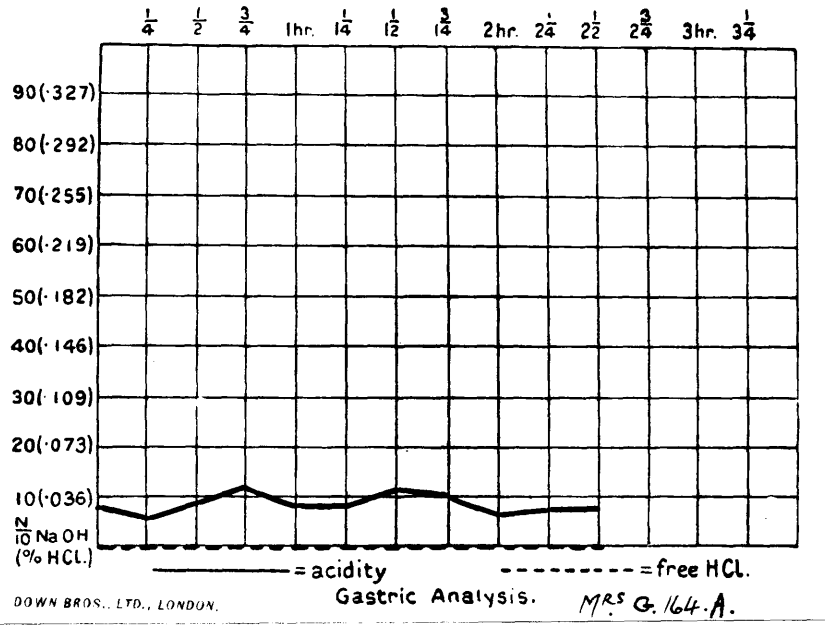
(A)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS C. 140. A.

(B)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRC C. 140. B.

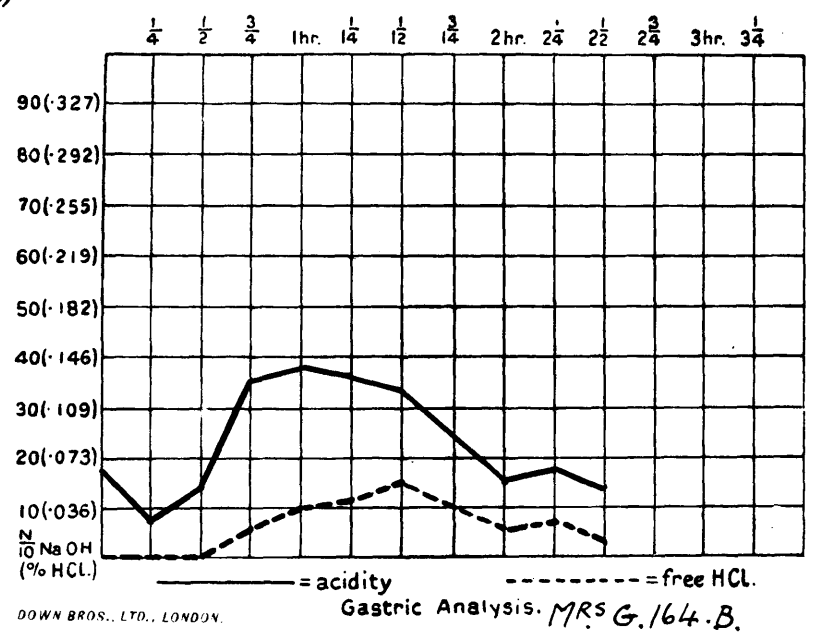
(A)



DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS G. 164. A.

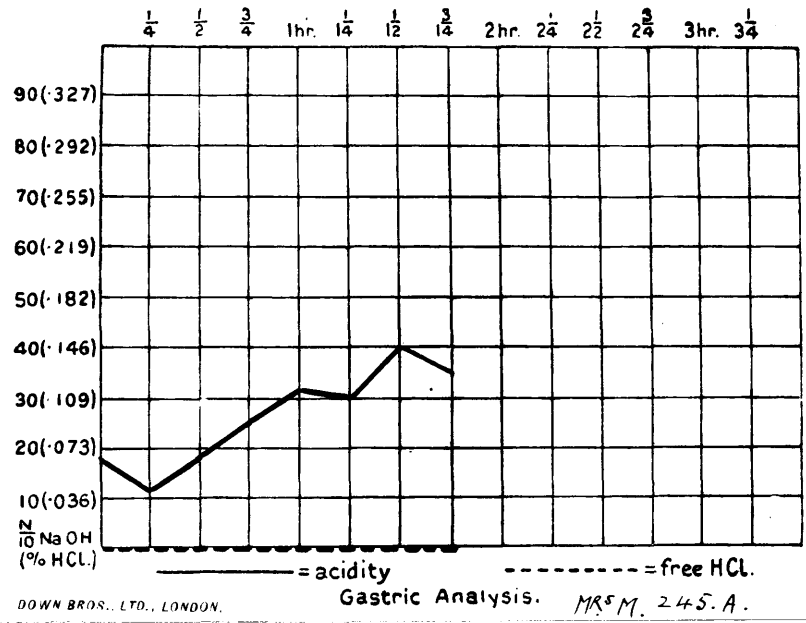
(B)



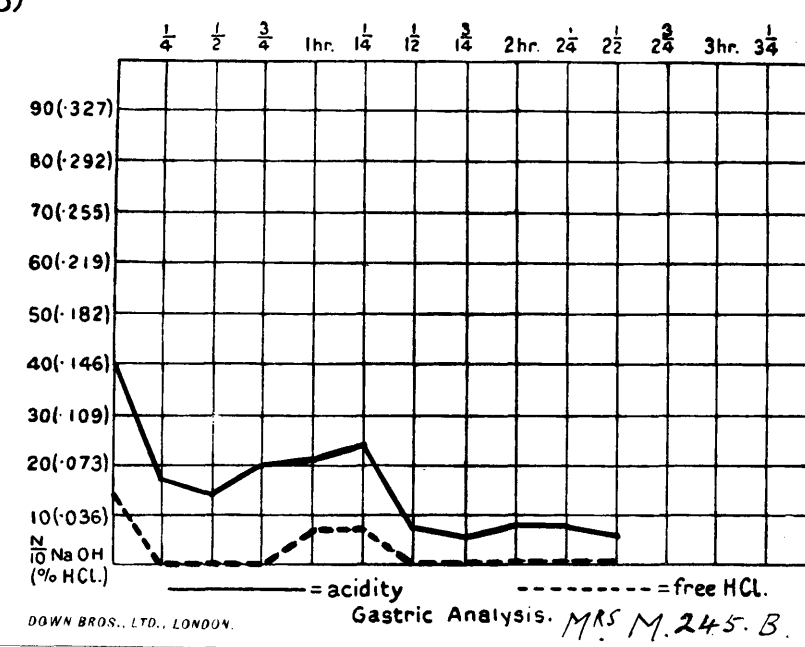
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS G. 164. B.

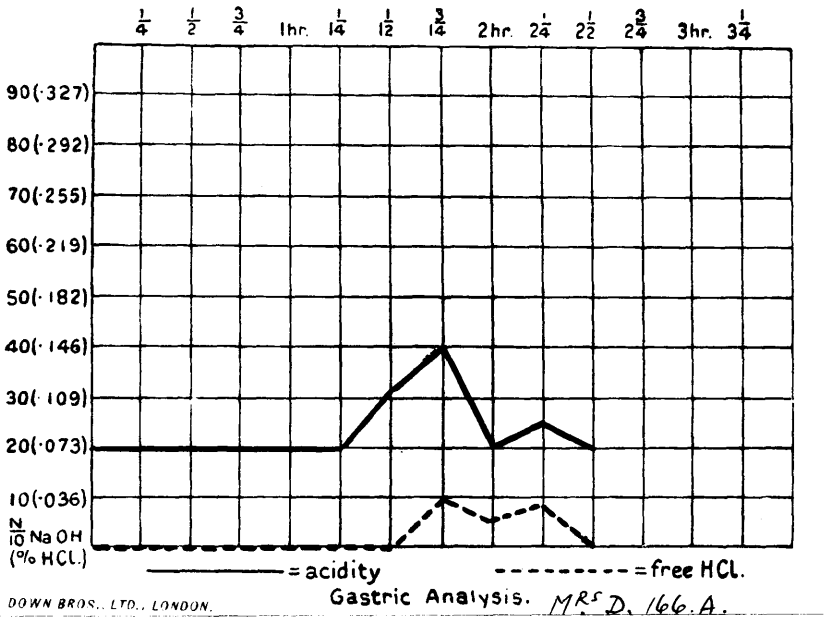
(A)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS M. 245. A.

(B)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS M. 245. B.

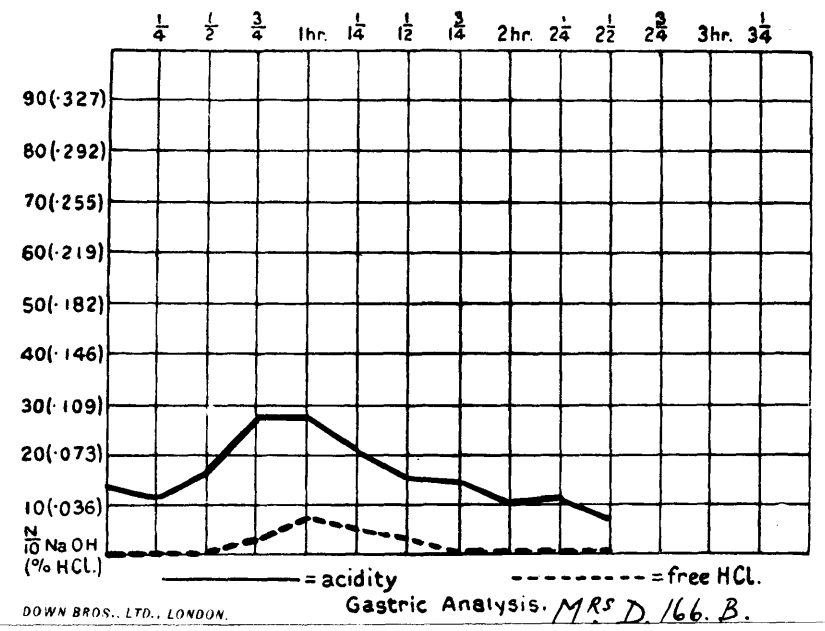
(A)



DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS D. 166. A.

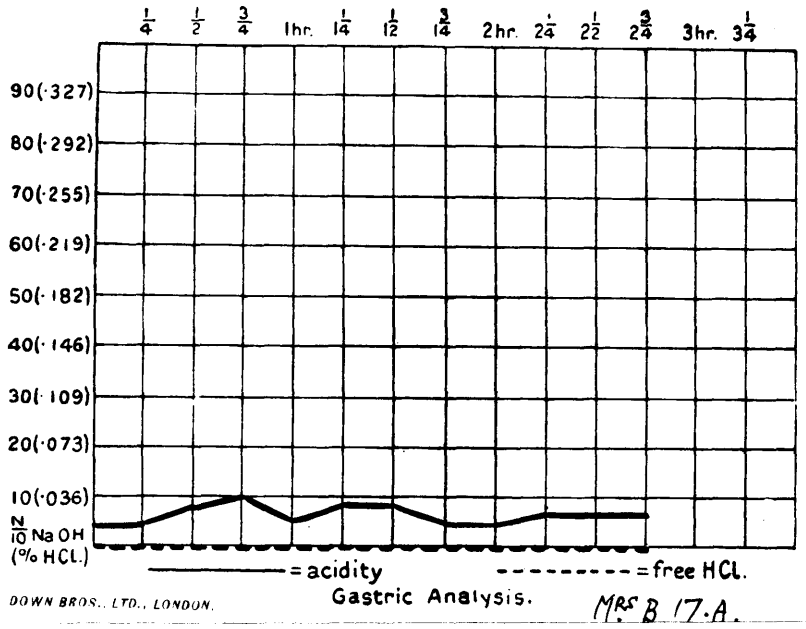
(B)



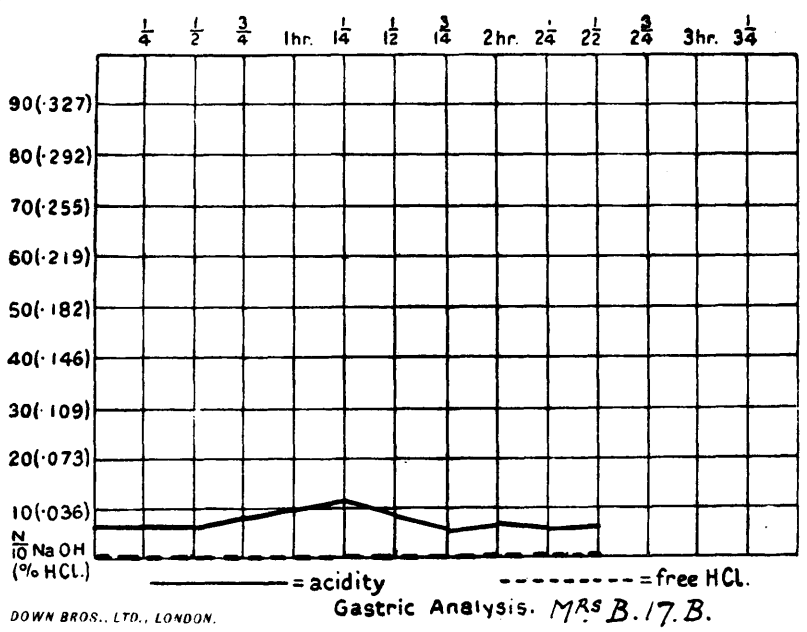
DOWN BROS., LTD., LONDON.

Gastric Analysis. MRS D. 166. B.

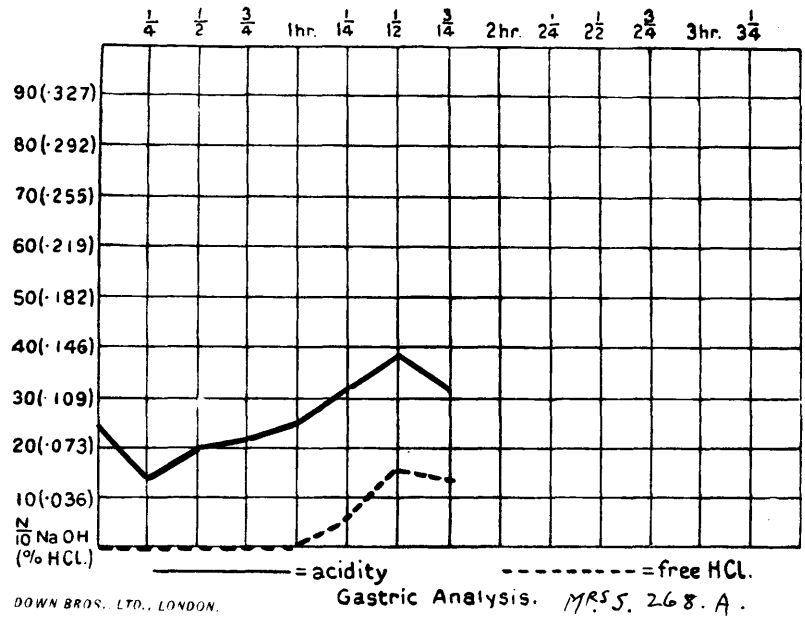
(A)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis.
MRS B 17.A.

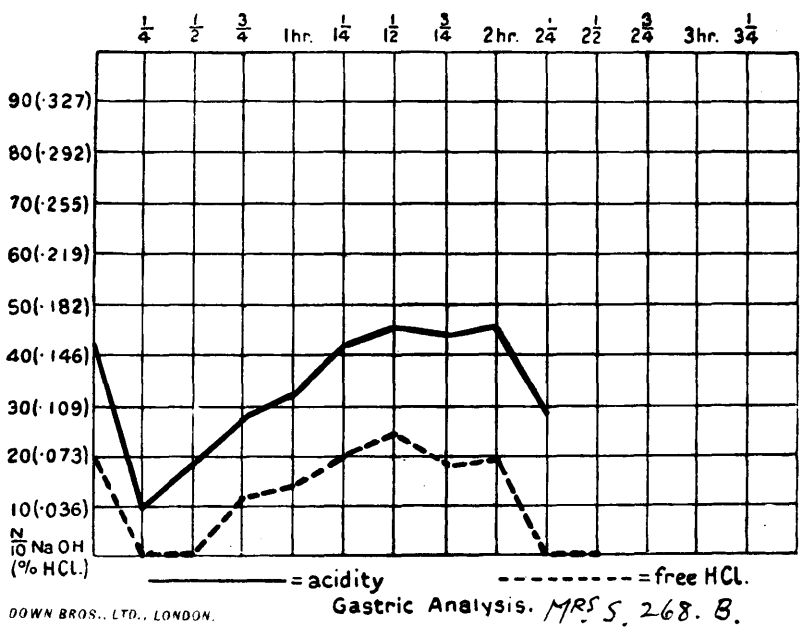
(B)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS B. 17. B.

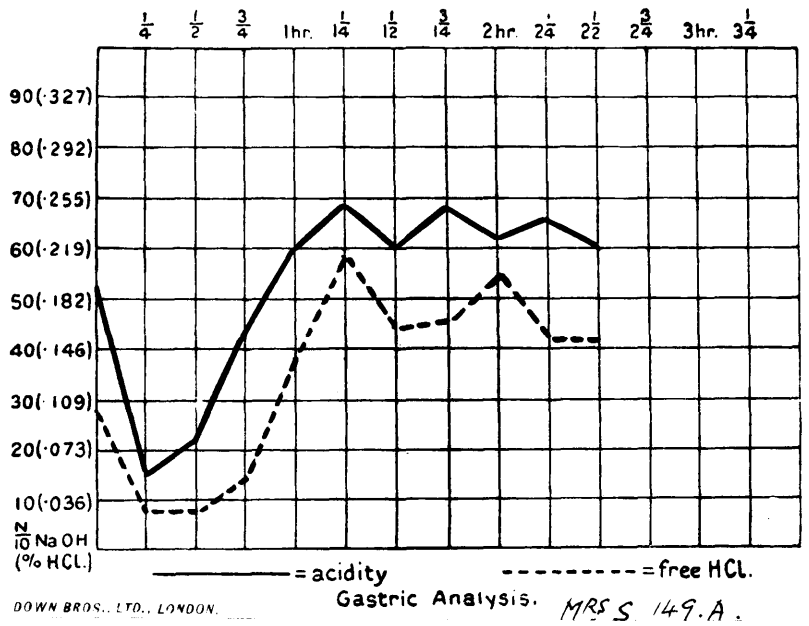
(A)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS S. 268. A.

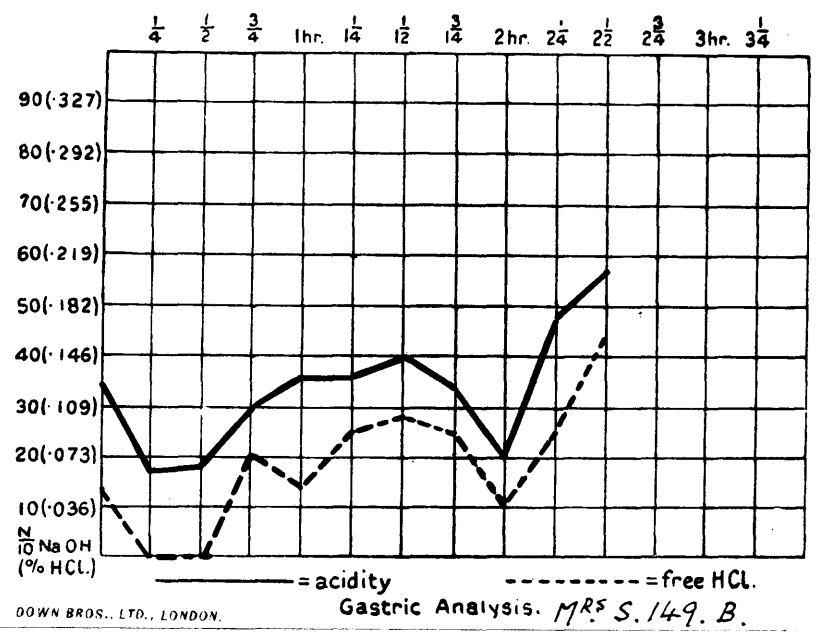
(B)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS S. 268. B.

(A)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS S 149. A.

(B)


¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr. 3¼
90(·327)
80(·292)
70(·255)
60(·219)
50(·182)
40(·146)
30(·109)
20(·073)
10(·036)
N/10 Na OH (% HCl.)
= acidity
= free HCl.
DOWN BROS., LTD., LONDON.
Gastric Analysis. MRS S. 149. B.

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XII. ON THE LATER TOXAEMIAS OF PREGNANCY.

CLINICAL MANIFESTATIONS.

The woman who has successfully weathered the storm of the early months of pregnancy is not yet out of danger, as the uterine contents may be a source of trouble in the later months of gestation. Pregnancy is a merciless detective and is ruthless in its exposure of hidden weakness. Thus, in a woman with an old-standing but quiescent lesion of the kidney, symptoms of toxaemia soon appear as the result of the aggravation of the renal damage: in such a case, pregnancy is merely an incident in the course of a chronic disease, and the unfortunate woman after delivery is in a worse plight than before. Toxaemic manifestations in the early months are related to the digestive system, whereas those of the later stage cause attention to be focussed on the renal apparatus.

In this communication, acute yellow atrophy and nephritic toxaemia will not be considered, so that attention may be concentrated on the pre-eclamptic and eclamptic states, both most frequent among primigravidae.

Let us consider first the pre-eclamptic syndrome. In such a case, the toxaemia appears to be primarily due to the pregnant state, occurring as it does in a woman in whom no trace of damage, renal or otherwise, can be detected. The order of development of these pre-eclamptic manifestations has received much attention of late. So often the patient when first observed presents the complete clinical picture, making it impossible to determine which was the initial departure from normal. Symptoms may be conspicuous by their absence when definite signs are in evidence.

It has been pointed out by Browne (1932) and others

that one of the earliest warnings of a developing toxaemia is an elevation of blood pressure. An observation such as this can be confirmed daily in the out-patient department: quite frequently a patient protests that she feels perfectly well, no abnormality beyond a raised blood pressure can be detected, yet that single departure from normal is significant and warrants the closest supervision of the case.

Another sign which is often noticed in the absence of any other abnormality is oedema of the feet and ankles — and occasionally of wider distribution. Other causes of oedema have, of course, to be ruled out before ascribing to this development a toxaemic origin. Such patients, when admitted to the wards from the ante-natal clinic, quite frequently develop in the course of a few days other pre-eclamptic phenomena such as raised blood pressure and proteinuria.

Oliguria and the detection of protein in the urine may first direct attention to the fact that all is not well with the patient. "Proteinuria" is the more accurate definition in as much as both albumin and globulin are present, but we shall continue to use the term familiarised by long usage, viz. "albuminuria".

In certain instances, haematuria is the only warning sign.

Symptoms are also important. Complaint of headache, particularly in the frontal region, is frequently made. Lassitude and back-ache may be conspicuous. The patient may wonder why her morning sickness has returned. The recurrence of vomiting in the later months of pregnancy should always be regarded as a toxaemic manifestation and the precursor of more significant departures from the normal state unless suitable

treatment be instituted. Toxaemia of bacteriological origin, as in pyelitis, must of course be excluded. Visual disturbances may be troublesome: these may be associated with oedema of the retina, but not with the characteristic appearances of "albuminuric retinitis". Should blindness develop, there is found to be partial or complete detachment of the retina. Epigastric pain should be looked upon as a serious pre-eclamptic symptom; and, on occasion, mental disturbance may be the only indication of the serious condition of the patient.

In the early detection of pre-eclamptic signs and symptoms lies one of the greatest opportunities of preventive medicine. It is impossible to over-stress the supreme importance of observing the first departure from normal. The patient may well be instructed to report forthwith any development such as headache, vomiting, visual disturbance or epigastric pain, but frequently these phenomena are absent in the early stages of the condition. Emphasis must be laid on the duty of the medical attendant to detect the signs, particularly elevation of blood pressure, oedema and albuminuria. Ante-natal care worthy of the name necessitates frequent estimations with the sphygmomanometer, together with periodic examination of the urine and routine inspection of the patient. The development of the complete clinical picture of pre-eclampsia need not be awaited before instituting treatment: the presence of any one of these signs is ample warning for the exercise of the utmost care.

What is the inevitable result of the over-looked pre-eclamptic sign and symptom? Neglect involves multiplication and aggravation of these until the toxaemia finally becomes so marked that the unfortunate woman is precipitated into that most

dreaded of all the toxaemias of pregnancy, eclampsia. Emphasis is laid on these pre-eclamptic manifestations, because it is only by the early recognition of a departure from the normal and the prompt treatment of the patient that the probable sequel of eclampsia can be averted. In most cases of eclampsia there is ample warning over a period of time if cognisance of the various manifestations already indicated is taken; and even in the fulminating type of eclampsia, if the patient be observed sufficiently closely, some unusual feature will attract attention. Pre-eclamptic phenomena, it is satisfactory to know, as a rule disappear rapidly under simple treatment, and, should the progress of the patient not be all that is desired, steps may be taken to terminate the pregnancy. The abatement of these signs and symptoms is comparatively easily accomplished and is relatively simple when contrasted with the Herculean efforts which may be made to rescue an eclamptic patient from the jaws of untimely death without any assurance of success.

Three illustrative cases, recently under observation, may be cited.

I. A woman, aged 23 years, pregnant for the second time, was kept under close supervision in view of the fact that, in her previous pregnancy, eclampsia had developed at the stage of 7 months. She was seen one afternoon at the ante-natal clinic when eight months' pregnant, and, as on previous visits, she felt perfectly well and had no complaint. No abnormality was noted with the exception of a blood pressure of 164/110 mm. Hg. Previous readings had not exceeded 120/70 mm. Hg. In view of this she was sent into hospital. The same night, at 11.10 p.m. she had a convulsive seizure, followed by another at 11.45 p.m. The catheter specimen of urine then obtained showed albumin present to the extent of Esbach 8 parts per 1,000. Spontaneous delivery of a dead child weighing 5 lb. occurred the following day at 5.35 a.m. In all, fifteen fits occurred — two intra-partum and thirteen post-partum. During the acute stage, the systolic blood pressure never exceeded 154 mm. Hg. The patient made a satisfactory recovery, the albumin in the urine dropping to a trace on the first day of the puerperium, and being absent thereafter. The blood pressure, too, was normal on dismissal.

In this instance, the type of eclampsia could justifiably be

classed as "fulminating", and yet there was a solitary warning sign in the presence of an elevated blood pressure.

II. About the same time there was admitted to hospital with eclampsia of the ante-partum variety a primigravida aged 17 years, the size of the uterus indicating pregnancy of seven months' duration. Albumin and blood were present in the urine and the blood pressure registered 160/124 mm. Hg. There was no oedema. In all, twenty-three fits occurred, and the patient died undelivered exactly twelve hours after the onset of convulsions. The history given was that, apart from scarlet fever at the age of 8 years, she had always been healthy. During pregnancy she enjoyed good health, and at no time had any complaint until 10.20 p.m. on the night before admission when, in a tram-car, she developed severe epigastric pain, became sick and vomited. The first fit occurred at midnight.

One cannot tell in a case such as this how long danger signals such as elevated blood pressure and albuminuria had been present, but the only symptom occurred 100 minutes before the first convulsive seizure.

III. A primigravida, aged 32 years, was admitted to hospital on account of intra-partum eclampsia. During pregnancy she had been perfectly well, but had noticed that for two or three weeks before term, her feet had become swollen. The urine showed albumin to the amount of Esbach 15 parts per 1,000, the blood pressure was 190/130 mm. Hg. and there was marked oedema of the lower extremities. A still-born child was delivered with forceps, and the following day the urine was clear while the systolic blood pressure was 120 mm. Hg.

The syndrome in this instance comprised oedema, albuminuria and elevation of blood pressure, but we do not know which was the initial symptom or sign. At any rate, oedema of the feet and legs for two or three weeks constituted ample warning, calling for the most careful observation of the patient.

THE RENAL FACTOR IN PRE-ECLAMPSIA AND ECLAMPSIA.

Abnormalities such as elevation of blood pressure, oedema, oliguria and albuminuria direct attention very forcibly to the renal apparatus. The factor or factors which maintain blood pressure at normal level are still imperfectly understood, consequently it is impossible to explain why the blood pressure should become raised in the pre-eclamptic state. In the first case cited, for example, elevation of blood pressure, followed

in a few hours by the appearance of albumin in quantity in the urine and by its equally rapid disappearance after delivery, would suggest the sudden action of a very powerful toxin on the renal epithelium and its abrupt withdrawal consequent upon the birth of the child. On the other hand, the slow liberation of toxin may have become suddenly accelerated, leading to the same result. The adjustment maintained between the maternal and foetal organisms appears to be so delicate that very little suffices to upset the equilibrium. Nothing is more dramatic in the pre-eclamptic or eclamptic subject than the rapid fall in blood pressure and disappearance of albumin from the urine very shortly after delivery.

Opportunity for post-mortem examination of the pre-eclamptic patient seldom presents itself, but, unfortunately, there is no such handicap in the case of eclampsia. Until recent years, attention has been directed more to the liver lesion than to the kidney damage. Baird and Shaw Dunn (1933) in a recent series of autopsies in eclamptic cases found it readily apparent in all instances that the hepatic lesions were of a very acute character, the changes being such as could easily have occurred within twenty-four hours. These observers have emphasised the importance of the renal factor in eclampsia, stating that the common lesion in the kidneys in fatal eclampsia is glomerular and characterised by thickening of capillary walls and of endothelium, leading to some degree of obstruction to blood-flow. Tubular changes they found to be less constant. They concluded that a degree of this renal lesion probably constitutes the anatomical basis of the albuminuria of pregnancy. It is important to note that the severity of the convulsions in eclampsia does not appear to bear any relationship to the degree

of the renal change.

The significance of the renal lesion becomes more marked when one reflects on the high incidence of recurrence of toxaemia in succeeding pregnancies shown by the woman who has been the victim of pre-eclampsia or eclampsia. Thus Young (1932) found a recurrence rate of 55·8 per cent. in a series of such cases, while Evans (1933) in a follow-up of 76 albuminuric patients discovered after-effects in two-thirds. Other investigations of this nature have yielded similar results. Women who have suffered from pre-eclampsia or eclampsia make an apparently perfect recovery, blood pressure returns to normal, albuminuria and other symptoms disappear, yet in a subsequent gestation toxaemic manifestations once more develop.

Experimental evidence has been brought forward by Browne and Dodds (1930) to show that chronic renal damage may exist during the intervals between pregnancies and yet give no clinical indication of its presence. In these cases, the subjects of occult nephritis, albuminuria appears towards the end of pregnancy. The observations of these workers suggest that in the so-called "recurrent toxaemias of pregnancy" there is all the while a mild degree of chronic renal damage which undergoes exacerbation with the strain of pregnancy, and that the "low reserve kidney" may be in the same category.

Furthermore, clinical evidence would suggest that successive normal pregnancies are not always without baneful effect. Not infrequently one encounters such a case in which a woman has passed through three or four pregnancies without the least upset, and has emerged apparently scathless, only to develop raised blood pressure, albuminuria, oedema, etc., in the fourth or fifth gestation. Such findings direct attention

once more to the renal apparatus: they suggest that a slight degree of renal damage has been caused by three or four apparently normal pregnancies, and that the fourth or fifth, as the case may be, has proved to be the limit of tolerance, with the result that the renal damage becomes manifest through the development of toxaemic signs and symptoms. It would seem that a woman cannot have an indefinite number of pregnancies without suffering the consequences, and that for many the normal limit is four.

Munro Kerr (1933) quotes a table showing that, in pregnancies subsequent to the fourth, there is apparent a higher rate of maternal mortality which increases steadily with increasing number of pregnancies thereafter. Observations such as these furnish a very strong argument against permitting women to have an indefinite number of pregnancies.

THE INCIDENCE OF ECLAMPSIA.

Eclampsia occurs more frequently in primigravidae than in multigravidae, and, of the three varieties, the ante-partum is the commonest. These facts are borne out in an analysis of 100 cases (Table I) in which it is shown —

(a) that 64 per cent. occurred in primigravidae;

(b) that 65 per cent. were of the ante-partum variety,
17 per cent. of the intra-partum variety, while
in 18 per cent. the onset took place during the puerperium.

A statement frequently made is that eclampsia is more prone to occur where the uterus is over-distended as in hydramnios and twin pregnancy. This is not corroborated by Table I (c) which shows that, in this series, 95 per cent. of the cases were associated with a single foetus, while twin pregnancy was noted

in 5 per cent., and hydramnios did not occur.

TABLE I — Analysis of 100 Cases of Eclampsia showing

(a) The high incidence among primigravidae;
(b) The preponderance of the ante-partum variety;
(c) The relative infrequency of multiple pregnancy.

(a)

Gravida.	Number of cases.
1 . . .	64
2 . . .	13
3 . . .	10
4 . . .	1
5 . . .	6
6 . . .	3
7 . . .	1
8 . . .	1
9 . . .	-
10 . . .	1

(b)

Variety of eclampsia.	Number of cases.
Ante-partum . .	65
Intra-partum . .	17
Post-partum . .	18

(c)

Single or Multiple Pregnancy.	Number of cases.
Single foetus	95
Twins	5

Eclampsia has also been encountered in cases of hydatidiform mole in which no trace of a foetus was discernible; hence it would appear that the presence of the actual foetus, or of more than one, cannot be directly related to the development of eclampsia.

No exact knowledge regarding the incidence of eclampsia can be obtained, and that mainly for three reasons.

(1) Convulsions and eclampsia are not synonymous terms. Patients may exhibit toxaemic signs and symptoms without convulsions and a fatal issue may result. Should a post-mortem examination be carried out, the finding of the characteristic renal and hepatic lesions points definitely to the existence of eclampsia. In the event of permission for autopsy being refused, an accurate diagnosis cannot be made. For example, a woman who had passed through several pregnancies uneventfully, was admitted to hospital with toxaemic manifestations, and a particularly marked elevation of blood pressure. One day she fell back dead without warning. At the post-mortem examination she was found to have a ruptured aorta and pronounced atheroma of the entire vessel. This catastrophe might have happened at any time apart from pregnancy, but the raised blood pressure incidental to her toxaemia undoubtedly hastened its occurrence. However, in addition, there were characteristic eclamptic lesions in liver and kidneys, although convulsions had never occurred.

(2) The occurrence of convulsions during pregnancy does not necessarily indicate eclampsia. Too frequently the discovery of pregnancy in convulsive states is automatically followed by the diagnosis of eclampsia when more accurate investigation would point to other causes such as epilepsy, hysteria,

meningitis, etc. Two illustrative cases may be mentioned. A woman, who was reported to have had several fits, was sent to a general hospital in an unconscious condition. There she was discovered to be pregnant and was thereupon transferred to the Royal Maternity Hospital as a case of eclampsia. The information elicited from the relatives was that the patient had passed through five pregnancies uneventfully, and that she had had no illness of note. For ten weeks she had complained of headache and earache, and the previous evening began to vomit. At 6 a.m. on the day of admission she was found unconscious.

Examination revealed pregnancy at the stage of six months: there was neither oedema nor albuminuria, and the blood pressure registered 122/74 mm. Hg. On lumbar puncture, the cerebro-spinal fluid was seen to be turbid and under tension: bacteriological examination showed a heavy pneumococcal infection and the diagnosis of pneumococcal meningitis was made. The patient died in a little over four hours after admission.

Similar features were noted in another case sent to hospital as post-partum eclampsia. Diagnostic lumbar puncture showed that the patient suffered from meningitis of the meningococcal type. She died ten minutes after admission.

(3) Eclampsia is not a notifiable disease, and therefore, while one can acquire accurate data as to the fatalities for which it is responsible, one cannot obtain reliable information as to the numbers developing this toxaemia who recover.

Doubtless most cases of eclampsia are concentrated in hospital, in urban areas at least.

TABLE II — Cases of eclampsia admitted to the Glasgow Royal Maternity and Women's Hospital during the years 1926 - 33 inclusive (574 in all).

Year	Total	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1926	69	2	5	9	3	5	8	10	4	13	5	1	4
1927	86	7	4	5	9	3	6	9	10	11	5	7	10
1928	74	6	7	8	5	6	6	9	4	7	8	3	5
1929	93	10	10	7	10	9	4	4	13	9	9	4	4
1930	59	1	3	3	10	5	2	7	8	6	4	10	-
1931	54	4	3	5	4	3	4	7	3	7	6	4	4
1932	73	10	10	6	5	7	9	6	4	3	3	5	5
1933	66	5	2	5	3	10	4	8	6	6	8	8	1
1926-33 incl.	574	45	44	48	49	48	43	60	52	62	48	42	33

TABLE III — Deaths occurring in Glasgow certified as due to eclampsia during the years 1926 - 33 inclusive (101 in all). Figure in brackets denotes those deaths which occurred in the Glasgow Royal Maternity and Women's Hospital (total 68).

Year	Total	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1926	11 (7)	—	2	2 (2)	—	1	1 (1)	2 (2)	—	2 (2)	—	—	1
1927	9 (7)	2 (1)	1 (1)	—	—	—	1 (1)	1	—	—	—	1 (1)	3 (3)
1928	15 (10)	1	1 (1)	1 (1)	3 (2)	—	1 (1)	3 (2)	2 (1)	1 (1)	1	1 (1)	—
1929	5 (4)	1 (1)	—	1 (1)	—	—	—	—	1	—	1 (1)	—	1 (1)
1930	16 (9)	2 (1)	—	3 (1)	2	1 (1)	1 (1)	1 (1)	2 (1)	—	—	3 (3)	1
1931	14 (8)	—	1	2	—	—	2 (1)	—	4 (2)	3 (3)	—	2 (2)	—
1932	19 (13)	1	1 (1)	2 (1)	—	—	3 (1)	2 (1)	3 (3)	1 (1)	2 (2)	2 (2)	2 (1)
1933	12 (10)	3 (2)	—	—	1 (1)	4 (3)	1 (1)	—	1 (1)	1 (1)	—	1 (1)	—
1926-33 incl.	101 (68)	10 (5)	6 (3)	11 (6)	6 (3)	6 (4)	10 (7)	9 (6)	13 (8)	8 (8)	4 (3)	10 (10)	8 (5)

Of the deaths in Glasgow certified as due to eclampsia, 67·3 per cent. occurred in the Royal Maternity and Women's Hospital. Over this period of 8 years, of 574 cases of eclampsia admitted, 68 died, the hospital death-rate for eclampsia being, therefore, 11·8 per cent.

Graph showing, during the years 1926-33 inclusive

(a) Variation according to months of 574 cases of eclampsia admitted to the Glasgow Royal Maternity and Women's Hospital _____

(b) Maternal deaths from eclampsia in Glasgow . . ---------

(c) Maternal deaths from eclampsia in the Royal Maternity and Women's Hospital . . . .

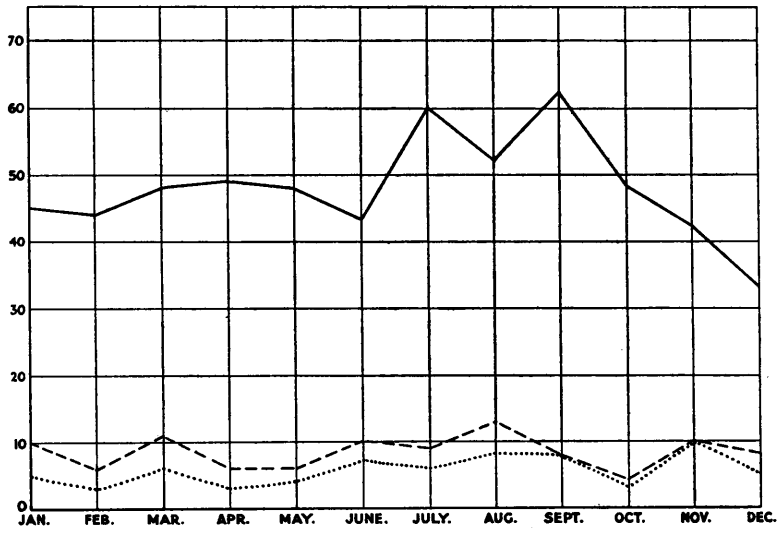

Table II shows the number treated in the Glasgow Royal Maternity and Women's Hospital during the years 1926-33 inclusive. The deaths from eclampsia in Glasgow during the same period are shown in Table III. The numbers vary in different months and from year to year, but from the graph it appears that, over the period indicated, the maximal incidence of eclampsia is in the months of July and September. Such an observation is not in accordance with the statement often made that eclamptic attacks are more frequent in cold and rainy weather and rare in warm, dry weather.

Sir Halliday Croom (1911-12), reviewing the cases of eclampsia in the Edinburgh Maternity Hospital during the years 1890 - 1911 (238), found the incidence to be greatest in the month of October. It is interesting that both Glasgow and

Edinburgh should find the condition most common at times which are at variance with the records of foreign hospitals. However, as Sir Halliday Croom points out, the cause of the varying incidence must be looked for, not in the actual seasons, but in the changes of temperature occurring in the various months.

Földes (1933) attempts to show that the pathogenesis of eclampsia is essentially the same as, and represents a special case of the pathogenesis attributed to epilepsy, and, in his view, the conception and term of toxaemia of pregnancy should be abandoned. In both conditions he considers that there is a general disturbance in the metabolism of water and minerals and a local predisposition in the brain, with the result that fluid accumulates in the tissues and spaces enclosed by the capsules of the brain, leading to increased pressure in these tissues and spaces and hence to irritation of the cortical centres. Atmospheric conditions have an influence on the frequency of epileptic attacks, and they are mentioned by him as being among the factors which may cause such disturbances of the water and mineral metabolism as may lead to eclampsia. "The causal connections," he proceeds, "may be understood by considering that a sudden drop of the barometric pressure associated with rainy weather leads to retentions, and that, in warm and dry weather, there is an increased perspiration which prevents retentions."

Heuss (1927) has shown that in Germany the incidence of eclampsia and meteorological conditions are closely related. It has been found that sudden alteration in temperature and rainfall, irrespective of season, affects the frequency of the disease.

The relationship of the early and late toxaemic

manifestations in pregnancy has often been discussed. Hyperemesis and eclampsia differ in that, in the former there is not the slightest suggestion of seasonal variation. They resemble one another in that they appear to have a regional variation: thus in Glasgow and Edinburgh hyperemesis and eclampsia are more frequent and of greater severity than in London. Differences in water supply have been invoked to explain this. In a book recently published, Porritt (1934) advocates the view that a potential cause of puerperal toxaemia and eclampsia is the saturation of the system by minute, infinitesimal doses of lead, extending over a long period of time, in districts where a plumbo-solvent water acts on the lead service-pipes, and conveys the metal not only into water drunk, but into all food consumed by dwellers in those districts. According to this view, the case of neuritis associated with pregnancy (p. 97) would be regarded as an example of subtle plumbism, as would also the toxaemic manifestations which followed.

TABLE IV — Glasgow Corporation Water Department.

Water Analyses.

(All results expressed in parts per 100,000.)

	Loch Katrine Water.	Gorbals Water.
Appearance	Clear & Bright.	Clear & Bright.
Free and Saline Ammonia	Free.	Free.
Albuminoid Ammonia	0·0041	0·0058
Chlorine	0·78	0·90
Oxygen absorbed in 15 minutes at 27°C.	0·059	0·734
Oxygen absorbed in 4 hours at 27°C.	0·162	0·189
Nitrogen as Nitrites	Nil	Nil
Nitrogen as Nitrates	Nil	Trace
SOLIDS IN SOLUTION.		
Mineral Solids	2·09	7·28
Volatile or Organic Solids	0·91	3·14
Total Solids	3·00	10·42
Hardness	1·18	5·30
Suspended Matter	None	None

(Received from City Analyst, January, 1931.)

The above results prove that the Loch Katrine and Gorbals water supplies represent a water of the highest standard of purity for domestic use and admirably suitable for trade purposes.

The difference in the characteristics of the waters drawn from the Loch Katrine and the Gorbals Water Works is confined to their relative degree of hardness.

The water from the Loch Katrine supply is an exceptionally soft water, registering only 1 degree of total hardness as measured by Clark's Standard Soap Solution.

The Gorbals supply, on account of its larger content of mineral substances in solution, is a harder water, registering 5·3 degrees of total hardness.

Loch Katrine water requires no filtration.

Gorbals water is filtered.

TABLE V — Edinburgh Corporation Water Works.

Water Analysis.

(Expressed in parts per 100,000.)

	East Area.	West Area.
Total solid matter	6·86	8·46
Organic and Volatile matter	2·29	2·20
Mineral matter	4·57	6·26
Chlorine in Chlorides	0·64	0·64
Phosphates	None	None
Iron	None	None
Lead or other poisonous metals	None	None
Nitrogen in Nitrates	None	None
Nitrites	None	None
Saline Ammonia	0·007	0·001
Albuminoid Ammonia	0.004	0·008
Oxygen absorbed at 80°F. in 4 hours	0·177	0·110
Total hardness	4·30	5·5
Temporary hardness	3·14	4·21
Lime (as CaO)	1·47	2·05
Magnesia (as MgO)	0·66	0·74

TABLE VI — Water Analysis — Dublin.

(Expressed in parts per 100,000.)

Total solids	5·0
Albuminoid Nitrogen	0·007
Ammoniacal Nitrogen	0·000
Nitrous Nitrogen	Absent
Nitric Nitrogen	Trace
Chlorine	1·3
Sulphates as Calcium Sulphate	Trace
Total hardness	2·0
Permanent hardness	
"Oxygen absorbed" in 3 mins. at 26·7°C.	—
"Oxygen absorbed" in 4 hours at 26·7°C.	0·142
Colour (Platinum Cobalt Scale)	20·0
Odour	None
General appearance	Clear & Bright
Ph. value	6·9

In Tables IV, V and VI are shown the official results of analyses of the water supplies of Glasgow, Edinburgh and Dublin. Examination of these figures shows individual variations, but gives no indication that any of these might serve as an aetiological factor in the production of pregnancy toxaemia.

It is frequently noted that failure of the thyreoid gland to hypertrophy during pregnancy is associated with pre-eclamptic manifestations: in such cases the administration of thyreoid extract often gives beneficial results. Such observations lead one to the consideration of water supply from the aspect of its iodine content. "The quantity of iodine in waters is usually expressed in terms of γ per litre of water, when 0·001 mg., i.e. 1/1,000,000 gm. = 1·0γ. It is really the same as parts per 1,000 million parts." So it is stated in the Twenty-fourth Annual Report of the London Metropolitan Board, in which the following figures, obtained at the Rowett Research Institute, Aberdeen, are contained.

TABLE VII.

Samples of Town Supplies. Iodine γ per litre.		Samples from Goitrous Areas. Iodine γ per litre.	
London (Thames – Hammersmith)	4·20	Cumberland (1)	1·30
London (Kent Chalk, Deptford Garden Well)	0·65	(2)	3·90
Manchester	2·00	(3)	2·45
Liverpool	2·00	Derbyshire (1)	1·66
Leeds	2·55	(2)	2·10
Shepton Mallet	2·58	(3)	1·87
Canterbury	2·14	(4)	1·84
Cambridge	0·80	(5)	1·40
Swindon	0·52		
Edinburgh	1·70		
Glasgow	1·90		
Aberdeen	0·63		

The Aberdeen workers point out that "It is true that the lowest figure (Swindon) is for water from a goitrous area, but the next one (Aberdeen) is not. The figures for Cumberland and Derbyshire, both goitrous areas, are not low."

"The examination of Aberdeen water, sampled direct at the intake and at the various stages in the process of purification, and of Edinburgh water before and after filtration, show that in each case there is a small loss of iodine. The loss is, however, too small to be of any significance and, in the case of Aberdeen water, is less than the fluctuations in iodine content which occur naturally from time to time."

"A much larger loss of iodine was found to take place in the process of softening a chalk water by Clark's process (addition of lime). Canterbury water before treatment was found to contain 4·32 γ per litre, and after softening, only 2·14 γ per litre."

It is seen that the figure for Glasgow is higher than that for Edinburgh, and neither is low. There is, therefore, no obvious fault in the water supply of Glasgow or Edinburgh which might be held responsible for the greater frequency and severity of toxaemic manifestations in pregnancy as compared with cities farther south.

It must be recognised that some women enjoy perfect health throughout pregnancy and suffer no unpleasant effects. Mention may be made of one such who did not even have nausea in the first two gestations; indeed, on the first occasion, she did not realise she was pregnant until she 'felt life'. In her third pregnancy, there was slight morning sickness during the third month, but she was not in the least upset: however, when seven months' pregnant, she was admitted to hospital with

eclampsia. It is possible that in this case two pregnancies proved to be the limit of tolerance, and that the toxaemic manifestations, early and later, in the third gestation represented the cumulative damage of two pregnancies on which had been superimposed the strain of another. On the other hand, it might be that the third pregnancy was especially 'virulent' as regards the destruction of maternal tissue, either on account of lowered resistance of the latter or excessive activity of the trophoblastic villi with the result that hormonal imbalance may have been more pronounced.

The fact remains that eclampsia has a distinct regional variation: it is more frequent in England than in France, and is very common in Glasgow and surrounding district. It is largely a disease of cities. Oxley (1930) reported that, among the last ten thousand consecutive confinements at the East London Maternity Hospital, only one woman developed eclampsia, that is, 0·01 per cent. During the year November 1, 1928 to October 31, 1929, there were admitted to the Rotunda Hospital, Dublin, nine cases of eclampsia. Consultation of Table II shows that, in the corresponding period, there were admitted to the Glasgow Royal Maternity and Women's Hospital ninety-three cases of eclampsia. Of course, differences in population must be taken into consideration. Table VIII shows that over a period of eight years, 1·7 per cent. of all admissions to the Glasgow Royal Maternity and Women's Hospital (33,234) were diagnosed as eclampsia.

TABLE VIII.

Year	Total admissions	Cases of eclampsia	Percentage of total admissions diagnosed as eclampsia
1926	3,653	69	1·9
1927	3,902	86	2·2
1928	3,941	74	1·9
1929	3,841	93	2·4
1930	4,469	59	1·3
1931	4,442	54	1·2
1932	4,391	73	1·7
1933	4,595	66	1·4
1926-33 incl.	33,234	574	1·7

Rickets is a disease of cities, and even among cities Glasgow has had an unenviable reputation on account of the prevalence of rickets. There appears to be a close analogy between the conditions, environmental and meteorological, giving rise to these two diseases.

It is well known that the toxaemias of pregnancy are very much less common throughout the East, if Japan be excepted, than they are in the West (Theobald, 1930). The clothing worn is light, and a generous portion of the body is exposed to the sun. The diet of the Siamese, nevertheless, is obviously deficient in vitamins A and B, as evidenced by the frequent occurrence of vesical calculi and beri-beri. The Siamese constantly eat lime with betel: this may provide the women with the necessary calcium, for there is certainly not much calcium in their food, and they never drink milk. Rickets is

practically unknown, its absence being due to the good effect of sunlight.

Eclampsia and allied conditions, it is worthy of note, occur mainly in the large cities of India, and eclampsia affects only those who lead a very secluded purdah life. Meat is eaten very sparingly by the average Indian. In Japan, on the other hand, the incidence of the toxaemias of pregnancy is as great as in this country. There the climate is about as bad as our own; large cities are found, and in these the people are tending more and more towards European habits and diet. The diet of the people is deficient in calcium because the Japanese do not drink milk, nor do they chew betel with lime.

CONCLUDING REMARKS ON PRE-ECLAMPSIA AND ECLAMPSIA.

In Tables IX and X are shown the results of blood analysis, carried out in conjunction with S.L. Tompsett, in 9 cases of eclampsia and 13 cases of normal and toxaemic pregnancy. The constituents estimated were the albumin, globulin, non-protein nitrogen, urea, inorganic sulphur, sodium chloride, sodium, potassium, phosphorus and calcium.

The methods employed were:-

For albumin and globulin, the methods of Folin and Wu (1919), Howe (1921) and Wu (1922), by which the normal albumin : globulin ratio is $\frac{2}{1} - \frac{3}{1}$.

For non-protein nitrogen, the method of Folin and Wu (1919), the normal limits being 20 - 40 mgm. per 100 c.c.

For urea, the method of Folin and Wu (1919), the normal values being 20 - 40 mgm. per 100 c.c. These methods for protein and non-protein nitrogen estimations are advocated by Hawk and Bergeim (1927).

For inorganic sulphur, the method described by Cuthbertson and Tompsett (1931), the normal values varying between 0·8 and 1·6 mgm. S per 100 c.c.

For sodium chloride, the method of Van Slyke (1923), the normal plasma chloride having a range of 560 - 620 mgm. per 100 c.c.

For sodium, the method of Kramer and Gittleman (1924), the normal for serum being 325 - 350 mgm. per 100 c.c.

For potassium, a slight modification of the method of Kramer and Tisdall (1921), (The precipitate of potassium cobaltinitrite was oxidised with a known excess of standard potassium permanganate solution, but the excess permanganate was determined by the addition of potassium iodide, and the liberated iodine was titrated with standard sodium thiosulphate.) The normal value is 18 - 21 mgm. per 100 c.c. serum.

For phosphorus, the method of Briggs (1922), the normal value for serum being 2 - 4 mgm. per 100 c.c.

For calcium, the method of Kramer and Tisdall (1921) as modified by Clark and Collip (1925), by which the normal serum value varies between 9·0 and 11·0 mgm. per 100 c.c.

TABLE IX — Cases of Eclampsia (9).

No.	Stage of pregnancy. Calendar months.	Variety of eclampsia.	Albumin. gms. per 100 c.c.	Globulin. gms. per 100 c.c.	Albumin / Globulin	N.P.N. mgms. per 100 c.c.	Urea. mgms. per 100 c.c.	Inorganic S. mgms. per 100 c.c.	NaCl mgms. per 100 c.c.	Na mgms. per 100 c.c.	K mgms. per 100 c.c.	Inorganic P. mgms. per 100 c.c.	Ca mgms. per 100 c.c.
1	4½	Ante-partum	—	—	—	50	58	2·6	585	309	29·2	5·5	8·7
2	5	Ante-partum	2·83	2·27	1·24	22	26	2·8	591	347	24·9	—	9·0
3	6	Ante-partum	—	—	—	32	22	2·0	—	318	20·2	3·8	7·4
4	7	Ante-partum	—	—	—	23	27	2·4	577	368	19·3	—	9·4
5	8	Ante-partum	—	—	—	18	20	0·3	582	368	26·7	—	8·3
6	9	Ante-partum	3.08	2·41	1·28	24	27	2·5	607	366	22·0	3·14	10·0
7	9	Ante-partum	3·03	2·33	1·30	21	26	1·9	591	300	23·1	4·2	11·2
8	9	Post-partum	4·50	3·37	1·33	30	27	2·2	532	314	26·6	—	9·8
9	9	Post-partum	4·03	1·91	2·11	50	54	2·3	572	299	23·1	3·9	9·9

TABLE X — Miscellaneous Control Cases (13).

No.	Stage of pregnancy. Calendar months.	Type of case.	Albumin. gms. per 100 c.c.	Globulin. gms. per 100 c.c.	Albumin / Globulin	N.P.N.	Urea.	Inorganic S.	NaCl	Na	K	Inorganic P.	Ca
								mgms. per 100 c.c.					
1	2½	Hyperemesis gravidarum	4·27	2·84	1·50	31	27	1·2	—	311	20·8	3·3	10·3
2	5	Nephritic toxaemia	2·73	1·86	1·47	—	105	2·7	547	310	20·8	4·8	10·0
3	6	Fulminating pneumococcal meningitis	—	—	—	31	24	2·7	608	304	18·6	1·2	10·1
4	7	Pre-eclamptic toxaemia	3·49	3·92	0·86	24	25	3·0	550	—	—	—	—
5	8	Pre-eclamptic toxaemia	2·90	4·41	0·70	39	24	2·5	567	—	—	—	—
6	9	Pre-eclamptic toxaemia in labour	—	—	—	39	25	0·7	626	328	18·3	3·4	8·9
7	9	Twin pregnancy	—	—	—	29	31	1·4	—	345	27·7	3·1	9·4
8	9	Normal pregnancy	3·65	2·60	1·40	24	28	1·4	—	209	18·6	3·1	9·6
9	9	Normal pregnancy	2·54	1·91	1·33	19	22	1·5	—	284	21·2	1·9	9·3
10	9	Normal pregnancy in labour	5·20	3·16	1·64	26	28	1·4	597	298	21·2	4·0	10·9
11	9	Normal pregnancy after delivery	3·70	1·93	1·91	—	28	1·7	562	295	26·3	2·8	10·3
12	9	Normal pregnancy after delivery	3·94	2·87	1·37	22	19	1·6	—	321	20·7	3·1	9·8
13	9	Normal pregnancy at term	2·93	2·63	1·11	—	22	1·0	631	284	19·2	2·8	10·9
		Normal pregnancy after delivery	4·21	1·78	2·37	39	38	1·5	529	284	23·1	3·3	9·7

The two outstanding features are those already emphasised, viz. the diminution in the serum calcium and the increase in the inorganic sulphur of the blood in eclampsia. These are the most constant; nevertheless they cannot be regarded as being primarily aetiological: rather must they be looked upon as accompaniments of the condition.

Anselmino, Hoffmann and Kennedy (1932) have carried out an important investigation, as a result of which they advance the hypothesis that "toxic albuminuria" of pregnancy and eclampsia are endocrine disturbances, probably of a pluriglandular nature, but in which great over-production of the hormones of the posterior pituitary dominates the picture. Not only do they state that they have been able to detect an increased content of posterior pituitary hormones in the blood of all their cases, but they have found it possible to demonstrate a relationship between the amount present and the severity of the symptoms. It is interesting to note that, by the injection of pituitrin experimentally, there have been produced many of the features of eclampsia, including diminution of blood calcium. There is added interest in the observation that the effect of the posterior pituitary has been found to be lessened by certain narcotics and hypnotics which happen to be the same drugs employed quite empirically in the Stroganoff treatment of eclampsia (1930).

Smith and Smith (1934) examined 46 sera and 44 twenty-four hour specimens of urine from 42 women in the last trimester of pregnancy for their content of gonadotropic hormone (prolan) and oestrin. Their conclusion was that a quantitative imbalance of these two hormones, due to excessive amounts of prolan and less consistently to subnormal levels of oestrin, is

typical of the toxaemias of late pregnancy.

During the early months of pregnancy the anterior lobe of the pituitary exhibits increased activity, as shown by the Zondek-Aschheim test, and this probably inhibits posterior lobe activity. Later on faulty balance may permit the activity of the posterior lobe to manifest itself at an earlier stage and to a greater extent than normal. Thus toxic albuminuria of pregnancy may be the result of hormonal imbalance due to premature and excessive activity of the posterior lobe of the pituitary. The development of eclampsia may coincide with some sudden and still more pronounced increase in posterior lobe secretion or with the superimposition of some additional factor. For some time the conception that abnormal endocrine activity must be responsible for the development of the later toxaemias of pregnancy has been gaining ground. Now that it has received confirmation through the work of Anselmino, Hoffmann and Kennedy and of other observers, it is hoped that an efficient antidote (perhaps in the form of a potent anterior lobe preparation) may be found to counteract the excessive activity of the posterior lobe.

Meanwhile, there is no specific for the treatment of eclampsia. It is a common experience that many recover with the ordinary routine treatment, while others succumb in spite of this and more energetic measures. Conservative treatment, in which attention to elimination and the judicious administration of sedatives figure prominently, gives the best results. More radical procedures should be reserved for such cases as make an unsatisfactory response.

In the early detection and prompt treatment of pre-eclamptic manifestations, as has already been stressed,

preventive medicine has one of its greatest opportunities, but the treatment of eclampsia is still empirical and the results problematical at the best. In the pre-eclamptic state, quite simple treatment quickly yields beneficial results: if not, the pregnancy can be terminated before the patient's condition becomes critical. Prophylaxis it is impossible to over-emphasise, because, in the present state of our knowledge, it is only by the exercise of <u>really adequate ante-natal supervision</u> that eclampsia can be prevented and a considerable decrease in maternal mortality thereby secured. The astounding results in the clinics in which the patients receive very complete ante-natal supervision justify the claim that eclampsia is, save in a few instances, a preventable disease.

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