THE TOXÆMIAS OF PREGNANCY.

I.—Early.

By DAVID FYFE ANDERSON, M.B. (Glas.), M.C.O.G.

Assistant to the Regius Professor of Midwifery, University of Glasgow; Assistant Obstetric Surgeon, Glasgow Royal Maternity and Women's Hospital; Surgeon to Out-patients, Royal Samaritan Hospital for Women, Glasgow.

The toxæmias of pregnancy have constituted a baffling problem throughout the ages, and to-day the mystery remains obscure. For the toxæmias of pregnancy no common ætiological factor has been demonstrated save one—the fact of pregnancy.

In every pregnancy profound changes in maternal metabolism early occur: evidence of this is furnished by the Zondek-Aschheim test. In most pregnancies the first disturbance is morning sickness, which may manifest itself before amenorrhœa is noted. There may be no actual vomiting, 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 occurs between twelve and seventeen days from the onset of the preceding menstrual period. If it be accepted that about seven days elapse between fertilisation and imbedding, it follows that the occurrence of sickness corresponds in time to the process of imbedding of the zygote.

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 gravidarum as is apparently the case with the typical toxæmia of the later months, viz., eclampsia. Underlying the so-called “normal” morning sickness there is a basis of toxæmia. One should not dismiss such cases lightly, airily attaching the label “neurotic vomiting.” It must ever be borne in mind that, with very few exceptions, the most pernicious vomiting begins as emesis gravidarum. Even morning sickness is a toxæmic 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.

Pregnancy is a physiological process characterised by its extreme liability to become pathological. Broadly speaking, in a healthy woman, the period of pregnancy 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. During the fourth, fifth and sixth months the equilibrium seems to be restored. In the average case, this may be said to be a period of comparative well-being.

3. In the last three months of gestation toxæmic 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.

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 overproduction 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 activity of the villi may be said to run riot, is in a very large proportion of cases associated with pronounced toxæmic 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.

This idea of the causes of the initial disturbances in pregnancy is a line of approach that Professor Munro Kerr has for many years presented to his students; his views are briefly summarised in a recent paper.⁽³⁾

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 toxæmia, and one would imagine that a larger amount of this toxic product might be found in the vomitus. 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.

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 intraperitoneally and intravenously without apparent harmful effect and without demonstrable histological change in any of the organs. Furthermore, attempts made to fortify pregnant women against toxæmia 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 toxæmic 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.

The vomitus (collected over a period of 24 hours) in the majority of patients suffering from hyperemesis gravidarum is found to contain no free hydrochloric acid, while in the remainder a very low concentration is noted.⁽¹⁾ Observations repeated at intervals of several days give identical results, hence it appears that little or no acid is lost from the body in the vomitus, and there seems to be no sufficient ground for the belief that such cases suffer from a relative alkalosis.

TABLE I.

Results of fractional test meals grouped according to the maximal concentration of free hydrochloric acid. (78 cases).

	No. of cases	Achlorhydia	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 ...	28	6	3	7	7	5	—
Hyperemesis ...	22	10	2	5	1	1	3
Pyelitis ...	9	—	4	2	2	1	—
Albuminuria ...	10	1	1	4	1	2	1
			(previous hyperemesis).				
Eclampsia ...	9	2	—	1	4	1	1
Total	78	19	10	19	15	10	5

TABLE II.

Number of cases of achlorhydia falling into age groups.

Age group	Achlorhydia	10 per cent and under	11 to 20 per cent	21 to 30 per cent	31 to 45 per cent	Above 45 per cent
19 to 25	10	5	8	8	3	3
26 to 30	6	—	5	3	2	1
31 to 35	2	2	6	3	3	1
36 to 42	1	3	—	1	2	—

TABLE III.

Comparison of results of fractional analysis in hyperemesis gravidarum in the active stage and on recovery. (certain selected examples).

Type of case.	Type of free hydrochloric acid curve.	
	In the active stage.	On recovery.
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 1½ 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.

On fractional analysis of the gastric contents after test meals, the most striking finding is the frequency of achlorhydria and hypochlorhydria in emesis and hyperemesis gravidarum. Patients with pyelitis as a complication of pregnancy frequently have vomiting, and such must be carefully distinguished from examples of toxæmic vomiting. It has been the experience of the writer that pregnant women suffering from pyelitis associated with vomiting exhibit a tendency to hypochlorhydria, but achlorhydria has not been demonstrated in this group. No marked incidence of achlorhydria in albuminuria or eclampsia has been shown to exist. Thus from Table I. it will be seen that, in a series of 50 cases of emesis and hyperemesis gravidarum, achlorhydria occurred in 16 (32 per cent.), while hypochlorhydria was noted in a fairly large proportion of the remainder.

An interesting case for comparison was a girl who suffered from habitual premenstrual 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: a fractional test meal during menstruation disclosed normal acidity curves. Incidentally, such a case lends corroborative evidence to the view that sickness is associated with endometrial changes and hormonal variations (menstrual).

Bacteriological examination of the vomitus and of the gastric contents removed for fractional analysis has shown that, in the presence of free hydrochloric acid, however low the concentration, there is a scanty flora, whereas achlorhydria is invariably accompanied by the appearance of abundant organisms. Thus is a vicious circle established. Oral sepsis and constipation, while occurring with notable frequency in hyperemesis gravidarum, cannot be stressed as being peculiar to the condition. Nevertheless, in an already established toxæmia, oral sepsis and intestinal stasis are certain to contribute to its aggravation. 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.

From Table I. it will be observed that, in the series investigated by the writer, there were 3 cases of hyperemesis in which hyperchlorhydria was exhibited—cases in which, judging by the severity of the symptoms, one would have expected achlorhydria or hypochlorhydria. It is recognised that, apart from pregnancy, one occasionally meets a case presenting the typical picture of the "achlorhydric syndrome" in which a test meal discloses a hyperacidic condition instead of the anticipated hypoacidity. In the writer's experience, fatal results have been recorded only in those patients whose gastric secretion showed achlorhydria or hypochlorhydria.

In all save one of these cases associated with achlorhydria, the total acidity curve was low, hence combination of acid with protein cannot be advanced as the reason for the disappearance of free hydrochloric acid from the gastric secretion. 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 in the fractional test samples. The psychic effect of the test meal has been quoted as accounting for the achlorhydria or hypochlorhydria in cases such as those under review. It would appear, however, 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. Repeated observations have testified to the ease with which Ryle's tube is retained 'in situ' even in severe examples of hyperemesis gravidarum,

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: the psychological value of the administration of a drug may be apparent in some instances. An essential therapeutic measure, especially in hyperemesis is the supply of nourishment, and particularly the exhibition of glucose which may be given orally, rectally or intravenously, according to the severity of the case. Liver extract and dilute hydrochloric acid have been employed, and, in our experience, these given together are well borne by the patient and apparently do not contribute to the already existing nausea. It is important to observe, however, that with the disappearance of symptoms, no matter what aids may have been invoked to produce this result, there is a change in the gastric secretion. In those patients who have previously been of the achlorhydric class, there is a return of free hydrochloric acid in low concentration: in patients who have had hypochlorhydria, there is noted an increase in the percentage of free acid. Typical examples are shown in Table III., where it will also be seen that, in a case of hyperemesis where hyperchlorhydria was in evidence, recovery was coincident with a fall in the percentage of free acid. The return of free hydrochloric acid to the stomach in those cases where it has previously been absent would seem to indicate that the achlorhydria or hypochlorhydria is intimately related to the disturbance of gastric function, but the vicious circle may be more complicated than we imagine.

A large amount of work has been done in connection with blood analysis in emesis and hyperemesis gravidarum. It would appear that variations in the composition of the blood are not characteristic of this toxæmia as contrasted with other toxæmias. 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 toxæmia at which the blood is examined. For example, an interesting study is the estimation of the ketone content of the blood in different types of pregnancy toxæmia. The high values obtained in hyperemesis are merely indicative of the degree of ketosis, which again is a starvation phenomenon dependent upon the duration of vomiting. It is important, however, having made such estimations, and having recognised the considerably raised values, to take appropriate prophylactic and therapeutic measures to counteract this tendency. Thus, should operative intervention be necessary, the choice of anæsthetic is obviously of great moment. Chloroform is especially dangerous because of its well recognised toxic action on the liver. The safest anæsthetic for such a case is undoubtedly gas and oxygen. Far from having any ætiological significance, 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.

The relationship of the early and late toxæmic manifestations in pregnancy has often been discussed. Hyperemesis and eclampsia differ in that, in the latter, a seasonal variation is noted. 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, but no satisfactory evidence has so far been adduced.

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 toxæmic 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 main features of another case, recently under observation, may also prove of interest. 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 when she was 6 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 œdema. 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 lbs. The puerperium was uneventful.

This woman would not admit any previous ill health. Throughout the three preceding pregnancies, she was perfectly well. In none of the four gestations had she experienced sickness: even nausea had been conspicuous by its absence. Constipation had not been troublesome, and aperients were not required. In view of the absence of any other ætiological factor, one is constrained to regard the loss of power of the right upper limb as a toxæmic manifestation of pregnancy and label the case accordingly as toxic neuritis of pregnancy. This is a rare

toxæmic 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 toxæmic disturbance. There is added interest in the fact that this rare toxæmic manifestation was succeeded by the more common toxæmic syndrome in the latter part of pregnancy, *viz.*, headache, albuminuria and raised blood pressure, in that order of development. 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 toxæmic manifestations in the fourth constituted the proof thereof, inasmuch as they represented the cumulative damage of three gestations on which had been superimposed the strain of a fourth. Munro Kerr⁽⁴⁾ 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.

From an early stage of pregnancy there is pronounced hormonal activity, as evidenced by the positive Zondek-Aschheim and Friedman tests. It is now possible to prognosticate the sex of the unborn child with a remarkable degree of accuracy by injecting rabbits, fully three months old, in which the testicles are in the inguinal canal, with urine from women five or more months' pregnant, the basis for the prognosis being the microscopic changes in the testicle of the rabbit noted forty-eight hours after injection.

A case, suggestive of the pronounced endocrine activity during pregnancy may be mentioned.⁽²⁾ A primigravida, aged twenty-two years, subject to bouts of paroxysmal tachycardia, did not have a single paroxysm throughout the entire period of gestation. On the seventh day of the puerperium, there commenced a paroxysm which persisted without remission at the rate of 220 per minute for over five and a half days. This was the most protracted paroxysm from which the patient had ever suffered. Attacks have occurred frequently since, and, although more than two years have elapsed since the birth of the child, the woman has not again been pregnant. Definite enlargement of the thyroid gland was observed in this case. There seems to be no doubt that endocrine activity was concerned in the abeyance of attacks throughout pregnancy, and that, with the waning of this activity shortly after delivery, the control over these paroxysms was lost.

Such examples are cited merely to illustrate the far-reaching and potent influence which is exerted through the endocrine system in pregnancy, and that from a very early stage. The connection between the ductless glands and the late toxæmias of pregnancy has been shown: reference will be made to this in a subsequent communication. Proof of the ætiological relationship of abnormal endocrine activity and the early toxæmias of pregnancy has yet to come, but it is certain to be demonstrated in due course.

In conclusion, emphasis ought to be laid on the following factors:—

- (1) Hormonal activity (initiated by the zygote).
- (2) Imbedding of the ovum with destruction of endometrium.
- (3) Metabolic disturbances resulting therefrom.
- (4) Faulty adjustment between the maternal organism and the developing ovum.

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

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