hernia repaired in childhood and only one of them had a testicle removed at the age of 4. All had amenorrhœa, absent pubic and axillary hair. They were tall and feminine looking with normal breast glandular tissue. Blood testosterone and œstrogens were of male pattern and concentration of testosterone in the testicular veins was ten times that of the blood concentration. All these patients had their testicles removed and post-operatively there were no post-menopausal manifestations, which suggests that the removal of testicles before puberty might not have any influence on sexual development. The cases have been fully reported by Deshpande *et al.* (1965, *Steroids*, **6**, 437) and McMillan (1966, *J. Path. Bact.*, in press).

**Dr L Haas** (*Torbay Hospital, Torquay*) wished to raise three points. First, he commented on the high incidence (reported by some to be 10%) of malignant change in the inguinal testicles of patients with the testicular feminization syndrome. In spite of the fact that the testicles were the only source of œstrogen secretion in these cases, he wondered whether bilateral orchidectomy was not indicated. Passing on to the adrenogenital syndrome, he then questioned the need, or indeed the desirability, of removal of the phallus in every case. Finally he quoted a case of hydrocolpos where the membrane had ruptured spontaneously, without any surgical intervention, leading to uninterrupted recovery of the patient.

---

*Meeting January 28 1966*

# President's Address

## Pre-eclampsia and Eclampsia: The Disease of Theories

by Professor T N A Jeffcoate FRCSED FRCOG
(*Department of Obstetrics and Gynæcology, University of Liverpool*)

Although not recognized by all, and especially by the younger obstetricians and gynæcologists, the opportunities for clinical as distinct from laboratory research are endless and recurrent. They present regularly because observations made in any one era are inevitably limited by the knowledge and the diagnostic aids available at that time and interpretation is coloured by current views. What appear to be established facts to one generation may be completely upset when re-examined by its better informed successors. Thus it was long ago shown that pre-eclampsia and eclampsia complicate 20–25% of all cases of polyhydramnios; from this it was natural to conclude that unusual distension of the uterus may play a part in causing these diseases but, now that the ætiology of polyhydramnios is better understood, a different picture emerges. Modern observations, whilst confirming that the overall incidence of toxæmia is four or five times increased when polyhydramnios is present, indicate that this is related to the cause rather than the presence of the abnormal amount of liquor. When polyhydramnios is the result of multiple pregnancy, diabetes, pre-diabetes and hydrops fœtalis, toxæmia occurs in 15–50% of cases, depending on the condition present. When the increased collection of fluid is determined by some simple mechanism, such as failure of the fœtus to absorb liquor through the alimentary tract as in anencephaly and œsophageal atresia, the incidence of toxæmia is no greater than expected (Jeffcoate & Scott 1959, Hibbard 1962*b*). The logical conclusion is that it is not to polyhydramnios that pre-eclampsia and eclampsia are due but to certain of its causes, namely multiple pregnancy, maternal diabetes and hydrops fœtalis which also operate when they are not complicated by polyhydramnios.

Confused observations attributable to limitations of knowledge may in large part explain why the countless biochemical and pathological studies carried out during the last fifty years have so far failed to reveal the cause of toxæmia of pregnancy. The laboratory worker, dependent on the obstetrician for his material, was often investigating a wide variety of diseases whilst under the impression that he was dealing with one. Cases of hyperemesis, ketoacidosis, acute liver necrosis, infective hepatitis and even chloroform poisoning were included with pre-eclampsia and eclampsia and the results of biochemical studies were inevitably conflicting. Even today a basic scientist, researching in this field, is handicapped by the fact that he is asked to accept as pregnancy toxæmia examples of nephritis, nephrosis, antepartum hæmorrhage, ischæmic renal necrosis and chronic hypertension of various types and causes. Is it surprising that eclampsia, with its fore-runner pre-eclampsia, remains a 'disease of theories' and that one of the shields on the walls of the Chicago Lying-in Hospital still remains blank for the name of the discoverer of the cause of eclampsia?

In one of the last articles which he wrote, the late Professor F J Browne (1958) expressed the opinion that all the essential facts about preg-

nancy toxæmia are now available and that all that is required to solve the problem is to fit them together in the right order, like the pieces of a jigsaw puzzle. This is a view for which I have the highest respect but it remains to question whether all the pieces of the jigsaw have been accurately cut and whether the difficulties in assembling them arise because we are attempting to make them into one picture instead of several.

*What are Pre-eclampsia and Eclampsia?*

What is meant by the terms 'pre-eclampsia' and 'eclampsia'? For want of better criteria the diagnosis of pre-eclampsia is made when a pregnant woman develops at least two of three arbitrary signs, namely hypertension, proteinuria and œdema. But such signs characterize diseases of all kinds, affecting many systems. Even though it is now somewhat easier to distinguish nephritis, nephrosis and pyelonephritis from pre-eclampsia, confusion between hypertension complicated by pregnancy and true pregnancy toxæmia remains rampant. It is this more than any other single factor which hinders the collection of reliable clinical data and prevents reaching the right conclusions.

Another source of muddle is abruptio placentæ. It was long ago noted that women already suffering from this complication of late pregnancy often have proteinuria and sometimes hypertension and œdema; in the typical case of severe abruptio placentæ or concealed accidental hæmorrhage the incidence of proteinuria is as high as 30–40%. The finding of this and other signs of 'toxæmia' led to the assumption that they must have been present before the placental detachment occurred and so to the idea that abruptio placentæ is a complication of pre-eclampsia, thence to the inclusion of 'toxæmic antepartum hæmorrhage' as a type of toxæmia.

Study of the events prospectively rather than retrospectively makes this concept no longer tenable. Women known to suffer from pre-eclampsia during the antenatal period are no more likely to sustain abruption of the placenta than those who are free from the disease; the same is also largely true for chronic hypertension (Hibbard 1962*a*, 1964, Hibbard & Hibbard 1963). Proteinuria and hypertension, when found in association with abruptio placentæ, follow rather than precede placental separation, the first being a manifestation of ischæmic injury to the kidney, resulting from the utero-renal reflex, the second being evidence of a physiological and protective response to hæmorrhage and shock. The presence of œdema in these cases betokens a pre-existing anæmia, usually caused by a defect in folate metabolism which is the important predisposing ætiological factor in abruptio placentæ (Hibbard 1964, Hibbard & Jeffcoate 1966). There is in fact no such condition as toxæmic antepartum hæmorrhage and statistics dealing with toxæmia which do not recognize this are misleading.

In assembling a jigsaw puzzle it is all too easy to delay the solution by misplacing one component: a piece coloured blue may be put in the sky when it ought to be in the sea. This happened when the finding of placental infarction in cases of pre-eclampsia and eclampsia gave rise to theories to the effect that the liberation of thromboplastin, menotoxin or other toxins from the infarcts causes the disease. But the infarcts in question are red, recent and so short lived that, when they occur, they must follow and not precede the toxæmia. The placenta with white and old infarcts comes from the woman suffering from chronic hypertension or nephritis.

The maternal blood flow to the placenta is decreased in pre-eclampsia and the blood vessels in the placental bed show histological changes but, again, the evidence suggests that ischæmia of these tissues is the result of hypertension and not its cause (Browne & Veall 1953, Dixon & Robertson 1958). This view is also supported by observations on placental and fœtal size which will be referred to later.

There seems as yet little reason to question that eclampsia is closely related to pre-eclampsia and that it constitutes, in most cases at least, an end-result of this condition. But the diagnosis of eclampsia also rests on arbitrary criteria, namely the occurrence of fits or coma or both, in a pregnant woman showing evidence of pre-eclampsia. Although denied by authorities in the past, it is said that eclampsia can sometimes occur in women who do not show hypertension, albuminuria or œdema. Nevertheless, when fits or coma develop in the absence of these, a disease other than toxæmia should be suspected. Moreover, the presence of one or other of the signs of toxæmia is not diagnostic. Thus, irrespective of its ætiology, cerebral hæmorrhage can *cause* hypertension as well as fits or coma.

It is traditional to regard pre-eclampsia and eclampsia as clinical syndromes but the question now arises as to whether they are clinical or pathological diagnoses. Women dying without ever having had coma, convulsions or proteinuria sometimes at autopsy show changes in the liver or kidneys which are regarded by pathologists as being characteristic of the lesions found in eclampsia. The pathologist, to the amazement of the clinician, may then conclude that a woman who, in life, showed no evidence of the disease, nevertheless died from eclampsia. Are such lesions specific to eclampsia? The evidence suggests the opposite. All observers agree that they are not always present in women dying from eclampsia whereas they are not uncommonly

found in pregnant women who clearly died from other causes.

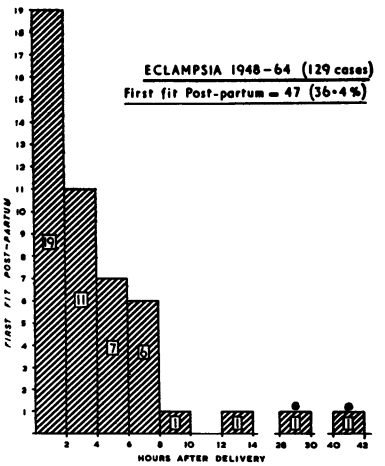
*Pregnancy as a Cause*

The one fact over which there can be little controversy is that the basic cause of pre-eclampsia and eclampsia is pregnancy: these diseases do not occur in any other circumstances. Conservative treatment never results in complete resolution of the signs and, in the case of eclampsia, is often attended by recurrence of fits. The only certain means of cure so far known is removal of the pregnancy. Once the affected patient is delivered, except there be some underlying chronic hypertension or some complication such as cerebral hæmorrhage, all symptoms and signs of toxæmia disappear within days if not hours. The same generally happens if the fœtus dies *in utero* but there are exceptions, explained probably by the fact that cure depends on placental rather than fœtal death. For there is strong evidence to show that it is the placental rather than fœtal elements of pregnancy which are primarily responsible for the disorder. Thus, pre-eclampsia commonly complicates hydatidiform mole, a condition characterized by the presence of active chorion and the absence of a fœtus.

As long ago as 1909 Holland concluded that 'the placental theory heads the field today'. Few would now deny that the basic cause of pre-eclampsia and eclampsia lies in the placenta, and most would agree that the role played by this organ is a positive one. Nevertheless it has been suggested (Browne 1958) that the placenta normally protects the woman from toxæmia and that this disease only occurs when its protective function is defective. The main evidence brought forward to support this view is the onset of eclamptic fits for the first time after the placenta is delivered. Thus it is commonly stated that eclampsia can occur three to five days after delivery and sometimes later.

The occurrence and timing of post-partum eclampsia is all-important to the reaching of any conclusion about the ætiology of pregnancy toxæmia. In the past, post-partum eclampsia represented 15–25% of all cases and this figure still applies in certain areas and hospitals. But where the standards of antenatal care have improved,[1] the proportion of cases (not the total number) in which eclamptic fits occur for the first time after labour has increased in recent years. In the hospitals in which my unit works there were 129 cases of eclampsia during the years 1948–64 inclusive. In 47 of these (36·4%) the first fit occurred after the completion of the

[1]Some have suggested that the relative increase in the number of cases of post-partum eclampsia is attributable to the routine use of ergometrine after delivery. This is unlikely to be the explanation since in the earlier era pituitary extracts which included vasopressin were employed equally frequently



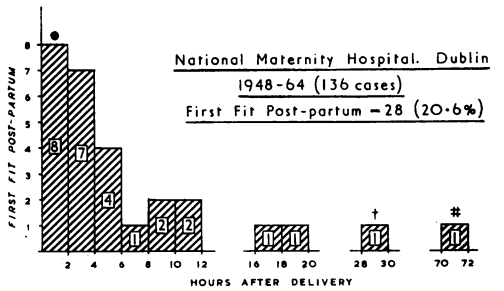

*Chronic hypertension ; recurrent toxaemia in both cases

Fig 1 *The time of onset of the first fit in 47 cases of post-partum eclampsia occurring in a consecutive series of 129 cases of eclampsia (Mill Road Maternity Hospital and Liverpool Maternity Hospital, 1948-64)*

third stage of labour. Except in 2 cases, however, the onset of fits was never delayed for longer than fourteen hours after delivery (Fig 1). In the exceptional cases eclampsia was first diagnosed at 29 and 42 hours after labour respectively. Both patients were multiparous and suffered from chronic hypertension; one was psychologically abnormal and the second was considered to be a possible epileptic.

During the period under review there were several other cases in which the onset of fits and coma relatively late in the puerperium resulted in an initial provisional diagnosis of eclampsia. But in each one of these, subsequent investigations and developments revealed other causes for the symptoms. These included epilepsy, primary cerebral venous thrombosis, hypertensive encephalopathy, cerebral hæmorrhage and phæochromocytoma. Indeed one of the cases of phæochromocytoma reported by Gemmell (1955) only came to be diagnosed as such because I refused to believe that coma occurring three days after labour could be caused by eclampsia. This view resulted in the search for another cause.

At the National Maternity Hospital, Dublin, a hospital chosen because it still deals with a relatively large number of cases of eclampsia and reports them in detail, 136 cases of eclampsia were treated during the years 1948–64 inclusive. Unlike the changing situation in Liverpool, however, there were only 28 patients (20·6%) in whom the first fit occurred after delivery. In 26 of these the disease was manifested within the first twenty-four hours, usually much earlier (Fig 2); in the remaining 2 cases symptoms first appeared at twenty-nine hours and at seventy-two hours after delivery respectively. In the first the patient was multiparous and, except for one fit, showed no




● Exact time unknown in 2 cases – soon after delivery at home

† 2-para without any signs of P. E.T., probably epilepsy

# 6-para, 'fit' preceded by unexplained pyrexia

Fig 2 *The time of onset of the first fit in 28 cases of post-partum eclampsia occurring in a consecutive series of 136 cases of eclampsia (National Maternity Hospital, Dublin, 1948-64)*

evidence of toxæmia at any time and the final diagnosis was 'probably epilepsy'. In the second, when fits occurred on the third day of the puerperium of a 6-para who had no previous history of toxæmia in any pregnancy, the clinical features as recorded are quite atypical, the first evidence of abnormality being unexplained pyrexia.

The conclusion is that unequivocal signs of eclampsia rarely appear later than twenty-four hours after delivery and never later than forty-eight hours. Observations made in the past to the effect that eclampsia can develop several days after delivery are almost certainly explained by errors in diagnosis resulting from limitations in knowledge and means of investigation available at the time.

It may not be insignificant that in the 2 cases in the Liverpool series in which signs of what was regarded as possible eclampsia appeared relatively late, both patients were multiparous and were known to suffer from chronic hypertension. The 2 late and doubtful cases of puerperal eclampsia in the Dublin series also concerned multiparous women. Considering that eclampsia is a disease of primigravidæ, the parity of all these four women is itself enough to raise doubts about the diagnosis. It may be that the rare apparent examples of late post-partum eclampsia, for which other organic causes are not found, are explained by hypertensive encephalopathy. In this respect it is not without interest that Vartan (1958) said that women with chronic hypertension rarely develop eclampsia and Theobald (1955) expressed the view that, when they do, the fits always appear after and not before labour.

The occurrence of post-partum eclampsia might be accounted for by supposing that the tumultuous activity of the uterus in the last phase of labour encourages the entrance of a substance of placental origin into the maternal circulation, there to exert its ill effect within the succeeding few hours. This, for reasons mentioned later, is a highly improbable explanation. A more likely one is that the stress of labour and of the immediate post-partum period fires off the fits in a nervously susceptible woman before there is time for the maternal organism to escape from the effects of the previously acting placental influence. This picture also satisfies the fact that general anæsthesia and sedatives administered during labour tend to defer the onset of fits by a few hours.

Whichever explanation is accepted, the timing of post-partum eclampsia supports rather than refutes the view that the placenta plays a positive role in causing the disease. Those who believe otherwise and regard the placenta as protective need to explain why it is rare to see post-partum pre-eclampsia which, if their concept is correct, should be very common.

Does the placenta cause toxæmia by the release of some vasopressor or other noxious agent which has a direct effect on the maternal vascular apparatus? Or does it act indirectly by stimulating the release of such agents from the maternal endocrine and other organs? The answers to these questions are suggested by examining what, within the limits of present-day knowledge, appear to be established ætiological factors as seen by the clinician.

*The Known Factors*

*Hyperplacentosis:* A common misconception is that the placenta is small and inefficient in cases of pre-eclampsia and eclampsia. It is not. Browne (1957) found that the average weight of the placenta was 1 lb 9 oz in cases of pre-eclampsia as compared with 1 lb 6 oz in cases of normal pregnancy. The baby too, in these cases, is generally of reasonable size for its maturity. For the placenta to be small there must be operating some condition present throughout the whole of or the greater part of pregnancy; whereas pre-eclampsia and eclampsia are diseases which generally make themselves manifest only after placental and fœtal growth are well established. The puny malnourished baby with its small and chronically inefficient placenta is the offspring of the woman whose basic trouble is chronic hypertension.

There is now clear evidence that the occurrence of toxæmia is sometimes related to excessive size and activity of the placenta, irrespective of parity and other factors. Three and possibly four states of hyperplacentosis, as it has been called, are so far recognized:

(1) Hydatidiform mole: In cases of hydatidiform mole the chance of toxæmia developing is increased ten times, the overall incidence being approximately 50%. Moreover, the bigger and more active the mole the more frequent and more severe the toxæmia (Chun *et al.* 1964).

(2) Hydrops fœtalis: The rare but interesting state of hydrops fœtalis is also complicated by pre-eclampsia in approximately 50% of cases. In this condition the placenta is not merely hydropic; its trophoblast shows unusual activity, especially of Langhans' cells. The activity is illustrated by the fact that the excretion of chorionic gonadotrophin in the urine is increased and may reach levels similar to those found with hydatidiform mole. Indeed, the hydropic placenta can present both macroscopic and microscopic appearances very similar to those of a mole (Scott 1958, Jeffcoate & Scott 1959) and is a vigorously growing structure (Crawford 1959). The occurrence of toxæmia in cases of hydrops fœtalis is directly related to placental size. The heavier the placenta in relation to fœtal weight (the placental co-efficient) the more likely is pre-eclampsia to occur (Jeffcoate & Scott 1959).

The development of pre-eclampsia is not determined by the cause of the hydropic changes in the placenta. Incompatibility of the blood groups of the mother and fœtus does not, in general, increase the risk of toxæmia, except only when it results in hydrops fœtalis. In the 25% of cases in which hydrops fœtalis has a cause other than iso-immunization the risk of pre-eclampsia remains at 50%.

(3) Multiple pregnancy: The chance of a woman developing toxæmia of late pregnancy is increased if she carries more than one placenta, although the extent of the increase is a matter of differing opinions. Parviainen (1945) said that with twins the risk is doubled and with triplets trebled and our experience coincides roughly with this. At Mill Road Maternity Hospital, Liverpool, during the years 1958–64 there were 23,563 deliveries, 5·9% of these being complicated by pre-eclampsia and eclampsia, 1·6% by chronic hypertension. Amongst 424 cases of multiple pregnancy proceeding beyond 28 weeks, the incidence of toxæmia was 13·2%[1] and of chronic hypertension 1·4%. It has to be recognized, however, that multiple pregnancy is more often seen in multigravidæ who are less prone to toxæmia so its effect may be greater than these overall figures suggest. When a primigravida has twins, her risk of developing pre-eclampsia or eclampsia is said to be increased six times.

(4) Diabetes mellitus: Maternal diabetes mellitus raises the incidence of toxæmia of late pregnancy from the expected 5% to one of 15–45%, the exact figure probably depending on the efficiency with which the diabetes is treated (Peel 1962). The association between uncontrolled diabetes and toxæmia may have more than one explanation: the presence of the disease betokens an already disturbed function of the pituitary-adrenal system and a tendency to hypertension and vascular degeneration. Nevertheless over-activity of some of the placental functions may be concerned, since the trophoblast, in cases of maternal diabetes, can show certain histological features similar to those found in the hydropic placenta and the urinary excretion of chorionic gonadotrophins is sometimes increased.

*Chronic hypertension:* Irrespective of her parity, the woman who suffers from essential hypertension has a 20–50% chance of developing pre-eclampsia in pregnancy, the wide reported range probably being explained by differences in the standards adopted for the diagnosis of hypertension. Not only established hypertensives are prone to toxæmia but also those women who, without so far showing evidence of the disease, give a strong family history of hypertension and who, presumably, have an inherited predisposition. Moreover, the girl born of an eclamptic mother is herself more likely to develop toxæmia when she in turn conceives (Chesley 1960).

The conclusion is that those women who have an actual or potential tendency to vasomotor spasm are particularly liable to develop pre-eclampsia but the diagnosis of toxæmia in such women is not always secure. The appearance of protein in the urine of a hypertensive pregnant woman may ordinarily indicate the development of pre-eclampsia but when the proteinuria is transient and recurrent it can reflect episodes of placental infarction. The occurrence of each infarct presumably sets in motion a weak utero-renal reflex with resulting temporary and mild damage to the renal glomeruli. The possibility of this happening immediately raises doubt about some of the observations recorded in regard to pre-eclampsia superimposed on chronic hypertension; it again illustrates how the mere association of two signs such as hypertension and proteinuria does not necessarily mean a diagnosis of pre-eclampsia.

*Gravidity:* Pre-eclampsia and eclampsia are diseases of the primigravida (abortions excluded) and do not recur in subsequent pregnancies unless the patient suffers from chronic hypertension. Recurrent toxæmia is always evidence of an underlying and persisting hypertensive state.

When pre-eclampsia appears for the first time in a multigravida it always has one of two possible explanations: the first is that the pregnancy is complicated by a state of hyperplacentosis; the second is that the patient has for some reason developed chronic hypertension or diabetes mellitus since her previous pregnancy.

*Nutritional status:* There are good grounds for believing that the woman who is obese or becomes obese during pregnancy has a greater than average chance of developing toxæmia.

[1]The present-day practice of admitting women carrying twins or triplets to hospital for rest between the 32nd and 36th weeks of pregnancy may be lowering the incidence of pre-eclampsia

Indeed, it is claimed that by controlling weight gain in pregnancy eclampsia and severe pre-eclampsia can be virtually abolished. In line with such findings may be observations to the effect that wartime conditions, resulting in severe restriction of foodstuffs, reduced the incidence of eclampsia in certain communities but the evidence in this respect is confusing. Malnutrition can apparently be associated with either a low or a high incidence of pregnancy toxæmia. It may be that the reported discrepancies are explained by the fact that it is a specific, rather than a general, deficiency state or an unbalanced diet which operates.

The influence of the nutritional status of a woman on her proneness to develop pre-eclampsia and eclampsia therefore remains ill defined and caution in drawing conclusions is all the more necessary because blood pressure recordings taken from arms which are unduly fat or unusually thin can be unreliable.

*Racial and familial characteristics; geographical considerations:* Not only does toxæmia of pregnancy affect certain families rather than others, it shows considerable variations in incidence from one race to another, from one country to another and even from area to area in the same country. For example, there is less pre-eclampsia and eclampsia in London than in other parts of Britain (MacGillivray 1961) and, when it occurs there, it tends to be less severe. The fact that the toxæmia incidence is low in certain countries such as Thailand, Ethiopia and Central Africa and high in India, Ceylon and Europe is probably explained either by inherent racial characteristics or by the dietetic habits of the peoples concerned. It is not attributable to geography and climate because, in countries like Fiji and the West Indies, where different races live in the same environment, one is prone to toxæmia while another is relatively immune. Those of Polynesian stock in Fiji and of African stock in the West Indies are less likely to develop pre-eclampsia and eclampsia than are those of Indian stock living in the same countries.

*The Clinical and Pathological Features of Toxæmia*

The essential pathological change in pre-eclampsia and eclampsia is one affecting the peripheral blood vessels, the small arterioles and the capillaries. The latter show endothelial thickening which, in minor degrees, is probably normal for pregnancy but tends to be exaggerated in toxæmia (Govan 1954); the former are in spasm, continuously or intermittently. Indeed, the characteristic lesions found in the liver, kidneys, spleen, pancreas, adrenals, heart, retina, brain and even the placenta are vascular ones and are the result of thrombosis or vasospasm which cause small or large areas of hæmorrhagic or ischæmic necrosis. The clinical findings of hypertension and proteinuria are presumably explained, the first by peripheral vasospasm and the second by ischæmic injury to the epithelium of the renal glomeruli and tubules.

*The Cause of Pregnancy Toxæmia*

Even though the exact effects are unknown there is no doubt that the introduction of the placenta, with its powerful and varied influences, results in modifications in the behaviour of all the maternal endocrine glands – the pituitary, thyroid, adrenal, ovary and the pancreas. Liver function is also changed (Tindall & Beazley 1965). These and probably other organs too have to adapt themselves to a new situation if the pregnancy is to proceed normally. The impact on the endocrine system is well illustrated by the fact that pregnancy exacerbates diabetes mellitus or reveals it for the first time, a disease which itself is mediated through the pituitary and the adrenals which control insulin antagonists.

As has been many times suggested in the past, the clinical features of pre-eclampsia in some ways resemble those of Cushing's syndrome in the nonpregnant woman. That the adrenals are concerned in the manifestations of toxæmia is supported by the finding of raised levels of corticosteroids in the blood and urine of affected women. Moreover I am informed that, except when replacement therapy was over-enthusiastic, none of approximately 100 reported cases of pregnancy occurring in women with Addison's disease was complicated by signs of toxæmia (H H Francis 1966, personal communication). The functions of the adrenal cortex cannot be separated from those of the hypothalamic-pituitary system and the latter might be directly involved by way of its production of either ACTH or its vasopressor and antidiuretic factor. Such a concept of a complex and multiple pituitary-adrenal upset as a basis for pre-eclampsia and eclampsia was first postulated many years ago, notably by Hofbauer (1918), but remains far from proven.

Toxæmia is not explained merely by the action of corticosteroids, because its occurrence is not related to the presence and number of striæ gravidarum and it cannot be induced by overdosage of the nonpregnant women with cortisone. Nor can it be attributed to a simple direct action of placentally produced œstrogen and progestogen: otherwise it would be expected that toxæmia might sometimes complicate pseudopregnancy deliberately induced by the administration of large amounts of those hormones. Similarly, quantitative variation in the production of chorionic gonadotrophins is an unlikely explanation of pre-eclampsia and eclampsia, otherwise these diseases would appear early in

pregnancy when the gonadotrophin levels are high and not in the middle or third trimester when they are low.

An immunological or allergic maternal reaction to the placenta is also an unacceptable basis for toxæmia because this would be expected to operate in early rather than late pregnancy. Moreover, there is now evidence that the trophoblast is non-immunogenic (Solomon 1965).

Any theory which envisages the production by the placenta of some vasopressor, sensitizing, inactivating or neutralizing agent which causes pre-eclampsia by a *direct* action on the maternal vascular system is also difficult to entertain. For there is no good reason why the emission of such a product should be the prerogative of a woman's *first* placenta and, if it had such a basis, toxæmia should occur as frequently in multigravidæ as primigravidæ. Moreover, if such a chemical were in circulation it might be possible to induce the disease in unaffected women by transfusing them with the blood of patients suffering from eclampsia – which it is not (Page 1948). Again, the agent would have to be one which in no circumstances can ever pass the placental barrier without being inactivated. Those who aim to discover the cause of eclampsia and its forerunner cannot afford to neglect the remarkable fact that the fœtus itself never shows signs, histological or clinical, of toxæmia.

This fact is one more pointer to the conclusion that pre-eclampsia and eclampsia are essentially the result of an unfavourable reaction of the maternal tissues to the presence of the placenta, rather than to an abnormal function of the placenta itself. These diseases represent what may be termed a failure of adaptation to the chorionic influence and they occur under two possible circumstances.

(1) *When the maternal powers of adaptation are impaired:* The primigravida is exposed to a situation to which she is not accustomed. She may fail to cope with it the first time but, having once profited from the experience, proves more efficient on every subsequent occasion. So pre-eclampsia and eclampsia do not normally recur. The woman suffering from diabetes mellitus already has a disturbed endocrine system. The one who is deprived of certain foodstuffs or is starved, as also the one who is obese, already has her metabolic processes working at a disadvantage. So any of these factors are handicaps when it comes to adaptation to the placenta. Women of certain families and races are, because of inherent traits or dietetic habits, better able to tolerate pregnancy than others. The observation that those of African stock are less likely to develop toxæmia might be related to the fact that they have relatively small and less active adrenals (Stirling & Keating 1958).

The woman who is hypertensive or is predisposed to hypertension already has an over-active or unduly sensitive vasomotor system. It is not, therefore, surprising that she is less able to cope with the placental impact. Moreover her defect is a persistent one, which means that toxæmia is likely to be recurrent in each and every pregnancy.

(2) *When the placental influence is unusually strong:* A woman's metabolic and endocrinological resilience, although adequate when exposed to a normal placental stimulus, may fail in the face of one which is unusually powerful; so, even if she has had several single pregnancies successfully, she may still develop toxæmia when exposed to two normal placentæ instead of one or to the unusually active chorion which characterizes hydrops fœtalis and hydatidiform mole.

When the circumstances are such that impaired powers of adaptation are combined with an excessive placental influence, the chance of the occurrence of pre-eclampsia is further increased. Thus multiple pregnancy carries a higher risk of toxæmia for the primigravida than for the multigravida. Both mechanisms may also operate in cases of diabetes mellitus.

*Differing Responses to Failure in Adaptation*

Many have suggested that, even excluding chronic hypertension, nephritis and nephrosis, there remains more than one type of toxæmia. Theobald (1955), having reviewed the evidence, concluded: 'There is not one eclampsia but several.' We have previously pointed out that, although the woman with a hydatidiform mole or a hydropic placenta commonly suffers pre-eclampsia of severe degree, it rarely proceeds to eclampsia (Scott 1958, Jeffcoate & Scott 1959). Nevertheless I have since had experience of one case of convulsive toxæmia complicating a mole and Chun *et al.* (1964) recorded eclampsia in one out of 135 cases of toxæmia associated with this condition. Moreover one out of 136 consecutive cases of eclampsia treated in the National Maternity Hospital, Dublin, occurred in a multiparous woman carrying a hydropic fœtus and placenta. Further clinical observations are required before it can be concluded that there is more than one type of toxæmia. Meanwhile it appears more rational to explain any clinical variants by postulating that a failure in adaptation to the presence of the chorion can manifest itself in different ways in different women, according to their make-up.

For example, an inherently disturbed or unstable nervous system may be the background to the occurrence of fits and coma and only those women who have this ever develop eclampsia, no matter how severe and neglected their pre-eclampsia may be. When toxæmia is characterized by hæmorrhage and degenerative changes in the liver, the explanation may be that the liver is

already vulnerable by reason of dietetic or other errors in metabolism. The absence of a pre-existing liver fault and the presence of an abnormal central nervous system could account for those cases of eclampsia in which, at autopsy, no liver lesion is found. An underlying vasomotor instability could explain those cases in which hypertension dominates the clinical picture; some defect in the renal vasculature might be the basis for heavy proteinuria as the leading manifestation of toxæmia.

*Conclusion*

The fact that post-partum eclampsia never occurs later than twenty-four to forty-eight hours after delivery might at first sight suggest that the cause of toxæmia must be a placental chemical agent which has a direct action on maternal blood vessels, rather than one whose effect is mediated by the reactions of the maternal endocrine and other organs. Such reactions, it might be argued, would take some time to resolve even after their stimulus is removed. In fact other evidence indicates that the endocrine system shows a major degree of recovery from stimulants in a very short time: thus, if the adrenal is exposed to injections of ACTH its return to normal function, as measured by all except very sensitive tests, is practically complete within forty-eight hours. It may not be insignificant that this is the same as the time limit for the onset of puerperal eclampsia.

Although it would be of considerable interest and of indirect value to know which is the placental agent which calls for maternal adaptation, it is unlikely to be very rewarding to continue enquiries as to whether it is acetylcholine, cholinesterase, monoamine oxidase, 5-hydroxytryptamine (serotonin), histidine, histaminase, oxytocinase, renin, thromboplastin, one of the hormones or some product not yet identified. Indeed, it is probable that there are multiple placental influences at work. Nor should biochemists hope to find some difference between the metabolic processes of the placenta from the case of pre-eclampsia and those of the placenta obtained from an uncomplicated pregnancy. All the evidence suggests that the placenta in cases of toxæmia is essentially normal in its function; even a state of hyperplacentosis probably represents increased rather than altered activity. The difference between normal pregnancy and pregnancy complicated by toxæmia lies in the response of the maternal system to stimuli which are basically normal.

This is not the first nor will it be the last Presidential Address on pregnancy toxæmia. Amand Routh in 1911, and again in 1913, appealed for investigations to be carried out by physiological and pathological chemists, as being the main hope of elucidating the ætiology of 'pregnancy albuminuria and eclampsia'. His first Address resulted in leading articles on 'The return of chemistry' by the *British Medical Journal* (1911), and on 'Where chemistry and medicine meet' by the *Lancet* (1911). The biochemists have responded to this and similar appeals and the fact that their work has so far proved unrewarding is, partly at least, because it has not always been channelled in the right directions by obstetricians. If progress is to be made it would seem that they and all other scientists concerned should be studying the woman rather than her placenta. Moreover, in providing cases for this, as well as for their own clinical observations, it behoves obstetricians to be extremely critical and logical in diagnosing pre-eclampsia and eclampsia.

*Acknowledgments:* For the evidence on which these arguments are based I made extensive use of the masterly reviews published by Mr G W Theobald (1955) and Mr T L T Lewis (1964). The references to individual authorities quoted by these writers are for the most part not repeated here. I am also grateful to Dr K O'Driscoll, Master of the National Maternity Hospital, Dublin, for permission to quote from the annual reports of that hospital.

REFERENCES

**British Medical Journal** (1911) ii, 1118
**Browne F J** (1958) *Lancet* i, 115
**Browne J C McC** (1957) *Proc. R. Soc. Med.* **50**, 787
**Browne J C McC & Veall N** (1953) *J. Obstet. Gynæc. Brit. Emp.* **60**, 142
**Chesley L** (1960) *Brit. med. J.* ii, 144
**Chun D, Braga C, Chow C & Lok L** (1964) *J. Obstet. Gynæc. Brit. Commonw.* **71**, 180
**Crawford J M** (1959) *J. Obstet. Gynæc. Brit. Emp.* **66**, 885
**Dixon H G & Robertson W B** (1958) *J. Obstet. Gynæc. Brit. Emp.* **65**, 803
**Gemmell A A** (1955) *J. Obstet. Gynæc. Brit. Emp.* **62**, 195
**Govan A D T** (1954) *J. Path. Bact.* **67**, 311
**Hibbard B M** (1962*a*) *J. Obstet. Gynæc. Brit. Commonw.* **69**, 282
(1962*b*) *Clin. Obstet. Gynec.* **5**, 1044
(1964) *J. Obstet. Gynæc. Brit. Commonw.* **71**, 529
**Hibbard B M & Hibbard E D** (1963) *Brit. med. J.* ii, 1430
**Hibbard B M & Jeffcoate T N A** (1966) *Obstet. Gynec.* **27**, 155
**Hofbauer J** (1918) *Zbl. Gynäk.* **42**, 745
**Holland E** (1909) *J. Obstet. Gynæc. Brit. Emp.* **16**, 255, 325, 384
**Jeffcoate T N A & Scott J S** (1959) *Amer. J. Obstet. Gynec.* **77**, 475
**Lancet** (1911) ii, 1085
**Lewis T L T** (1964) Progress in Clinical Obstetrics and Gynæcology. London
**MacGillivray I** (1961) *Path. Microbiol.* **24**, 507
**Page E W** (1948) *Obstet. Surv. Baltim.* **3**, 615
**Parviainen, S** (1945) *Acta obstet. gynec. scand.* **25**, 32
**Peel J** (1962) *Amer. J. Obstet. Gynec.* **83**, 847
**Routh A** (1911) *Proc. R. Soc. Med.* **5**, Sect. Obstet. p 1
(1913) *Proc. R. Soc. Med.* **6**, Sect. Obstet. p 348
**Scott J S** (1958) *J. Obstet. Gynæc. Brit. Emp.* **65**, 689
**Solomon J B** (1965) In: The Early Conceptus, Normal and Abnormal. Ed. W Park. Edinburgh; p 83
**Stirling G A & Keating V J** (1958) *Brit. med. J.* ii, 1016
**Theobald G W** (1955) The Pregnancy Toxæmias. London
**Tindall V R & Beazley J M** (1965) *J. Obstet. Gynæc. Brit. Commonw.* **72**, 717
**Vartan C K** (1958) In: A Symposium on Non-Toxæmic Hypertension in Pregnancy. Ed. N F Morris & J C McC Browne. London; p 81