



## Some Notes on the Pathology and Theories of the Aetiology of Pre-Eclampsia and Eclampsia

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### **Abstract**

From a Dissertation delivered to the Royal Medical Society

Eclampsia and its precursor, pre-eclampsia, is an interesting and puzzling disease: for decades past, a great deal of study has been devoted to it, and yet its cause is still uncertain. This article attempts to summarise the features of the disease, together with some of the theories that have been submitted as to its aetiology.

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# SOME NOTES ON THE PATHOLOGY AND THEORIES OF THE AETIOLOGY OF PRE-ECLAMPSIA AND ECLAMPSIA

From a Dissertation delivered to the Royal Medical Society  
by R. Marshall.

Eclampsia and its precursor, pre-eclampsia, is an interesting and puzzling disease: for decades past, a great deal of study has been devoted to it, and yet its cause is still uncertain. This article attempts to summarise the features of the disease, together with some of the theories that have been submitted as to its aetiology.

## CLINICAL FEATURES

The classical clinical features are too well-known to need much description. Pre-eclampsia is characterised by hypertension, oedema and proteinuria, or a combination of these, appearing in the second half of pregnancy without any other obvious cause such as kidney disease. The state of eclampsia is said to be reached when convulsions and coma supervene, but so far as can be discerned by microscopic examination of the affected organs or by any other means, there is no other difference between pre-eclampsia and eclampsia: they are different stages in the same disease. For convenience, therefore, the term "toxæmia" will be used throughout the rest of this paper to mean pre-eclampsia and eclampsia together, although this is not the standard, accepted, nomenclature.

Certain other signs and symptoms may be present, including visual disturbances and retinopathy, oliguria, pulmonary oedema, cyanosis and cerebral disturbances.

Retinal changes are a very constant and important finding in both pre-eclampsia and eclampsia. Constriction of the lumen of the arterioles is the first change seen: it may be either localised, giving a linked-sausage appearance to the vessel, or long and spindle-shaped.

Less constantly, papilloedema may occur, and in some severe cases retinal detachment.

As a rule there is marked improvement after the birth of the child, or after its death in utero. Proteinuria and oedema vanish within 4 or 5 days, and hypertension is usually gone after a fortnight.

## PATHOLOGICAL HISTOLOGY

(a) *Liver.* On gross examination, irregular, reddish areas of hæmorrhage are seen beneath the capsule and on the cut surface. The organ looks mottled.

Microscopically, peripheral hæmorrhagic necrosis of the lobule is seen associated with extensive thrombosis in the small vessels in the periportal

connective tissue. It has been suggested that extravasated blood or plasma finds its way into the peripheral bases of the columns of liver cells, and causes them to be pushed up inside their surrounding "tubes" or "sleeves" of connective tissue.

At the bases of the columns, fibrin masses form, distending the sleeves and so compressing the blood sinuses. Large deposits of fibrin are characteristic of these lesions, which have a focal distribution.

The liver lesions are characteristic of toxæmia, but vary very much in extent and severity. Both autopsy and biopsy studies have shown that the degree of liver involvement is not related to the clinical severity of the disease.

(b) *Kidney.*

Three characteristic abnormalities are found :

- (1) Swelling of the glomerular endothelial cells.
- (2) Deposition of amorphous material against the normal basement membrane by the endothelial cells. (Formerly, before the use of the electron microscope, it was thought that the basement membrane itself was thickened).
- (3) An increase in the number of intercapillary cells between the capillary loops.

All of these reduce the capillary lumens, and may account for the fall in glomerular filtration rate that is a feature of this disease. The glomeruli are usually all enlarged, by about 20%, and the outside diameter of the capillary loops varies from less than normal to about twice as big as normal.

Lesions are also seen in the tubules, but probably only represent congestion of the cells with protein reabsorbed from the glomerular filtrate. There are often casts, both of protein and haemoglobin derivatives, in the collecting tubules.

Rarely, thrombosis of the intralobular arteries may lead to complete bilateral cortical necrosis. This may be due to renal artery spasm, causing thrombosis and anaemic infarcts.

(c) *Brain*

In fatal eclampsia, involvement of the brain is likely. This may take the form of oedema, hyperaemia, anaemia, thrombosis or haemorrhage. Thrombosis of small cerebral vessels is common. Haemorrhage may range from small petechiae to massive bleeding, and is often associated with arteritis or arteriolitis.

(d) *Heart*

The heart is involved in most fatal cases, haemorrhages and areas of necrosis being found in the myocardium.

(e) *Lungs*

Pulmonary oedema is usually present. About 50% of cases coming to post-mortem have evidence of aspiration pneumonia, and some have lung abscesses.

(f) *Adrenals*

The adrenal glands are sometimes damaged, with a necrotic and haemorrhagic appearance. When this happens, nearly all the cortical tissue is usually destroyed, and adrenal insufficiency is probably a terminal factor in some cases of eclampsia. The adrenals are affected in an extraordinarily "all-or-none" sort of fashion: minor lesions are not seen.

(g) *Placental Changes*

In normal full-term placentae the incidence of "infarcts" is about 60%. This is raised in toxæmia, and is thought to indicate premature ageing of the organ. Some syncytial degeneration is characteristic of the normal placenta

at term, but only 10 - 50% of the small terminal villi are affected. All of them may be affected in toxæmia.

In the first stage of syncytial degeneration, clumping and autolysis of nuclei in the cytoplasm are seen, leaving clumps of dark-staining masses without cell outlines or nuclei. Later, all nuclei disappear from the syncytial layer, leaving the villi surrounded by a thin layer of hyaline material.

There is thus a great variety of clinical and pathological manifestations of this disease. They occur together so often, clearly as part of the same syndrome, that it seems reasonable to suspect that one pathological mechanism may be common to them all.

Now one common and constant observation in toxæmia is vasospasm; this may be seen directly in the ocular fundi, the nail beds, and the conjunctivæ, and can account for most of the changes observed. Being widespread, it can of itself account for the hypertension. It may cause focal areas of hypoxia in the different organs. Circulation in the vasa vasorum is probably disturbed, causing damage to the vessel walls. The hæmorrhages, necroses, and most of the other pathological changes can thus be explained by this one underlying condition.

### *Disorders of Function*

Again, vasospasm can account for most of the disorders of function found in toxæmia.

It is well-known that constriction of renal blood-flow causes immediate proteinuria: it has been suggested that there are "leaks" in the glomerular capillaries due to transient hypoxia. Some authorities have suggested that there is a generalised disturbance of capillary permeability, of which albuminuria is a local renal manifestation. This would directly account for the generalised oedema. Eclamptic convulsions may be due to cerebral hypoxia, or cerebral oedema, or a combination of the two.

But vasospasm, although it satisfactorily explains most of the clinical and pathological phenomena of pre-eclampsia and eclampsia, is not the answer to all the mysteries of this disease. It must itself be caused by something—and its cause remains in doubt.

Biochemically, the classical feature of toxæmia is the excessive retention of salt and water. This is the basis for the usual treatment of pre-eclampsia with a low-sodium diet, with or without a diuretic; such treatment has excellent results in improving oedema. The ability of the kidney to concentrate sodium chloride is impaired in pregnancy, a feature that is exaggerated in toxæmia. Salt tolerance tests on mild pre-eclamptics have suggested that most (80%) are worsened by large doses.

Why salt and water should be retained is not fully understood. The sex steroids help to bring about retention of salt and water in normal pregnancy, but they are found to be decreased in the early stages of pre-eclampsia. Modern methods of assay have failed to implicate pituitary ADH; and while aldosterone may possibly be the cause of sodium retention it cannot be shown to be the primary factor.

Other biochemical changes in severe toxæmia include hæmoconcentration (serum proteins, hæmatocrit and hæmoglobin all rise as a result in decrease in the plasma volume), and in eclampsia, acidosis. The latter is due to a build-up of lactic acid and other acid metabolites during the muscular exertion of the convulsions.

### *Actiology*

First let it be said that most authorities credit toxæmia with being an independent entity, as opposed to the mere unmasking of such inherent traits

as essential hypertension. On this assumption, many hypothesis have been advanced to account for it.

To be satisfactory, any theory must explain certain observed facts, of which these are a few :

(1) The predisposing influence of primiparity, multiple pregnancy, hydatidiform mole, and (perhaps) hydraminios.

(2) The disease is commoner in certain localities and in the lower social classes.\*

(3) The increasing incidence as term approaches.

(4) Repeated eclampsia is rare.

(5) The classical signs and accompaniments of toxæmia.

(6) Improvement after the birth of the child, or its death in utero—although post-partum eclampsia may occur.

(7) The virtual elimination of the severer forms by good ante-natal care.

(8) The fact that pre-eclampsia and eclampsia are peculiar to pregnancy.

The earliest explanations of eclampsia, were on mechanical grounds, and may at once be dismissed. There was thought to be an increased intra-abdominal pressure that damaged the kidneys by compression of the renal vessels and ureters.

Many toxins have been suspected as the cause of pre-eclampsia and eclampsia—hence the name “toxæmia”—including uræa, ammonium carbonate, carbonic acid, creatine and creatinine, besides many more. Against all of these is the fact that blood from toxæmic patients has no effect when transfused into normal pregnant women; however, some workers have suggested that the trouble lies in the absence of antitoxins to counteract normally-present toxins, but none of the substances named above can be shown to be the cause of this disease.

Other early theories incriminated infection, which is not acceptable, and foetal metabolic products. The latter cannot be the cause, for toxæmia can occur with hydatidiform mole. Another early hypothesis, that toxæmia is brought about by incompatibility between maternal and foetal blood, can very easily be shown to be incorrect.

Among contemporary hypotheses, Sophian *et al.* have presented a theory based on the “Tructa shunt mechanism”, postulating a utero-renal reflex whereby sudden distension of the uterus causes a diversion of the blood-supply from the cortex to the medulla of the kidney. While this would no doubt account for many of the observed phenomena of pre-eclampsia and eclampsia, it cannot be shown that the Tructa Shunt in fact occurs in the human kidney. However, this theory still has many agonists.

As the placenta is a complicated organ that we still have much to learn about, it is hardly surprising that many workers have sought, and are seeking, a cause for toxæmia there. It has not been possible to incriminate a placental endotoxin, because although syncytial cells can become detached and enter the maternal bloodstream, deposits of these have been found at post mortem in the organs of women dying for other reasons, who had not had toxæmia.

The so-called placental “infarcts” have been incriminated as the source of toxins by some workers, who take the view that in the “red infarct” stage these lesions are proteolysed, and that their products, which are partly absorbable, are nephrotoxic. They are not in fact infarcts at all, being merely signs of senescence of the placenta, and are present in about 60% of all cases. Whether the extent of infarction and the severity of toxæmia are at all related is still a matter of considerable controversy; and the incidence of toxæmia with hydatidiform mole, where infarcts are not found, is evidence

\* Footnote.—This may be due to variation in antepartum care.

against this theory. It seems more probable that infarcts are an effect rather than a cause of toxæmia.

The most widely-held theory at the present time is that of Uterine Ischaemia. This postulates that in an ischaemic state of the uterus, a placental or decidual substance with hypertensive properties is released in much the same way that an ischaemic kidney produces renin. What such a substance might be is not known, but histamine has been suggested, and more recently Hunter and Howard have reported the presence of a pressor polypeptide, "hysterotonin", in the decidua and amniotic fluid of toxæmic women. They find that plasma and decidual extract from patients with pre-eclampsia or mole cause contraction of smooth muscle, and have a pressor effect on the pithed cat. Again, Sandler & Coveney have suggested that placental monoamine oxidase activity may be diminished in toxæmia, with the resulting reduction of inactivation of endogenous amines leading to vasospasm and anoxia.

This theory fits many of the facts :

(1) In primigravidae, the uterine vessels have not undergone hypertrophy. Also there is greater tone in the abdominal wall, possibly causing pressure on the uterus.

(2) Multiple pregnancy and mole—excessive or sudden expansion of the uterus might make it outgrow its blood-supply.

(3) Aggravation of pre-eclampsia in labour—there is uterine ischaemia with the contractions.

(4) The increased incidence as term approaches.

(5) The characteristic liver lesions, which are explained in this way: the placenta is the richest source of thromboplastin in the body, and if it were injured by ischaemia it would very probably suffer cytolysis of the syncytial epithelium, allowing the entry of thromboplastin into the maternal circulation. There, it might conceivably contribute to the large deposition of fibrin seen in the liver lesions.

This is probably the most widely-held theory at the moment, as was remarked above. Why uterine ischaemia should occur in some women and not others, aside from any of the predisposing factors such as multiple pregnancy, etc., is not clear: it is suggested that they have a pre-existing hypoplasia of the uterine vasculature, but this is not universally accepted.

Other theories have suggested that toxæmia was purely an endocrine disorder. It has been ascribed to thyroid malfunction, which can be swiftly dismissed, to hyperfunction of the posterior pituitary, which there is little evidence to support, and to hyperfunction of the adrenal cortex. Pregnant women are thought to produce more corticosteroids in the last trimester than non-pregnant women: some workers hold the view that in patients with pre-eclampsia or eclampsia a poorly-functioning placenta fails to inactivate these hormones. Variations are also noted in the amounts of oestrogen, progesterone, and chorionic gonadotrophin produced in toxæmic patients, but no endocrine disturbance can be shown to be a primary cause of the disease.

Mention must be made of the nutritional theories. Theobald has pointed out that many bizarre and unfamiliar syndromes may result from deficiency of particular food factors or groups of food factors, as was demonstrated vividly in Japanese prisoner-of-war camps in the last war, for example. Dietetics is a subject of great complexity, and is not yet fully understood: it is possible

to live on far less than the "standard" requirements, but in such circumstances a variety of pathological phenomena are liable to become evident. It seems not unreasonable to suppose that the enormous metabolic task of producing a full-term infant might create a deficiency of certain dietary constituents in a woman who is very well fed by ordinary standards: it also seems fair to suppose that some women may have inborn metabolic idiosyncrasies which make such a task much more difficult for them than for others. Might such a deficiency manifest itself as pre-eclampsia or eclampsia?

Oedema can be produced, in a little-understood way, by malnutrition. Liver damage can result from the absence of certain amino acids. A lack of vitamin B can cause ovarian disfunction, and as ovarian hormones are needed for the successful implantation of the placenta, the premature senility of that organ may be the result of a degree of malnutrition. (It is of interest that Dalton has had good results from giving prophylactic progesterone in early pregnancy, before pre-eclampsia has become established.) Theobald considers that convulsions may be caused by cerebral oedema, changes in the Ca/Mg ratio, a sudden slight fall in the blood sugar, or electrolyte imbalance—all possible consequences of malnutrition.

But what of hypertension? Theobald considers this to be no more than a red herring in pre-eclampsia and eclampsia, claiming that when it is found in pregnancy it is merely the result of an underlying essential hypertension.

The obvious argument against this theory is that, if pre-eclampsia and eclampsia are evidence of a dietary deficiency disease, why should non-pregnant women—or even men—be immune? Presumably the other special circumstances of pregnancy—hormonal, mechanical, etc.—might be such that this syndrome can only manifest itself in such women.

Certainly this is a very interesting theory, and one that cannot be lightly dismissed.

Present methods of treating pre-eclampsia and eclampsia, although very successful as a rule, are quite empirical. It is to be hoped that eventually the mysteries of this disease will be solved, and that a more specific line of treatment or prevention will become available. Then, perhaps, this common and serious hazard of pregnancy will at last be overcome.