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STUDIES IN THE ETIOLOGY OF ECLAMPSIA.

by

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The purpose of this essay is in the first place to present a critical review of the literature dealing with certain aspects of the eclampsia problem and secondly to expound in some detail the placental theory of origin, with which what of original work has been done has been principally concerned.

Since the discovery by Lever in 1843 of albumen in the urine of eclamptic patients an immense literature has accumulated round the subject - the year 1908 alone produced considerably over 100 scientific papers dealing with it - and so numerous have been the views advanced that the condition well merits the title of "The disease of theories" given it by Zweifel. The explanation of the amount of work done is to be sought partly in the baffling nature of the problem and partly in the advances that have been made in our knowledge of the general metabolism of the body, the theories of immunity, the action of intra-cellular ferments and the physiology of the ductless glands. Speaking generally, the theories proclaimed and the methods employed by the host of investigators busied with the elucidation of the problem accurately mirror the scientific tendencies of their day.

In strange contrast to the completeness of our knowledge/

knowledge along clinical lines, the paucity of facts bearing upon the etiology is indeed striking. Moreover the investigations which have been undertaken have brought forth so many apparent contradictions that in attempting to gain information of value from the contributions made, a serious difficulty has been to distinguish good work from bad.

It would be beyond the compass of this paper even to mention all the theories from time to time advanced and in the following pages attention will be directed only to those views which have attracted greatest interest and which seem to have most significance from the reviewer's point of view.

The theories which have appeared worthy of consideration are the following. 1. Metabolic Auto-intoxication. 2. Bacterial. 3. Aberration in function of the Ductless Glands. 4. Mechanical. 5. Anaphylaxis. 6. Placental.

Metabolic Auto-intoxication. Riviere in 1888 was the first to suggest that eclampsia was an auto-intoxication, its presence being shewn by an increase in the toxicity of the blood serum and a decrease in that of the urine. By the term metabolic auto-intoxication is understood the disturbance produced/

produced by products of metabolism which have been formed within the tissues. A harmful accumulation of metabolic products or an auto-intoxication may result from any of the following conditions (Wells).

- (1) Failure of elimination because of abnormal conditions in the eliminating organs, e.g. uraemia.
- (2) Failure of neutralisation by chemical combination, presumably due to abnormalities in the organs or tissues through whose activities the neutralisation is normally accomplished, e.g. diseases of the liver.
- (3) Failure of the chemical transformation of the metabolic products; this may result either from abnormalities in the functioning tissues or through a checking of the normal steps of metabolism by failure of elimination of the end products.
- (4) Excessive formation of toxic chemical substances; e.g. autolytic changes in an organ such as the liver.

It is impossible to classify eclampsia under any of the above headings, but so complex and so far reaching are the anatomical and chemical changes met with, that probably all four may be looked on as factors of importance.

That the process of building up a foetus of six
or/

or seven pounds weight, as well as the provision of a suitable lodging for it by the growth of the uterus, must inevitably lead to an increased metabolism is natural. Accurate measurement of the degree of increased metabolism has been made possible by the introduction of the measurement of the basal metabolism rate. This may be defined as the measurement of the energy metabolism of the individual at complete rest and in the post-absorptive state (Baer).

It is determined by ascertaining the heat production or gaseous interchange in such a subject during a certain period and expressed in calories per Kilogram of body weight. The investigations of Baer in 44 carefully studied cases of pregnancy show a gradual rise from + 26 in the 34th week, to + 33 in the 40th week, dropping to + 15 on the 3rd day after labour, to + 5 on the 7th day, and becoming normal on the 15th day of the puerperium. These are average figures and refer to normal cases. Two further cases observed by Baer, which shewed symmetrical thyroid enlargement without symptoms, gave figures below the series average in metabolic rate, which appears to support the view as to the primarily compensatory nature of thyroid enlargement during pregnancy. In five cases of eclampsia also the metabolic rate was determined; in only two of these was variation from the average figure noted, though in what direction is not indicated.

Granted that there is an increased metabolism during pregnancy the strain of this must inevitably fall on such organs as the liver and kidney, especially the former. Expressed in simple language, the hypothesis advanced by those who seek to find in disordered metabolism an explanation of the phenomena of eclampsia, is that an auto-intoxication results through failure of the elaborate system of defence with which the body is provided to deal with the more or less toxic waste products resulting from an increased metabolism. What the exact nature of this auto-intoxication is and the processes by which it is brought about involve problems of bio-chemistry extremely complex and baffling for the average obstetrician, the more confusing as contributions of different observers giving the results of blood and urine analysis, and of tests of renal and hepatic functional efficiency have not always been in agreement.

The rôle which the foetus may play will be dealt with in a later section, meantime it may be asserted that of possible toxic products of foetal metabolism we have as yet no definite knowledge, nor do we know to what extent foetal metabolism throws an additional strain on the maternal excretory organs.

No clue as to the ultimate cause of the disease has/

has been forthcoming from research on the disordered metabolism which accompanies eclampsia; and hopes that by blood and urine analysis not only could the tissue changes be satisfactorily explained, but even the toxin or group of toxins responsible be isolated have proved abortive. As the ultimate solution of the problem however will probably be arrived at along lines of biochemical research, an outline of recent work done is warranted here. The observations made can be conveniently recorded under the following headings: (1) The Acidosis factor. (2) Renal and Hepatic function in eclampsia. (3) The rôle of alimentation.

1. Acidosis.

By acidosis is understood a condition in which an abnormal quantity of organic acids escape oxidation and remain free in the body where they may be detected in the blood and urine. Work on acidosis as the cause of the toxæmias of pregnancy dates back to the investigations of Zangemeister who in 1903 estimated the alkalinity of the blood in normal pregnancy and eclampsia and found it slightly reduced in the latter. In the following year Zweifel offered his theory that eclampsia resulted from over-production of lactic acid by the foetus.*

* The injection of lactic acid into animals causes no disturbance. It is probably a disintegration product of proteid and of no special significance.

More recently Ewing and Wolf finding leucine and tyrosine in the urine suggested that amino-acids incompletely catabolised in the liver were actually the cause of the toxaemia and the abnormal nitrogen distribution. Hasselbach and Gammeltoft in 1915 from a careful study of ten pregnant women, came to the conclusion that in normal pregnancy a slight acidosis is present. They found that during the course of pregnancy the ammonia-coefficient rose steadily and that this rise was accompanied by a corresponding fall in the alveolar CO_2 tension. Later, Slemons, Emge, Losee and Van Slyke investigated the alkaline reserve of the blood plasma by testing the CO_2 combining power of the blood plasma. They found it reduced and corroborated the results of Hasselbach and Gammeltoft that in pregnant women a slight acidosis is normally present. The same observers carried out a similar blood investigation in eclampsia and the pre-eclamptic state and found figures practically within normal limits. As far as a state of acidosis can be determined by blood analysis, the slight and constant diminution in the alkaline reserve of the plasma does not support the view that acidosis should be looked on as the underlying cause of toxaemia in the later months. Analysis of the urine, moreover, judging from the figures of Ewing and Wolf and later of Slemons, Losee and/

and Van Slyke, shews a comparatively small rise in the ammonia-coefficient in cases of eclampsia as distinct from hyperemesis, a finding which supports the same view.

2. Renal and Hepatic function.

Since the investigations of Gscheidlin and Spiegelberg (1870) who estimated the urea and ammonium carbonate in the blood, and Butte (1894) who estimated the urea in the blood, methods of testing renal function have advanced considerably and in investigating renal impairment have been applied widely without adding very materially to our knowledge of the nature of eclampsia. The normal level of the blood urea in pregnancy is disputed. Folin (1917) from an investigation of 100 cases states that the blood urea is abnormally low. Losee on the other hand found figures similar to those of non-pregnant individuals. Hester, Zangemeister, Farr, and P.F. Williams have reported the blood urea and the total non-protein nitrogen of the blood normal or only slightly increased in women suffering from eclamptic toxæmia. Losee recently reported the creatinin blood content of 13 patients with eclampsia between 1.45 and 3.15 mg. per 100 cc., figures only slightly above normal.

Lisle/

Lisle Williams (1921) has drawn attention to the increase in uric acid in the blood of toxæmic patients. With the exception of Slemons and Bogert (1917) who reported uric acid in excess of normal in the blood of two patients with eclampsia and three with pre-eclamptic toxæmia, there were few references in the literature concerning the uric acid blood content of pregnant women, especially those with symptoms of toxæmia, before Williams' paper appeared. Williams carried out a chemical analysis of the blood of twenty-five patients suffering from different types of pregnancy toxæmia and demonstrated that in the blood of these patients the amount of uric acid regularly exceeds the normal, whereas the other non-protein nitrogen constituents are not usually increased. His table is of sufficient interest to reproduce.

TABLE./

Non-Protein Nitrogen Constituents. - m.g. per 100 cc.

	Urea N.	Non-protein N.	Uric acid.	Creatinin.
Group I. Eclampsia: 5 cases average	17.2	40.1	7.84	2.67
Group II. Pre-eclamptic toxæmia: 13 cases average	15.8	51.9	5.9	1.57
Group III. Normal Pregnancy at various months average	12.76	26.68	1.94	1.38
Non-pregnant individuals.	12-23	20-35	1.3-3	0.7-1.5

A group of seven cases of pernicious vomiting has not been included.

Lisle Williams lays great stress on uric acid excess; he suggests absorption of foetal urine as a possible source.

The diastase content of the urine has been dealt with specially by Mackenzie Wallis.* In normal pregnancy he found a diastase content of 10 - 33 units, the figure usually given for non-pregnant urines. In eclampsia and the pre-eclamptic state he found the diastase content abnormally high, sometimes reaching 200 units, a figure which, with the exception of certain pancreatic disorders is not met with in any other conditions. In pyelitis and nephritis a low diastatic excretion is present and he therefore believes the test to be of value in differentiating true pregnancy toxæmia from nephritis complicating pregnancy. He asserts further that the high diastase values in eclampsia indicate that there is little impairment of renal functional efficiency in this condition, a view corroborated by Farr and Williams who failed to demonstrate impairment of kidney function in/

* The measurement of the diastatic activity of the body fluids, especially of the urine, has been applied to clinical purposes for about ten years. It was originally introduced by Wohlegemuth as a means of diagnosis in pancreatic disease; later it was shewn that whereas in pancreatitis the urinary diastase tended to be increased above normal, conversely in the presence of renal lesions the excretion of diastase in the urine was usually diminished.

in eclampsia by the phenol sulphonephthalein test.

Methods of estimating the functional activity of the liver are unsatisfactory and little progress has been made in this direction in the study of the toxæmias of the later months of pregnancy. Reduced urea output has been regarded as evidence of failure of the urea-forming mechanism of the liver. The work of Folin and Denis suggests however that there is an efficient extra-hepatic urea forming mechanism. The extraordinary persistence of urea-forming function of the surviving liver in spite of the action of such poisons as phosphorus is illustrated by the recent work of Löffler, and Van Slyke found in a case of Acute Yellow Atrophy that despite almost complete destruction of liver parenchyma a large proportion of urea was still formed. Losee and Van Slyke were unable to demonstrate any rise in the amino-nitrogen of the blood or urine in eclampsia as compared with normal pregnancy and conclude that there is no evidence of impairment of desaminating function in the liver. (De Wesselow).

No evidence of deranged carbohydrate metabolism through impairment of liver function is afforded by blood-sugar estimations. These have been carried out by Slemons, Losee, and Mackenzie Wallis, all of whom find normal values. In passing, Wallis draws the interesting/

interesting deduction that this negatives the hypothesis that the toxæmias of pregnancy are associated with abnormal activity of the endocrine glands, disturbance of function of these glands being almost invariably reflected in an altered blood sugar content.

Recent work shews that the marked accumulation of urea and other nitrogenous waste products so frequently seen in acute and certain types of chronic nephritis is absent in eclampsia and allied conditions. The non-protein nitrogen and the blood urea are frequently within normal limits. Absence of definite nitrogen retention is indeed one of the most characteristic features of the disease and serves to differentiate eclampsia from cases of uraemia due to chronic interstitial nephritis complicating pregnancy (Wallis). Fourteen years ago Holland reviewing the literature wrote "the outstanding feature of eclampsia is an auto-intoxication of the body by the toxic products of protein disintegration". More recent biochemical research has cast doubt on the correctness of this view and Slemons (1918) in the light of recent work has stated "The results of blood analysis give no indication of a derangement of protein metabolism; the evidence not only fails to support the protein metabolism hypothesis but even favours its abandonment".

3. The rôle of alimentation in eclampsia.

Although laboratory research appears to demand modification of the metabolic autointoxication theory, reference must be made to certain clinical facts which seem to support it. In opening his presidential address before the Obstetrical section of the Royal Academy of Medicine, Ireland, said "the cause of eclampsia is no longer a mystery" and proceeded to state that "during pregnancy ordinary food becomes poisonous and may produce eclampsia".

The Dublin method of treatment which, compared with statistics from other centres yields such good results, is based on Tweedy's hypothesis. The effect of a diet poor in proteid was seen in the lowered incidence of eclampsia during the latter years of the war. In an analysis of cases of eclampsia occurring in the Edinburgh Royal Maternity Hospital during the years 1912-1921, the writer found a marked decrease in the years 1916-1918. Bela Varo of the University of Buda Pesth working on a considerable material reported a marked fall in the number of cases of eclampsia during the war years. This fall was more marked in Germany than in Austria, a fact which the writer correlates with the more marked under-development of the German population. In Hungary he found that/

that the percentage incidence and mortality remained unaltered during the war among the classes who were able to maintain their standard of living. The maternal mortality fell from 24 per cent before the war to 14 per cent during the war years. Gessner noted a steady fall in the Baden statistics of eclampsia from 1913-1918. His figures which are representative of many Continental clinics may be quoted.

	Births.	Cases of Eclampsia.	Incidence.
1913	60901	119	0.19
1914	60621	103	0.17
1915	45643	58	6.13
1916	32358	42	0.13
1917	29779	24	0.08

Warnekros refers to an article by Mayer on the marked falling off of eclampsia at the Tübingen clinic and quotes a similar state of affairs at Berlin. In addition to the importance of war diet as a factor he makes the extraordinary suggestion that the disease in question may have been aggravated by "supersaturation of the female organism with the male fertilising principle, a factor largely eliminated by protracted absence of the men at the front"! Bumm has noted that strong heavily built women are more likely to suffer/

suffer from the disease than the opposite type and ascribes the higher incidence and more severe form of the disease in northern latitudes to the extra consumption of meat and fat. In spite of bio-chemical observations these clinical facts strongly suggest that the dietetic factor is of the first importance, if not in the aetiology of the pre-eclamptic state, certainly in its aggravation and in the development of eclampsia.

An attempt has been made in the preceding pages to outline recent advances which seem to throw light on the disordered metabolism which accompanies eclampsia. Our knowledge is as yet insufficient to allow of definite conclusions being drawn; the metabolic factor however, does not in eclampsia appear to possess the significance which must be assigned to it in the pernicious vomiting of the earlier months.

Linked up with the theory of metabolic poisoning are certain other theories and miscellaneous observations which can be reviewed more conveniently in a later section.

THE BACTERIAL THEORY.

The occasional sudden onset, the occurrence of cases in groups, and certain other considerations made it inevitable that a bacterial theory should be propounded. Déloir and Rodet of Lyons in 1884 were the first to suggest bacterial invasion as the responsible factor. Doléris in 1885 and, following him, a large number of observers claimed to have cultivated various organisms from the blood, urine and tissues of eclamptic patients, but their results were so contradictory as to be of little value (W. Williams). On the other hand Haegeler (1892), Döderlein (1893), Schmorl (1893), Lubarsch (1896), Bar and Guyeisse (1897) and Whitridge Williams obtained uniformly negative results. As a consequence of these observations the bacterial hypothesis fell into disfavour and in a critical review on the etiology of eclampsia published by Holland in 1909, among the numerous theories of origin quoted organismal infection is not mentioned. More recently, probably because of the introduction of improved methods of investigation, a number of papers have appeared in which positive findings have been claimed. It must be admitted however that the results on the whole are not convincing. Speaking generally the arguments advanced in favour of the theory are.

1. The marked genus epidemicus.
2. Its prevalence in populous centres.
3. The accompanying fever.

4./

4. The relative immunity conferred by one attack.
5. Its occasional resemblance to an acute infection, occurring explosively or after a prodrome.
6. The accompanying leucocytosis.*

In only one communication has a definite organism been particularised. C.F. Dick and G.R. Dick (1915) investigating the urine from a case of eclampsia were able to cultivate many slowly growing pin-point transparent colonies consisting of Gram-negative bacilli about the size of the influenza bacillus. Intravenous injection of the organisms, however, produced no apparent effects in dogs, and obviously a communication based on the investigation of a single case has no value.

More recently Talbot (1919) has contributed his views in a lengthy article based on a study of a series of/

* Although it is germane to the present subject, the leucocytosis of eclampsia is of sufficient interest to deserve a passing notice. Whereas a white blood count of 10 - 12,000 is normally found in the later months of pregnancy, with a further increase during labour, in eclampsia the leucocytosis is much greater than in normal pregnancy. Dienst found an average of 26,000 before labour and 40,000 immediately after labour; a similar increase was noted in the albuminuria of pregnancy. He considered the leucocytosis a factor of supreme importance in eclampsia and looked on the disintegration of leucocytes as the origin of fibrinogen which he regarded as the direct cause of the disease and accountable for all the lesions of eclampsia; he, therefore, advised the employment of hirudin (to inhibit coagulation) in the treatment of eclampsia.

of 97 consecutive cases of eclampsia in which from purely clinical as distinct from laboratory observations he has come to the conclusion that in all cases a septic focus of origin may be found if searched for. In all 97 cases, without exception, he found evidence of chronic sepsis in the teeth or gums and believes that the poisons of a chronic infection (in) being filtered from the blood stream by the kidneys, damage their excreting mechanism and cause a reduction in their reserve power. He bases his argument on the assumption that the symptoms of eclampsia and the pre-eclamptic state are caused by a retention of the normal physiological waste products of the developing pregnancy, this retention being due to the damaged functional efficiency of the kidneys; and further argues that the increased incidence of the disease in those individuals who have a pre-existing chronic nephritis proves the intimate relation between the occurrence of symptoms and the damaged excretory function of the kidneys, instancing the similarity of symptoms of eclampsia to those of chronic kidney disease as suggestive of a common cause.

Without questioning the accuracy of Talbot's clinical observations as regards the presence of a septic focus in all his cases, a high incidence of eclampsia, as distinct from uraemia, in individuals suffering from chronic kidney disease is a point on which/

which all obstetricians are by no means in agreement. Further, as has been indicated above, metabolic intoxication on which his hypothesis essentially rests does not appear to play more than a subsidiary rôle from an aetiological standpoint; nor, in the light of the work of Wallis, Slemons, Lisle Williams and others are we warranted in believing that in eclampsia and the pre-eclamptic state the efficiency of the kidneys is markedly impaired; the observers mentioned, making use of modern tests of kidney function, are agreed on this point.

Without adducing laboratory evidence in support of his view La Vake (1916) has also expressed himself convinced of a bacterial origin of eclampsia and has described thirteen cases of pre-eclamptic toxæmia in all of which a history or evidence of infection, acute or chronic, could be elicited.

As far as one can judge, no satisfactory evidence has as yet been brought forward in support of a bacterial origin of eclampsia nor can one speculate as to a possible rôle played by organismal infection until observations are available which are much more elaborate and reliable than any which have so far been recorded.

THE ENDOCRINE SYSTEM AND ECLAMPSIA.

It may seem premature to broach the question of anomalies of endocrine function during gestation when the nature of the function under physiological conditions remains a secret, but in view of the increasing importance being attached to the interaction of the internal secretions one feels warranted in placing on record the views which have from time to time been advanced concerning the part played by the various ductless glands in relation to eclampsia and the pre-eclamptic state.

1. Thyroid. Lange in 1899 was the first to draw attention to the enlargement of the thyroid gland which so frequently accompanies normal pregnancy and to suggest that in its absence the albuminurias of pregnancy were of more frequent occurrence. Out of 133 pregnant women Lange found thyroid enlargement in 108 and attributed this to a compensatory hypertrophy to meet the demand for increased thyroid secretion as the result of increased metabolism. Of the 108 who shewed thyroid hypertrophy only 2 had albuminuria and in these there was a history of renal disease prior to pregnancy. Of the remaining 22, 16 had albuminuria and tube casts, which /

J *the cause*
~~which~~ in six instances terminated in eclampsia. Lange removed four-fifths of the thyroid gland in eleven cats, six of whom were pregnant and 5 non-pregnant; of the former, five died, three of them with convulsions, and in all albuminuria, and post-mortem, characteristic kidney and liver lesions were noted. Of great interest also are those cases reported by Pineles, Erdheim, and Thaler in which a thyroid-ectomised animal apparently recovered completely from the operation and, becoming pregnant weeks or months afterwards developed symptoms suggestive of eclampsia, with oliguria, albuminuria, and sometimes convulsions. Lange's observations formed the basis of a clinical investigation by Oliphant Nicholson who emphasized the antagonistic relationship between the internal secretion of the thyroid and that of the suprarenal, especially in regard to their action on the blood-vessels and their influence upon the metabolic processes. He believed that whereas thyroid extract powerfully stimulated both metabolism and elimination, increasing the secretion of urine and excretion of urea, suprarenal extract lowered the general metabolism and might lead to partial or complete suppression of urinary secretion. Nicholson suggested that where the normal physiological thyroid hypertrophy failed to develop, suprarenal overactivity was allowed and was responsible for/

for the high blood-pressure, oliguria and other phenomena of eclampsia through producing a spasmodic contraction of the arterioles of the body generally and in particular of those of the kidney; on this assumption he claimed good results by re-establishing diuresis by means of thyroid extract.

Fruhinsholz and Parisot (1921) have reported a series of animal experiments in which the influence of the thyroid gland on gestation, parturition and the post-partum state were studied by removing as much of the gland as possible without destroying life or preventing fecundation. Their results were uniform and appeared to show that the pregnant animal was much less able to stand the operation than the non-pregnant; where pregnancy followed extirpation albuminuria and convulsions were frequent, and where death occurred, suggestive changes in the kidney and liver were commonly found. Such phenomena did not follow extirpation in non-pregnant animals. In 1922 in a further communication Fruhinsholz reported four cases of pregnancy in women with typical abortive myxoedema; he was impressed by the constancy of renal disturbances in these cases; eclampsia in the first, albuminuria in the second, eclampsia in the third, and oedema in the fourth. Although the numbers quoted are small these observations lend support to Nicholson's suggestions./

suggestions. The effect of myxoedema on pregnancy is variable. Kocher, to whom one looks for guidance in all questions related to the thyroid, affirms that as a rule pregnancy aggravates the symptoms of myxoedema or reveals them when they are latent. On the other hand, Adam, Walter, Wetz, Siredey, Ley, and others have reported cases in which the condition was either unaffected or even improved by the pregnancy.

The conclusions which suggest themselves from a survey of the literature are that a physiological enlargement is common during pregnancy, especially in the later months; that where pregnancy occurs in a myxoedematous woman, the symptoms may be relieved or aggravated according to the response which the gland is able to make to the demand for increased secretion. When symptoms do appear, they are those of albuminuria and the pre-eclamptic state. In the majority of cases of thyroid inadequacy, however, pregnancy is apparently able to develop along normal lines, so that in the meantime it is difficult completely to correlate the results of animal experiments with that of clinical experience.

Hunter from a review of McCarrison's work agrees that thyroid insufficiency is frequently met with in eclampsia and suggests that the function of this gland is disturbed by bacterial toxins having their origin in/
in/

in the alimentary canal. One effect of this, he believes, is to interfere with the production of that thyroid hormone on which depends the efficiency of the selective or barrier function of the choroid plexus, the result being that endogenous products of metabolism are permitted to enter the cerebro-spinal fluid, producing irritation and convulsions. This view presupposes that in eclampsia the toxic agent is to be found in the cerebro-spinal fluid, which has not yet been proved.*

2. Parathyroid. It was asserted some years ago by Italian investigators that there was an analogy between the tetany following the removal of the parathyroids and eclampsia, and the extract of these glands was recommended for the treatment of the disease. They were able to demonstrate/

* The only reference I can find to the histological changes found in the thyroid gland in eclampsia is in a communication of Pottet and Kernilly (quoted by Holland). These observers examined the gland in four fatal cases. In three they found somewhat complex changes the chief of which were the presence of many young embryonic vesicles, cirrhosis of the connective tissue, and increased fluidity of the colloid substance. In one case the gland was of normal histological structure. Changes similar to the above were found in three fatal cases of puerperal sepsis.

demonstrate that if hypoparathyroidism is produced in dogs by partial removal of the glands, the animals, if fed on bread and milk, show no tetanic tendency, but if given meat convulsions develop. From this it was argued that the parathyroids either themselves were active in reducing products of metabolism to excretable substances, or that they activated the liver in this function; and further, that failure to reduce these substances evidenced either a deficient activity of the parathyroids, or that an excessive task was thrown upon them resulting in their break down and failure to function.

Thaler and Aden making use of rats also removed the parathyroids from a large number of animals and noted the appearance of tetany exclusively among the pregnant females, the others being unaffected.

3. Pituitary. In a communication entitled "eclampsia: evolution as a causative factor"

S.E. Kark has propounded an ingenious theory that aberration of pituitary function is responsible for the disease. He believes that the prodromal symptoms are due solely to the over-activity of the anterior lobe, on the hormone of which the physiological requirements of pregnancy normally depend, and emphasizes the resemblance between these prodromal symptoms and acromegaly. Pre-eclamptic symptoms, he suggests, are due to hypertrophy of both parts of the/

the gland, the increase in size of the gland, through pressure on the optic chiasma being responsible for the visual symptoms. The phenomena of eclampsia itself, which usually coincide with the onset of labour, result from overactivity of the posterior lobe, which normally is brought into play at this time. The convulsions are due to its pressor action resulting in spasm of the cerebral blood-vessels; a similar explanation for the high blood-pressure is adduced. Kark attempts to explain the post-mortem appearances in the various organs as the result of a generalised arterial spasm having its origin in overactivity of the posterior lobe of the pituitary. He concludes "eclampsia is essentially a physiological process overdone, due to an excess rather than a perversion of an essential product.

Why nature should, in the process of gestation overshoot her mark and thus defeat her own aim is due to the comparatively short evolutionary experience she has had of this her newest experiment in reproduction - the placental form". The high blood pressure which so frequently accompanies the kidney of pregnancy (occurring as a rule at a period of pregnancy when according to Kark's theory the anterior lobe is active and the posterior passive), the fact that labour commonly does not coincide with the onset of convulsions, that symptoms resembling those of eclampsia and the pre-eclamptic state never follow the therapeutic/

therapeutic administration of pituitary extract in large doses and over long periods for example in the treatment of certain types of menorrhagia, and the fact that extract of the post lobe of the pituitary has a distinctly stimulating effect on the renal secretory cells inducing diuresis in contrast to the oliguria of eclampsia are a few of the many flaws which make Kark's theory untenable.

4. Corpus Luteum: In the search for the fons et origo of eclampsia the corpus luteum has not escaped calumny. In 1907 Lambert and Busquet and in 1911 Champy and Gley injected corpus luteum extract into animals and produced paralysees and convulsions. Later, Devraigne and Chirié reproduced their experiments and concluded that the effects produced were of the nature of anaphylaxis. Westermark in 1919 advanced anew the theory that in the corpus luteum was to be found the primary source of the eclamptic poison. He had been impressed with the relative frequency with which toxic symptoms accompanied hydatid mole (which is associated with exaggerated lutein activity) and with the severity of eclampsia when it developed in these cases. He conducted a series of experiments in which corpus luteum extract was injected into animals and found that in non-pregnant animals, while repeated injections usually/

usually proved fatal, the post-mortem appearances were neither constant nor suggestive of eclamptic lesions. In pregnant animals, however, he claims that the microscopic findings were in every respect similar to those of eclampsia. In all, eighteen experiments were carried out, the injections were intravenous, and consisted of 3 cc. of fresh corpus luteum suspended in four times its volume of physiological saline. The injections were repeated at intervals of 3 - 5 days and four injections were usually sufficient to cause death. Westermarck's results, in that the injections were made intravenously are open to question, for, as Weichardt, Pilz and others have shown, intravenous injections may prove fatal, not as the result of toxic action, but merely consequent on the introduction of free cellular elements into the circulation.

Experiments of a similar nature have recently been carried out by Mackenzie Wallis and Everard Williams. These workers used clear protein free solutions of corpus luteum obtained from freshly killed pigs and from human ovary removed by operation. They report a series of eight experiments in which injections were followed by definitely toxic results, and produced lesions which they claim to be identical with those found in patients dying of eclampsia. They attribute special significance to the occurrence of hypercholesteraemia/

hypercholesteremia during pregnancy, especially as this increase occurs about the fourth month of gestation, at a time when the corpus luteum is most active. Injections of corpus luteum increase the cholesterol content of the blood. Further, in eclampsia, much higher figures are found for cholesterol than during normal pregnancy. Mackenzie Wallis and Williams believe that the excess of cholesterol represents an attempt on the part of the body to neutralise the toxic substances elaborated by the corpus luteum.

M.L. Bory (1918) attributes to the corpus luteum a different function in its relation to eclampsia. He is convinced of the correctness of the theory advanced by Fieux and Mauriac, who claimed to have demonstrated the presence of specific toxic bodies elaborated by the placenta and of equally specific antibodies in the blood of pregnant women. Bory is impressed by the coincident and parallel development of the corpus luteum and of these antibodies which are found in greatest concentration in the second and third months of pregnancy, and attributes to the corpus luteum the function of maintaining the equilibrium between these antibodies and the toxins they are called forth to suppress. His view, therefore, differs essentially from that of Wallis and Williams in that he believes that luteal inadequacy, through failure to preserve this equilibrium may result in eclampsia./

eclampsia. Our knowledge of the physiology of the corpus luteum is as yet too scanty to admit of scientific criticism of the views outlined above as to the rôle this organ may play in eclampsia. While experimental investigation suggests that the corpus luteum does contain a toxic substance which in moderately large doses causes death in animals, the theory that toxæmia developing in the late stages of pregnancy, when the corpus luteum has almost completely disappeared, should be caused by overactivity of that gland appears improbable.

A MECHANICAL EXPLANATION OF THE ORIGIN OF ECLAMPSIA.

Before proceeding to discuss the relationship of anaphylaxis to eclampsia which serves as an introduction to the consideration of the placental theory mention may be made of a view advanced by Paramore of Rugby who has attempted to explain the phenomena of eclampsia along mechanical lines. Paramore's conception is that the lesions in the maternal viscera precede and give rise to the toxæmia; he regards the toxæmia which ends in eclampsia simply as an aberration of normal metabolism and eclampsia simply a uræmia, distinguishable from other acute uræmias only in its method of production. Given the maternal kidney/

kidney and liver lesions it is unnecessary to look for a strange toxin arising from elsewhere, and everything in eclampsia except those lesions is, he claims, explained.* Paramore suggests that the kidney and liver necrosis is ischaemic in nature, due to a shutting off of the blood supply, determined by an occlusion of the capillaries, this occlusion being produced not by thrombosis but by pressure. The thrombosis is secondary, not primary, to the necrosis. The pressure is an exaggerated intraabdominal pressure produced in certain cases of pregnancy, to which rises in pressure induced by activity and especially by labour are superadded. During the performance of a Caesarian section for eclampsia, with a manometer in position, Paramore made the following readings of rectal pressure. Before opening the abdomen the pressure was 35 mm. Hg. (in the normal non-pregnant it is 10 mm. Hg.); on opening the abdomen the abdominal pressure dropped to 30 mm., and after removal of the child to 10 mm. In a series of pregnant women in whom the intra-abdominal pressure was gauged by means of a manometer and pressure bulb in the rectum, two/

* Other workers have believed that the maternal visceral lesions were primary. Lever in 1843 believed that puerperal convulsions resulted from undue pressure of the pregnant uterus on the renal veins causing interference with the function of the kidney.

two were suffering from eclamptic toxaemia and in these two the highest pressures were found.

As arguments supporting his theory Paramore instances the high incidence of eclampsia in primigravidae, in the unmarried because of tight-lacing, in multiple pregnancy, in hydramnios, in concealed accidental haemorrhage, in all of which the intra-abdominal pressure is unduly high, and finally in strong muscular women, and asks "are we to suppose that the strong muscular type are specially prone to develop strange toxins from placenta, intestine, thyroid, or breast while the weak and diseased react otherwise? Moreover if the disease is due to failure of chemical adaptation, it should occur in the early rather than in the later months of pregnancy. The real explanation is to be found in interference with visceral metabolism caused by the pressure changes incident to pregnancy".

Two obvious fallacies in the way of acceptance of this attractive theory are first, that eclampsia occasionally does occur at the sixth or seventh month of pregnancy when the intraabdominal pressure must be less than is common at full term; and second, that with rapidly growing abdominal tumours or with rapidly developing ascites the intraabdominal tension may be as high as at the full term of pregnancy without the production of any symptoms suggestive of eclampsia. Without embarking at this stage of my paper on any exposition/

exposition of the placenta theory, Paramore's findings with regard to increased intraabdominal pressure may have this significance that such a factor may predispose to venous stasis and consequently to placental degeneration.

THE RELATION OF ANAPHYLAXIS TO PREGNANCY AND ECLAMPSIA.

While the suggestion that eclampsia is of the nature of an anaphylactic phenomenon has been practically discarded, in view of their bearing on some aspects of the placental theory, it is proposed to outline in brief the principles which underlay this hypothesis. By anaphylaxis is understood the serious and frequently fatal attack, mainly convulsive, which follows the second inoculation, under specific conditions of time and quantity, of certain complex albuminous substances, not of themselves toxic when administered in the same quantity as a single dose (Leith Murray). Although anaphylaxis is not always associated with convulsions, it was perhaps inevitable that the convulsive nature of eclampsia should direct attention to the possibility of its being of this nature. The first suggestion that eclampsia was anaphylactic in character was given by Anderson and Rosenau to whom it occurred that the blood or some protein/

protein substances in solution from the foetus or placenta might first sensitise the mother and a subsequent introduction into the system of the mother of a similar substance explain the convulsions. In their experimental investigations pregnant and non-pregnant guinea-pigs received a first and, after an appropriate interval, a second injection of guinea-pig foetal blood. Their results were invariably negative. When placenta which had been allowed to autolyse for three hours at 37.0°C . was used, anaphylaxis was readily induced. Leith Murray's experiments (1910) seemed to prove that it was the autolytic rather than the purely placental element which produced the anaphylaxis. Three guinea-pigs received intraperitoneally $\frac{1}{2}$ cc., 1 cc., and 2 cc. respectively of a fresh emulsion of guinea-pig liver, and three weeks later 10 cc. of a fresh emulsion of guinea-pig liver without obvious result. On the other hand two guinea-pigs receiving at the same interval of time the same amounts of liver which had been allowed to autolyse for 24 hours in an incubator at 37.0°C . shewed undoubted anaphylaxis. Theis (1910), Lockeman (1911), and Gräfenburg (1911) experimented on the injection of foetal serum into pregnant and non-pregnant animals, and came to the conclusion that the mother was sensitised during pregnancy by small quantities of foetal protein, and that the sudden introduction into her circulation of a quantity/

quantity of foetal blood would produce an anaphylactic reaction. They claimed that the liver and kidneys, in cases where death followed, presented lesions characteristic of eclampsia. Eisenrich (1914) on the other hand, as the results of previous investigations had been inconclusive, attempted to decide the question by the passive transmission of hypersensitisation. He sensitised guinea-pigs by the intra-peritoneal injection of maternal serum; after 24 - 36 hours he gave an intravenous injection of foetal serum. Of fifty guinea-pigs treated in this way, forty-one shewed no symptoms, the remaining nine shewed non-characteristic "pseudo-anaphylactic" symptoms. Sixteen guinea-pigs that had been treated with the serum of eclamptic mothers and children shewed the same symptoms as these last. No animal died of shock.

The most recent paper on the subject is that of Zweifel (1921) who has repeated the experiments of Grafenburg, Lockeman, and Theiss, but with absolutely negative results. Working with guinea-pigs and rabbits he found that foetal serum, and serum from the placental blood did not sensitise the animals of the same species. He gives reasons for not regarding eclampsia as an anaphylactic phenomenon, such as its non-occurrence in guinea-pigs, and the unfavourable conditions for its production in pregnancy where the mother is constantly exposed to foetal protein and should/

should rather pass into an anti-anaphylactic state.

Although neither clinically nor in post-mortem appearances is there other than a superficial resemblance between the two conditions, the evidence seems to be clear that an animal can be sensitised by an injection of placenta from its own species. In other words, placenta of a species on injection into a member of that species acts exactly like horse serum in the guinea-pig experiment. Placenta alone seems to have this property, for example liver extract under the same conditions will not do so. There is apparently some factor in the placenta of any species which is alien to the blood of that species. Murray claims to have proved that pregnant animals are already sensitised to placenta, i.e. whereas in a non-pregnant animal two doses of placental extract are necessary to produce anaphylaxis, in a pregnant animal a single dose (corresponding to the second injection of horse-serum in the guinea pig) will suffice, and deduces that the animal is actively protecting itself from something injurious in its own placenta, (a suggestion, the significance of which will appear when the placental theory of eclampsia is reviewed). While the conferring of anaphylaxis on such an animal is an interesting confirmation of the fact that the animal was sensitised, Murray agrees that from the dissimilarity/

dissimilarity of the two conditions eclampsia cannot be regarded as an anaphylactic reaction, a view endorsed by the experiments of Eisenrich, Fellander, and R.W. Johnstone.

These observations prepare the way for the consideration of the placental theory which may be said to hold the field to-day.

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THE PLACENTAL THEORY OF ECLAMPSIA.

The fact that eclampsia appears solely during or shortly after pregnancy demands that in its ultimate source the poison must be sought in the placenta or foetus. By the passage of foetal metabolic products into the maternal circulation, the foetus has frequently been held responsible. Fehling (1899) and Dieust (1902) advanced this theory and have had many supporters. The arguments commonly given in favour of this view - that a child born of an eclamptic mother may itself show signs, clinically and post-mortem, of a similar poisoning, and that delivery of the child, or its death in utero, is commonly followed by an abatement of symptoms are not convincing, and are/

* For much information with regard to the earlier researches on the placental theory I am indebted to Holland's critical review.

are open to other interpretation. In the presence of a profound maternal toxæmia the wonder is that the child is so frequently born unscathed; intra-uterine death is not always followed by a cessation of convulsions; moreover when the child dies the placenta commonly becomes detached from the uterine wall, so that the phenomenon gives equal support to the placental theory of origin; the same explanation obviously applies to the beneficial effects of delivery. The most recent advocate of this (the "foetal") hypothesis is Bory (1918) who reviews in a critical manner the theories from time to time advanced in favour of a placental origin. In particular he deals with the specific reaction in the maternal tissues which may be elicited by an injection of placental extract. This reaction which will be dealt with more fully in its appropriate place is more marked, as shewn by the researches of Fieux and Mauriac in the earlier months of pregnancy and in the later months is usually absent; Bory therefore concludes that exaggerated syncytial activity in any of its forms (Veit, Weichardt, Pilz, Shenk etc.) whether or not it may account for the "toxæmias" of the earlier months cannot possess aetiological importance as regards eclampsia. The fact that no reaction can be obtained in the later months and that in eclampsia, premature senility in the form of infarcts is/

is so often found, suggested to him the idea that eclampsia resulted from placental insufficiency, in that it failed to deal with noxious foetal waste products and allowed the maternal organism to be flooded by them. "L'éclampsie est au placenta ce que l'urémie est au veïn, l'ictère grave à la gland hepaticque". The strongest argument against the theory is of course the occurrence of eclampsia in hydatid mole of which numerous cases have been recorded; and as Holland points out, when one considers that eclampsia usually occurs in primigravidae and in young women and vesicular mole in multiparae and older women, eclampsia in the later months, and vesicular mole in the earlier months, it follows that the incidence of eclampsia associated with hydatid mole is relatively great. Whitridge Williams however denies that this contention is well founded, as it is quite conceivable that the metabolic processes incident to the continued growth of the chorionic villi may be practically identical with those of the normal foetus.

When Ehrlich propounded his side-chain theory of immunity, this conception was eagerly seized by Veit and his school and upon it they based an elaborate structure founded upon numerous clinical and experimental/

experimental investigations. * Veit (1901) believed that during pregnancy minute portions of placental villi were constantly "deported" into the maternal blood stream and were there dissolved by the blood fluids of the mother. The hypothetical solvent he called a lysin, or more specifically a syncytiolysin. Under normal conditions this sequence was physiological, but where an undue quantity of villous fragments was deported into the maternal blood stream, the syncytiolysins being insufficient to deal with them, they acted on the maternal organism as an unneutralised toxin producing, according to the degree of excess of placental cells over syncytiolysin, varying degrees of toxaemia. In support of his view Veit and Sholten (1902) found that serum drawn from rabbits/

* Schmorl was the first to point out that in eclampsia, the presence of the placental cells in the vessels of the lung was a constant feature. He at first affirmed that they were a feature peculiar to eclampsia and were never found otherwise. Later however his views were modified; out of 150 cases of pregnancy in which they were present, only 83 were eclamptics, so that they were relatively common in women dying from causes other than eclampsia. They were markedly abundant in two cases of abortion at the 2nd month who died of sepsis. It is now known that this "Zottendeportation" is commonly found in pregnancy both normal and abnormal, but it was Schmorl's discovery which really gave Veit the initial idea in formulating his "placental theory" of eclampsia.

rabbits into whose peritoneal cavity had been introduced pieces of fresh human placenta deprived as far as possible of all foetal and maternal blood agglutinated and partially dissolved a suspension of human placental cells.

Ascoli (1902) and Weichardt (1902) working on the same general principles as those of Veit offered different interpretations. Ascoli prepared artificial syncytiolysins which on injection into animals produced marked nervous phenomena, and concluded that eclampsia resulted not from an excess of circulating placenta cells but from overproduction of the lytic substances evoked to dissolve them. It is of significance however, that it was only when the serum was injected subdurally that any effect comparable to eclampsia was produced, intravenous and subcutaneous injections being innocuous. Weichardt on the other hand explained the mechanism as similar to that found in certain bacterial diseases. He agreed that syncytiolysins were formed both experimentally and in pregnancy, and that placental elements circulating in the blood were destroyed by them, but suggested that eclampsia was caused by endotoxins liberated by the cytotoxicity of placenta cells. These toxins he termed syncytiotoxins.

Weichardt's account of his experiments and results is the reverse of convincing and Wormser (1904),
Pollak/

Pollak (1904), and Liepmann (1902) who repeated them, obtained uniformly negative results. In Liepmann's experiments cotyledons were aseptically removed from the placenta and placed in a sterile bowl with sterile salt solution. The pieces were then passed through a sterile mincing-machine and finally filtered through a fine sieve. The resulting emulsion was washed repeatedly in sterile salt solution until all blood had as far as possible been removed. The intraperitoneal injection into rabbits of large doses of the emulsion produced albuminuria in two cases only out of sixteen, its appearance in these two cases being attributed merely to the presence of excess of protein and not regarded as a toxic phenomenon.

On the other hand Liepmann pointed out a new phenomenon. He prepared a specific serum by injecting an emulsion of placental cells into the peritoneal cavity of rabbits and deduced the presence of specific placental antibodies by testing this serum against human placental extract, a precipitin resulting. To meet the objection that the precipitin indicated merely a general human species reaction, in a second series of experiments he removed the precipitate resulting from the addition of human blood serum and then obtained a further precipitate with placental extract (partial precipitation). This specific precipitin/

precipitin reaction together with the constant presence during pregnancy of placental cells in the mother's circulation suggested to Liepmann that he had discovered a serum test for the diagnosis of pregnancy.

The observations of Kawasoye (1904) seemed to lend further support to the view that the syncytium acted as a toxin within the maternal organism and that it served to induce the production of specific antibodies. This worker placed human placental cells in the serum of pregnant women and obtained a cloudy precipitate and partial dissolution of the cells, a reaction which appeared to indicate the presence of a lysin in the blood of gravid women. The precipitin reaction was negative with the serum of non-pregnant women and of males.

When finally Freund (1907) as the result of a large series of experiments announced that the injection intravenously of placental extract caused the death of rabbits preceded by convulsive seizures and attended with widespread thrombosis, his observations apparently confirming the results of Weichardt and Pilz, the chain of evidence seemed complete. Meanwhile, however, doubting voices were heard, and subsequently the whole course of experimental research was of an adverse nature and appeared to shew that although a definite species reaction undoubtedly existed/

existed and could be demonstrated by biological tests, organ or cell specificity (as, for instance, a particular lysin or precipitin for placenta, liver or kidney cells) became more and more problematic.

1. Liepmann's work was adversely criticised by Opitz who attributed Liepmann's failure to obtain positive results with his injections to the repeated washing and mincing of the placenta, a proceeding probably resulting in much loss of syncytium. Opitz removed blood from the placenta by passing salt solution through the umbilical arteries under pressure of one and a half metres of water, the superficial layer of the decidua was then shaved off and the remaining placenta ground in a mortar with sterile salt solution: a "specific serum" was then prepared by the intraperitoneal injection into animals of this emulsion. He completely failed to obtain a distinctive precipitin on adding serum of pregnant women to this specific serum. He could detect no difference in the reaction given by serum of pregnant women, of eclamptics, of non-pregnant women, of foetuses and of men.

2. Wormser as the result of numerous experiments expressed himself in total disagreement with the results claimed by Veit, Ascoli, Wiechardt, and Liepmann. Wormser carried out two sets of experiments. In the first he prepared the specific serum by injecting/

injecting placental extract manufactured according to Liepmann's technique; in the second series the placental emulsion was prepared by the method advocated by Opitz. The experiments of Veit, Ascoli, Weichardt and Liepmann were repeated using both types of placental extracts. The results obtained by these observers were criticised as follows: (a) Veit's theory. On general grounds untenable; if eclampsia were a direct poisoning by excess of syncytium over syncytiolysin it should be possible to produce it in every pregnant animal by injection of placental cells of a corresponding species; but pregnant animals are not more affected by such an injection than non-pregnant females and males. In addition uniformly negative results were obtained in attempting to produce syncytiolysis in vitro. (b) Ascoli's theory. If eclampsia were due to an excess of syncytiolysins, the serum of an eclamptic patient should cause cytolysis in vitro of fresh human placental cells; such was not the case. Moreover Ascoli's experiments were valueless, and in repeating them Wormser only obtained one positive result out of six where the injection was subdural, in this case death being due to a direct cerebral injury from the canula. (c) Weichardt's "syncytiotoxin" theory. Repeated fifteen times with uniformly negative results. (d) Liepmann's precipitin reaction. No difference could be detected between the action of specific and normal sera.

3. Pollak (1904) and Aronson (1905) both failed to detect syncytiolysis and precipitation with specific sera, and Pollak repeated Weichardt's experiments with uniformly negative results.

4. An important communication was published in 1907 by R.T. Frank who immunised rabbits against human placental emulsion using three different extracts prepared from placenta; (a) a maceration of human placenta made as bloodless as possible by washing with large quantities of normal saline solution; (b) a maceration of human placenta made blood-free by washing in plain running water; (c) a solution of nucleo-proteid from human placenta.* With these sera all the tests previously employed individually by other investigators were carried out (precipitation, agglutination, haemolysis, cytolysis against placental cells) upon placental extracts, human blood serum, serum obtained from the umbilical cord blood and from retroplacental blood, urine from pregnant women with and without albumen etc. In addition the Boret-Gengou reaction (complement fixation test) was used for the first time in this connection, because it was regarded as even more delicate than the precipitin reaction./

* Placental nucleo-proteid was used because Beebe and Bierry and Pettit had shewn that if the nucleo-proteid prepared from cells, instead of the cells themselves, was injected, a serum was obtained, which was much more sharply specific and gave much less of a "general human" reaction.

reaction. Frank's results constitute a damaging criticism of the observations of Veit and his co-workers, for all the tests shewed that when any positive reaction was obtained, it was a "general human" species reaction, but that not the slightest evidence of a specific placental reaction could be found; he concluded that "he felt justified in making a positive statement that no experimental proof of a specific placental immune reaction could be demonstrated by our present biological methods".

Frank's observations were apparently confirmed by the work of Frankl (1909) and later by Schenk(1910). Frankl's investigations consisted for a series of experiments, in substance identical with those of Frank, and with the same negative outcome. Further he employed the Wassermann reaction, using the blood serum of patients as amboceptor and placenta as antigen. Schenk also made use of the complement fixation test with placenta as antigen and failed to find evidence of a specific placental antibody.

The negative results just enumerated almost sufficed to render untenable Veit's hypothesis that Eclampsia was due to a specific placental toxin. One other symptom - complex however remained to be accounted for. This was the occurrence of convulsions following intravenous injection of placental extract, such/

such as were obtained by Weichardt and Freund.

Weichardt and his supporters believed that the widespread thrombosis found post-mortem resulted from a special toxin elaborated by the placenta.

1. Mathes (1908) criticising Freund's observations was able to shew that the concentration of the extract and the rate of its injection had considerable influence on the production of intravascular coagulation, and while agreeing that placental extract had toxic properties was able to prevent thrombosis by dilution and slow injection. 2. Englemann and Slade (1909) however, from a large series of experiments denied that the rate of injection affected the result. They affirmed that the chief effect, and that a toxic one, was a widespread intravascular coagulation; and that death, when it occurred was due to this alone they attempted to demonstrate by introducing along with a fatal dose of placental extract a quantity of hirudin (leech extract) to prevent vascular coagulation; out of fourteen animals thus injected only two died, one from air embolism. 3. Lichtenstein (1909) denied altogether the toxicity of placental extract and offered a different explanation for the occurrence of thrombosis. He obtained an emulsion of placenta by grinding it in a mortar and passing it through a series of sieves of graduated texture; where a very fine sieve was used no result followed; with one less/

less fine widespread intravascular coagulation was the result. Moreover this latter occurrence could be exactly reproduced by the intravenous introduction of inorganic particles (a suspension of fine clay was used). Lichtenstein concluded therefore that death, when it occurred, was produced purely by foreign body effect, through the occurrence of multiple emboli followed by thrombosis, and was in no sense due to toxic properties in the placenta. While the intravascular coagulation which follows intravenous injection of placental extract may be partially attributed to the contained cell debris, it has long been known that nucleo-proteid, prepared from any organ, when injected intravenously is followed by a similar result. That it could be produced by injecting nucleo-proteid prepared from placenta was demonstrated by Acconci (1904) and Dryfuss (1908).

These researches shew that the work of earlier observers and the results obtained by intravenous injection must be regarded in a restricted sense.

Frank's work has already received attention; it may be recalled that as the result of an elaborate research he concluded that no evidence of a specific placental reaction could be obtained. In contrast to this must be mentioned the observations of Fieux and Mauriac (1910) who, also making use of the Bordet-Gengou/

Gengou (complement-fixation) reaction, claimed to have demonstrated the presence of specific toxic bodies elaborated by the placenta, and of equally specific antibodies in the blood of pregnant women. These investigators instead of using the serum of pregnant rabbits, immunised against human placenta as the amboceptor, as most other workers had done, employed the blood serum of pregnant women in this rôle, exactly as human serum is used in the Wassermann reaction, and as antigen they used extract prepared from the villi of early ova (taking the place of syphilitic liver in the Wassermann test) instead of full term placenta. Fieux and Mauriac tested the blood serum of fifty-five women, of whom thirty-four were pregnant, the remainder being used as controls. The subjoined table shows the results obtained.

Number of Cases.	Period of Gestation.	Results		
		Positive	Negative	Doubtful
5	3rd - 5th week		5	
11	2nd - 3rd month	11		
7	3rd - 4th month	1	4	2
21	4th - 9th month		21	
<u>10</u>	Non-pregnant		<u>10</u>	
54		<u>12</u>	<u>40</u>	<u>2</u>

What/



What impresses one immediately is that positive reactions were obtained only in twelve cases out of fifty-four, all of them during the second and third months of pregnancy, where their association with the fullest development of the trophoblast is obvious. After the third month a negative reaction was uniformly noted. In passing, as far as this individual research is concerned, it seems to negative very definitely the possibility that eclampsia is due either to an excess of syncytial toxin, as Veit and his followers conceived it, or to a deficiency of protection developed.

With the results of Fieux and Mauriac, Frank and Heimann (1911) expressed themselves in complete disagreement. Frank's earlier paper has already been noted, and in view of the results claimed by Fieux and Mauriac, the second research was undertaken to vindicate the observations previously made. Frank and Heimann, therefore, decided to repeat the experiments of Fieux and Mauriac, employing the same technique as had been used by them. In their investigations eighteen sera were examined; of these, nine were obtained from women who were in the second or third month of gestation, the other nine were drawn from patients who were in the later months of pregnancy. Uniformly negative results were obtained with all sera, /

sera, with the exception of one where the reaction was doubtful. Apart from the suggestion offered by Frank and Heimann that Fieux and Mauriac might unwittingly have performed a true Wassermann reaction for syphilis, in that their antigens might have contained luetic inhibitory substances and their sera luetic antibodies, it is difficult to explain such a variance in results.

In the light of more recent work it is probable that Frank and Heimann went too far in denying altogether that there is in the placenta some body or antigen which is capable of producing antibodies in the species, i.e. of stimulating the body tissues and fluids to immunise themselves. Murray, whose earlier work in relation to anaphylaxis and eclampsia has already been referred to was able to adduce convincing evidence that pregnant animals are already sensitised to placenta; whereas in a non-pregnant animal two doses of placental extract were necessary to produce anaphylaxis, in a pregnant animal a single dose (corresponding to the second injection of horse serum in the guinea-pig) would suffice. And, as lending support to Fieux and Mauriac's observations, he found that the anaphylaxis induced in a pregnant animal by a solitary injection of placental extract was much more severe in early pregnancy and might be rapidly fatal/

fatal in a pregnancy so early as to be microscopic.

Obata of Tokio (1919) has recently published results of a similar investigation. His technique was as follows: As soon as the placenta was expelled the umbilical cord was cut off together with the portion of placenta surrounding its attachment. As much blood as possible was then expressed from the placenta and the decidual tissue removed. A portion of the remainder of the placenta was then cut in pieces, ground in a mortar and mixed with 0.85% saline solution, in proportion of 1 in 3 by weight. The mixture was stirred and allowed to stand for half-an-hour at room temperature, and then filtered through fine silk. The filtrate was then centrifuged and the supernatant fluid, designated placental extract, was used for the experiments. The extract had a pale pink colour, but contained no solid particles. As a rule freshly prepared extracts from placentae taken immediately after birth were employed. The animals used for injection were Japanese dancing-mice and the placental extract was injected into their caudal vein. In the majority of cases after an interval of 30 - 60 seconds the animal became excited, and convulsions followed by death rapidly developed; occasionally however death occurred after an interval of hours or days. The lesions found in the bodies of animals who succumbed were/

were broadly similar to those present in fatal cases of eclampsia in the human. The placental extract was found to kill in a dose of 0.025 - 1.5 cc. in the case of normal placentae and in a dose of 0.019 - 0.1 cc. in the case of eclamptic placentae. The toxicity of eclamptic placentae, accordingly, was hardly to be distinguished from that of placenta from normal cases. Obata then proceeded to determine the relative capacity of fresh serum of normal and of eclamptic patients respectively to neutralise the toxicity of placental extract. 1 cc. of the latter was placed in contact with amounts of serum varying from 0.7 to 0.025 cc., physiological saline being added to bring the mixture up to 2 cc. and the fluid injected after being left for one hour at 37°C. He found that serum either of normal men or of normal non-pregnant or normal pregnant women possessed a power practically uniform of neutralising the poisonous properties of placental extract, 0.2 - 0.3 cc. of such serum sufficing to neutralise 1 cc. of the extract. This neutralising power was found to be considerably reduced in the serum from women during an eclamptic attack, as much as 0.6 cc. being then required to neutralise the toxicity of the placental extract, although after recovering from eclampsia 0.3 - 0.4 cc. and sometimes 0.2 cc. of the patient's serum was sufficient. Experiments made to determine whether the neutralising/

neutralising power was increased during normal pregnancy were negative. Hence no evidence was found to indicate that the neutralising power was due to an immunological process. Obata concluded that eclampsia consisted in an intoxication of the maternal organism by a placental poison which was made possible by the failure of the maternal blood to supply an efficient neutralising principle. It is of interest to note in passing that fresh serum from normal persons when injected intravenously into mice produce symptoms which differ only slightly from those produced by placental extract. No substantial difference moreover was found between the serum of normal and of eclamptic gravaidae in this respect, nor could any increase in toxicity be found in the serum of a patient during an attack of eclampsia and after recovery from that condition. Obata's technique is very similar to that first used by Liepmann and adversely criticised by Opitz; his experiments are in nature essentially those carried out by Freund in 1907 and are therefore open to the same criticism (of results following intravenous injections) as were advanced by Mathes, Engelman, Slade and Lichtenstein. In general they lend support to the view that the introduction of placental extract under certain circumstances may result in a reaction more or less specific, but as regards the etiology/

aetiology of eclampsia they do not seem to any appreciable extent to advance our knowledge.

Such then is the placental theory of eclampsia as conceived originally by Veit and elaborated by the numerous investigators who followed him. Sufficient alone to cast grave doubts on its correctness are the diametrically opposite conclusions arrived at by different observers working along practically the same lines. While it seems clear from the researches of Fieux and Mauriac, of Murray, and of Abderhalden that a specific maternal reaction, of the nature of antibody formation to placenta as antigen may occur, it is equally clear that this is most marked in early pregnancy, completely disappearing during the later months, and that the hypothesis that eclampsia may be due either to an excess of syncytial toxin (as Veit and his followers understood it) or to deficient development of protection against it, is a theory not supported by sufficient evidence to warrant its existence.

To Liepmann belongs the credit of first advancing the view that it is in the eclamptic placenta that one must look for the cause of the disease.*

Hoping/

* The following account of Liepmann's work is taken from Holland's Critical Review.

Hoping to produce a specific antibody for eclampsia analogous to the immunity which Weichardt and Opitz had been able to produce against large doses of normal placentae by the injection of small doses, Liepmann was working with a dry powder, manufactured from eclamptic placentae, which he injected into the peritoneal cavity of rabbits. To his surprise the animals quickly died, with all the symptoms of a severe intoxication. Control experiments made with normal placentae gave negative results. He drew the conclusion that in the eclamptic placenta existed a poison not present in normal placentae. His technique was as follows:- The placentae of eclamptic patients were minced, dried in vacuo, and ground into a fine white powder. Of this powder a suspension in salt solution was made and a definite dose, usually 1 gm., of powder was injected into the peritoneal cavity of rabbits. Of seventy animals injected only thirteen lived, and these shewed severe disturbances shortly after the injections. As regards the manner in which the toxin exists in the placenta, experiment shewed that it was firmly combined with the protoplasm of the cell. The juices of the eclamptic placenta were separated from the pulp in a Buchner's press. Injection of the placenta pulp proved fatal, whereas the juices of the same placenta, when injected intravenously/

intravenously produced no bad effect. But in placentae from cases of very severe toxæmia a smaller proportion of the toxin was found in the extracted juices as well. Further, it was found that the extract, when toxic, could be deprived of its toxicity on the addition of reagents which precipitate albumen; they either precipitated the toxin or carried it down with the precipitate. That the toxin was very labile and difficult to preserve was shewn by trials of the same placenta powder at different dates; the powder which proved fatal on one day was innocuous on the day following. Attempts to extract the toxin by chemical means failed. In further experiments Liepmann found that extracts of placenta from severe cases of eclampsia were less toxic than extracts from milder types, and deduced from this that the greater the amount of toxin that was passed over into the organism and the more the number of fits that occurred, the less was the amount of toxin found in the placenta; conversely, the placenta was so much the richer in toxin the fewer the fits that occurred.

Although objection may be taken to Liepmann's work on the ground that his placentae were prepared in a factory on a large scale and therefore must have run the risk of decomposition before the powder was finally ready, he escapes the criticism which may be passed on the results of many other workers in that he/

he obtained positive results by means of intra-peritoneal and not intravenous injection; the fallacy attached to this latter method has already been indicated. Further, in directing the search for the source of toxæmia to the eclamptic rather than to the normal placenta he broke new ground.

Many workers have sought to find the source of eclampsia in a study of the placental ferments which are exceedingly numerous and complex and are apparently increased in activity in eclampsia. Savaré (1906) claimed to have discovered a ferment which might be responsible through its powerful action in causing intravascular coagulation. Mohr and Freund (1908) were able to extract from the placenta a lipoid with strongly haemolytic properties. Hofbauer (1918) in a series of lengthy articles regards the placenta as the seat of ferments which under certain conditions may become altered and produce autolytic degeneration in the liver. Finally Schönfeld (1921) attributes eclampsia to the perverted activity of a lipoid normally present in the placenta. This substance he was able to isolate and claims by its intravenous introduction to have produced eclampsia in animals.

The foregoing review, while it does not pretend to be completely comprehensive, embraces the bulk of/

of the work on the etiology of eclampsia carried out in recent years with the exception of the research of James Young who seeks to explain the phenomenon as resulting from the liberation of products of early autolysis of the placenta, a theory which I shall endeavour to substantiate. Before Young published his results autolysis of the placenta had received considerable attention from Mathes (1901), Basso (1905), and in particular Dryfuss (1907) who investigated very fully the autolysis of normal and of eclamptic placentae from the chemical standpoint without drawing conclusions as to its rôle in the production of the eclamptic state.

THE ECLAMPTIC PLACENTA.

Before proceeding to a detailed consideration of Young's theory, with which the remainder of this paper is principally concerned, it is expedient to bring under review certain changes which may be met with characteristically in the eclamptic placenta, for, on the significance of these Young's hypothesis essentially rests. The appearances found may be grouped as follows:-

(1)/

(1) Changes in the chorionic epithelium.

Proliferation of the epithelium in the form of projecting buds of granular syncytium has been described by various authors (Fink, Hermann, Sitz etc.) as characteristic of the albuminuric or eclamptic placenta. The condition has been described in detail by Brindeau and Nattan-Larrier, who do not however consider this budding peculiar to eclampsia, but merely an exaggeration of the physiological condition. In my own series of eclamptic placentae I have noticed it frequently.

(2) Epithelial Plates.

J.L. Brenner (1918) has called attention to certain thin epithelial plates to be found in the surface layer of the placental villi in intimate connection with the underlying foetal capillaries, "similar in appearance and relations to the epithelial plates of the visceral layer of the capsule of the renal or mesonephric glomerulus", and claimed to shew that such plates were present in the placenta only during the absence or degeneration of the mesonephros in any particular type of embryo. He suggested that the presence of these plates shewed the ability of the placenta to remove from the foetal blood certain excretory substances and to assume for the foetus the function/

function of glomeruli. Normally the plates are scattered and only found after careful search. In eclamptic placentae, Brenner states, their numbers are greatly increased, and their detection correspondingly easier.

(3) Haemorrhagic lesions.

These have been variously termed: apoplexy (Cruveilhier, Jacquemier, Gierse, Meckel, and Williams; haematoma (Klebs); haemorrhage, (Kuehnel, Simpson, Brindeau and Nattan-Larrier); red infarcts (Williams, Young and others), these last will be considered under the heading infarction.

Brindeau and Nattan-Larrier describe three forms of haemorrhage (a) the haemorrhagic nodule or cyst, (b) diffuse haemorrhage into the substance of the placenta, or placental apoplexy, (c) the retro-placental haematoma; this last type will be considered under ante-partum haemorrhage. The former two varieties are stated by Brindeau and Nattan-Larrier to be due to rupture of the villous vessels consequent on their overdilatation, in other words the haemorrhage is foetal in origin. McNalley and Dickmann (1922) on the other hand, who have also studied these intraplacental haemorrhages, have decided in favour of a maternal origin and stated that they probably result from back pressure due to venous stasis from thrombosis, the/

the size of the lesion being in proportion to the extent of the interference with the return flow. This explanation was suggested by Young in 1914. Such intraplacental haemorrhages while very frequent in eclampsia may of course be met with in other conditions. Their significance is uncertain. In thirty-two eclamptic placentae investigated by myself they were present in twenty-one. An area of haemorrhagic extravasation may, probably through interference with the maternal blood supply to the underlying portion of the placenta, be subtended by an arc of infarcted tissue.

(4) Infarction.

Placental disease of the nature of infarction has been recognised as a common accompaniment of the toxæmic states in the later months of pregnancy since Fehling first drew attention to the connection in 1886. The typical case of long-standing pregnancy albuminuria always shows multiple areas of infarction varying in age and appearance. Their relative frequency has been variously estimated by different observers. Rouhaud, in 1882, noted that 40 per cent of the cases which had albuminuria had red infarcts. Rossier found infarction in 60 per cent of albuminuric placentae. Meyer stated infarction to be four times more frequent when the patient was albuminuric than when the urine was/

was healthy (although he only found a percentage of 6.7 albuminuric patients were delivered of infarcted placentae); Cagny found infarction in 33 per cent of placentae obtained from albuminuric patients; Martin in 47 per cent. Williams from whom the figures are quoted found infarction in 63 per cent of a series of five hundred placentae, though he does not state in what proportion of these albuminuria was noted.

Haffner (1921) has recently reported the results of an examination of a consecutive series of four hundred placentae and investigated the relative incidence of albuminuria and infarction. In seventy-three albuminuric patients infarction was found in 56 per cent; of one hundred and eighty-five placentae shewing infarction 77 per cent were obtained from women in whose urine no albumen was detected, moreover in 30 per cent of these placentae the infarctions were recent. Haffner concludes accordingly that there is insufficient justification for believing that any direct relationship exists between albuminuria and placental infarction.

In spite of Haffner's adverse opinion, the mass of evidence suggests that, however the relationship be explained, infarction and albuminuria are closely associated. With this view my personal observations are/

are in accord. The material employed consisted of two hundred and forty-six cases observed from the point of view of albuminuria and the changes met with in the placenta. The examination of the placenta consisted in inspection of the maternal surface after it had been washed free of blood clot, and in careful palpation of the organ to detect areas of greater resistance; such a superficial examination may be sufficient to make out the larger or older brick-red or yellow infarcted areas. The very recent infarction however may differ only slightly in consistence and colour from that of the normal fresh placental tissue and may escape notice. In addition, therefore, as a routine each placenta was thoroughly sectioned with a long-bladed knife and examined under running water, thus rinsing the inter-villous blood out of the healthy parts of the placenta; the deep red or purple colour of recently infarcted areas (in which the blood is clotted and therefore not removed by washing) being thus thrown into relief against the paler surrounding tissue their detection, otherwise sometimes difficult, was simple.

This technique was found more satisfactory than the usual formalin method. Further, in the majority of cases, all areas showing anything unusual were submitted to microscopic examination. Two hundred and forty-six patients were classified as follows:-

1./

1. Cases admitted to the Maternity Hospital immediately preceding, or during labour, whose history as regards the condition of the urine during pregnancy was unknown; these numbered one hundred and sixty-seven.
2. Cases admitted whose previous history as regards the urine was accurately known; there were seventy-nine patients in this category.

The following table shows at a glance in what proportion albumen was present and the incidence of infarction.

TABLE. /

	Urine.		Infarction.	
1. Cases admitted with no previous record	167	Albumen absent 74	12	= 16.2%
		Albumen present 93	68	= 73.1%
2. Cases whose previous history was known	79	Albumen absent 32	63	= 18.7%
		* Albumen present 47	34	= 72%

* This includes cases which had albumen present on admission to hospital or a history of albuminuria at some time during the later months of pregnancy.

The 140 albuminuric patients were further classified as far as possible as follows:-

1. Cases of true albuminuria of pregnancy. These numbered 67 and were restricted to cases presenting definite symptoms of toxæmia. In 62 cases (92.5 per cent) infarction was present. One of the remaining five was a case of fulminating eclampsia, coming on with no prodromal symptoms; the placenta was apparently normal; the explanation of this apparent paradox will be suggested later.

2. Cases of nephritis complicating pregnancy. These numbered four. All had a long history of previous kidney trouble and the condition of the heart and bloodvessels suggested chronic Bright's disease. In two the placenta was abnormal.

3. Cases shewing a symptomless albuminuria, more or less transient. These numbered 69 and are of certain interest. In 38 cases (55 per cent) the placenta contained recent infarcts, most of them small, varying in size from a pea to a filbert. This type of symptomless albuminuria, present in 28 per cent of cases in my series of 246 deliveries, is usually looked on as physiological in nature, the result of the fatigue incident to labour; moreover such infarction as was present in the placentae of these cases is commonly, and without doubt correctly regarded/

regarded as a normal occurrence, "a sign of senility in a short lived organ" (Eden). While fatigue, anaesthesia etc. no doubt do play a part in the production of these transient albuminurias, in the light of Young's work the question obtrudes itself as to whether a direct association may not exist between this so-called physiological albuminuria and the slighter degrees of infarction which may be met with in the average full term placenta. In other words, is not the trace of albumen sometimes toxic in nature? The question cannot be satisfactorily answered until a more delicate test for the presence of toxæmia than albumen in the urine is available.

THE PATHOLOGY OF INFARCTION.

This has been fully described by Whitridge Williams, Eden, McNalley and Dieckmann and especially by Young. The principal pathological changes in an infarcted area of placenta, as described by these observers may be summarised as follows:- (1) Coagulation in the intervillous spaces. This according to Young is due to blockage of the corresponding maternal vessels, and is not secondary to an area of necrosis. This feature is/

is by no means invariably present; occasionally neither blood nor fibrin can be found in the intervillous spaces. (2) Congestion of the vessels of the chorionic villi. This is early and characteristic. The expansion of the vessels causes a swelling of the villi which become closely packed together so as to form a solid block resting against the decidual surface, and sharply differentiated from the surrounding spongy placental substance. This "hepatisation" is not entirely due to the turgescence of the individual villi. Eden explained it as due to a "progressive diminution of the blood supply to a part of a cotyledon by the obliteration of a maternal artery, which would cause the villi to become crowded together because there would not be sufficient blood in the part to maintain them at their normal distance from one another," and suggested further that the pressure exerted by the rest of the placenta "would drive the villi together into a closely crowded consolidated mass". With this explanation Young is in agreement and writes "the infarcted block is thus really an area of collapsed placental tissue comparable to collapse of a portion of the lung following occlusion of a corresponding bronchus". (3) Necrosis. The earliest indication of this appears to be a proliferation of the syncytial nuclei forming masses of darkly staining/

staining tissue, later the cellular elements of the villi undergo disintegration and may finally be represented by mere ghost-like outlines.

The naked eye recognition of infarction is simple when the condition is fully established. The pale and brick-red varieties are so distinctive that they form a prominent feature of the cut section of the placenta. The more recent variety, in colour only differing slightly from that of the surrounding placenta, may escape notice unless carefully searched for when a cut section is washed under running water. Young, so far as I know, was the first to point out that the various appearances included under the term "infarction" are different stages in one and the same process and not, as often stated, independent pathological states; he suggested as explanatory of the change in colour from red to white, that the haemoglobin was gradually removed from the blood contained in the affected portion.

Young's views are in disagreement with those of Whitridge Williams but have been endorsed in a recent article by McNalley and Dieckmann. These authors while agreeing that the white infarct generally represents a further or older stage of the red variety describe a further type of lesion which results from the conversion of a collection of pure blood into structures/

structures that in the gross have the identical appearance of white infarcts but in whose formation villi play no part. This condition has also been described by Dieulafoy who writes "The lesion is characterised by the appearance of haemorrhages which are converted into white infarct. The primary lesion is haemorrhagic, the white infarct is secondary. If the infarct is incised it appears to be formed of fibrin, more or less dense in appearance and sometimes disposed in a series of concentric lines" Cruveilhier and De Lee have made similar observations.

AETIOLOGY OF INFARCTION.

The factors responsible for infarction are disputed. Whitridge Williams from an examination of five hundred placentae concluded that in the great majority of cases the main factor in the production of infarction was to be found in an obliterative endarteritis of the villous vessels. His observations were thus in accordance with those already made by Eden, Ackermann and others. Young on the other hand agreed with Hofmeir that the degeneration was due to some interference with the maternal blood supply, and pointed out that the villi were not dependent for their nourishment on the foetal blood and that they could/

could live and proliferate when this was absent, as in the earlier stages of development, or in hydatid mole, and therefore that villous necrosis must be the result of some process other than obliteration of the villous vessels.

Young's observations receive support from the work of Goodall who has shewn in his investigation on the involuting uterus that obliteration of the maternal vessels does take place before labour; "in the smaller veins of the placental area" he writes "there is usually a complete obliteration due to the building of a thrombus". Goodall pointed further to the connection between these changes and the presence of placental infarcts.

That infarction results from interference with the maternal blood supply is shewn clearly by the frequency with which a retroplacental clot is accurately subtended by an area of infarction. Underlying old clots old yellowish or white infarctions will be found, while under a recent haematoma the area of infarction is deep red or purple; such infarction as this last commonly accompanies accidental haemorrhage, especially of the concealed variety, and I have repeatedly found it in the separated portion of a placenta praevia.

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In many instances, in fact in the majority of cases of eclampsia, no evidence of placental separation or of retroplacental bleeding may be present, the local impairment of blood supply that results in placental infarction being probably due to thrombosis in the vessels of the placental site.

THE AETIOLOGICAL RELATIONSHIPS OF INFARCTION
AND THE ALBUMINURIA OF PREGNANCY.

This has been much disputed. Holland, while admitting that infarction was more frequent in albuminuria and eclampsia, wrote "they may be looked on as the result of a chronic toxæmia; as to their connection with eclampsia, they are merely accompaniments not consequences. The presence of the chronic degenerations in eclamptic placentae has been investigated by Brindeau and Nattan-Larrier who give them no special significance". Whitridge Williams, while recognising their association with eclampsia and albuminuria stated that at present we could not satisfactorily account for the relationship between them. More recently Hoffbauer has denied that the two conditions are in any sense associated. Until Young's paper in 1914 one may summarise the position by saying that placental disease of this nature was looked/

looked on merely as the accompaniment or as the result of the toxæmic state. This attitude was the natural outcome of the variable and confusing changes which might be found in the placenta in toxæmic cases. In some cases of toxæmia marked placental infarction is obvious; in others there is no apparent change; in a third group one may find an extensive degree of infarction and yet at the time of delivery no clinical evidence of toxæmia. The natural inference from such irreconcilable data was that no constant association between the two conditions existed. A logical explanation however has been offered by Young. What first led him to the interpretation of this apparent paradox was the discovery that although obvious placental disease might be absent in the placenta of a fulminating eclampsia which ended in rapid labour or death, in the other less virulent type in which some days or weeks elapse between the inception of the toxæmia and the birth of the placenta there is always massive necrosis visible to the naked eye. In my own series of cases I have seen no exception to this rule. The obvious deduction from this observation was that in an albuminuric or eclamptic toxæmia a degenerative change is always present in the placenta but that some days must elapse before it can evolve into the form of naked eye infarction. Quoting from his/

his 1914 papers (p.4): "It is this that explains why in an albuminuria which becomes established gradually and persists for some time, one is more likely to find marked placental disease. It is just the comparatively slow involvement of the placenta that allows of the continuance of the pregnancy and the evolution of the infarcted regions. Where there is a sudden and extensive involvement of the placenta, the toxæmia is so fulminant that the pregnancy ends before any naked-eye changes in the placenta are produced."

If these observations are correct they indicate that if the necrotic areas are the source of the eclamptic poison, this poison is produced during the early autolysis of the disintegration process, and whilst the structure of the placenta as yet shews little or no change. Gradual piecemeal involvement of the placenta may produce in the end an extensive infarction consisting of small isolated necrotic areas of different ages but "under these circumstances the absorption of toxic products from the dying patches is so gradual and at any one time so small in amount that it is tolerated and may occur with little outward effect". (Young)

In that type of case mentioned above, in which, despite the presence of obvious infarction, no toxæmia/

toxaemia is evident at the time of delivery, we are dealing with a toxaemia which was present earlier in the course of pregnancy and has been recovered from. In such, the infarction will obviously be other than recent.

ACCIDENTAL HAEMORRHAGE AND TOXAEMIA.

Retroplacental haemorrhage is a common cause of placental degeneration, and is of special interest on account of the frequency with which it is associated with toxaemia. The frequency of albuminuria in accidental haemorrhage is given by different authors in figures varying from 30 to 80 per cent. In my own series the ratio is twenty-four times in a series of thirty-one cases - i.e. 77.4 per cent.

This common association suggests either that the haemorrhage results from the toxaemia, as is commonly urged, or that the haemorrhage precedes, and through the coincident placental infarction, originates the toxaemia. The following considerations render the validity of the common interpretation questionable.

(1) If accidental haemorrhage is provoked by the common toxaemia of the later months of pregnancy, it should be specially common in primigravid women. It is, however, relatively much rarer in these than in multiparae.

(2) In a certain proportion of cases, especially those in which delivery is rapidly accomplished, there may be no evidence of toxaemia.

(3) That the toxaemia is secondary is shewn by the fact that one may occasionally observe its development subsequent to the haemorrhage. In four of my cases an examination of the urine within a few hours of the bleeding was negative, whereas at a later examination an albuminuria was revealed: (an albuminuria develops so rapidly after the separation of the placenta, however, that it is usually present by the time the patient is admitted to hospital). It may be urged of course against this argument that cases of toxaemia, in which the urine till a comparatively late stage remains albumen-free, are not unknown.

(4) A study of the aetiology of accidental haemorrhage and especially of the pathological picture presented in cases of the concealed variety suggests strongly that in many cases a mechanical factor is in operation. One hesitates to quote trauma as an etiological factor of importance; in four of my cases, however, the haemorrhage followed the performance of such severe exertion as the washing of clothes, or it succeeded an accident, such as falling downstairs.

In/

In all these cases there was albuminuria, and in two it developed after the bleeding. In most cases of accidental haemorrhage the bleeding occurs in the site of least resistance - namely in the retroplacental area. In other cases, however, the bleeding is widespread, and, coincident with the retroplacental extravasation there may be a deep infiltration of the muscular wall of the uterus and of the broad ligaments, a condition which has been called "diffuse uteroplacental apoplexy". In my series there were three cases of this remarkable condition. The appearances are exactly those that would be produced by a sudden blockage of the ovarian vein. Young suggested this as a possible factor and has described one case of concealed haemorrhage in which thrombosis of the right ovarian vein was found. This observer has also drawn attention to the resemblance which the intense congestion of the uterus in such cases bears to a pedunculated ovarian or fibromyomatous tumour with acute torsion of the pedicle.

Without entering into a description of the appearances found in the uterine wall in these cases, it is of interest to note the resemblance they present to changes found in cases of so-called spontaneous rupture of the uterus in which fragmentation of muscle and extensive vascular infiltration of the muscular wall/

wall occurs. W.A. Scott, describing two cases, writes "In the light of the findings of J. Whitridge Williams in cases of accidental haemorrhage where there was a diffuse haemorrhagic infiltration separating the uterine muscle fibres, it is possible that a common underlying cause may account for both early spontaneous rupture and premature separation of the normally situated placenta". It may be recalled that cases of concealed haemorrhage are almost invariably associated with profound toxæmia, and if Scott's suggestion is correct the significance is obvious.

A study of the placenta in cases of accidental haemorrhage provides another series of considerations in support of the theory which Young has advanced. Cases of accidental haemorrhage may be divided into two classes: (a) Those in which the placenta shews little or no evidence of degeneration; and (b) those in which the placenta exhibits degeneration of the detached area.

(a) Here sufficient time has not been allowed for the full development of infarction. This category includes cases in which the birth of the placenta follows quickly on the onset of the bleeding, and in it are numbered most cases of external bleeding. Toxæmia is inconspicuous and, if present, is represented by a slight transient albuminuria.

(b)/

(b) Here the placenta throughout the detached area shews the signs of early infarction. The placenta has been retained in the uterus for some time, and whilst one part of the organ has remained intact and healthy, the other part has become transformed into a mass of degeneration. The best example of this type is the retroplacental haematoma, subtending which there will always be found an area of infarction. Toxaemia is the dominating feature in this class of case. The most severe toxaemias in my series of accidental haemorrhage belong to this class. It includes five cases of eclampsia.

It is apparent that, if these observations are correct, in order that a toxaemia may develop the placenta must necessarily maintain its attachment to one part of the uterine wall. Only thus can it receive and pass into the maternal blood stream the products of the adjacent necrosis.

PLACENTA PRAEVIA AND TOXAEMIA.

It sometimes happens that in placenta praevia the detachment of the placenta commences some days before the delivery of the uterine contents. If the thesis I am attempting to substantiate be correct such cases should be associated with a toxaemia.

It/

It was decided therefore to conduct an investigation along these lines.

A rise in blood-pressure is probably the earliest definite sign of a toxæmia that we possess. In cases of severe hæmorrhage however, despite the presence of toxæmia this indication may obviously be wanting, and in this investigation the presence of albumin in the urine was taken as a test.* In all the cases the bleeding had commenced before admission of the patient to hospital.

My series consists of fourteen cases of placenta prævia. Of these seven had no albuminuria throughout. In seven cases (50 per cent) albuminuria was found. In one only a trace was present and quickly disappeared. In two it increased from a trace at the first examination to a heavy deposit at subsequent examinations. In two the albuminuria was absent at the first examinations and only developed later. In one case, an eleven-para, labour was induced at the seventh month for placenta prævia; her health, previously perfect, now deteriorated and violent headaches and other evidence of toxæmia such as marked albuminuria developed. After delivery her condition only partially improved; and some months later/

* For this investigation, as for the similar investigation of the cases of accidental hæmorrhage, a catheter specimen of urine was obtained as soon as possible after the admission of the patient to hospital and also at subsequent intervals thereafter.

later she was admitted to the Medical Wards of the Royal Infirmary with an acute recrudescence of kidney mischief from which she died. In one case which I have described elsewhere, the patient, a seven-para, developed eclampsia.

Toxaemia has, so far as I know, never been recognised as bearing any aetiological relationship to placenta praevia, though a number of cases, in particular one by Holland, have been recorded in which low implantation of the placenta was combined with albuminuria. The concurrence has been, however, considered as a chance phenomenon. Recently Jardine and Kennedy reported a series of eleven cases of toxaemia so severe as to lead to complete suppression of urine, and in two of these there was placenta praevia. These conditions are each so rare that unless there is a possible mutual dependence they should occur together only once in several hundred thousand cases.

These records are striking and, although the series is too small to warrant any far-reaching conclusions, go towards the confirmation of Young's argument. As a control I examined four cases of severe haemorrhage, other than obstetrical, and in each case the urine gave negative findings.

The association of albuminuria with placenta praevia is admittedly less frequent than with accidental/

accidental haemorrhage; my ratio of fifty per cent no doubt considerably exceeds the average findings. If placental separation, provided the case does not rapidly terminate in labour, induces a toxæmia, how is one to account for this relative infrequency of toxæmia in placenta prævia? There are two considerations which may be adduced in explanation.

(a) For the production of a moderate degree of toxæmia it is probably necessary that a considerable extent of the placenta should undergo degeneration. Young has suggested that for an eclamptic seizure it is necessary that one half or one third of the placenta be infarcted. In the majority of cases of placenta prævia, however, the area of separated placenta is comparatively small and the resulting toxæmia correspondingly inconspicuous. For the same reason eclamptic toxæmia in abortion or in extra-uterine pregnancy is seldom met with. (b) As compared with placental separation in accidental haemorrhage, the possible channels for the exit and absorption of toxic products in placenta prævia are comparatively limited. In the former, best exemplified for my purpose in the retro-placental hæmatoma, the area of degeneration is completely surrounded with living placental tissue and a ready access into the systemic circulation of any toxic material is thus/

thus allowed. In placenta praevia however, if one excepts the completely central variety, the separated portion is in limited contact with healthy placenta and the diffusion of poisonous material elaborated in the infarcted area is inevitably less free.

OTHER CAUSES OF PLACENTAL DEGENERATION AND TOXAEMIA.

It has been shewn above that mechanical factors may cause a detachment of the placenta from the uterine wall, and, as in certain cases of placenta praevia and accidental haemorrhage, such a mechanical detachment is the cause of the degeneration that ends in toxæmia. It often happens however, that in cases of ordinary infarction of the placenta the exact cause of the impairment of the maternal blood supply is difficult or impossible to discover by an anatomical examination. In some such instances there is a thrombosis in the decidual vessels, and in the light of Goodall's work, this factor probably operates in a number of cases. Localised degeneration in the placenta must be due to blackage of the corresponding maternal vessels. Of this we can be certain, but the ultimate explanation must remain of a theoretical nature until we have a more intimate knowledge of the vascular conditions/

conditions that obtain in the abdomen and pelvis during pregnancy. Is it possible that the increased intra-abdominal pressure which Paramore claims to have shewn is present towards full term especially in primigravid women may tend to cause venous stasis with consequent thrombosis?

S U M M A R Y.

Eclampsia still remains "die Krankheit der Theorien" nor does this essay claim to offer a comprehensive review of all the theories propounded. Its purpose is merely to indicate lines along which work has been done, and to adduce certain arguments in favour of James Young's explanation of the phenomena. None of the suggestions hitherto propounded have met with any general acceptance and in no case have they been based on such incontrovertible evidence as to offer a firm foundation for rational treatment and prophylaxis. Young's theory, which seems to offer the reviewer the most logical interpretation may be summarised as follows:

- (1) Eclampsia and pre-eclamptic toxaemias are due to the products of the early degeneration of a piece of placenta, the blood supply of which has been interfered with.

- (2) Infarction of the placenta may be due to mechanical detachment of the organ from the uterine wall, as in placenta praevia and in some cases of accidental haemorrhage.
- (3) Where time is allowed for the elaboration of toxic elements from the detached placenta toxæmia develops. In concealed accidental haemorrhage, therefore, toxæmia is conspicuous. Absorption of placental poisons only occurs if and whilst part of the placenta remains attached to the uterine wall.
- (4) The toxæmia commonly develops after the haemorrhage; it is therefore not the cause of bleeding in accidental haemorrhage.
- (5) The major symptoms of eclampsia are probably due to the flooding of the mother's system with the breaking-down products of liver cells (and perhaps of other tissues), which were killed some hours or days previously. A considerable interval may elapse therefore between the initiation of the toxic process and its clinical manifestation. This possibility of delayed action may explain the occurrence of post-partum eclampsia.

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