TOXÆMIAS OF PREGNANCY

Human and Veterinary

Editors

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TOXÆMIAS OF PREGNANCY

HUMAN AND VETERINARY

A Ciba Foundation Symposium

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FOREWORD

By

The Rt. Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P.

THE decision of the Ciba Foundation to publish in book form the recent symposium on the Toxæmias of Pregnancy, held under its auspices, will, I feel sure, be welcomed. The discussions, under distinguished Chairmanship, occupied five sessions and were spread over three days. The contributors included men and women of accepted international repute in the subject. These facts speak for the authenticity of the present book as a presentation of our knowledge of the subject to date.

Professor Pickering draws attention to the looseness of our accepted nomenclature in this field. He points out that the use of the term "Toxæmia of Pregnancy" gives a spurious sense of unity to the conditions actually met with and implies that these are due to the action of a chemical poison or toxin. One of the useful purposes this book may serve is to correct this impression. At the same time its perusal will show how different in their essential pathology are some of the most common expressions of a gross deviation from the physiological state of pregnancy.

Further research, biological, chemical and clinical, will doubtless clarify the position. In the meanwhile here is—I think it will be agreed—an excellent basis from which these researches may develop.

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OPENING ADDRESS

A. S. PARKES

IT falls to my lot to take the chair at the first meeting of this symposium on the toxæmias of pregnancy, and I need hardly say that I am very pleased to do so. I am always attracted by a programme which seeks to integrate man and animals. Perhaps I should say man and *other* animals, because to a biologist man is an animal, albeit a very distinctive kind of animal, and often a very peculiar one.

The symposium has another attraction; it seeks to bring different branches of knowledge to bear on a complicated problem. Toxæmia of pregnancy is certainly complicated; it crops up regularly in man and in other animals, and it is of interest to the pathologist, physiologist, biochemist, and many others, whether medical, veterinary, or just ordinary.

A glance at the programme shows that a remarkable range of knowledge and experience is being brought to bear on the problem, and we are particularly fortunate in having several distinguished workers from abroad to take part in our discussions. We may confidently expect that a most stimulating build-up of ideas will result. The great possibilities of the symposium obviously derive from the potentialities of the subject, but the fact that it is taking place is due entirely to the insight and enterprise of the organizers. Of these, the moving spirit was Professor Huggett who deserves our very best thanks for his initiative. In making the arrangements, Professor Huggett has been much helped by the Ciba Foundation who have not only provided accommodation, and helped with the office work, but have done so in a most generous and hospitable way. No doubt more will be heard of this at the end of the proceedings.

The session this afternoon opens with a paper on the physiology of pregnancy, and here there is a tragic note. This paper was to have been given by the late Professor W. H. Newton, whose early death has robbed the scientific and academic world of a most valuable life and a most endearing personality. Professor Huggett, with characteristic determination that, come what may, the symposium shall go on, has stepped into the breach himself. I will therefore call upon Professor Huggett to read his paper on the Physiological Changes in Pregnancy.

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THE PHYSIOLOGY OF PREGNANCY

A. St. G. HUGGETT

In his last (1949) publication before his untimely death less than a month ago, Newton has described pregnancy as a maternal syndrome, in which he puts several conditions which occur in animals or man, apart from the presence of a developing ovum in an enlarging uterus. These are :—

1. The inhibition of œstrus.
2. The maintenance of corpora lutea of pregnancy.
3. Maintenance of increasing weight with a loss after parturition.
4. The development of the mammary glands.
5. The appearance of the normal interpubic ligament (in mice only).
6. Mucification of the vagina (in rats and hamsters only).
7. The occurrence of parturition at a normal time.

The outstanding work of the last fifteen years of his life was the demonstration that these phenomena were controlled by the endocrine system of the body and that the largest part of this control was due to endocrinal action of the placenta, which he and others demonstrated to secrete at least three hormones, chorionic gonadotrophin, progestrone and œstrone. The evidence for this has been reviewed recently (Newton, 1949 ; Huggett, 1950), and need not be given here in detail.

There are, however, certain well-substantiated major changes in function (in addition to many minor ones) associated with normal pregnancy. The mechanism by which these changes are brought about is not always clear, nor have their physiological implications been fully worked out. One will, therefore, indicate some of the more important now, and

discuss in detail those which may have a bearing on this subject of pregnancy toxæmia.

These changes in the pregnant organisms are :—

Increase in Body Weight with Retention of Nutrients. These include water, nitrogen and mineral salts ; of these water is gravimetrically by far the most important [Dewar and Newton (Newton, 1949)].

Water and Vascular Changes. The water retention is in the extracellular water and includes 1.2 litre extra (60 per cent) in the plasma volume and 3.3 litres increase (33 per cent) in the interstitial water. This results in a rise in blood volume, a relative anæmia, and an increased heart output, but no increase in the arterial blood pressure.

Metabolic Changes. These include metabolic rate alterations, retention and storage of protein, of calcium, of phosphorus, and of mineral salts.

Respiratory Changes. There is apparently a primary over-ventilation with an acidosis without, however, any normal ketosis. There is, therefore, a compensated acidosis : which comes first, the primary over-ventilation or the base excretion is uncertain.

Histological Changes. There is a true hypertrophy of the anterior pituitary (Comte, 1898), of the suprarenal cortex, of the parathyroid and of the thyroid glands. In the thyroid new vesicles form, and in the suprarenals, the zona fasciculata is outstanding in growth.

The Endocrinal Control of Pregnancy

The cardinal point about this is that the syndrome of pregnancy, as described by Newton, is maintained by the placenta. Should the fœtus die or be destroyed experimentally and be aborted or absorbed, then the syndrome persists so long as the placenta or the chorionic portions thereof persist in the uterus. It has been shown that healthy placenta will grow after fœtal death so long as it has been fully formed and the primary layers are present, the decidua, the ectodermal trophoblast and the mesodermal substance of the chorion

(Huggett and Pritchard, 1945; Pritchard and Huggett, 1947).

The Weight Increase and Retention of Water

The outstanding alteration in the mother is the increase in weight, which amounts at term to 20.0–22.5 per cent of the weight at conception; an average increase of about 25 lb. or 11 kg. Of this, 3–4 lb. is deposited in the first trimester; 11–12 lb. in the last three months of pregnancy (Stander and Pastore, 1940; Chesley, 1944). The distribution of this weight increase is seen in Table I.

Table I

PREGNANCY: DISTRIBUTION OF WEIGHT INCREASE.

	lb.	Kg.	Percentage
Ovum (Fœtus, Placenta and Fluids)	11.0	5.0	44
Reproductive Weight:			
Uterus	2.5	2.5	10 } 22
Breasts	3.0		12 }
Net Maternal Weight Gain:			
Blood	6.0	3.8	24 } 34
Tissues	2.5		10 }
	25.0	11.3	100

The main source of this weight increase is water, as has been clearly shown by Dewar and Newton (Newton, 1949).

The water retention in pregnancy is almost entirely in the extracellular water which rises from 12 litres to 18.5 litres. Of this, 2 litres are in the ovum fœtal fluids; 1.2 litre in the plasma (60 per cent increase); and 3.3 litres in the maternal tissues (33 per cent increase).

The mechanism of this water retention is unknown. There is enlargement of the suprarenal cortex but no change in size of the posterior pituitary. The role of desoxycorticosterone in this condition has got to be assessed accurately. Further,

nothing is known of the effect of the salt changes in the diluted blood or the production of the antidiuretic hormone of the blood.

The Vascular Changes in Pregnancy

While there is an increase in cell volume and of hæmoglobin content in the total circulating blood, the 60 per cent dilution of the plasma results in a decrease in the cell volume and hæmoglobin per 100 c.c. of blood. Further, there is a decrease in the protein and electrolyte concentrations in the plasma, but a rise in sedimentation rate. The most complete analyses of the blood changes in pregnancy are due to Dieckmann and his collaborators.

Table II

PREGNANCY: BLOOD CHANGES.

Blood and Plasma Volume—Both Increase.

	Blood Vol. %	Plasma Vol. %	Hb g./100 cc.
Non Pregnant	100	100	13.9
3rd Month	116	118	13.8
6th Month	—	—	12.2
Term	123	125	12.4
8 weeks Post Partum	107	109	—

Cell Volume per 100 c.c. Blood	decreased
Hb per 100 c.c. Blood	,,
Total Cell Volume	increased
Total Hb	,,
Proteins per 100 c.c. serum	decreased
Electrolytes	,,
Viscosity	,,
Sedimentation rate	increased

Concomitant with these changes are the rise in venous pressure in the femoral vein from 6–24 cm. water pressure, increased cardiac output, but no expansion of the normal arterial blood pressure beyond the limits of the normal range.

Nitrogen Retention

It was in 1887 that Baumm first discovered that diet which

Table III

PREGNANCY: VASCULAR CHANGES.

1. Heart-Minute Volume Increased.	Output litres per min.
Before Pregnancy	3.55
During Pregnancy	4.30
During Pregnancy	5.02
Post Partum	4.40
Four months later	3.90
2. Pulse rate increased.	
3. Arterial Blood Pressure unaltered.	
4. Venous B.P. increased 6–24 cm./H_2O.	
5. Heart Work—Increases.	

yielded constancy of weight in a non-pregnant woman permitted an increase in weight if she became pregnant. Our best knowledge of this is derived from the work of Hoffström (1910), and of Hunscher and her colleagues (1935). These changes are shown in Table IV.

Table IV

PREGNANCY: NITROGEN RETENTION.

1930 Coons and Blunt—Nitrogen Balances.

Wk.	Intake g.	Output g.	Retention g.	Average
12	8.16	7.30	+0.86	
20	13.97	11.25	+2.72	
28	13.56	8.46	+5.10	2.0 g. per day
33	10.04	8.74	+1.30	
39	8.13	6.77	+1.36	

Maximum at 6th–7th Month.
Coincident P and S Maxima.

Distribution—grams.

	Total	Fœtus +fluids	Reproductive Wt.		Nett Maternal Wt.
Hoffström	310	101	51	209	158
Hunscher	511	151		360	

Coincident with this nitrogen retention there is a coincident peak of phosphorus and sulphur retention, signifying protein formation and deposition. It is significant that the peak is at the 28th week, which is three months before full term and before the age of maximal fœtal growth. It is, therefore, a maternal deposition which is occurring.

Mineral Retention

Calcium, magnesium, sodium, potassium, chlorine, sulphur and phosphorus are all retained and in excess of the fœtal needs, forming a large maternal store. These facts have been well brought out by the careful and accurate studies of Coons and Blunt (1930). Table V shows that, while there is a peak in the nitrogen and phosphorus balances at the 28th week, there is a peak in the calcium retention balance at the 39th week, and that between the 28th and 39th weeks the phosphorus retention does not drop to the same extent as the nitrogen, suggesting that it is retained for deposition with the calcium.

Table V

Ca and P Retentions in Pregnancy.

Wk.	N. Bal/Day	P. Bal/Day	Ca. Bal/Day
12	+0.86	−0.14	−0.05
20	+2.72	+0.31	+0.14
28	+5.10	+0.53	+0.11
33	+1.30	+0.21	+0.14
39	+1.36	+0.21	+0.28

There is an increase in iron retention to the extent of 1,000 mg. in complete pregnancy, of which 400 mg. goes to the fœtus and 600 mg. to the mother; that is, there is a daily retention of 3.57 mg. (Coons, 1932). In Table VI we see that the intake determines the retention per day.

At first sight it would appear that an intake of 14 mg. per day would suffice. In fact, however, many women become

anæmic on this amount, over and above the relative anæmia due to blood dilution, and an intake of 17 mg. is desirable for full prevention.

Table VI

PREGNANCY : IRON METABOLISM.

1. Intake and Retention per Day.

mg.	mg.
9.69	0.88
14.0	3.57
17.45	5.71
19.45	6.97

2. Total Fe intake in pregnancy = 1 gram.
   of this 400 mg.→Fœtus.
   600 mg.→Mother.

Although the mother may be anæmic, the infant at birth is not so. It has, however, been shown by Helen Mackay (1931) that these infants develop an anæmia while at the breast and develop infections. Strauss (1933) showed that this could be protected against by fortifying the diet of the mother with iron during pregnancy. That is, the infant can store iron if it is administered to the mother.

This is not so in the pigling, as shown by Venn, McCance and Widdowson (1947), nor in the rat (Huggett and Widdas, 1950 ; Widdas, 1949), where the main source of iron for the neonatal life appears to be the iron of the milk and not the iron which has traversed the placenta and been stored in the fœtal body.

Hammond's Theory of Partition of Nutrients

Hammond (1944) has emphasized how tissues of high metabolic activity, such as the placenta, fœtus and brain, can draw from depleted nutrients at the expense of the maternal tissues of low metabolic activity, so that in nutrient

shortage there is an actual loss of weight in the maternal tissues other than brain, placenta and fœtus (Fig. 1).

In consequence, apparently healthy infants can be born of somewhat malnourished mothers. Only in gross maternal malnutrition, as in famine, does this result in even the placenta and fœtus being under weight at term. This unproven working hypothesis is convenient as such; it is applicable to all nutrients and is of supreme importance in all considerations

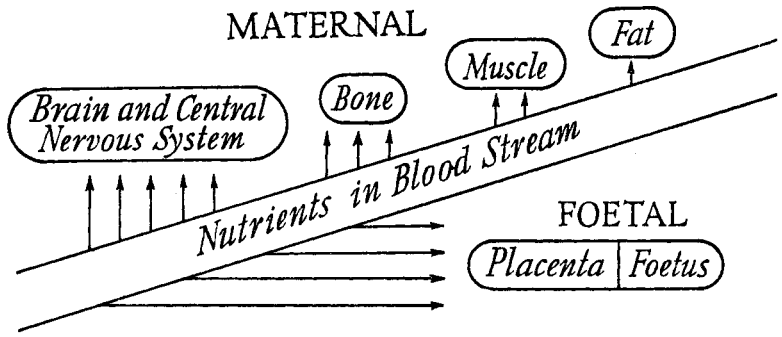

Fig. 1. Illustrating Hammond's (1944) Theory of Partition of Nutrients. The number of arrows pointing to each tissue illustrate the relative metabolic rate demands of the cells of the tissue in question.

of protein, iron, minerals, vitamins and lipotropic factors. In shortages of all these nutrients the fœtus is born healthy in most cases, whereas the mother shows impairment of function in one way or another.

Metabolic Changes in Pregnancy

The basal metabolic rate drops in the first trimester by about 4 per cent but recovers and rises by full term to about 10 per cent (Rowe and Boyd, 1932).

The carbohydrate metabolism is marked by an apparent normality. Carbohydrate is not retained in excess, but there is a decreased sugar and lowered galactose tolerance (Rowe, Gallivan and Matthews, 1931).

Fat metabolism is unaltered except in so far as there is an increase in all lipid fractions in the maternal blood (Slemons and Stander, 1923). At this stage it is important to note the work of Himsworth and Glynn. Any shortage of lipotropic factors, such as lecithin, choline or methionine, or increase in cystine, can be expected to lead to fatty infiltration of the liver. On the other hand, a grossly low protein diet with or without high fat content can be expected, arguing by analogy from rats, to lead to periportal hæmorrhagic necrosis, as found in eclampsia. Further, cystine deficiency, especially if accompanied by tocopherol shortage in rats, can lead to massive hepatic necrosis, which has a greater incidence in women than in men, especially pregnant women (Himsworth, 1947).

While there is no ketosis normally present in pregnancy, it is clear that we are dealing in this condition with an organism in which a relative shortage of nutrients by reason of fœtal priorities can easily be produced that will lead to disorders of fat and carbohydrate metabolism akin to those occurring in toxæmias not only in humans but in farm animals.

Placental Degeneration

It is important to note that in many species the placenta reaches its maximum weight some time before birth ; in sheep at the 120th day (full time 150 days) (Elliott, Hall and Huggett, 1934) ; at the 16th and 24th days in the rat (Huggett and Pritchard, 1945) and rabbit (Lochhead and Cramer, 1908) respectively. In man it slows its rate of growth (Westermark, 1926) showing degenerative changes. In the rodent it likewise shows degenerative changes but maintains a constant weight. It has therefore long been thought that products of disintegration of the placenta are possible sources of a toxin affecting the mother. One exponent of this school is C. L. Schneider, who has shown that thromboplastin is present in the placenta and that it will cause lesions resembling those of eclampsia when injected intravenously.

Similarities between Pregnancy and Lactation

In man, eclampsia is occasionally seen in the puerperium: in cattle and in sheep, ketosis tetany and extreme variations in blood calcium are seen both before and after delivery. Any consideration of toxæmia of pregnancy must therefore give consideration to similar conditions in the puerperium.

The outstanding similarities between pregnancy and the puerperium are the need for supplements of protein and calcium, best supplied as milk, together with a good plentiful balanced diet. In both conditions there is a prolonged formation of protein and in both cases there is formation of calcium and compounds.

The Anterior Pituitary, Pancreas and the Adrenal Cortex

In all these three organs there is hypertrophy and excessive activity. The anterior pituitary shows an increase in both basophils (associated with gonadotrophin formation) and in acidophil cells in pregnancy (Severinghaus, 1937). These latter cells are associated with the production of growth hormone. Cotes, Reid and Young (1949) have shown that pure growth hormone is diabetogenic and it is now known that the diabetogenic factor of the anterior pituitary lobe is identical with the growth hormone. We can therefore take note of Young's (1948) thesis that this hormone causes nitrogen retention and protein deposition. If the islets of Langerhans are adequate in response, then there is conversion of carbohydrate to protein and storage, or oxidation of the carbohydrate. If the response by the islets of Langerhans is inadequate, then neither the storage nor the oxidation can occur and the carbohydrate goes to sugar in the urine. At the same time the adrenal cortex is hypertrophied and it has been observed by Ingle, Li and Evans (1946) that the adrenocorticotropic hormone of the pituitary is diabetogenic. Now Venning (1946) has demonstrated two peaks in normal human pregnancy of excretion of urinary corticoids, which are

responsible for carbohydrate metabolism and protein storage, one at the 80th day coinciding with the excretion of gonadotrophin and one at the 220th day coinciding with the period of maximal maternal tissue deposition (Fig. 2).

Lastly, there is the work of Hench, Kendall and their colleagues at the Mayo Clinic (1949) on the relief to rheuma-

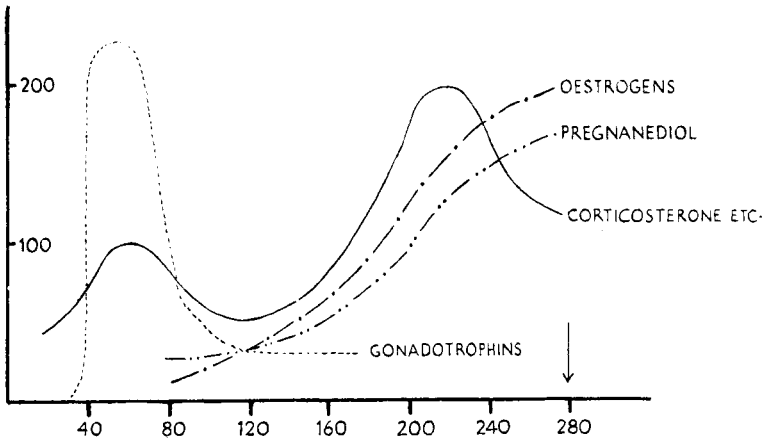

FIG. 2. After Venning (1946). Ordinates represent units of corticoids abscissæ, days of pregnancy in the human female.

toid arthritis in pregnancy, and arising out of this its relief by cortisone and A.C.T.H.

Conclusion

It would appear, therefore, that in considering the physiology of pregnancy and lactation in relation to toxæmias, we are dealing with a group of simultaneous changes in the maternal organism.

There is the retention of water and of foodstuffs, notably protein and mineral matter. There is the endocrine hypertrophy, notably the adrenal cortex and anterior lobe of the pituitary body, which correlate with the deposition or growth of maternal tissues and provide an explanation of the increased

maternal needs. At the same time the fœtus and placenta are exhibiting a high metabolic rate and appear to compete with the mother for nutrients, with success in cases of malnutrition and nutrient deficiency. Finally, the placenta in all species shows degenerative changes and slowing of growth in the last part of pregnancy, and in many species shows cessation or even loss of weight which would lead to the liberation of metabolites of potential toxicity to the mother on being absorbed into the blood stream. The tissue growth and endocrine change, the fœtal demand for nutrients and the placental necrosis and atrophy are ready for investigation.

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PATHOLOGICAL LESIONS IN THE HYPERTENSIVE TOXÆMIAS OF PREGNANCY

H. L. SHEEHAN

THE subject of this communication will be limited to the lesions of preeclampsia and eclampsia. Various other related subjects will be excluded from consideration: vomiting of late pregnancy, jaundice at delivery, hypertensive shock, accidental hæmorrhage, massive liver necrosis and so on. In addition no analysis will be made of pseudo-eclampsia due to cerebral thrombosis, embolism, glioma, etc.

Kidney

Ordinary Eclampsia

It is simplest to begin with a description of the renal lesions in ordinary eclampsia as seen in a young primipara at about term. To the naked eye the cortex is usually rather broad and pale while the medulla is congested. The appearance is not characteristic and is easily overlooked.

Microscopically, the essential lesion is seen in the glomeruli. All the glomeruli are equally affected. They are slightly enlarged, to about 1.2 times their normal diameter, and often pout out into the neck of the tubule. The capillary loops show very great variation in their size. Some are ballooned out to about twice the normal diameter; some are narrow and rather beaded. Inside the loops, the endothelial cells are rather swollen and lay down fine fibrils, sometimes under the basement membrane and sometimes as a network between the cells. These fibrils give certain of the staining reactions of collagen. The appearances are often misinterpreted as a thickening and reduplication of the basement

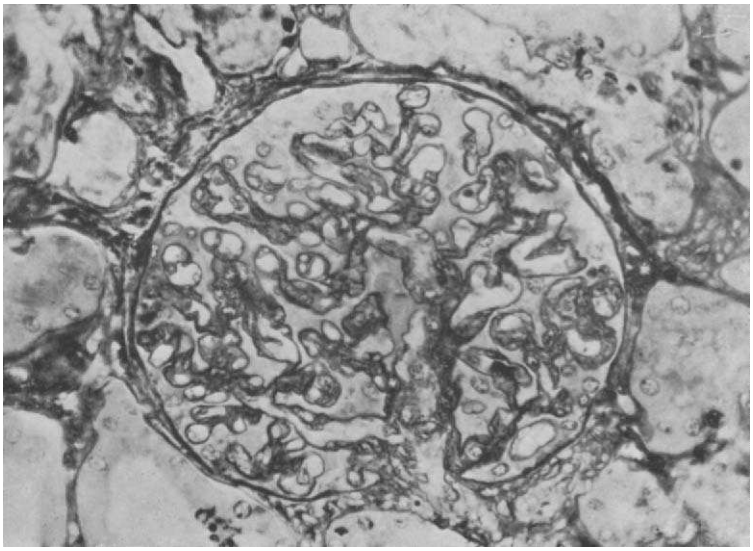

FIG. 1. Low power view of eclamptic glomerulus.

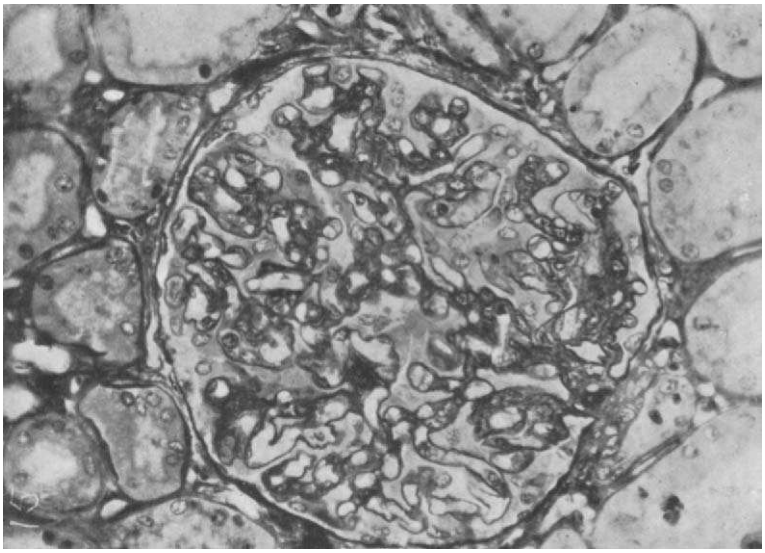

FIG. 2. Low power view of eclamptic glomerulus.

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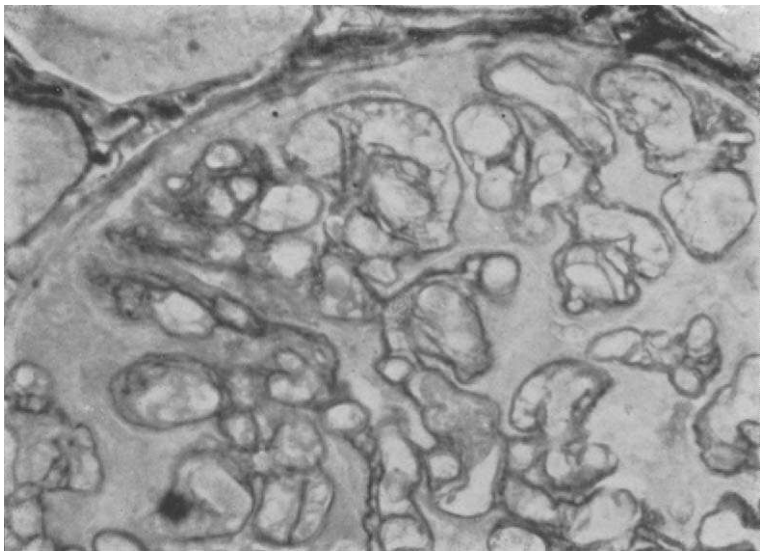

FIG. 3. Collagen stain of part of eclamptic glomerulus showing fibrils in capillary loops.

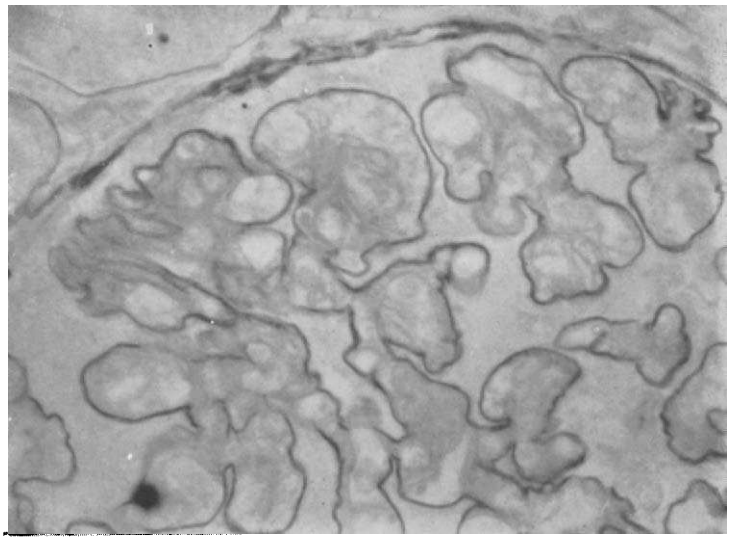

FIG. 4. Basement membrane stain of Fig. 3 showing no abnormality of basement membrane.

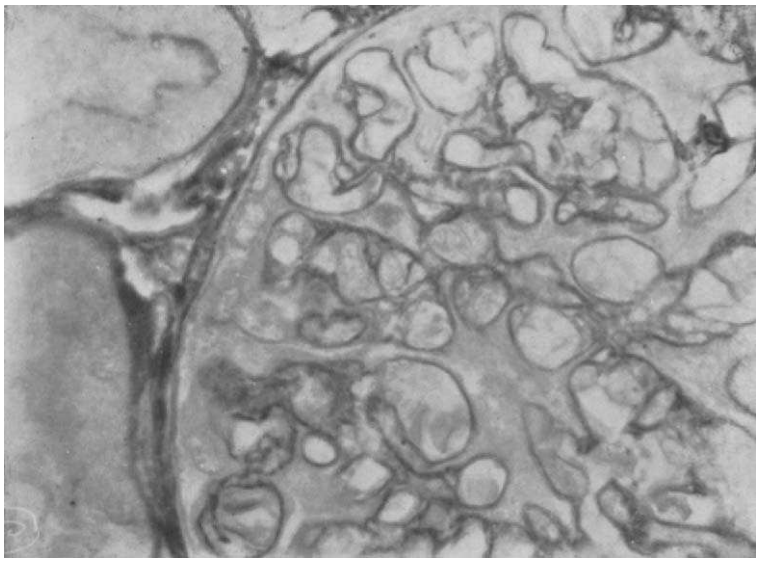

FIG. 5. Collagen stain of part of eclamptic glomerulus showing fibrils in capillary loops.

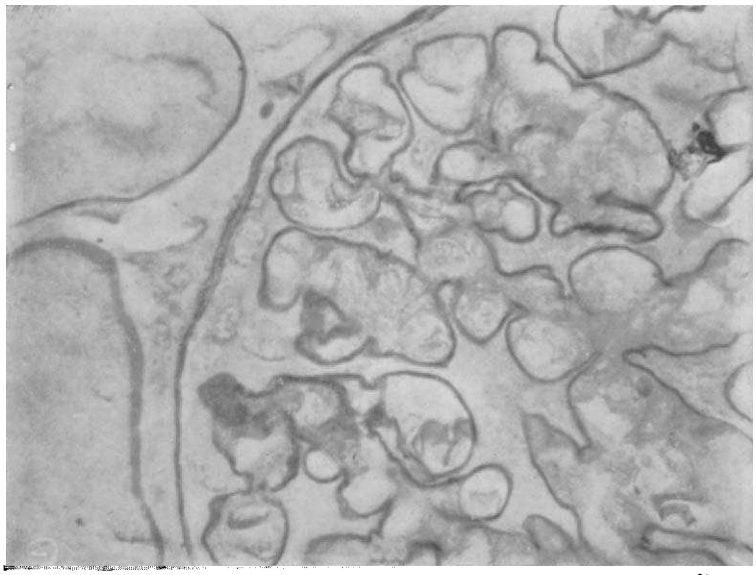

FIG. 6. Basement membrane stain of Fig. 5 showing no abnormality of basement membrane.

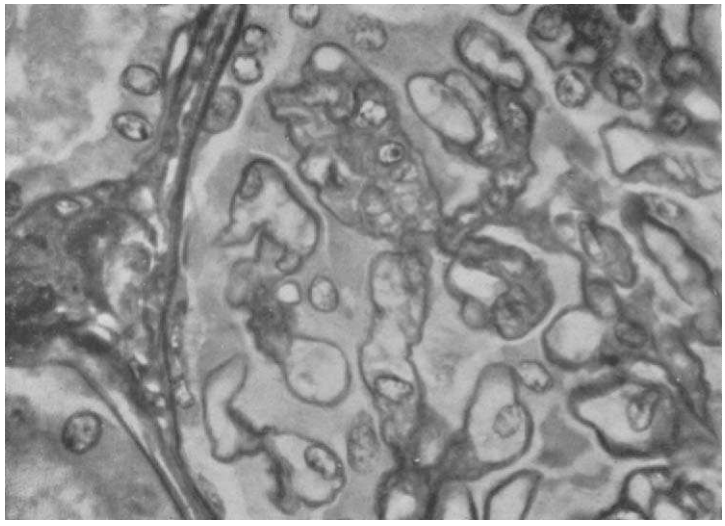

FIG. 7. Eclamptic glomerulus showing thickening of epithelium over capillary loops.

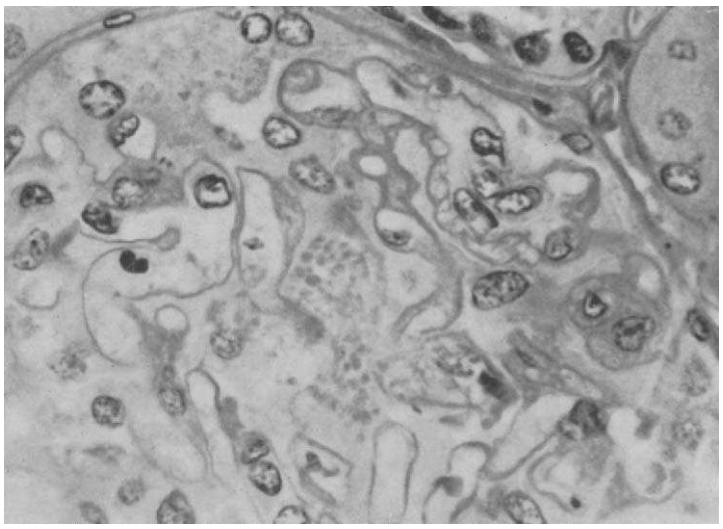

FIG. 8. Eclamptic glomerulus showing hyaline droplets in epithelium over capillary loop.

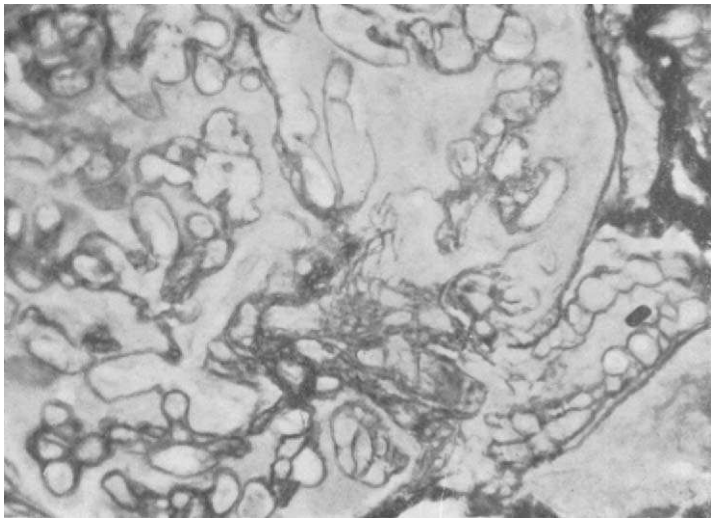

FIG. 9. Collagen stain of stalk of eclamptic glomerulus showing fibrils in main vessel.

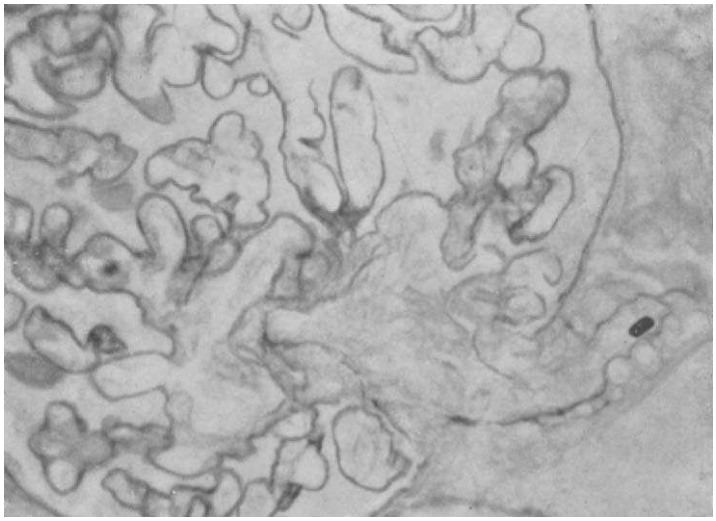

FIG. 10. Basement membrane stain of Fig. 9.

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membrane of the loops but, in fact, the basement membrane remains unchanged. The epithelial cells over the loops become greatly thickened as a result of an increase of their cytoplasm. Some of these cells contain large numbers of hyaline droplets ; others become filled with fat. The main afferent vessel in the stalk of the glomerular tuft usually shows the same endothelial fibril formation that is seen in the loop capillaries. The afferent arteriole leading to the glomerulus shows no significant change. (Figs. 1 to 10)

The first convoluted tubules have a rather flattened epithelium with an excellent brush border, and their lumen contains a fine deposit of protein from the albuminuria. Occasional first convoluted tubules have some hyaline droplet change in their cytoplasm, but there is no necrosis in an uncomplicated eclampsia. The collecting tubules often show considerable cast obstruction, sometimes of protein type but sometimes of hæmoglobin derivatives. The latter type of casts produce the standard epithelial damage locally and, if the patient lives for a few days, foci of monocytes in the boundary zone.

The glomerular lesions are of a type which could develop within a day or two, though they might certainly remain unchanged for many days. After the delivery the glomeruli return to a histological normal within about a week.

The association of albuminuria with the glomerular lesions is not surprising. The manner of production of the lesions is rather uncertain, but it seems quite possible that they may be the result of intermittent periods of spasmodic contraction of the afferent arteriole or the vessels in the glomerulus. Such a condition could be related to the oliguria and to the hypertension. The lesion of the lower segments of the tubules accounts adequately for the post-partum oliguria that occurs in some cases.

Special Types of Eclampsia

In eclampsia developing in multiparæ or elderly primiparæ, the histological changes in the glomeruli tend to be rather

exaggerated. In addition, a few of the glomeruli show a further development. An occasional loop enlarges until it comes into contact with the capsule. When this happens, the basement membrane and the endothelial fibrils in the loop swell up and become a coarse hyaline network, with staining reactions different from those of either of the original structures. The epithelium of the loop and the capsule proliferate at the site of the adhesion and form a small crescent there.

Associated with this, there is an exaggeration of the fibrillary change in the afferent vessel of the stalk, and this vessel is often dilated. The afferent arteriole outside the glomerulus frequently has small localized swellings of its internal elastic lamina like small hyaline beads. The media of the arteriole is sometimes rather hyalinized.

These differences from the lesions of ordinary eclampsia are essentially differences of degree, possibly related to the age of the patient or to the duration of the vascular disturbance.

The other variant of eclampsia is that associated with prolonged hypertension in rather older patients. These patients have much hypertrophy of the left ventricle and tend to develop eclampsia at about six months gestation, usually after a few weeks of increasing dyspnœa and of systolic blood pressure over 180 mm. Hg. The kidneys of these patients show the changes of malignant hypertension superimposed on the eclamptic lesions. There is fibrinoid necrosis of arterioles associated with various degrees of infarction of glomeruli. In addition there are foci of older hypertensive lesions in the kidneys.

Other Findings

In ordinary hypertensive toxæmia which has not culminated in eclampsia, the kidney usually shows little alteration. There are sometimes very minor glomerular lesions of the type seen in eclampsia, but the tubules appear normal.

There appears to be no real histological basis for the description of the "pregnancy kidney" in the older literature.

Furthermore it should be noted that chronic nephritis, though often diagnosed clinically, is a very rare pathological finding in patients with toxæmia of pregnancy. In the present series, pyelonephritis, which is a fairly common condition in obstetrics, did not show any obvious pathological relationship to the toxæmias.

Liver

In the liver there are almost always quite specific periportal lesions in any type of eclampsia. In most cases the existence of these lesions can be recognized with the naked eye by the presence of rather scanty tiny red petechiæ on the outer surface of the liver, though the lesions cannot usually be identified on the cut surface. In severer cases the outer surface shows numerous petechiæ, and the cut surface may show patches similar to a recent venous congestion of the liver. In very severe cases there may be obvious diffuse hæmorrhages.

Microscopically the lesions may be very numerous or so few that several slides must be examined to find a single example. They are seen as small areas of blood or fibrin beside the portal tracts, sometimes surrounding the whole tract but more commonly only on one side of it. The lesions are of two main types, focal or diffuse.

Focal Lesion

This is produced by the escape of blood constituents into the base of the columns of liver cells where they abut on the portal tract. This pushes the column of liver cells up in its sleeve of connective tissue, rather like a piston in a cylinder. The lower end of the sleeve may be distended by red blood corpuscles or by plasma which coagulates very rapidly to a mass of fibrin. The distended lower ends of these sleeves compress the blood sinuses between. Not infrequently there is necrosis and disintegration of the two or three liver cells which are in contact with the blood at the

base of the column. Less commonly the blood sinuses appear to be obstructed and there is degeneration of the liver cells further up the column. These minor necroses are clearly secondary to the hæmorrhages of blood or fibrin at the base of the columns. It should be pointed out that these focal hæmorrhagic lesions are often described rather inaccurately in the literature as capillary ectasias or thrombosis of sinuses or periportal necroses.

If the patient survives long enough, the lesions show a transient moderate infiltration with polymorphs which are subsequently replaced by large mononuclear phagocytes. The complete repair of the lesion takes about two weeks.

Diffuse Lesion

This is merely a variation on the focal lesion. The plasma or blood bursts in the same way from the sinuses into the base of the liver column. But, instead of pushing the liver cells up like a piston, it runs up inside the connective tissue sleeve of the liver column, stripping the liver cells from their support so that they form a thin band down the centre of the artificial blood channel. In many cases the blood flows up this channel and erupts into the sinuses again near the central vein, and it seems probable that this extravascular circulation may continue to function for some time. The channel inside the connective tissue sleeve of the liver columns may contain red blood corpuscles, or may carry only plasma. In rather striking contrast to the condition in the focal lesion, the plasma does not coagulate, so that fibrin is practically never seen in the diffuse lesion. The column of liver cells down the centre shrinks in width and the cells always show early necrobiotic changes, but the cells do not separate from each other so that the continuity of the column is maintained.

This diffuse lesion is often very extensive and is seen particularly in the cases where the cut surface of the liver shows obvious hæmorrhages to the naked eye. It appears to indicate a very severe eclampsia which is always fatal, so that late stages of it have not been observed.

Significance

It seems probable that the majority of the focal lesions which are seen in the liver in fatal eclampsia have occurred during the last day or so. They are certainly not produced by the eclamptic convulsions, because they are found in other severe toxæmias of the same general group, such as "eclampsia without fits." Their extent is not obviously related to the severity of the preceding symptoms either of the preeclampsia or of the eclampsia, and they are occasionally found in patients who die suddenly at delivery without any previous indication of a toxæmia. Nevertheless they are related to the mortality of eclampsia; they are found in nearly all patients who die of this condition but in only about a quarter of the patients who recover from the eclampsia itself and die of other causes in the puerperium.

Brain

In about one third of the fatal cases of eclampsia, there are cerebral lesions which are recognizable to the naked eye. There may be a single hæmorrhage in the pons, the basal ganglia, or in the subcortical white matter; such a hæmorrhage may be quite small or may be very massive and clearly the cause of death. (These cerebral hæmorrhages are very striking phenomena in view of the youth of the patients.) Sometimes there may be small areas of early softening in the basal ganglia, but the identification of these lesions is often rather uncertain. Tiny capillary hæmorrhages are sometimes found in the cortical grey matter, usually confined to one part of the cortex. This lesion is of considerable interest in that it indicates that there has been a vascular disturbance in the cortex of a patient who has had convulsions. Microscopically the cerebral capillaries not infrequently contain peculiarly colloid-looking thrombi, and their walls may show fibrinoid or fatty changes. A naked-eye appearance of cerebral œdema is not seen unless the post-mortem has been delayed a couple of hours or more so that autolytic changes have occurred.

However, the subject has not been investigated by weighing and desiccation so that no definite statement can be made on this point.

Other Organs

These will only be mentioned briefly.

The lungs usually show multiple tiny areas of hæmorrhage and œdema, and sometimes an early bronchopneumonia. The heart sometimes has subendocardial hæmorrhage on the left side of the interventricular septum, of the type seen in shock or in acute cerebral disturbances. There may be areas of hæmorrhage or necrosis in the suprarenals or, less commonly, in the pancreas, but these lesions are not specific and are seen in patients without toxæmia. The retinal lesions are more easily studied by an ophthalmologist than by the pathologist.

Œdema of the legs and body is seen in very many of the patients with preeclampsia, and the eclamptic patients often have a peculiar œdema of the maxillary region. Sometimes there is a moderate œdema of the parametrium, and less commonly a gross œdema of the retroperitoneal tissues.

Conclusions

Leaving out the unsolved problem of the œdema in these cases, all the remaining pathological lesions appear to be evidence of a type of vascular disturbance which is peculiar to the hypertensive toxæmias of late pregnancy. The lesions themselves can easily be linked up with many of the prominent symptoms such as albuminuria, oliguria, convulsions and coma, or the terminal slight hæmolytic jaundice of some patients. But the pathogenesis of the fundamental vascular disturbance remains obscure.

TOXÆMIAS OF PREGNANCY: HUMAN AND VETERINARY
Edited by JOHN HAMMOND, F. J. BROWNE and G. E. W. WOLSTENHOLME
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THE TOXÆMIAS OF PREGNANCY IN WOMEN

G. W. THEOBALD

I INTEND to limit my contribution to the presentation of clinical facts concerning the pregnancy "toxæmias" in women, which I do not think can be challenged. I shall not mention the "pernicious vomiting" of pregnancy which is now but seldom encountered or acute yellow atrophy of the liver. Neither do I propose to refer to the hypothesis I have advanced, although I confess that I am more convinced than ever that it alone can offer an explanation of all the known facts, which fall conveniently into four main groups :—

(1) Geographical and other factors external to pregnancy which have a marked influence on the incidence of eclampsia.
(2) Facts relating to hypertension, albuminuria and œdema.
(3) Observations on the pathological changes, particularly in the liver and placenta, which may be associated with pregnancy.
(4) Clinical facts about eclampsia.

Part I

In 1930 (*a*) I drew attention to the geographical incidence of eclampsia which I myself had observed on my travels, and at a later date our distinguished visitor Professor Dieckmann (1938) collected figures from all over the world which substantiated this fact.

Between the years 1926–1929 Bangkok was a city of some 700,000 inhabitants and I was in charge of the largest obstetric service in the city, larger than all the other obstetric services

in the country put together. During these three years I saw but eight cases of eclampsia, and only five other cases of severe pregnancy toxæmia. During the next year my successor Professor Carl Bachman reported eight cases of eclampsia. Such recent figures as I have been able to obtain suggest that the eclampsia rate in Siam is now very much higher than it was—and this I prognosticated to my students when I was there.

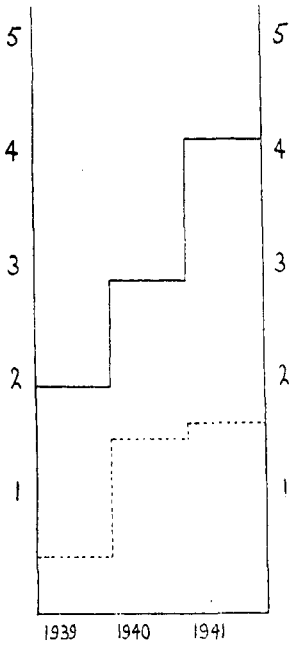

FIG. 1. This figure illustrates the more than 200 per cent rise in the incidence of the pregnancy toxæmias in the Hong Kong hospitals that occurred between the years 1939–1941. The incidence of beri-beri also rose and gross malnutrition was prevalent in the island.

In Ceylon, the other eastern country in which I have worked, the eclampsia rate is probably the highest in the world. Wickramasuriya (1941) showed that the incidence of eclampsia in Ceylon was 28 per thousand live births in 1935, and that this figure had fallen to 16.5 by 1939. He showed that eclampsia occurred much more frequently in patients who suffered from chronic malaria and/or ankylostomiasis. The interesting point is that the meteorological conditions, mode of life, and the standards of hygiene and sanitation are extremely similar in those two countries.

King and Ride (1945) (Fig. 1) reported that more than twice as many patients suffering from the pregnancy toxæmias were admitted to the Hong Kong hospitals in 1941 as there were in 1939. They stated that gross malnutrition was rife in the colony but, for various reasons, were disposed to attribute this increase in the pregnancy toxæmias to deficiency of Vitamin B.1 in the diet. This explanation cannot be accepted for

the very simple and adequate reason that the incidence of beri-beri was very high in Bangkok, where the incidence of the pregnancy toxæmias was low, whereas there is practically no beri-beri in Ceylon where the incidence of the pregnancy toxæmias is so high.

Prof. E. C. Crichton (1947) has drawn attention to the marked variations in the incidence of eclampsia in different areas of South Africa.

It is well known that there was a remarkable fall in the incidence of eclampsia in the cities of Austria and Germany during the latter half of the 1914–1918 war. There is also some evidence that there was a considerable increase in the incidence of eclampsia in Russia during the same period of time (Westmann, 1935; Varo, 1920; Hermann, 1929; Gessner, 1929).

During the second world war the incidence of pre-eclampsia and eclampsia was more than halved in Brussels, Leyden, Rotterdam, and in the whole of Western Holland, where the daily wartime intake for pregnant women was below 800 calories. Nearly all the authors in occupied countries have reported a marked increase in the incidence of pre-eclampsia and eclampsia since food again became more plentiful (Snoeck and Hubinont, 1947; Holmer, 1947; Ten Berge, 1947).

Finally, let us turn to our own islands. There are no figures relating to the incidence of eclampsia, and we must perforce be content with mortality rates. It is, however, instructive to note that well over 100 years ago the Rotunda Hospital reported an incidence of 30 cases of eclampsia in 16,000 confinements, a considerably lower incidence than obtains today in spite of ante-natal care (Dieckmann, 1941).

No comparable specific figures for eclampsia were published by the Registrar General for England and Wales until 1939 or by the Registrar General for Scotland until 1941. I therefore show graphs indicating the combined mortality rates for all the pregnancy toxæmias, excluding only those for pernicious vomiting. It is clear that between the years 1911 and 1930 the mortality rates for eclampsia and the

albuminuria of pregnancy were remarkably constant and were unaffected by the 1914–18 war (Fig. 2). From 1935 to 1940 the combined mortality rate for the pregnancy toxæmias remained but little altered until 1940, when the first significant drop occurred, and since 1942 the fall has been progressive except during the years 1945 and 1946. The combined mortality rate in 1948 was less than half that for 1940 (Fig. 3).

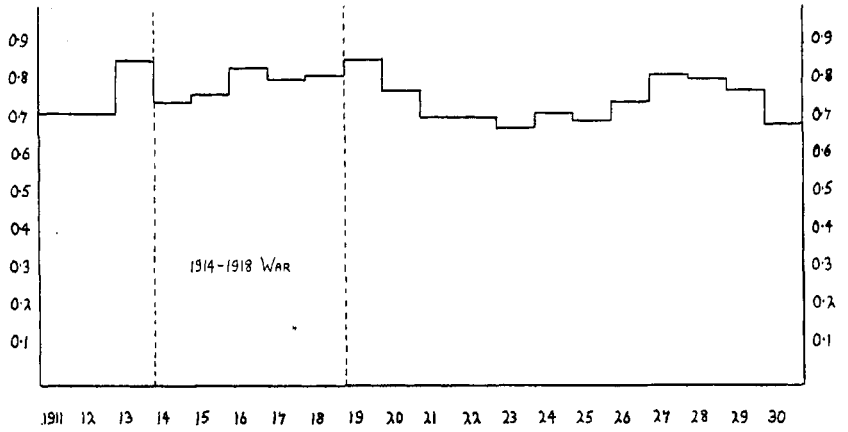

FIG. 2. This graph illustrates the fact that the mortality rate for puerperal "albuminuria and convulsions" in England and Wales remained almost unaltered in spite of ante-natal care between the years 1911 and 1930. It will be noticed that the rate rose slightly during the 1914–1918 war.

The mortality rates for the pregnancy toxæmias were consistently higher in Scotland than in England and Wales, but since 1942 they have fallen dramatically. The mortality rates for "albuminuria and convulsions" (which includes all the pregnancy toxæmias except pernicious vomiting and possibly acute yellow atrophy of the liver) per 1,000 live births were 1.12 in 1911, 1.03 in 1941 and 0.23 in 1948 (Fig. 4).

This fall in the mortality rates both in England and Wales and in Scotland is all the more remarkable because the figures for the latter years include a considerably higher proportion

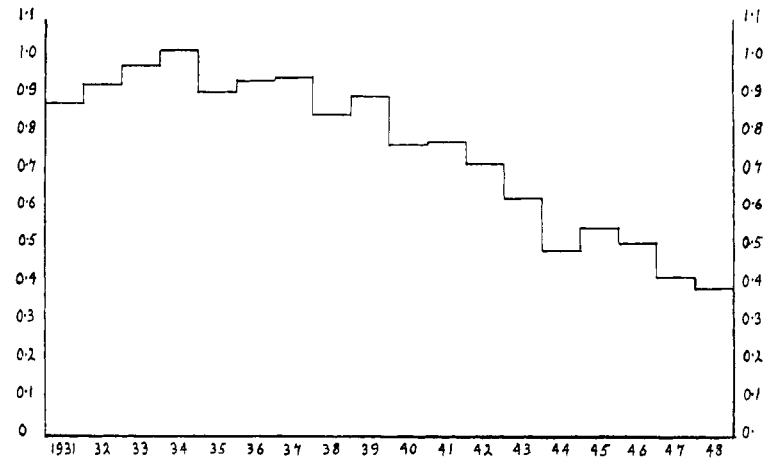

FIG. 3. This graph illustrates the remarkable fall in the combined mortality rates for the pregnancy toxæmias which has occurred in England and Wales since 1939.

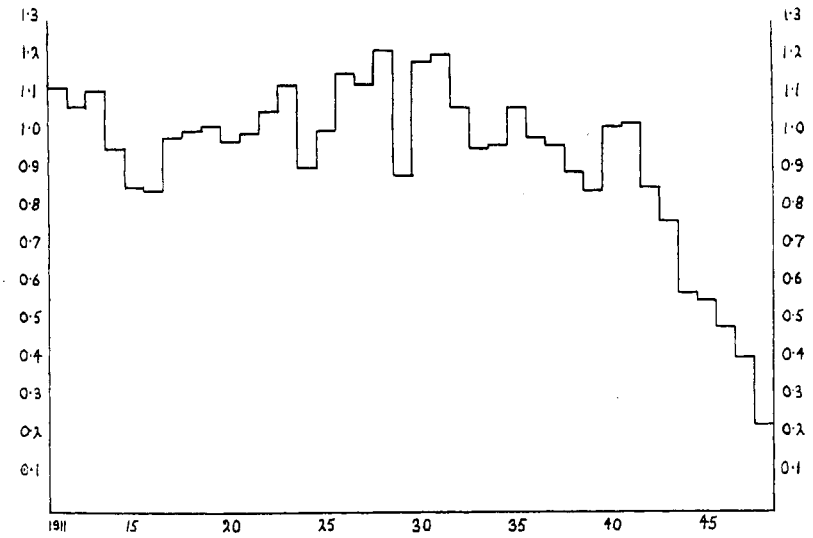

FIG. 4. This graph illustrates the dramatic and continuous fall in the combined mortality rates for the pregnancy toxæmias which has occurred in Scotland since 1941.

of primigravidæ, and what is more important, elderly primigravidæ, and this fact would be expected to operate in the opposite direction.

Finally I would stress the fact that chronic malaria, ankylostomiasis and, to a lesser degree, diabetes are prone to cause a pregnant woman to suffer from the pregnancy toxæmias.

A geographical incidence varying between 0 and 28 per thousand live births, an incidence which alters more than 100 per cent because of war conditions ; an incidence so affected by co-existent disease—these facts challenge attention and demand an explanation. My colleagues regard this striking evidence as so contradictory as to be valueless, whereas I suggest that it conforms to a strict understandable pattern and provides the most important key to our understanding of eclampsia.

Part II. Hypertension, Albuminuria and Œdema

Hypertension

The arbitrary standard I have chosen to denote hypertension is a blood pressure of, or above 140/90 mm. Hg., occurring on at least two separate occasions during the course of the pregnancy. There is some divergence of opinion as to whether the diastolic pressure should be taken when the note changes—or when it disappears. There may in consequence be a variation of up to 10 mm. Hg. in the published diastolic figures—and this is important.

I would ask that when we speak of hypertension—we confine ourselves to hypertension, and when we speak of hypertension in association with albuminuria we should bear this distinction in mind. No advances can be made if we confuse our terms and it is important to eschew preconceived ideas, fancies, and arbitrary divisions, whether of degree or time of onset. Until more information is available it must

be assumed that the general level of the blood pressure is the measure of angiospasm present in the body, for there is no warrant for the assumption that localized spasm may affect a limited number of blood vessels supplying specific organs, such as the kidneys.

During the last three years I have treated 916 cases of hypertension in Bradford. On no occasion was labour induced before term. One patient had one fit immediately after delivery, but no albumin was discovered in her urine. In this group there were 28 stillbirths and 15 neonatal deaths in hospital which gives an uncorrected gross mortality rate of 4.7 per cent. Surprisingly enough the prematurity, stillbirth and neonatal mortality rates were lower for patients showing hypertension than for the rest of the patients delivered in hospital who showed no hypertension (Figs. 5, 6, 7, 8). The average weight of the babies born to hypertensive patients whose blood pressure exceeded 160 mm. Hg. during the year 1947–48 was 7 lb. 4 oz. (Fig. 7).

All these patients were kept on a high protein diet supplemented with various minerals and vitamins. They all performed daily exercises in bed. It will be observed that the great majority of the patients admitted with hypertension did not develop albuminuria. The patients have been grouped in degrees of severity of the hypertension, each group exceeding the preceding by 10 mm. Hg., and not until the blood pressure reached or exceeded 190 mm. Hg. did the majority of patients classified to a group show albuminuria (Fig. 5). It is important to recognize that the blood pressure in hypertensive patients may vary considerably during the day, even while they are at rest in bed.

Hypertensive Patients and the Puerperium. It is common for the blood pressure to fall immediately after delivery. It then usually rises again and may subsequently drop rapidly to a normal level, or take several days, weeks or even months to do so. It may continue to rise after delivery and attain a higher level than at any time during pregnancy or labour.

	BOOKED PATIENTS.															
	Systolic B.P. 140–149 mm.Hg.		Systolic B.P. 150–159 mm.Hg.		Systolic B.P. 160–169 mm.Hg.		Systolic B.P. 170–179 mm.Hg.		Systolic B.P. 180–189 mm.Hg.		Systolic B.P. 190+ mm.Hg.		Emergency Admissions with Hypertension		Total Admissions	
	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.
Total No. . .	113	11 8.9%	143	14 8.9%	49	22 30%	31	14 31%	21	11 34%	7	13 65%	27	36	391	121
Maternal Deaths . .	1	0	1	0	0	0	0	0	0	0	0	0	0	1	2	1
Stillbirths .	3	0	5	2	2	0	2	0	0	3	1	5	1	9	14	19
Premature Births . .	6	1	6	4	6	3	4	1	0	1	2	7	2	10	26	27
Infant deaths in Hospital	2	0	0	4	2	1	1	1	0	1	0	1	2	2	7	10

FIG. 5. This table illustrates the fact that hypertension, whether it pre-exists the pregnancy and is exacerbated by it, or occurs for the first time during the pregnancy, is three times more common than hypertension associated with albuminuria. It must however be noted that although the stillbirth, premature birth, and neonatal death rates are so much higher when the hypertension is associated with albuminuria, 9 out of the 19 stillbirths and 10 of the 27 premature births occurred in the 36 emergency admissions.

ST. LUKE'S MATERNITY HOSPITAL
BRADFORD

Cases of Hypertension and Hypertension + Albuminuria

1947 and 1948

	Systolic B.P. 140–149 mm. Hg.		Systolic B.P. 150–159 mm. Hg.		Systolic B.P. 160–169 mm. Hg.		Systolic B.P. 170–179 mm. Hg.		Systolic B.P. 180–189 mm. Hg.		Systolic B.P. 190 + mm. Hg.		Emergency Admission with Hypertension		Total Admission	
	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.	Without Alb.	With Alb.
No. of Cases	207	24	242	27	108	38	47	37	25	19	8	18	32	67	669	230
No. of Stillbirths	6	1	7	2	3	3	2	4	0	3	1	6	1	13	20	32
No. of Premature Births	10	3	11	5	12	6	5	8	0	2	2	10	2	16	42	50
No. of Infant Deaths In Hospital	2	0	2	4	3	3	1	1	0	1	0	3	2	3	10	15

Hypertension = 140/90 mm. Hg. in above on at least 2 occasions.

FIG. 6. This table is similar to that shown in Fig. 5.—but shows the results for two years. It is not without interest that in the group showing hypertension between 180 and 189 mm. Hg. there was no stillbirth, no premature birth, and no infant death.

ST. LUKE'S MATERNITY HOSPITAL
BRADFORD

Combined Figures for
1947 1948 1949

CASES OF HYPERTENSION

(Blood Pressure of or exceeding 140/90 mm. Hg. on at least 2 occasions)

Total No. of cases	Induction of labour	Stillbirths	Infant deaths in Hospital	Total unconnected foetal mortality
919	0	27	14	41 or 4·5 per cent
HYPERTENSION + ALBUMINURIA				
101		53	19	72 or 18 per cent

Average weight of babies born to mothers with Blood Pressure of or exceeding 160 mm. Hg = 7 lb. 4 oz.

Average weight of babies born to mothers with B.P. of or exceeding 160 mm. Hg. + Albuminuria = 6 lb. 11 oz.

FIG. 7. This table is self explanatory and makes clear the markedly increased fœtal wastage when hypertension is associated with albuminuria.

	"Hospital" Incidence	Incidence in cases of Hypertension	Incidence in cases of Hypertension associated with Albuminuria
Stillbirths . .	3.6 per cent	3.6 per cent	15.7 per cent
Premature Births . .	7.1 per cent	6.6 per cent	22.3 per cent
Infant deaths in Hospital .	3.3 per cent	1.7 per cent	8.3 per cent

FIG. 8. This table again accentuates the significant difference that the association of albuminuria with hypertension makes to the loss of fœtal life. The "hospital incidence" is the incidence occurring in patients who manifested neither hypertension nor albuminuria during the course of pregnancy and labour.

The most interesting and little recognized, although by no means rare fact is that a blood pressure which has been normal or but little elevated throughout pregnancy and labour may suddenly reach a level of over 200 mm. Hg. at any time between the third and eighth days of the puerperium (Fig. 9).

B.S. *æt.* 43. Primigravida. Booked at 32 week—B.P. 158/90 mm. Hg. B.P. settled to 140/85 mm. Hg. and remained fairly constant. Delivered ♂ 7 lb. 8 oz., on 22.1.49. B.P. suddenly rose to 210/110 mm. Hg., on fifth day of puerperium and then gradually fell to 118/76 mm. Hg. and was at this level when she was discharged. Four months later her B.P. was 220/140 mm. Hg. and it has since persisted at a high level. Her blood urea was normal, and no casts were found in her urine.

Albuminuria

Albuminuria may occur as the result of :—

Mechanical factors.
Lowered osmotic pressure of the plasma colloids.
Altered permeability of the glomerular tufts.
Alterations in the molecular sizes of the plasma proteins.
Electrolytic changes in the blood plasma.
Pathological changes in the kidneys.

Albumin and casts in the urine may be associated with large rapidly growing ovarian tumours and disappear after they are removed (Theobald, 1930*b*). If the pressure in the inferior vena cava above the points of entry of the renal veins exceeds 10 mm. Hg., albumin and red blood corpuscles are likely to appear in the urine and retention of chlorides and phosphates might occur (Theobald, 1931). Albuminuria is easily provoked in both men and women by maintaining them in the lordotic position. The albuminuria so provoked comes from both kidneys (Theobald, 1931 ; Bull, 1948).

It is a remarkable fact that small amounts of albumin are more likely to be discovered in the urines of healthy college girls than in those of women less than 24 weeks pregnant (Theobald, 1932*a*).

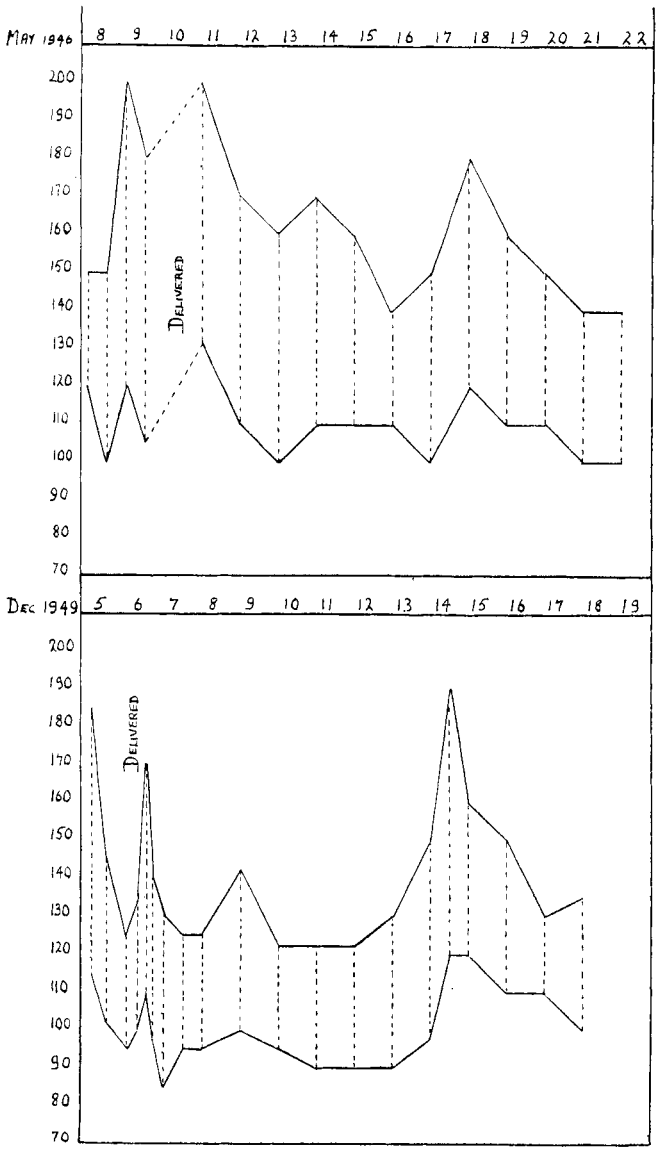

FIG. 9. In her first pregnancy this patient suffered from eclampsia. A marked rise of blood pressure on the 8th day of her puerperium is shown in the upper tracing. A similar rise occurred on the 8th day of her puerperium following the delivery of her second child (lower tracing). Her blood pressure during her second pregnancy had remained at a level of about 140 mm. Hg. The upper line in each tracing represents the systolic blood pressure and is linked by vertical hatched lines to the lower which represents the diastolic blood pressure, both being expressed in mm. Hg.

The onset of albuminuria during pregnancy may occur apart from either œdema or hypertension. I show a slide of a patient who showed 0.4 gm. per cent of albumin (four parts in Esbach) when her blood pressure was 110/66 mm. Hg. This disappeared from her urine while in the ward although her blood pressure rose to 130/72 mm. Hg. The albuminuria recurred when she went home for Christmas (Fig. 10).

Albuminuria may appear, disappear, and then after an interval appear again while the patient is kept under close observation in the ante-natal ward. I can show records of an eclamptic patient who had over 2 gm. per cent (20 parts in Esbach) of albumin in the urine one day and none the next. It then reappeared and more slowly disappeared from the urine. This fact suggests extra-renal rather than renal causes for the albuminuria.

If an in-dwelling catheter is left in the bladder for three or four days and every specimen of urine collected at four-hourly intervals is put up in an Esbach's tube, rapidly fluctuating amounts of albumin may be discovered in the various specimens.

Whereas it is true that if the blood pressure equals or exceeds 180 mm. Hg. albumin is likely to be present in the urine, it is equally true that the great majority of pregnant women who suffer from albuminuria do not show extreme elevations of the blood pressure, and that the blood pressure of eclamptic women may never exceed 140 mm. Hg.

Pregnant women suffering from chronic malaria or ankylostomiasis, are very prone to suffer from albuminuria, and this is true to a lesser degree of diabetes.

Œdema

Some degree of water retention is almost invariably associated with the third trimester of pregnancy. The weight of the pregnant uterus causes water to be retained, particularly in the lower extremities by day, which is excreted by night so that the N/D ratio of urine secretion may exceed unity. It

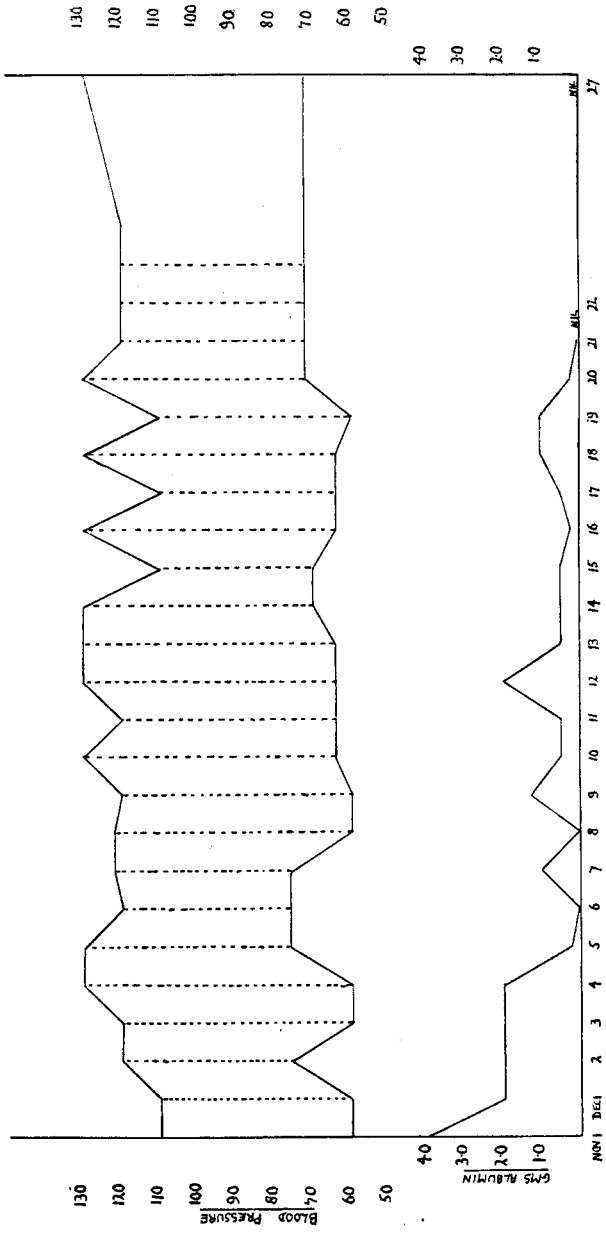

FIG. 10. The upper tracings linked together by vertical hatched lines show the systolic and diastolic blood pressures expressed in mm. Hg. The lower tracing shows the amount of albumin in the urine expressed in parts per thousand. (*Esbach.*)

is generally agreed that œdema confined to the feet and ankles which disappears with rest in bed, is of no significance.

Water may be retained (*a*) in the circulation, (*b*) in the tissue spaces and (*c*) in the cells themselves. The factors leading to water retention may be either mechanical or a relative increase in the osmotic pressure in the tissues. In either of these cases the water would not be presented to the kidneys for excretion.

Alternatively, and possibly coincidentally, some anti-diuretic factor might prevent the excretion of the water presented to the kidneys.

If œdema of the lower extremities persists for several weeks during pregnancy, it disappears after delivery so long as the patient remains in bed. The œdema of the lower extremities tends to recur when she gets up, and may persist for weeks.

Although œdema may not be observed in cases of either pre-eclampsia or eclampsia, it may be the first noted sign of the onset of eclampsia.

Severe œdema may occur apart from any toxæmic symptoms :—

B.R. *æt.* 40. Gravida 8, was admitted with œdema, a blood pressure varying between 140/70–160/80 mm. Hg. and 0.025 gm. per cent of albumin in the urine. On the 8.11.47, four days later, there was no albumin in the urine, the blood pressure varied between 130/70—150/80 mm. Hg., and the vulva was the size of a balloon, from which approximately 0.5 litre of fluid was withdrawn on two separate occasions. She was delivered of twins on the 12.11.49 and the following day her output exceeded the intake by 82 oz. or 2.3 litres.

Œdema may manifest itself and disappear again without any significant alteration occurring in the volume of the body fluids. This shift of the water in the tissues is remarkable and may occur apart from any shift in the packed blood cell volume.

I would again stress the fact that œdema, amounting to anasarca, is very common in pregnancy associated with either chronic malaria or ankylostomiasis. It should be particularly

noted that neither malaria nor ankylostomiasis is commonly associated with œdema—except in pregnant women.

Lastly the water diuresis which begins on the first or second day after delivery may be very marked. I have already mentioned a case where the output exceeded the intake by 2.3 litres in the day after delivery. In another case (A.T.), the output exceeded the intake during the second to the fifth day of the puerperium by 238 oz., or 6.7 litres.

Hypertension, Albuminuria and Œdema

The association of hypertension and albuminuria, whether or not œdema is present, is of more serious importance than when either state is present singly. Indeed a blood pressure of 150/90 mm. Hg. associated with albuminuria is probably of more significance than a blood pressure of 200/110 mm. Hg. without albuminuria. Nevertheless, pregnancy was not terminated except in the rare cases which demonstrated changes in the retina.

The woman may continue with her pregnancy for several weeks, in spite of a high blood pressure, marked albuminuria and widespread œdema and give birth to a living child.

The fœtus frequently dies *in utero*, with or without an immediate subsequent amelioration of the patient's condition (Figs. 5, 6, 7, 8). The death of the fœtus may or may not be associated with major or minor degrees of *abruptio placentæ*.

Retinal changes occasionally (very rarely) make it necessary to terminate the pregnancy.

The woman may develop eclampsia and four of the 401 cases suffered from a mild attack. In my experience, however, it is not the intensity of the hypertension, or the albuminuria or the œdema which precipitates the crisis, but the three following symptoms (1) headache; (2) vomiting; and (3) abdominal pain.

The following brief histories illustrate some of the points I have raised :—

N.D. æt. 38. Gravida IV.

Albuminuria when 17 years old. Was found to have hypertension and albuminuria six years ago at a routine medical examination.

1944. Hypertension, albuminuria, induction of labour, infant death.

1947. Hypertension, albuminuria. Living child.

1948. Hypertension, albuminuria. Living child.

1949. Booked at 22nd week. B.P. 180/106 mm. Hg. Albuminuria. Admitted for 17 days, 30th August–17th September. B.P. remained unaltered. Readmitted 2.10.49. B.P. 170/120 mm. Hg. fell at end of month to 140/90 mm. Hg.

Readmitted 1.12.49. B.P. 170/108 mm. Hg.

22.12.49. B.P. 140/96 mm. Hg., Alb. one part in Esbach.

General condition good. B.P. did not subsequently rise above this level. Delivered of healthy child.

P.M.W. æt. 19. Gravida I.

Booked *13.1.48.* B.P. 160/85 mm. Hg. Œdema of legs and thighs ++. Alb. nil.

16.1.48. Albumin 0.9 gm. per cent (nine parts in Esbach).

2.2.48. B.P. 155/95 mm. Hg. Alb. ++.

9.2.48. B.P. 145/95 mm. Hg. No albumin. (Carefully checked.)

12.2.48. Alb. ++. Took her own discharge and subsequently refused to come into hospital.

Eclampsia (1)

3.4.48. B.P. 200/130 mm. Hg. Three fits. Alb. +++.

Eclampsia (2)

9.4.48. Four fits—then almost continuous fits controlled by 0.5 gm. Pentothal injected intravenously. 3.2 gm. per cent of albumin (32 parts).

10.4.48. Delivery ♂ 3 lb. 9 oz. Did very well. Œdema so bad she could not open her eyes. B.P. 170/110 mm. Hg. Blood urea 30 mg. per cent. Hyaline and granular casts.

18.4.48. 0.95 gm. per cent of albumin (9.5 parts). Is very well—baby thriving.

4.1.50. B.P. 165/110 mm. Hg. Cloud of albumin but no casts in urine. Both mother and baby very well.

V.M. æt. 23. Gravida I.

Admitted *4.2.48.* Hypertension, albuminuria, œdema of ankles and eyelids. B.P. 185/135 mm. Hg. Albumin 2 gm. per cent (20 parts).

5.2.48. Occipital headache, epigastric pain, vomiting.
Between 5.2.48 and 29.2.48. B.P. varied between 220/140 and 170/110 mm. Hg. *Urine.* Albumin varied between 2 gm. and 0.4 gm. per cent (20 and four parts in Esbach).
23.2.48. Eyegrounds. Still no hæmorrhages, no œdema, no exudate, but arterio-venous crossings show very clear evidence of the continued effects of hypertension.
24.2.48. B.P. 210/120 mm. Hg. Albumin 0.8 gm. per cent (eight parts in Esbach). Blood urea 60 mg. per cent. Granular casts and red blood cells in urine. Hysterotomy under local anæsthesia. ♂ 3 lb. died on fourth day. Question of sterilization arose.
On discharge B.P. 130/80 mm. Hg. Albumin 0.025 gm. per cent.
10.4.48. B.P. 130/70 mm. Hg.
10.7.48. B.P. 135/70 mm. Hg. } No albumin in urine.
6.8.48. B.P. 140/80 mm. Hg. Pregnant 16 weeks.

Second Pregnancy

At 28 weeks. B.P. 150/70 mm. Hg.
5.11.48. Admitted to hospital. B.P. varied between 140/70 and 150/80 mm. Hg. No albumin discovered in the urine.
6.12.48. Condition of fundi satisfactory.
23.1.49. Delivery ♀ 5 lb. 5 oz. Throve.
22.12.49. B.P. 140/78–82 mm. Hg. Neither albumin nor casts in urine. Baby thriving.

H.T. æt. 38. Gravida II. Three months in ante-natal ward. Hypertension, albuminuria, anasarca, hydramnios, diabetes.
19.8.49. Admitted.
August. B.P. level 120/80–140/90 mm. Hg., reached 160/100 mm. Hg. 30.8.49. Albumin disappeared from urine 25.8.49. Œdema +.
September. B.P. level 140/80–160/120 mm. Hg., reached 170/120 mm. Hg. 30.9.49. Albuminuria recurred 14.9.49. 0.25 gm. per cent.
October. B.P. level 150/90 → 165/120 mm. Hg. Albumin up to 0.8 gm. per cent (eight parts in Esbach). Œdema of legs, thighs, abdominal wall, back, anasarca. Frequent tappings of amniotic fluid caused temporary relief of acute discomfort.
November. B.P. 180/110 mm. Hg. 0.7 gm. per cent of albumin in urine. Anasarca +.

4.11.49. Cæsarean section. Baby throve. Diuresis second–fifth day of puerperium during which output exceeded intake by 238 oz., or 6.3 litres.
15.12.49. B.P. 104/70 mm. Hg. 0.1 per cent albumin in urine.

N.B. æt. 36. First pregnancy.
Eclampsia at 32nd week of pregnancy. Stillbirth.
Second pregnancy. Intrauterine death at 32nd week.
Third pregnancy (1949). Severe pre-eclampsia at 34th week.
19.10.49. Hysterotomy. Baby died third day.
25.11.49. B.P. 140/70 mm. Hg. No albumin in urine.

A.H. 1935. First pregnancy. Eclampsia.
1937, 1939, 1944, 1947. Full term pregnancies at home.
1949. Eclampsia, living child.

Part III. The Histological Changes in the Liver and Placenta

There is no doubt that specific histological changes were almost invariably found in the livers of women dying from eclampsia between the years 1886 (when they were first described) and 1930 (Jürgens, 1886 ; Pilliet, 1890 ; Schmorl, 1893 ; Konstantinowitsch, 1907 ; Acosta-Sison, 1931 ; Davidson, 1930-31 ; Theobald, 1932*b*). Wooldridge (1889) produced these classical hepatic lesions in dogs by injecting tissue fibrinogen intravenously and Schmorl confirmed his results.

It is just as important to recognize that eclampsia can cause specific changes in the liver as it is to admit the fact that in recent years the livers of women dying from eclampsia may show relatively normal histological appearances.

Young, Bartholomew, Falkiner and others have stressed the significance of placental infarcts and we are all looking forward to hearing Dr. Falkiner's contribution.

Quite recently Poliakoff and Bartholomew (1949) have reported a case of "Convulsive seizures, questionably eclamptic, diagnosed solely by placental examination." Reading

this report convinces me that areas of "E" infarction can occur in cases of normal pregnancy.

Lesions occur in the lungs of patients suffering from pulmonary tuberculosis, but these cavities are not the cause, but part of the expression of the disease. May it not be that the histological changes in the livers and placentas of women dying from eclampsia are concomitant rather than causal?

Part IV. Eclampsia

This syndrome has been recognized for well over 2,000 years, and I have already made some observations on its incidence. More than half of all cases occur in primigravidæ, and there is a much higher incidence in association with multiple pregnancy. It occurs but rarely before the 30th week of pregnancy, but does occasionally supervene in cases of hydatidiform mole. It would, however, be unwise to exclude the possibility that the so-called eclampsia associated with hydatidiform mole might have a very different ætiology from that of true eclampsia. Eclampsia is certainly not associated with chorion epithelioma.

Eclampsia may occur with overwhelming suddenness* in a patient, who previous to the attack had been normal by every known standard, or it may terminate a short or long period of pre-eclampsia characterized by hypertension, albuminuria, œdema and a diminished secretion of urine. In the latter event prodromal symptoms (i.e. headache, disturbance of vision, vomiting and epigastric pain) usually manifest themselves before the actual attack occurs. In cases of pre-eclampsia rapid amelioration of the symptoms may occur shortly

*In a twelve-hour period during the week following this symposium, three eclamptics were admitted under my care. One, M.K., *æt.* 25, a primigravida, was seen at the ante-natal clinic at about 11 a.m. on the 19.1.50. Her blood pressure was 120/80 mm. Hg. There was no albumin in her urine and no œdema was detected. She was 34 weeks pregnant and had lost 2 lb. in weight during the preceding week. Her blood pressure had never exceeded the above figure. Less than fifteen hours later she had the first of her eight eclamptic fits. She was delivered of a living child twelve hours after her first fit. The maximum blood pressure during the eclampsia was 170/130 mm. Hg.

after the death of the fœtus, but by no means always. I have no record of a case in which eclampsia occurred subsequent to the death of the fœtus.

Although the name derives from the fits which characterize the syndrome the patient may pass into coma without having a single fit. She may lie in deep coma in between the fits, or conversely she may be easily aroused, notwithstanding the fact that she has a large number of fits.

The blood pressure may remain at or below the standard I have mentioned (140/90 mm. Hg.) both before and throughout the attack.

Albumin may not appear in the urine until after a number of fits have occurred. There may be no œdema, or the woman may be so bloated as to appear but half human. In other cases œdema may come and go, or its intensity may vary within considerable limits during the course of the attack.

The patient may recover from her attack and subsequently pass through a number of normal pregnancies. Conversely, the patient may demonstrate pre-eclamptic symptoms in every succeeding pregnancy, and may even have two or more attacks of eclampsia sandwiched in between apparently normal confinements.

The secretion of urine usually becomes almost suppressed, and the small amounts passed are commonly loaded with albumin. In a small percentage of cases the secretion of urine is relatively normal and may at no stage contain more than 0.1 gm. per cent of albumin (one part in Esbach).

Eye changes, other than those seen in hypertension, have not been commonly encountered in association with eclampsia during the last three years in Bradford.

Neither routine biochemical nor hæmatological investigation have proved of much service in determining which patient is likely to develop eclampsia. In particular I would observe that neither packed blood cell volumes nor estimations of blood uric acid have proved of any service.

The blood urea has risen to very high levels in two cases

of antepartum hæmorrhage, and in one case of hyperemesis gravidarum but not in a single case of eclampsia.

I have so far attempted to describe the signs and symptoms of eclampsia which may be matched less by similarity than by contrast. I turn now to the two most extraordinary features of this baffling syndrome.

The first is that it is a self limited disease. The treatment I have adopted is simply to give morphia, and to nurse the patient on her side in a dimmed room. During the last three years I have treated between 50 and 60 cases of eclampsia. In only one case did fits occur in such rapid succession that it was found necessary to give 0.5 gm. of penthothal intravenously to control them. Two consecutive cases, both of whom demonstrated hyperpyrexia, died, and one further death has occurred since this paper was written.

I am not claiming any merit for this line of treatment, but the point I wish to stress is that a condition which at one time carried a mortality of over 50 per cent can be successfully treated merely by the exhibition of morphia. I know of but one other condition in medicine where it can be said that if the patient can be kept alive without suffering irreparable damage to any vital organ for twenty-four hours he or she will survive, and that is surgical shock. I know of no other condition in which the patient who stands in very real jeopardy of her life can almost invariably be saved merely by the injection over a period of twenty-four hours of some $2\frac{1}{2}$ gr. of morphia.

The second remarkable fact about eclampsia is that it may be intercurrent. Lichtenstein (1911) collected 64 examples from the literature in which the woman recovered from the eclampsia and subsequently gave birth to a living child and 56 in which she recovered and at a later date gave birth to a dead or macerated fœtus. Since then many such cases have been reported. During the last three years I have had under my care seven patients each of whom recovered from a severe attack of eclampsia, occurring at about the 36th week of pregnancy, continued with her pregnancy and subsequently gave birth to a living child some three weeks later. Indeed

two of these patients had two attacks of eclampsia separated in each case by an interval of six days.

I have shown that hypertension, whether it pre-exists and becomes exacerbated during the pregnancy, or whether it manifests itself for the first time during the latter half of the pregnancy, is of no immediate significance to the mother, and of none to the fœtus. It is clear that the association of albuminuria with the hypertension very considerably increases the risk to the fœtus, and to a lesser degree enhances the risk to the mother. Seeing that a woman may show a marked elevation of the blood pressure, serious proteinuria and extensive œdema for many weeks and subsequently give birth to a living child, and conversely that eclampsia may come literally "out of the blue" and prostrate an apparently healthy woman, the possibility cannot be excluded that eclampsia is something other than the sum total of hypertension, albuminuria and œdema.

Clinicians must play for safety until more is known of the pregnancy toxæmias, but from the investigator's viewpoint it is essential that no assumptions be made. I would, therefore, urge that terms such as "mild toxæmia," "severe toxæmia" and "pre-eclampsia" be eschewed and that instead we should speak of hypertension, hypertension and albuminuria, and of hypertension, albuminuria and œdema, the intensity and duration of each state being recorded.

Any hypothesis which purports to elucidate the genesis of eclampsia must therefore explain :—

(1) Why the incidence of eclampsia was so low in Bangkok in 1926 and why it was so high in Ceylon, in spite of the fact that the meteorological conditions, mode of life, living conditions and sanitation were so very similar.
(2) Why the incidence of eclampsia has risen steeply in Siam during the last few years.
(3) Why the incidence of the pregnancy toxæmias increased more than twofold in Hong Kong during the first two years of the second world war.

(4) Why the incidence of eclampsia fell during the last two years of the first world war in the large cities of Germany and Austria and throughout Belgium and Holland during the second world war.

(5) Why the incidence of eclampsia rose during the first world war in Russia and in the cities of Belgium and Holland after their liberation at the end of the second world war.

(6) Why the mortality rates for the pregnancy toxæmias have been consistently higher in Scotland than in England and Wales.

(7) Why ante-natal care had so little effect on these mortality rates until 1942 and why they have fallen so dramatically since that date.

(8) Why chronic malaria, ankylostomiasis and diabetes occurring in association with pregnancy predispose a woman to the pregnancy toxæmias. In particular, why anasarca and albuminuria are so commonly encountered in pregnant women suffering from chronic malaria and ankylostomiasis when neither of these states is associated with these diseases when uncomplicated by pregnancy.

(9) How it is that eclampsia can occur with great suddenness in women whose pregnancy has been normal and who show neither hypertension, albuminuria nor œdema.

(10) Conversely, how it comes about that a pregnant woman may show a high blood pressure, a marked degree of albuminuria and œdema amounting to anasarca over a period of eight to twelve weeks, and give birth to a living child without developing eclampsia.

(11) The cause of the sudden onset of headache, abdominal pain, vomiting and œdema of the face and why they are so often the prodromal symptoms of eclampsia.

(12) Why eclampsia is peculiar to pregnancy and why it is particularly associated with primiparity and multiple pregnancy.

(13) How it is that a woman can recover from eclampsia and then several weeks later give birth to a living child.
(14) How it is that a woman suffering from eclampsia, in imminent peril of her life, can be cured simply by giving morphia.
(15) How eclampsia can occur up to four days after delivery.
(16) Why the blood pressure in some cases reaches its highest level three to eight days after delivery.
(17) The hepatic lesions which are peculiar to pregnancy; and what is equally important why it is that in recent years many fatal cases of eclampsia have occurred without these specific histological changes being discovered.

Any hypothesis which fails to offer an explanation for all these facts or is contradicted by any one of them should be ruthlessly discarded.

There is no slur on obstetricians for not finding an acceptable explanation for the genesis of this baffling syndrome, but they do incur reproach for tabulating so many hypotheses (and expecting students to learn them) which most obviously fail to account for most of the clinical facts.

For my part I have long advocated that biochemists, biophysicists and physiologists should be appointed to the staff of a maternity hospital and that they should be expected to do the clinical ward rounds with the clinician in charge of the beds. Only by this means will it be possible for the laboratory workers to become fully acquainted with the clinical problems, and the clinicians to envisage the help that those trained in the laboratory can afford. It is in the clash of divergent mental attitudes that truth may emerge.

ADDENDUM

The Dietetic-Deficiency Hypothesis of the Toxæmias of Pregnancy in Women

The two factors concerned are :—

(1) The state of nutrition of the expectant mother, her diet, and the nutritional demands of the fœtus.
(2) The mechanical factors occasioned by the weight and bulk of the uterus.

Eclampsia represents a break-down in physiological mechanisms and there is no need to postulate any toxin.

(1) The safest diet during pregnancy is one low in animal proteins and fats. The more animal protein taken the greater is the need for protective vitamins. Eclampsia is more likely to be caused by multiple partial deficiencies than by the deficiency of any one vitamin. A woman may become adjusted to a very low diet and her metabolism may be upset by any sudden alteration in it, even though the added substances are in themselves good.

(2) The weight and bulk of the pregnant uterus, particularly during the last trimester, cause :—

(*a*) An increase of pressure in the veins of the lower extremities, and this leads to water retention by day which should be excreted by night. This diurnal mechanism may break down.
(*b*) The assumption of the lordotic position when sitting and walking—and this predisposes to albuminuria.
(*c*) The bulk of the uterus indirectly tends to cause distension of the pelves of the kidneys, particularly on the right side. This can largely be prevented if a water diuresis is assured once or twice daily.
(*d*) The diaphragm becomes elevated—and this may facilitate the onset of albuminuria.

(*e*) The stomach is unable to expand normally, and this leads to a certain amount of indigestion which may indirectly upset the metabolism in many ways.

It is obvious that multiple pregnancy operates adversely in two ways: it increases the mechanical disadvantages and twins demand more of the maternal nutritional stores. The same applies to a large fœtus. Primigravidity tests the physiological mechanisms for the first time, and the necessary adjustments may prove beyond the maternal resources.

A woman suffering from chronic malaria, ankylostomiasis, severe malnutrition or diabetes is less likely to meet the physiological demands of pregnancy than a well nourished woman. A woman with incipient Bright's disease is liable to manifest hypertension during pregnancy, and this is the more likely the older she is when pregnancy first occurs.

Post partum eclampsia—occurring up to two to four days after delivery—may be explained on the assumption that the woman just escapes an attack of eclampsia during labour and that the scales are finally tipped against her by the deposition in the breast tissues of the substances necessary for the formation of milk.

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ÆTIOLOGY OF PREECLAMPSIA-ECLAMPSIA

II. The Effect of Intravenous Injections of Sodium Chloride and Lactate in Preeclamptic Patients*

Wm. J. DIECKMANN et al.

THE inability of some pregnant patients to normally excrete sodium chloride has been thought, by many investigators, to be the cause of preeclampsia and eclampsia for the last fifty years.[1] This delay in the elimination of sodium chloride has presumably caused the retention of water (sometimes evident as œdema) and the complex syndrome of the disease. The result of such beliefs has been that for almost twenty-five years, preeclampsia has been treated by a limitation of the sodium intake and by a high protein diet in an endeavour to increase the concentration of the serum proteins and thereby raise the colloid osmotic pressure of the blood.

In a previous report[2] we stated that there is sufficient evidence to indicate that there are no lesions pathognomonic of eclampsia in the liver, kidneys or any other gland. We also stated that there is an abnormal physiology of the liver, kidney and many of the glands of internal secretion. Our purpose in these studies is to determine the cause of pre-eclampsia-eclampsia.

We have stated that preeclampsia-eclampsia is a salt and water retention due to an abnormal capillary permeability, but that we do not know which is primary. Some patients in addition develop hypertension (which may be compensatory), proteinuria, and a very few have various other symptoms and signs due to cerebral anoxia culminating in

*This study was supported in part by the Chicago Lying-in 50th Anniversary Research Fund on Eclampsia.

convulsions and/or coma. We have stated that since eclampsia-preeclampsia is an entity peculiar to the human race, studies as to the ætiology and treatment must be made on pregnant patients and not on animals.

In 1940 the senior author[3] reported that during the early puerperium of preeclamptic patients there was a negative balance for sodium, potassium and chloride, indicating that there had been a retention. Sodium may be both extra- and intracellular ; in the latter instance, displacing potassium from the cell. As the concentration of sodium increases in the extracellular fluid, water and potassium salts leave the cell in an endeavour to establish isotonicity, and sodium enters the cell. There can be a transient difference in isotonicity between the intra- and extracellular fluids, with resultant impairment of cell function. This is particularly important in the brain where any disturbance in cell function will result in generalized effects such as convulsions, increase in blood pressure, coma, hyperpyrexia, etc.

We have all seen eclamptic patients with no demonstrable œdema at the initial examination, within a few hours develop œdema of such magnitude that the eyes are closed and the legs pit easily. Since the patient had not been given any fluid, the only source was from her own tissues where it could have been intracellular.

A vast literature has accumulated during the past two decades on the importance of water for the normal functioning of the body. Extracellular water comprises some 20 per cent of the body weight and intracellular amounts to 50 per cent. Obviously a positive water balance will cause increased pressure in the kidneys, liver, and the brain with its bony walls, thus producing many of the serious symptoms and signs associated either with an excess or a decrease in the normal amount of water within or between the cells.

Water is absolutely essential for life.[4] Too much or too little, depending upon the climate, soon produces systemic changes which, if continued, may terminate in death in a few hours to several days. A failure of water to reach the

kidney, even though there may be anasarca, is as dangerous as absolute dehydration. Œdema may be a protective mechanism for a time. These physiologic changes, together with alterations in weight as well as various symptoms and signs, may be obvious within an hour. The longer the abnormality in water balance persists, the greater the changes in the body.

Haldane and Priestly[5] in 1914 noted in experiments on themselves that excessive drinking of tap water could result in dizziness, vomiting and an unpleasant sense of fullness. If the hydration continues, convulsions, coma, hypertension, anuria and death will occur. These observations have been confirmed by various observers. Periodic ingestion of water together with repeated injections of posterior pituitary solution have been suggested by McQuarrie[6] and others as a therapeutic test for epilepsy.

Studies with deuterium oxide, radioactive chloride and sodium indicate that intracellular, extracellular and plasma water and electrolytes are exchanging every few minutes and that concentrations of the various electrolytes fluctuate.

Thompson and Pommerenke[7] in three pregnant women reported an average daily retention of 14.7 meq. per litre of sodium and 7.9 of potassium. Coons *et al.*[8] report a daily mean retention in normal pregnant patients of 0.877 gm. of chloride, 1.265 gm. of sodium, and 0.508 gm. of potassium.

If normal pregnant women have daily retentions such as these throughout pregnancy, one would expect all pregnant patients to have œdema. A period during which sodium and/or potassium ingestion are increased or the excretion decreased, perhaps because of a diminished intake of water (cool weather), could easily be the predisposing factor which would result in the development days or weeks later of pre-eclampsia. Furthermore, a similar course of events in a patient with preeclampsia could result in the onset of convulsions and/or coma. We have not purposely precipitated eclampsia but we believe that conditions as described could have such a result. To date, two patients, while being

investigated, have had convulsions and coma although somewhat similar studies in the remainder have not given such dramatic results.

The legs and thighs of a human body comprise 37 per cent of the total weight. Smirk[9] concluded that the lower extremities acted as a depot for water. It is true that the legs and thighs can contain a huge amount of fluid without showing pitting œdema. This fluid may be both extra- and intracellular and we have studies in progress to determine the extent and frequency of this type of water and electrolyte retention. We are determining the volume of the leg and thigh, measuring the maximum circumference of each, determining sodium, potassium, chloride and phosphorus balances, obtaining total body water, plasma volume, extracellular fluid volume and accurate body weights (Fig. 1).

Any abnormal condition which interferes with water or cellular metabolism will intensify the normal delay in water and electrolyte excretion. Some of these factors are anæmia, a slight decrease in the concentration of serum albumin, cardiac disease, glomerulonephritis, multiple pregnancy, polyhydramnios, etc.

The stimulus to urinary secretion is an excess amount in the blood of water, an electrolyte or non-electrolyte. The excretion of water by the kidney is dependent upon a relatively abrupt blood dilution and a decrease in the concentration of the antidiuretic hormone (A.D.H.) in the blood.

Verney[10] states that the post-pituitary A.D.H. is released in the living animal by emotional stress or an increase in the osmotic pressure of the arterial blood. This release is inhibited or suppressed by an increase in sympathetic activity associated with the animal's discomposure. He has shown that sodium chloride produces a marked secretion of A.D.H., while other substances such as glucose and urea produce little or no secretion.

Various reports indicate that especially the hormones of the adrenal cortex and to a less degree the thyroid gland, through effects on electrolyte and water excretion, renal

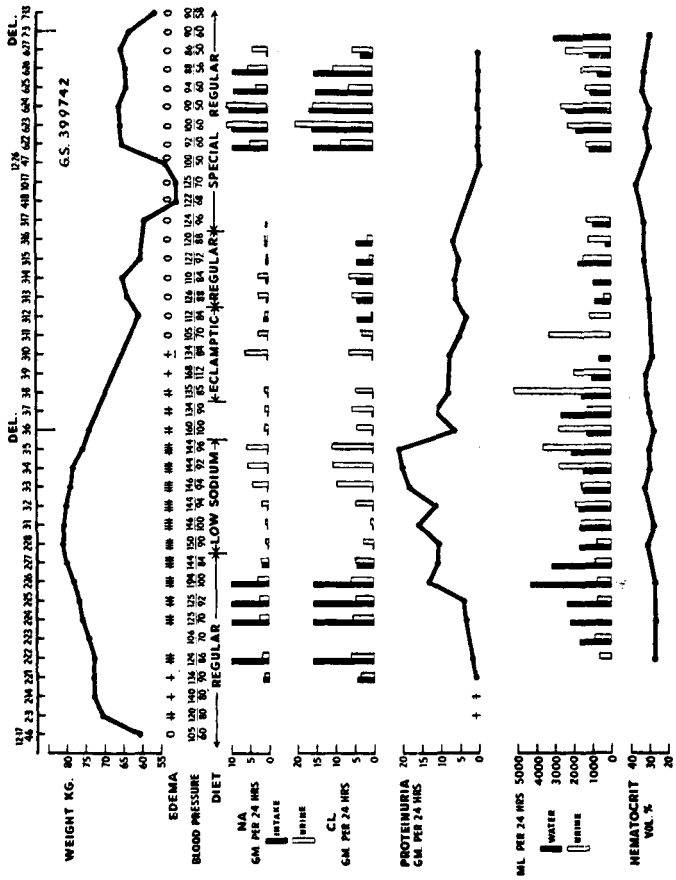

FIG. 1. Patient No. 1. Na and Cl retention and increase in weight, œdema, blood pressure and proteinuria caused by injections of NaCl solution. Marked proteinuria persisted after delivery in first pregnancy. Similar NaCl injections in the second pregnancy caused no retention or abnormal signs and symptoms.

function, permeability, etc., have an important regulating influence on the metabolism and distribution of body water.

The normal kidneys can excrete up to 1,200 ml. of urine per hour for a short time but owing to fatigue, the diuresis soon decreases to approximately 750 ml. per hour.

The pregnant woman has a delayed excretion of water and sodium which may be due in part to the increased deposition and delayed absorption from the legs and thighs caused by the high venous pressure in the lower extremities as well as to changes in the amounts of posterior pituitary and adrenal cortical hormones. This delayed excretion of water is greatly intensified in severe preeclamptic and eclamptic patients. Œdema of varying degrees occurs in at least two-thirds of normal pregnant patients. If we had more exact means of determining œdema, the incidence would be higher. Oliguria or anuria are characteristic of eclampsia and severe pre-eclampsia and the persistence of these signs is associated with increasing mortality.

Previous studies[2] seem to indicate that if there is a constant diuresis, thus perhaps preventing any stimulus for the release of A.D.H., the urine volume will remain fairly constant, and there will be a negative water balance.[11] However, if the A.D.H. increases there is a delay in water excretion in the normal individual which becomes exaggerated in the toxæmic patient ; thus accounting for the oliguria or anuria. Adrenal cortical hormones are also involved in the excretion of urine, sodium, potassium, and chloride.

Where there is evidence of extensive water retention, there is also an increased amount of water in the kidney, thereby adding an additional impediment to renal work. The amount of water in the liver is also increased with a resultant impairment in its function to detoxify substances absorbed from the intestinal canal and brought to it from other portions of the body (A.D.H. and other hormones). An increased amount of fluid either inside or between the brain cells may produce an increase in the amount of A.D.H., or a failure in its removal or neutralization. A small increase in the intra- or extra-

cellular fluid of the brain will result in an increased irritability and other symptoms and signs associated with anoxia of the brain, namely, headache, dizziness, diplopia, nausea, vomiting, convulsions, etc. A still greater increase will result in coma, hyperpyrexia and death.

Stewart and Rourke[12] have shown that the continuous intravenous injection of 5 per cent glucose solution to relatively normal postoperative patients over periods ranging from 36 to 144 hours not only resulted in an increased elimination of sodium in the urine but caused a diminution in the volume of the extracellular fluid of 1,960 ml. in one patient. One patient actually became comatose because of the decreased concentration of sodium in her blood and tissues. In other words, she suffered from water intoxication although she was dehydrated. Another patient was given 26.7 litres of 0.9 per cent sodium chloride solution over 96 hours with a 7 kilo increase in weight and an increase in the interstitial fluid of 9,890 ml., and of 1,722 ml. in plasma volume without any evidence of œdema. This same patient had a maximum decrease of 23 per cent in the plasma protein concentration and a 21 per cent increase in the total amount of circulating plasma protein; thus indicating that there are stores of plasma protein presumably in the interstitial fluid. These observations of Stewart and Rourke indicate a possible new type of therapy for the markedly œdematous patient, namely a continuous injection of 5 per cent glucose solution for several days or longer.

In a previous paper[2] we reported our results with the Robinson, Power and Kepler test for Addison's disease not because we thought that preeclampsia and eclampsia were due to a hypofunction of the adrenal gland but because this gland is associated with sodium and water balance. We found that the elimination of water given by the oral or intravenous route is delayed in all pregnant patients but to even a greater degree in those with preeclampsia than in those with hypertensive disease. This delay may be due in part to the increased storage of the water in the legs and

thighs as the result of the high venous pressure in the lower extremities due to pregnancy. 82 per cent of the preeclamptic patients and 48 per cent of those with essential hypertension had a positive test before delivery; that is, they had less urine in the morning hourly specimens than in the night urine. The water factor was abnormal in 40 per cent of the preeclamptic patients, ante- and postpartum. Comparable figures for patients with essential hypertension are 12 and 17 per cent respectively; for normal pregnant patients, 17 per cent and 0, and nonpregnant, 9 per cent. We found a marked difference between patients with preeclampsia and hypertension which was primarily due to the low hourly urine characteristic of preeclampsia. The total elimination of water also showed a marked difference with a mean of 33 per cent for antepartum preeclampsia as compared with 66 per cent for hypertensive disease and 56 and 82 per cent, respectively, for the same patients postpartum.

Thompson and McQuarrie[13] noted that the ingestion of large amounts of sodium chloride by three diabetic children resulted in the development of hypertension. Torbert and Cheney[14] have also noted that the ingestion of a large amount of sodium chloride caused œdema, blood dilution, and some proteinuria.

Excessive amounts of parenterally injected sodium chloride solution will produce œdema, hypertension, convulsions and coma in animals and humans (Figs. 2, 3). The best example is the waterlogged patient with lower nephron nephrosis from an incompatible blood transfusion.

A restriction of sodium to lower the blood pressure of nonpregnant patients with hypertension is still experimental. Several investigators[15] state that some hypertensive patients placed on a low sodium diet or the Kempner rice diet, respond with a significant fall in blood pressure and the decrease in both cases is abolished by giving sodium chloride.

Jardine,[16] in 1900, lowered the mortality from eclampsia in the Glasgow Maternity Hospital from 47 per cent, which was the rate for the previous fifteen years, to 19 per cent by the

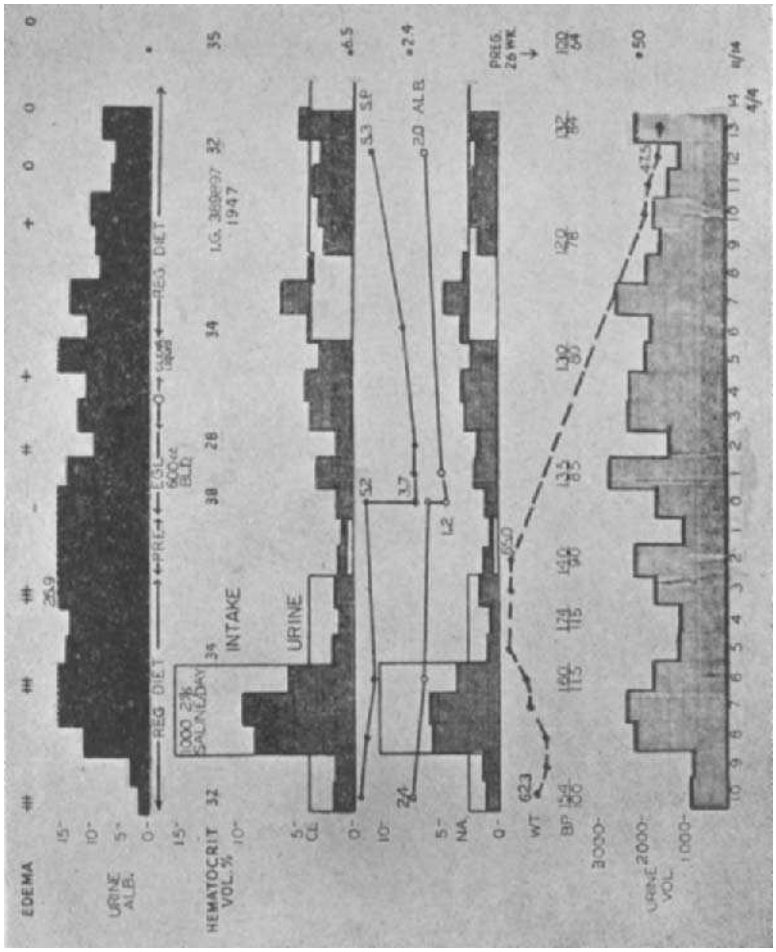

FIG. 2. Patient No. 2. Injections of NaCl solution caused a Na and Cl retention and increase in blood pressure, weight (no detectable change in œdema which was always ++), and proteinuria. Latter persisted throughout hospital puerperium.

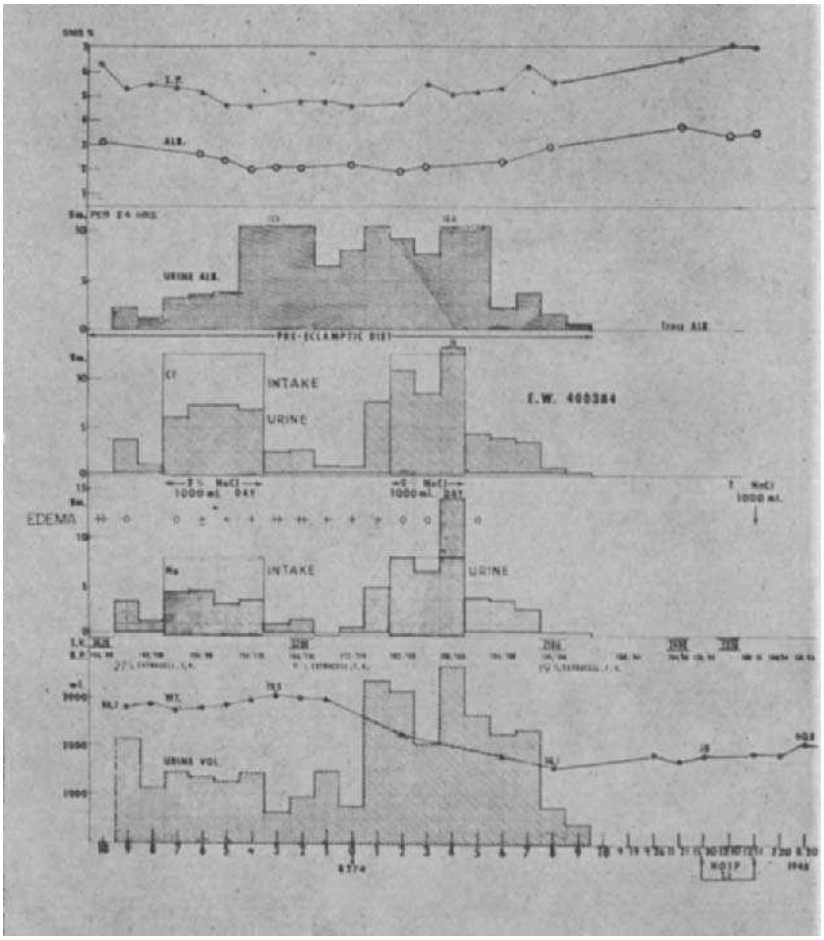

FIG. 3. Patient No. 3. The injections of NaCl solution caused the appearance of œdema, increase in weight, blood pressure, proteinuria, and extracellular fluid volume. A hæmodilution occurred but the blood and plasma volume decreased. Injections during the puerperium again produced a marked increase in the blood pressure.

subcutaneous injection of 1,000 ml. of a solution consisting of 0.8 per cent sodium chloride and 0.8 per cent sodium acetate. It was repeated if necessary.

Tweedy[17] modified the Rotunda Hospital treatment of eclampsia by adding 500 ml. of a 0.4 per cent solution of sodium bicarbonate to be injected beneath each breast or intravenously.

Zangemeister,[18] commenting on the well-known fact that many women have slight œdema of the ankles late in pregnancy, postulated that the cause of preeclampsia and eclampsia was an abnormally large retention of water. This condition (hydrops gravidarum) was accordingly regarded as a precursor of preeclampsia and eclampsia.

Harding and Van Wyck[19] gave sodium bicarbonate by mouth or injections of 10 per cent sodium chloride solution intravenously to toxæmic patients. They stated that both substances would result in an increase in weight and that the intravenous injection of 300 ml. of a 10 per cent sodium chloride solution would, in the susceptible individual, cause a marked increase in proteinuria, blood pressure and a recurrence of the eclamptic convulsions (one case). They decided that the experimental intravenous injection of 30 grams of sodium chloride was too dangerous to continue.

Strauss[20] gave normal pregnant and toxæmic patients 23 gm. of sodium bicarbonate or 16 gm. of sodium chloride (each salt contained 6.3 gm. of sodium) by mouth. He found that approximately 15 per cent of the toxæmic patients would show marked increases in weight, hypertension, proteinuria and some had symptoms as the result of the ingestion of these salts. He found a rough correlation between the decreased colloid osmotic pressure of the plasma and the previously described changes caused by the sodium salts. A low sodium intake was one means of eliminating undue water retention. He stated that preeclampsia and, presumably, eclampsia, may be prevented by maintaining the pregnant woman's plasma proteins at a normal level by an adequate diet and avoiding excessive sodium intake. However, ten patients

with preeclampsia in one pregnancy, who had been studied by him, were followed through a subsequent pregnancy during which a high protein intake was commenced early. Despite the increased protein intake, three of the women had an abnormal lowering of the plasma proteins. All were on a low sodium intake and none developed any manifestations of toxæmia. This has been the experience of most obstetricians, namely that true preeclampsia or eclampsia rarely recur in subsequent pregnancies although the patient's dietary habits rarely are permanently changed.

Fuster[21] gave an intravenous injection of a 10 per cent sodium chloride solution to a pregnant woman near term, who had anæmia, hypoproteinæmia and œdema early in the pregnancy. She soon developed headache, dizziness and at the end of two hours (80 gm. sodium chloride) became comatose which lasted for three hours. During this time two convulsions occurred. He stopped the injection when 800 ml. of sodium chloride had been injected. The patient recovered and delivered without any difficulty. A hypertension was present between the fifth and seventh postpartum days.

We began this study in 1946 but the work prior to the fall of 1948 lacks accurate weights because we were using the ordinary platform scale and we frequently had evidence that the patient's weight should be changing and yet we found either no change or a change inconsistent with the sodium balance. Since November, 1948, we have had an accurate beam balance and can be certain of the weight. Since the spring of 1949 we have a climate room which enables us to keep the patient at a constant temperature and humidity, thereby the insensible weight loss is constant with the same diet. Patients are comfortable in a temperature of 80–85°F. and a relative humidity of 25–35 per cent, and the insensible weight loss is markedly increased. A higher temperature will result in a still greater loss of water by lungs and skin. A relative humidity greater than 50 per cent becomes uncomfortable and patients complain of the heat even though the temperature has not been increased.

M.V. No. 388369, one of the first patients receiving saline solution, was a primipara, 21 years old, who had had severe preeclampsia with a hydatidiform mole. 1,000 ml. of normal sodium chloride solution was injected intravenously on September 4th, 1946, the fourth postpartum day, and repeated for eight days. The patient gained 1.7 kg. and the blood pressure increased again but then she lost weight and the blood pressure returned to normal. The other signs and symptoms continued to improve. She had a normal pregnancy and a baby twelve months after the mole was removed. We continued the postpartum injections in other patients and concluded that they could be given with safety to patients who had had preeclampsia and eclampsia without any demonstrable ill effect. We then began antepartum injections and in an endeavour to eliminate the water effect, we increased the concentration to 2 per cent and finally to 2.5 per cent. We found that 1,000 ml. of a 2.5 per cent solution of sodium chloride given daily for two or more times to a patient with preeclampsia would result in an increase in blood pressure, proteinuria, and in 31 per cent, the onset or recurrence of symptoms such as nausea, vomiting, headache, dizziness, scotoma and decrease in vision. The usual number of injections was five. In some patients we have given as many as twelve antepartum, without any significant effects (Fig. 4).

320 ml. of molar sodium lactate in 1,500 ml. of 5 per cent glucose have also been given to a number of patients but no marked effect as to increase in weight, proteinuria or blood pressure was demonstrable if the patient was on an intake of chloride less than 1.0 gm. per twenty-four hours.

Some patients received sodium chloride capsules by mouth and also intravenous injections (Fig. 5). Large doses of desoxycorticosterone acetate (DCA) for its sodium and water retention and occasional diuretic properties have been used in some patients. Solution of posterior pituitary (pitressin) and water ingestion have also been used. Large amounts of plasma and salt-poor concentrated serum albumin have been injected. Intravenous injections of heparin have been

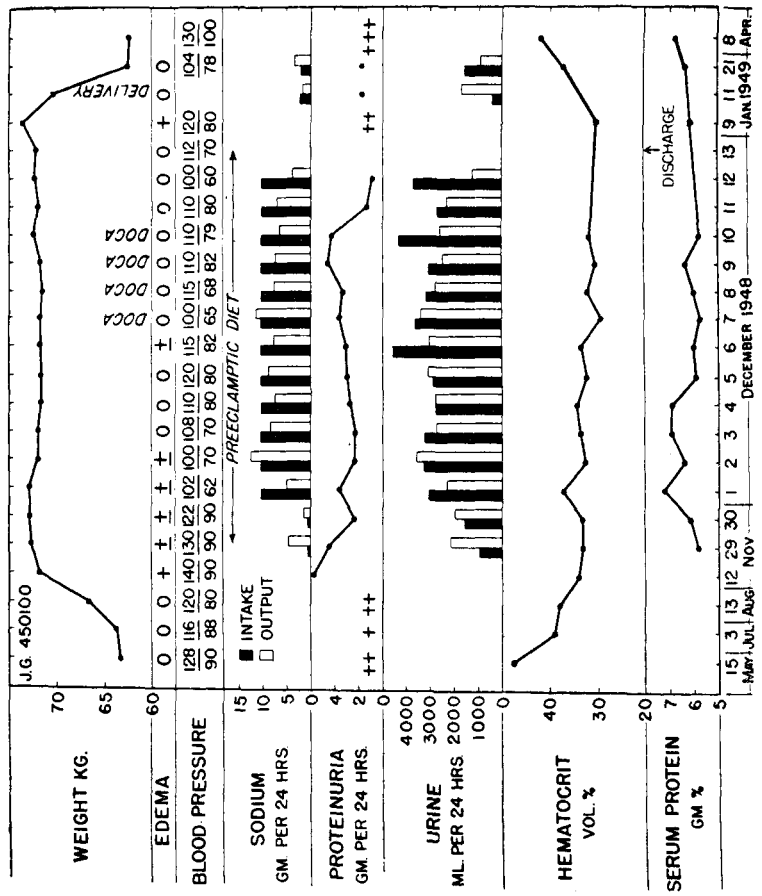

FIG. 4. Patient No. 4. Injections of NaCl for twelve days produced no change in weight but decrease in œdema and proteinuria, and a haemodilution. Water intake and urine were in balance.

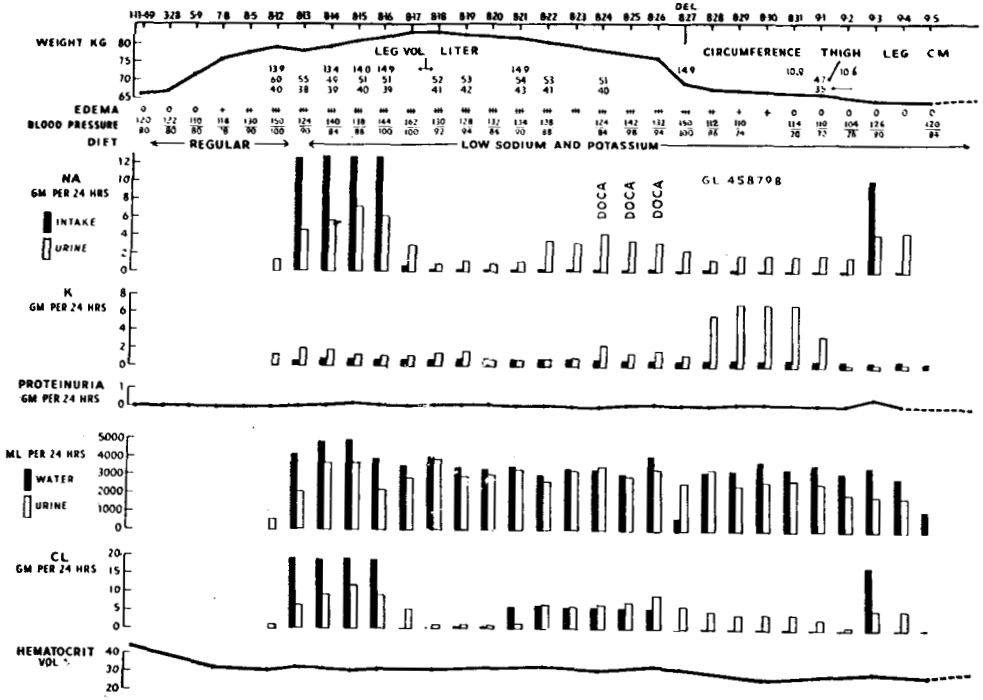

FIG. 5. Patient No. 5. Ingestion and injection of NaCl solution caused increase in blood pressure, in weight of 6.87 kg., and in leg volume and measurements but no demonstrable change in the degree of œdema or proteinuria. NH_4Cl in 10 gm. daily doses from 21/8 to 26/8 in addition to the low Na and K diet, resulted in a weight loss of 5.12 kg. but no detectable change in œdema or leg volume.

used. We are reporting the effect of intravenous injections of sodium lactate or chloride (Fig. 6).

A study such as we are making is wasteful in that many patients go into labour after one has made various control observations and most of the work is of little value. We have 56 patients who received two or more injections of sodium chloride intravenously during the antepartum period and 63 who received similar amounts in the puerperium. The actual number of patients and injections are given in Table I.

Table I

INTRAVENOUS INJECTIONS OF SODIUM SALTS.

Number	Antepartum		Postpartum
	Sodium Chloride	Sodium Lactate	Sodium Chloride
1	63		59
2	12	2	16
3	15	3	14
4	9	4	19
5	8	5	7
6	7		2
7–8	2		5
9–10	2		
11–12	1		
2 or more injections	Pts. 56	14	63

A few patients were deemed so critical on admission that we did not feel that it was safe to give them the test dose of 1,000 ml. of 2.5 per cent sodium chloride solution. However, we now feel that the test dose can be given to almost every patient; the only exception at present would be if evidence of pulmonary œdema were present.

Sodium chloride if given orally or intravenously in adequate amounts, even to normal non-pregnant subjects, will cause an increase in weight, hæmodilution, toxic symptoms and even

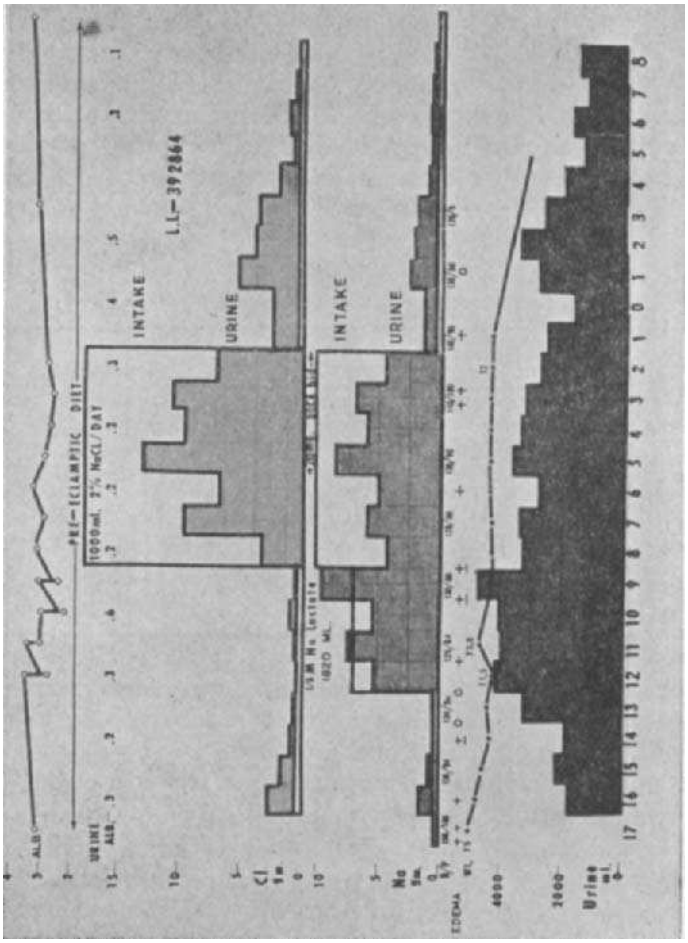

Fig. 6. Patient No. 6. Sodium lactate solution was given intravenously for four days and caused a slight increase in weight; then NaCl solution was given for seven days and caused an increase in edema and blood pressure but no change in proteinuria.

death if given in large enough amounts. The data in Table II–A illustrate the increases and occasional decreases in weight noted as the result of injecting sodium chloride or lactate solutions intravenously on two or more days before delivery. Some patients had 3 to 8 kg. increases in weight within a period of three to six days but these were exceptional and not all of these patients developed other signs and

Table II

WEIGHT CHANGES—PERCENTAGE OF PATIENTS.

Kg.	A Antepartum			B Postpartum		
	Increased	Decreased	No Change	Increased	Decreased	No Change
			2			2
0.1 – 0.49	18	7		5	2	
0.5 – 0.99	9			5	2	
1.0 – 1.99	23	5		12	23	
2.0 – 3.99	25				30	
4.0 – 5.99	9				12	
6.0 – 7.99	2				5	
10.0 –10.99					2	

symptoms. The detection of œdema is a gross measure and we could not make any close correlation between the weight gain and the amount of œdema.

Data in Table II–B show that in patients who had had œdema antepartum and were given daily injections of sodium chloride solutions during the early puerperium, 22 per cent had varying degrees of gain in weight rather than losses. The increases were not large but are probably significant since the weight would normally be constant or show a slight increase up to the fourth postpartum day,[22] when it begins to decrease.

The data in Table III–A indicate the effect on the œdema of two or more injections of sodium chloride before delivery. It is worth noting that 22 per cent of the patients showed no œdema and 36 per cent showed no detectable increase in œdema. 40 per cent showed increases varying from + to +++.

During the puerperium, Table III–B, almost without exception, the œdema decreased and sodium chloride injections would, in some instances, retard it but in general we could not cause an increase with the same amount of sodium chloride solution which had caused an increase during the antepartum period.

Table III

CHANGES IN THE DEGREE OF ŒDEMA—PERCENTAGE OF PATIENTS.

Increase or Decrease %	A Antepartum				B Postpartum			
	In-creased	De-creased	No Change	None	In-creased	De-creased	No Change	None
			36	22			9	64
+	27	2				25		
++	11					2		
+++	2							

Abdom. wall . 3 patients
Face . . . . 2 patients
Vulva . . . 1 patient

The effect on the systolic blood pressure is given in Table IV–A. 2 per cent of the patients showed no change in blood pressure. The percentage of patients for normal means that the systolic and diastolic blood pressures were less than 140/90 both before and after the saline injections but that there had been either an increase (still less than 140/90) or a decrease. In 77 per cent of the patients the systolic blood pressure increased and 57 per cent of the patients had systolic pressures of 140 or more. 51 per cent had a higher blood pressure as a result of the injections. 40 per cent had increases of 20 to as much as 70 mm. in the systolic pressure. 6 per cent of those with a hypertension had a lower blood pressure. 15 per cent of those with normal pressure had a decrease in the pressure after the injections of saline solution.

During the puerperium, Table IV–B, saline injections produced a higher blood pressure in 57 per cent of the patients and 14 per cent had increases of 20 mm. or more. The pressure

Table IV

CHANGES IN THE SYSTOLIC BLOOD PRESSURE—PERCENTAGE OF PATIENTS.

mm. Hg.	A Antepartum			B Postpartum		
	Increase	Decrease	No Change	Increase	Decrease	No Change
			2			7
Normal*	26	15		23	14	
1–9	2	2		9	7	
10–19	9	4		11	5	
20–29	11			7	7	
30–39	13			2	2	
40–49	7			5	2	
50–79	9					

*Blood pressure before, during and after injections was always less than 140/90.

was lowered in 37 per cent and showed no change in 7 per cent.

What was of great interest to us was the increase in proteinuria which occurred in most cases after several injections of sodium chloride solution. Data are given in Table V–A and B. 11 per cent showed no change and 23 per cent a

Table V

CHANGES IN THE PROTEINURIA PER TWENTY-FOUR HOURS—PERCENTAGE OF PATIENTS.

Change %	A Antepartum			B Postpartum		
	Increase	Decrease	No Change	Increase	Decrease	No Change
			11			5
10–49	9	11		12	17	
50–99	16	2		10	5	
100–199	11	2		10	21	
200–299	7	4			10	
300–399	9	4		2	5	
400–499	4			2	2	
500–599	7					
600+	2					

decrease before delivery. We did not see these increases after sodium lactate but the number of cases treated with the latter are fewer in number. There would be as much as a 600 per cent increase within twenty-four to forty-eight hours and it would persist long after delivery (Shevky and Stafford determination). Micro Kjeldahl determination gave approximately 60 to 70 per cent as much protein. Two of these patients have been studied in subsequent pregnancies and the kidney function and Addis counts are normal and there is no proteinuria. One was given repeated injections of sodium chloride in a subsequent pregnancy without any detectable disturbance. The other was followed through two pregnancies and in the second, intravenous injections late in pregnancy again produced no detectable disturbance. In the third pregnancy, at 37 weeks she was started on 7 gm. of sodium chloride by mouth in addition to her normal intake and she did gain weight rapidly and developed a 1 + œdema. Unfortunately, when sent into the hospital for repeated intravenous injections of salt solution, she went into labour. The urinary protein is serum protein as proved in one case by electrophoretic curves. These studies are still in progress. However, despite the marked proteinuria there was no decrease in the serum protein concentration. Once the normal postpartum diuresis started these patients would eliminate water and electrolytes with even still lower serum protein concentration.

The data in Table VI–A indicate the changes which occur in the serum protein concentration before delivery as the result of two or more injections of sodium chloride solution. We believe that changes of a half a gram per cent or more are not due to daily fluctuation or experimental error. 34 per cent of patients showed decreases of this magnitude or more and 7 per cent showed increases. The preeclamptic patient who is still having a urinary volume of 1,000 ml. or more and no symptoms (compensated or not severe) will show a steadily increasing plasma volume and a lowered serum protein concentration, but the opposite type of case (decompensated

Table VI

CHANGES IN THE SERUM PROTEIN CONCENTRATION—PERCENTAGE OF PATIENTS.

Gm. %	A Antepartum			B Postpartum		
	Increase	Decrease	No Change	Increase	Decrease	No Change
			2			13
0.1–0.4	18	39		22	13	
0.5–0.9	7	23		18	11	
1.0–1.4		9		16	2	
1.5–1.9		2		4		

or severe preeclampsia) will show hæmoconcentration, and an increased serum protein. Normally after delivery, the serum proteins decrease for two to seven days and then slowly return to a normal concentration. Data in Table VI–B demonstrate that 38 per cent showed an increase in concentration of 0.5 gm. or more instead of a decrease.

The data in Table VII–A depict the antepartum changes in the hæmatocrit which were presumably caused by two or more injections of sodium chloride solutions. Here again, a change of 2 volumes per cent or more is not due to the daily fluctuation or experimental error. Table VII–B demonstrates that 39 per cent of the patients had increases in the

Table VII

CHANGES IN THE HÆMATOCRIT—PERCENTAGE OF PATIENTS.

Volume %	A Antepartum			B Postpartum		
	Increase	Decrease	No Change	Increase	Decrease	No Change
			9			11
1	9	18		11	5	
2–3	14	25		21	21	
4–5	7	5		5	14	
6–7		5		2	9	
8–9	2	7				
10–11					2	

hæmatocrit instead of the usual decreases. The trend of change and explanations are similar to those given for changes in serum protein concentrations for both the antepartum and postpartum injections.

We know the sodium intake and the excretion in the urine. We did not determine fæcal sodium or sodium lost in perspiration. The data in Table VIII–A show very definitely that some patients retain relatively large amounts of the injected sodium. Here, too, it seems that individuals differ

Table VIII

SODIUM BALANCE—PERCENTAGE OF PATIENTS.

Retention Grams	A Antepartum		B Postpartum		
	Increase	Decrease	Increase	Decrease	No Change
					2
0.1– 0.9	2		2		
1.0– 3.9	9	2	12	5	
4.0– 7.9	9		21	12	
8.0–15.9	40		26	7	
16.0–23.9	24		7	2	
24.0–31.9	11			2	
32.0–39.9	2				

in their response to water, sodium, and chloride retention. Some will show systemic responses such as blood pressure elevation and symptoms of increased intracranial pressure with relatively small retentions of sodium and water; while others may have tremendous gains in weight associated with marked retention of sodium, chloride and water and yet show no pitting œdema or clinical evidence of it. This difference in response is what we are now studying, for it seems that if we can determine the reason for the response in one patient or the failure of response in the other, we may have the cause of preeclampsia.

Normally, twenty-four to forty-eight hours after delivery there is a spontaneous diuresis with a negative balance for sodium and chloride. Data in Table VIII–B show that in

68 per cent of the patients, sodium chloride injections caused a positive instead of the usual postpartum negative balance.

Patients 1, 2 and 3 (see Case Abstracts, page 78) show similar responses to intravenous injections of sodium chloride solutions. One and two were typical cases of preeclampsia as their abstracts indicate. Patient 3 was thought to have an essential hypertension. It is possible that she had a superimposed preeclampsia. She gave the most marked blood pressure increase as a result of postpartum injection of sodium chloride solution.

Patients 4 and 5 also seemed to be typical cases of pre-eclampsia but patient 4 did not show any increase in signs or symptoms despite the intravenous injection of 1,000 ml. of 2.5 per cent sodium chloride solution for twelve consecutive days (intake of 125 gm. sodium, positive balance of 29 ± gm. sodium). Injections of DCA did not have any demonstrable effect. The proteinuria did not increase but decreased slightly. Patient 5 showed an increase in weight and blood pressure but no increase in œdema or proteinuria. Leg measurements and volumes showed increases although we could detect no difference in the degree of pitting.

Patients 6 and 7 indicate that the intravenous injections of 1,820 ml. of 1/6 molar sodium lactate solution for four days do not cause significant increases in weight, blood pressure, proteinuria, etc., if the chloride intake is less than 1 gm. per day. The injections do cause an appreciable increase in the serum sodium bicarbonate and decrease in the serum chloride (Table IX).

Patient 6 was then given intravenous injections of 2 per cent sodium chloride solution for seven days, resulting in an increase in œdema and blood pressure but no change in proteinuria.

Patients who received two or more injections of 1,000 ml. of sodium chloride solution before delivery had changes in the twenty-four hour output of urine as follows :—

43 per cent had decreased volumes, and of these, all but 8 per cent had an increase in weight.

Table IX

Case 7.—L.P. No. 392846. INJECTIONS OF 1/6 MOLAR SODIUM LACTATE SOLUTION.

Date	Wt. Kg.	Œdema	B.P.	Protein-uria GM./24 hrs.	Hæmat. Vol. %	Serum		Serum–mM.		Sodium		Remarks
						Prot. GM.	Alb. %	$NaHCO_3$	NaCl	GM. Intake	Urine	
25.10.46	57	0	108/62	0	39							
24.1.47	66	±	126/66	0								Vertigo Headaches
21.3.47	70.5	++	154/100	0								Heartburn Headache
22.3.47	70	++	140/90	0.2	36	6.6	3.4					Hospita-lized. Low Na diet
24.3.47	69.0	±	148/100	0.4								
25.3.47	68.3	0	140/85	0.4		6.6	2.9			0.3	2.85	
26.3.47	67.8	0	135/100	0.7	a. 38	6.8	2.8	19	104	7.8	2.3	1,820 ml.
					b. 31	5.9	2.6	26	95			⅙ M sodium lactate
27.3.47	68.8	±	130/90	0.7	a. 40	6.1	2.9	25	99	7.8	3.8	1,820 ditto
					b. 31	5.4	3.1	33	91			
28.3.47	69.2	+	140/90	0.5	a. 33	6.5	3.3	28	95	4.1	3.4	1,160 ditto
					b. 30	5.8	2.8	30	91			
29.3.47	69.8	+	140/90	0.5	a. 34	6.2	3.1	28	95	4.1	4.1	1,160 ditto
					b. 32	5.5	2.8	29	91			
30.3.47	69.4	+	124/90	0.5						0.4	2.4	
1.4.47	Delivery		158/94	1.2	3,415 gm. baby					0	1.2	
2.4.47		0	144/84	0.7	31.5	5.8	2.6			2.2	2.6	Regular diet
4.4.47	60.6		134/88	0.3	33.0	6.5	2.8			2.2	0.85	
10.4.47	58.8		126/88		37	7.3	3.3					
10.10.47	57.5	0	126/66	0	41							Aborted?

"a" is blood obtained before injection and "b" obtained immediately at end.

35 per cent of the injected patients had increased volumes of urine and also weight gains greater than 1 kg. 22 per cent had an increased urine output but a weight gain of 1 kilo or less.

Oliguria and anuria can be caused by the excessive retention of sodium chloride.

It was only in 33 per cent of the patients that there was a parallelism for the retention of sodium, chloride and water, and the weight gain, œdema, hypertension, onset of symptoms and oliguria. Pulmonary œdema occurred in two patients but required no heroic treatment. There has been one death in a patient with toxæmia during the period of study (42 months). She died from pulmonary embolism on the eighth day after a cæsarean section.

Discussion

After several patients had had marked increases in blood pressure, proteinuria, œdema and typical preeclamptic symptoms caused by the antepartum intravenous injections of sodium chloride solution, the first thought was that these patients had difficulty normally in excreting sodium but we soon found that they could excrete it postpartum in a normal concentration. Furthermore, similar and even larger amounts of sodium chloride were used in subsequent pregnancies before delivery without producing any significant changes. One patient was started six weeks before term on a high sodium chloride diet and did develop œdema but unfortunately she went into labour earlier than anticipated. It seemed that the sodium chloride might be the ætiologic agent because of some possible toxic substance resulting from its purification. However, many patients were injected from the same lot number and we believe we have excluded any contaminant in the sodium chloride.

Preeclamptic and hypertensive patients have also had water forced by mouth or have been given 1,500 to 2,000 ml. of 5 per cent dextrose solution intravenously in addition to the oral ingestion for two to five days without any change.

Sodium lactate and sodium bicarbonate given for five to fourteen days cause no increase in blood pressure, œdema, proteinuria or symptoms if the chloride intake is less than 1 gm. in twenty-four hours. Sodium must be held primarily as sodium chloride to be effective.

Since sodium chloride, *per se*, seemed to be excluded, we considered the possibility that there could have been some toxic substance in the diet prior to admission. This possibility has not been excluded. We have had some patients on a weighed regular diet in the hospital but could not select any one food which seemed associated with systemic changes. We had in mind the epidemic dropsy peculiar to Bengal natives. These men and women develop a marked œdema of the legs and other signs as a result of intoxication from the Argemone Mexicana weed, a contaminant of mustard which is used in large quantities by them. A dietary toxic factor has not been excluded but since people rarely change their diet habits, one would expect preeclampsia to recur in subsequent pregnancies, which it rarely does.

Since the legs and thighs comprise approximately 37 per cent of the body weight, it is an attractive theory to consider them and the increased venous pressure in them as the basic cause. When the thighs and legs are bulging from water and electrolyte retention, which may be detected as œdema in some cases, a similar retention begins in the upper 60 per cent. of the body. Periodic determinations of the thigh and leg circumferences or volumes may reveal enlargement long before clinical œdema is visible. A sensitive scale is best. However, while too much water and/or too much sodium, potassium or chloride are toxic and even lethal, we think that the cause of preeclampsia is more complex. It probably begins as a salt and/or water retention which is general (not just in the legs) and soon there is an abnormal physiology of kidney, liver, endocrine glands, cardio-vascular system and brain. This abnormal body metabolism results in an intensified retention of water and/or electrolytes, thereby establishing a vicious circle. The deranged physiology can be controlled

in most patients by a low sodium diet and by delivery, but if neglected too long, the changes become irreversible and death occurs as a result of cardiac stoppage or failure, respiratory paralysis, hyperpyrexia, etc.

We have given various sodium salts by mouth and intravenously, and have learned the approximate amount which, in the susceptible individual, will cause not only a weight increase but also an elevation in blood pressure, marked and occasionally tremendous increases in the proteinuria, the onset of symptoms, etc. We have also learned the approximate time required for the excretion of injected sodium by the normal pregnant, the patient with essential hypertension in pregnancy, and the preeclamptic patient. We hope that we will be able to select those patients with too rapid weight gain, with or without œdema, but who can eliminate sodium in large amounts and in whom restriction of this ion is unnecessary. We have also learned that a number of patients with œdema, with slight hypertension and proteinuria, have no difficulty in excreting large amounts of injected sodium salts. Some of these patients were subsequently discharged from the hospital and not delivered for some weeks after the experimental injections. We believe that much effort and needless dietary restriction of sodium has been used in some of these patients.

Case Abstracts

Case 1. G.S.—399742. A 22-year old primipara was at term on 12.3.47, and was admitted to the hospital on 21.2.47 as a preeclamptic patient. Four intravenous injections of 1,000 ml. of 2 per cent sodium chloride solution in five days produced a weight gain of 8 kg., a marked increase in œdema, blood pressure, proteinuria and on 6.3.47 scotoma, a decrease in vision and epigastric pain. The cervix on vaginal examination was uneffaced and closed, therefore a cæsarean section under local anæsthesia was performed. The baby weighed 3,280 gm. The sodium and chloride retention amounted to 29 and 44 gm. respectively. The positive water balance is evident both from the increase in weight and difference in measured intake and urine volume. Repeated pituitrin tests were borderline. Thymol turbidity and serum bilirubin were

always normal. The cephalin flocculation test was abnormal on admission and normal by the eleventh postpartum day. Capillary fragility tests were normal. 40 gm. of concentrated salt-poor serum albumin caused a slight hæmodilution but a decrease in serum and blood volume.

She had a normal pregnancy in 1948 with no proteinuria. Five daily intravenous injections of 2.5 per cent sodium chloride solution, a weighed regular diet and 40 mg. of DCA were started on the fourth day of sodium chloride injections and were given for five days, resulting in a 0.2 kg. loss in weight, no increase in proteinuria, no change in hæmatocrit or serum protein concentration, and a decrease of the blood pressure from 115/70 to 80/46. She had a repeat cæsarean section on 3.7.48 at 39 weeks, the baby weighed 2,385 gm. The balance for sodium, chloride and water were normal and were markedly different from those in the first pregnancy. The urea clearance on 8.7.48 was 62 per cent normal, no proteinuria, but an increased number of erythrocytes and leucocytes (frequent finding after laparotrachelotomy). On 4.11.49 the patient was well, weighed 56 kg. and urine and blood chemistry were normal.

Case 2. I.G.—389897. A 20-year old primipara was at term on 4.5.47, and was admitted to the hospital on 11.3.47 because of +++ œdema and proteinuria, blood pressure of 174/120–154/110 and weight gain since 10.8 of 18 kg. Visits to the doctor had been irregular. On a regular diet and three daily intravenous injections of 1,000 ml. of 2 per cent sodium chloride solution there resulted a weight increase of 3.7 kg., an increase in the œdema especially in the face; scotoma, blurred vision, nausea and epigastric pain. She also showed an increase in the proteinuria to 28 gm. per twenty-four hours (Shevky and Stafford method), 17.4 gm. by micro Kjeldahl. 30 to 50 per cent of the urinary protein was albumin. Because of the marked proteinuria and increase in blood pressure, the saline injections were stopped. Thymol turbidity and cephalin flocculation tests were always normal. Serum bilirubin was increased after the saline injections. Labour began spontaneously and a 3,110 gm. baby was delivered by low forceps on 21.3.47 The proteinuria on 3.4.47 was still 7.6 gm. per twenty-four hours.

The second pregnancy was at term on 1.2.48. The hospital discharge weight on 4.4.47 was 47.5 kg. In November, 1947, when 26 weeks pregnant she weighed 50 kg. and on 17.1.48 she weighed 63 kg. but had no œdema or proteinuria. She was placed on a weighed regular diet and given six daily intravenous

injections of 2 per cent sodium chloride solution. There was a 19 gm. retention of sodium and 26 gm. of chloride, but no increase in weight (platform scale), proteinuria or blood pressure.

The third pregnancy was at term on 15.9.49 and was uneventful until 15.7.49 when her hæmoglobin was 8.9 gm. per cent. She was given a molybdenum iron complex. She was given 1 gm. enseals of sodium chloride on 22.7.49 and instructed to take seven per day. By 26.8.49 she had gained 1.56 kg. and had a + œdema. She was hospitalized on 26.8.49 for study (sodium chloride injections) but delivered a 3,380 gm. baby on 28.8.49. The enseals of sodium chloride, a weighed regular diet and one intravenous injection of 1,000 ml. and four of 1,500 ml. of 2.5 per cent sodium chloride were given daily in the early puerperium. The daily sodium and chloride intakes were over 19 and 30 gm. respectively. The normal weight loss was prevented but the œdema had disappeared and there was no increase in blood pressure or proteinuria. The sodium, potassium, and chloride retentions during this five-day period amounted to 37, 6, and 60 gm. respectively with a weight gain of 1.76 kg. The urea clearance on 16.12.49 was 110 per cent, the Addis count was normal, weight was 50.03 kg., hæmoglobin of 12.2 gm. per cent, and serum protein of 6.7 gm. per cent.

Case 3. E.W.—400384. A 28-year old gravida II, para I, was at term on 24.9.47. Family history: mother and one sister have hypertension and two sisters had toxæmia of pregnancy. The first pregnancy was supposedly normal The blood pressure was 144/96 when ten weeks pregnant, and labile thereafter with gradual increases. On 1.8.47 the blood pressure was 146/90 and œdema + but the weather was hot. On 16.8.47 the blood pressure was 160/103, ++ œdema and proteinuria ++ and she was admitted to the hospital. Ophthalmoscopic examination showed normal fundi. Sodium chloride injections caused a marked increase in the proteinuria and blood pressure, although weight increase (platform scale) was only 3 kg. There was a hæmodilution and increase in extracellular fluid volume but a decrease in plasma and blood volume.

Water clearance factor, water elimination after oral and intravenous administration, and delayed water excretion, are all characteristic of preeclampsia but hypertension appearing in early pregnancy and persistence for over one year postpartum are characteristic of essential hypertension. Both conditions may have been present. On 20.8.48 the blood pressure was 150/85, the weight was 61 kg. and no proteinuria.

Case 4. J.G.—450100. A 33-year old gravida III, para I, was at term on 6.1.49. She had a history of a 40 lb. gain and of œdema for four months in the first pregnancy. The urea clearance was normal but the Addis count was characteristic of chronic glomerulo-nephritis. She was hospitalized from 29.11.48 to 13.12.48 because of proteinuria of 5.9 gm. per twenty-four hours and slight hypertension. Twelve daily intravenous injections of 1,000 ml. of 2.5 per cent sodium chloride solutions caused no change in weight but a decrease in œdema and proteinuria. Definite hæmodilution as evidenced by a decrease in hæmatocrit and serum protein concentration. There was no increase in extracellular fluid volume. This patient was instructed to drink 200 ml. of fluid every hour while awake. The resultant large volume of urine enabled her to excrete most of the injected sodium chloride. The intramuscular injection of 40 mg. of DCA on the 8th, 9th, 10th and 11th days had no effect on the weight, sodium balance or plasma volume. The intravenous injection of 75 mg. of heparin at four-hour intervals on 12.12.48 for three injections had no effect. The proteinuria had decreased markedly before this injection. The patient was discharged and returned for an elective cæsarean section on 11.1.49 because of the persistent and marked proteinuria, which is frequently associated with intrauterine fœtal death. The Addis count was always abnormal and on 9.4.49 it was still suggestive of chronic glomerulo-nephritis. The clearance was 78 per cent and proteinuria of +++. Serum protein was 6.8 gm. per cent and hæmoglobin was 12.7 gm. per cent.

Case 5. G.L.—458798. A 34-year old gravida III, para nil, was at term on 23.8.49 and had a 10 kg. weight gain from 11.1.49 to 8.7.49; + œdema and no other signs. She was admitted on 12.8.49 having gained three more kg. and the œdema had increased to +++. The diet contained 0.23 gm. of sodium and 0.96 gm. of potassium. She was given seven enseals of 1.0 gm. sodium chloride and 1,000 ml. of 2.5 per cent sodium chloride solution intravenously for four days. There was an increase in the weight of 6.87 kg. in the blood pressure, but no change in proteinuria or in the degree of œdema, but the leg volume (small container—to middle of the thigh) increased from 13.9 to 14.9 litres (7 per cent increase) and the leg and thigh circumferences increased. They had decreased during the rest of the first night in the hospital. The sodium and chloride retention amounted to 28 and 41 gm. respectively. The potassium balance was negative for almost all of the antepartum days and markedly so during the early puerperium, the loss amounting to 33 gm. Ophthalmoscopic

examination on 13.8.49 showed vasospastic changes of preeclampsia but was normal on 29.8.49. The patient was in the climate room at 81°F. and a relative humidity of 61 per cent. The temperature was increased to 85° on 17.8.49. On 19.8.49 the relative humidity was increased to 80 per cent but the patient complained of difficulty in breathing and the humidity was decreased to 63 per cent. On 24.8.49 the relative humidity was increased to 73 per cent and the temperature was still at 85°F. 40 mg. of DCA daily for three days had no effect. The weight loss at delivery was 7.81 kg. Delivery was by outlet forceps. Pituitrin tests before delivery were 23 and 20 mg. Hg. increase (borderline) and no change after delivery. The patient drank 200 ml. of fluid per hour during the day throughout the hospital period, which may have prevented a greater retention of sodium. The water factor on the 9th postpartum day was 41 and the patient excreted 112 per cent of the ingested water. The urea clearance was 115 per cent. There was no proteinuria but the Addis count showed an increased number of erythrocytes.

Case 6. L.L.—392864. A 22-year old primipara was at term on 1.5.47. Between 29.10.46 and 25.4.47, she gained 12.6 kg. and then had œdema ++, blood pressure of 150/100 and no proteinuria. She was given intravenous injections of 320 ml. of molar sodium lactate diluted with 1,500 ml. of 5 per cent dextrose solution for four days and then 1,000 ml. of 2 per cent sodium chloride solution for seven days during the last four of which 40 mg. DCA were given daily. The sodium lactate injections caused an increase in weight of 2.1 kg. but the saline injections caused no increase in weight or proteinuria but a definite return of the œdema and an increase in the blood pressure. The pituitrin tests were normal. The serum sodium bicarbonate increased and sodium chloride decreased as a result of the lactate injections.

During the second pregnancy, at term on 12.3.49, there was a hypertension of 158/100, œdema + but no proteinuria. Ophthalmoscopic examination showed normal fundi. Twenty-four hours after delivery, 1 gm. enseals of sodium chloride were given seven times daily and 1,000 ml. of 2.5 per cent sodium chloride solution was injected intravenously for four days. The weight loss was not prevented. The blood pressure increased to 150/100 but soon dropped to normal. Urea clearance on 22.3.49 was 89 per cent, proteinuria + and a slightly abnormal Addis count.

Case 7. L.P.—392846. An 18-year old primipara was at term on 19.4.47. On 24.1.47 the caloric intake was reduced and on

28.2.47 she was placed on a low sodium (less than 0.5 gm.) diet. Two pituitrin tests gave negative results. Capillary fragility studies were normal. Thymol turbidity, serum bilirubin and bromsulphalein were always normal. Cephalin flocculation was borderline on admission, but was normal two days later. Ophthalmoscopic examination on 24.3.47 showed mild hypertensive retinopathy. From 22.3.47 to 25.3.47 she took 8 gm. of ammonium chloride daily. She was given two injections of 1,820 ml. of 1/6 molar sodium lactate but because of the marked increase in the serum sodium bicarbonate and decrease in the serum sodium chloride, the injection of lactate solution was reduced to 1,160 ml. of molar and 1,000 ml. of 5 per cent glucose solution. There was a retention of only 8 gm. of sodium for the period from 26.3.47 to 30.3.47 inclusive. There was a definite hæmodilution. Other patients have been given the total 1,820 ml. of 1/6 molar without any ill effect. The serum and blood volumes on 22.3.47 were 3,050 and 4,760 ml. respectively and on 10.4.47 were 2,270 and 3,610 respectively. Urea clearance on 10.4.47 was 75 per cent of normal, U/B was 56 and the Addis count was normal. There was no proteinuria.

Summary

Preeclampsia and eclampsia are the same disease, differing only in the occurrence of convulsions and/or coma in the latter condition.

Patients have different physiologic responses to abnormal balances of water, sodium, chloride and potassium which are associated with the signs and symptoms of preeclampsia-eclampsia.

Intravenous injections of adequate amounts of sodium chloride solution in some patients who apparently have preeclampsia, will cause marked increases in weight, œdema, blood pressure, proteinuria and the onset of the various symptoms and signs which either precede or are associated with eclampsia.

We no longer regard a proteinuria of 5 or more gm. per twenty-four hours (+++) in preeclamptic patients as an ominous sign.

The dietary restriction of sodium salts is not necessary in those patients who apparently have mild preeclampsia

but who can excrete large amounts of sodium. These patients probably have some other condition.

The ætiology of preeclampsia-eclampsia must be determined with the human subject. A relatively safe method is described for studying the physiologic changes associated with varying degrees of severity of preeclampsia and eclampsia without too much risk for the patient.

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TOXÆMIAS OF PREGNANCY IN THE DOMESTIC ANIMALS WITH PARTICULAR REFERENCE TO THE SHEEP

H. B. PARRY

Introduction

As I have been asked to introduce from the viewpoint of veterinary and comparative medicine the toxæmias of pregnancy as they occur in the domestic animals, I feel I should make a few introductory remarks, during which those of you who are familiar with the subject will I trust bear with me.

The so-called metabolic diseases we see in the domestic animals associated with reproduction fall into two main groups. The first group, which is widespread among the different species, comprises the neuromuscular disorders associated with disturbances of calcium, magnesium and phosphorus metabolism and observed chiefly at the time of parturition and the puerperium, more rarely at other times. They include milk fever and lactation tetany of cattle, lambing sickness of ewes, milk fever of mares and sows and eclampsia in the bitch. About these disorders I do not wish to say more, as they will be discussed in later papers this morning, but I do wish to stress the importance of distinguishing disorders of this group from those of the second group.

The second group of reproductive metabolic disorders are those confined to the pregnant animal and more properly termed toxæmias of pregnancy. The only species in which disease of this nature occurs as a well recognized entity is the sheep, although a similar entity has been reported in the pregnant bitch under experimental conditions, e.g. renal artery constriction (Dill and Erickson, 1938). However, I wish to confine my remarks to the syndrome in the sheep,

firstly reviewing very briefly the commonly accepted views, and secondly presenting the results of a large field experiment in Australia, the results of which, I think, make it essential that we enlarge our concept of the pathological physiology of this syndrome.

Pregnancy Toxæmia of Sheep

Occurrence

The syndrome known variously as twin-lamb disease, ketosis of pregnancy, ante-partum paralysis, etc., has been recognized since the last century as occurring in sheep in the latter two-fifths of pregnancy and in ewes carrying more than one lamb, although occasionally one single large lamb. The odd sporadic cases occur without any very obvious precipitating cause, but where a number of cases occur there is nearly always a history of a sudden change in the level of food intake—either semi-starvation after good food or very plentiful feeding after a period of semi-starvation. Often there is a history of sudden lack of exercise, such as sheep being fed in a yard after grazing on open pasture, or restrictions on movement, such as occur with heavy snow falls. No infective agent has been demonstrated and the animals will often recover if the fœtus is removed either by surgical means or by parturition (Groenwald *et al.*, 1941, *et seq.*).

The Clinico-pathological Syndrome

The principal signs are those of stupor, inappettence and a disinclination to move when animals are mustered. They often lie about in a coma and if forced to get up their gait is unsteady. There are in some cases some disturbances of vision. In many cases excessive quantities of ketone bodies occur in the blood and urine. The principal finding at autopsy is a yellow friable fatty liver, while the other internal organs appear normal.

Various hypotheses have been brought forward to explain the ætiology of the condition. One most favoured is that

the principal site of disorder is the liver and that due to the accumulation of fat in that organ its metabolism becomes disordered and hepatic insufficiency ensues. Another hypothesis stresses the importance of the ketosis and would attribute the syndrome to the high levels of ketone bodies in the blood.

Experimental Production of Pregnancy Toxæmia

Methods

The data I wish to lay before you today were obtained in Queensland in 1942 in some experiments which were designed by my old colleague, Dr. M. C. Franklin, of the McMaster Animal Health Laboratory, University of Sydney, to whom I am indebted for the biochemical data, and carried out with him and Mr. I. L. Johnston, B.V.Sc., of the C.S.I.R., Australia; the experiments were made possible by the generosity of Mr. Euston Young, of Noondoo, and the Australian Pastoral Company.

3,000 six years old Merino ewes were placed at our disposal. Without burdening you with the full details of the division of these animals into groups to control each stage of the experimental procedure, suffice to say that 510 ewes were finally selected as being pregnant, within three weeks of parturition and probably carrying twins. They were held in yards and partially starved for ten days, during which we observed some 100 cases of pregnancy toxæmia with a mortality of about 85 per cent. Of these, 70 cases were subjected to careful clinical, biochemical and pathological study, while eight normal ewes from a control group were killed as controls on the autopsy findings. It is a summary of these observations I should like to present to you very briefly now.

Clinical Signs

Cases began to occur on the third day of the regimen and reached a peak on the fifth day, declining until the tenth day. The earliest signs were inability to keep up with the mob

when mustered and a tendency to knock against gate posts. The appetite was capricious and rumination was usually suppressed. Later, when the syndrome was fully developed, anorexia was usually complete and there was no rumination, while the fæces, which are usually voided in the form of firm pellets, became soft and even unpelleted. The body temperature was often as high as 107°, and the respiration hyperpnœic, probably related to the intense solar hyperthermia ; the heart rate was accelerated, the femoral pulse was of small amplitude and soft tone, but the jugular venous blood pressure was maintained.

The most interesting signs, however, were related to functional deficits in the nervous system ; they were either general or local in distribution and persistent or transient in duration, and tended to occur in three or four clinical entities. These are illustrated in Plates I and II.

The obvious neurological signs were mainly concerned with the disturbances in the animal's awareness of its surroundings and the adoption of unusual postures. Animals would stand about in unusual postures for long periods at a time—some would sit in tins (Plate II, Fig. 3), others with their head rotated to one side (Plate I, Fig. 1), many attempted to force their head into the few available dark places, e.g. amongst the equipment boxes. Many showed no fear of man and could be approached in the open. Spasticity of the trunk and limbs occurred in some cases (Plate II, Fig. 4), occasionally being unequal between the two sides, so that the animal progressed in a circle. Disturbances in the visual system were constant ; they were often bilateral and symmetrical, but in a number of cases the defect was only apparent in one eye, while the opposite eye was unaffected. The pupils were constricted, with loss of the pupillary light reflex and the eye preservation reflex, while the corneal reflex and the conjunctival reflexes remained. The fundus was examined with the ophthalmoscope in a number of cases but no difference in the retinal blood vessels was noted between the affected and control animals.

PLATE I

NEUROLOGICAL SIGNS IN PREGNANCY TOXÆMIA OF EWES

(Photographs by Dr. M. C. Franklin)

FIG. 1. Abnormal standing posture with asymmetrical head rotation maintained for many hours without movement.

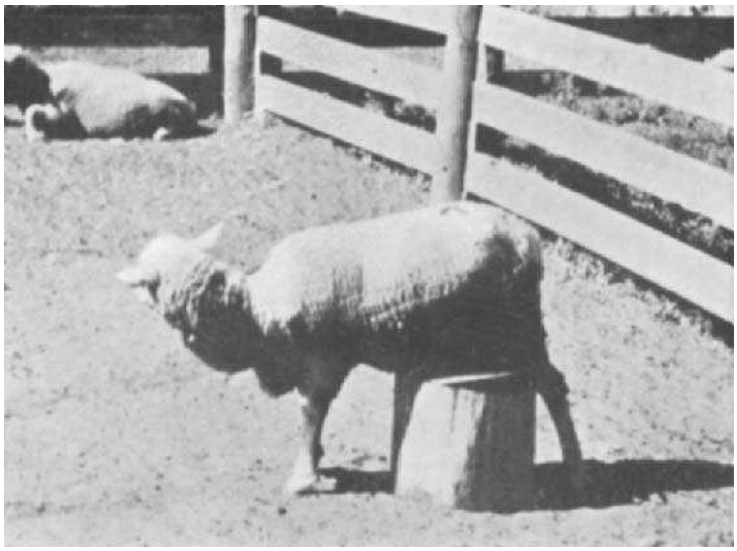

FIG. 2. Abnormal response to an obstruction with head rotation of transient duration.

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PLATE II

NEUROLOGICAL SIGNS IN PREGNANCY TOXÆMIA OF EWES

(Photographs by Dr. M. C. Franklin)

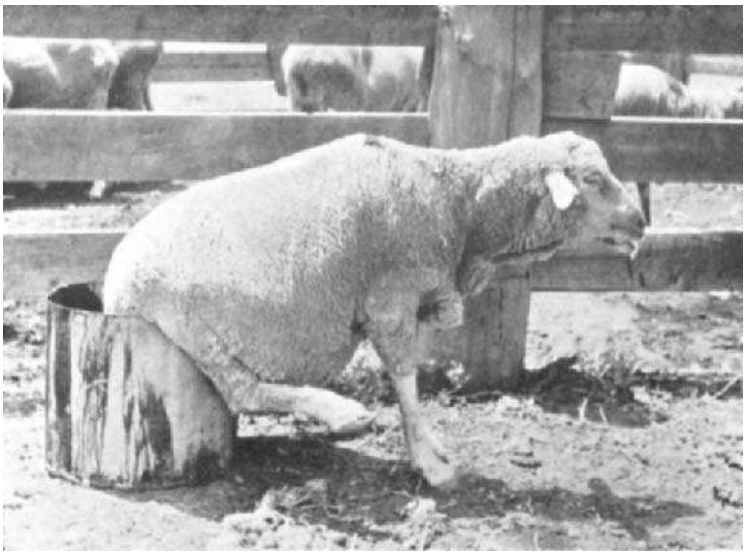

FIG. 3. Unusual sitting posture maintained on human approach. Note salivary discharge.

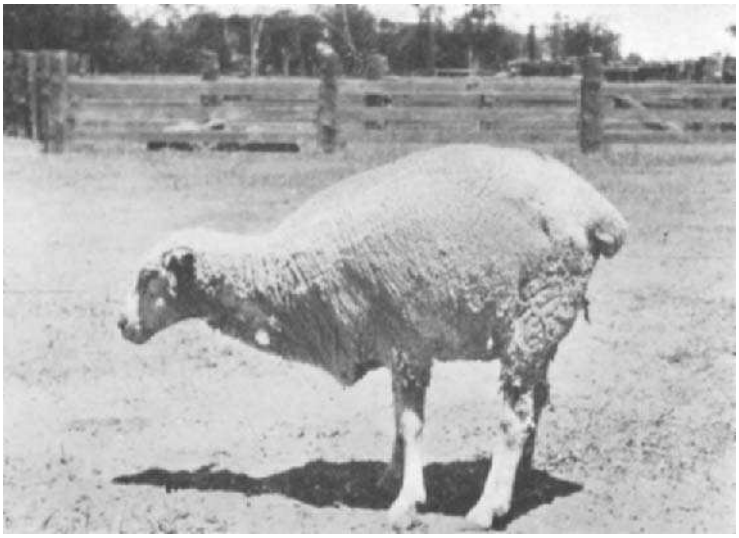

FIG. 4. Spasticity of limbs and trunk in an animal aware of human approach but immobilized by the rigidity of its limbs.

In some the neurological signs were transient and appeared for ten to twenty minutes only, so that unless the animals were under close observation these signs were easily missed. Such animals would walk backwards, would hold their head in an unusual posture with the nose elevated to one side (Plate I, Fig. 2), while occasionally twitching of one ear or a clonic spasm of the hind legs might appear for a few minutes at a time. Others would walk or run in circles. Between attacks, which were repeated at intervals in some cases, the animals appeared almost normal, apart from slight depression.

In the late stages of the disease, which lasted twenty-four hours to a week or ten days according to the severity, although most cases proved fatal in two to three days, the animal became prostrate or walked round in a stupor and died of some accident, such as falling into the watering place.

Biochemical Findings

Blood samples were taken before and during the disease in a number of animals and were analysed by Dr. Franklin for five main constituents, namely serum calcium, serum magnesium, blood sugar, blood ketones and non-protein-nitrogen. Briefly the serum calcium and serum magnesium values were within the normal range and we could detect no correlation between high and low figures and the clinical syndrome. The blood sugar levels were often below the normal lower range of 45–60 mg./100 ml., but a number of animals with values below 20 mg. were not particularly severely affected while a number of severely affected animals showed levels of 100 mg. and over. Many values for blood ketone levels were 30–40 mg./100 ml. but once again we could detect no correlation between the blood ketone level and the clinical syndrome and in several advanced cases the values were less than 10 mg./100 ml., i.e. within the range of our control animals. The non-protein-nitrogen values for the control ewes were about 40 mg./100 ml. In the early stages of the disease N.P.N. levels were 40–70 mg./100 ml. but there was a definite tendency for these to increase as the disease

progressed and shortly before death many animals had values of 100 to 180 mg./100 ml.

Urine samples were obtained from a small series of 14 animals including two controls and one recovered animal. Samples from the 11 affected animals all showed considerable amounts of protein, while the remaining three did not. Twelve of the samples, including two from the controls, were strongly positive for ketone bodies, while two from affected animals gave only a very slight reaction.

Autopsy Findings

In the majority of cases the most obvious feature was the pale friable fatty liver of a *café-au-lait* colour, but it must be stressed that this was not a constant finding and that in at least five cases the liver was a normal colour and consistency, while in the eight control ewes, seven of which had twins, three showed similar livers. More constant, but less spectacular, were changes in the kidney and adrenal glands, which were absent in the controls. In the kidneys the cortex was invariably pale with yellowish translucent streaks interspersed with pin-point reddish foci, while the medulla was a normal red colour. Histologically, Professor H. R. Carne was unable to detect any gross morphological abnormality to account for this cortical pallor, and it was not until the work of the Oxford group (Trueta *et al.*, 1947) was published that the possible significance of this became apparent. Even more constant than the kidney pallor was the pallor of the adrenal cortex ; in the normal sheep the colour of the cortex is darker pink than the medulla. However, without exception in our series, the cortices of the adrenals of affected animals were paler than the medulla, while those of the controls and recovered animals were the reverse.

The uterus was normal with twin, triplet or large single fœtuses and the membranes showed no gross abnormality. The fœtuses which were, in a number of instances, alive when the autopsy was carried out within half an hour of the ewe's

death, were normal, although in many instances the amniotic cavity was stained with meconium.

Discussion

I think that there is little doubt that the syndrome that we were observing was in fact identical with the naturally occurring toxæmia of pregnancy in sheep. The fact that a number of the clinical and especially neurological signs, as well as pathological changes, which we observed, have not been reported previously may be attributed rather to unfavourable conditions for observation than to the absence of these signs, since I have confirmed since my return to England that many of these neurological signs do in fact occur in affected animals in this country. Their occurrence and distribution make it essential that we reconsider the accepted ideas on the pathological physiology of the disease.

Our biochemical observations do not lend much support to the current theories of causation of the disease. The serum calcium and magnesium values indicate no severe disturbance of metabolism of these elements, although the calcium levels were low in some cases ; however, the clinical signs of hypocalcæmic states in the sheep are quite distinct and the parenteral administration of calcium had no influence in a small group of our cases. The importance of the low blood sugar levels is difficult to assess, but the failure to influence the course of the disease by feeding molasses, and the inconsistency of the low figures, together with the ability of the sheep to withstand phenomenally low blood sugar levels without showing clinical signs, which I know Dr. Phillipson has also observed, suggests that disturbance of blood sugar levels is merely a secondary effect. Similar considerations apply, we feel, to the interpretation of the elevated blood ketone levels. While awaiting Dr. Phillipson's paper with great interest, we must say we consider that the significance of elevated blood ketone levels has been over-emphasized by some workers in the past. It is difficult to explain in the light of Eden and Green's (1940) observations on cows, in

which they found blood ketone levels as high as 45 mg./100 ml. in clinically healthy animals, how similar levels can be responsible for the profound clinical effects we have observed in sheep, and for the unilateral and transient distribution of some of the neurological signs.

However, I would like to focus your attention upon the observations which suggest that a profound vasomotor disturbance is involved. The changes of colour in the adrenals and kidneys at autopsy, unassociated with morphological changes, indicate a tissue anoxæmia due to changes in the vascularity of these organs. Such a concept involving renal cortical anoxæmia would explain the presence of terminal renal insufficiency, which the N.P.N. figures and the presence of protein in the urine indicate. If, indeed, disturbance of vasomotor tone were the underlying disorder, vasomotor spasm in the cerebral circulation would serve to explain many of the anomalous and transient neurological signs. Indeed, it is difficult to understand how one can get unilateral reversible disturbance of function in the central nervous system in these cases unless some vascular mechanism was involved.

For the present this interpretation of the pathological physiology of pregnancy toxæmia in the ewe must remain entirely hypothetical, since we have been unable to demonstrate quantitatively changes in the vascular bed of the different organs. This is no easy matter unless one can observe directly changes in the retinal blood vessels; our failure to do so may be possibly due to lack of experience and somewhat difficult field conditions.

Conclusions

In conclusion I would make two points. First, that the accepted theories as to the ætiology of pregnancy toxæmia in the ewe are, in my view, quite inadequate to explain many of the observed facts, and that the hypothesis of primary vasomotor disturbance leading to secondary renal-adrenal insufficiency with subsidiary hepatic disorder is more in

accord with these facts. I shall await with great interest the comments of those primarily interested in human medicine, since I believe this new hypothesis does bring our concepts of the ovine disease more in line with those held regarding the toxæmias of pregnancy in women.

This brings me to my second point. We can now produce at will, given a little luck, the syndrome of pregnancy toxæmia in ewes. This does allow us to use a new experimental approach for the study of departures from the normal natural history of pregnancy, and should allow us to evaluate more accurately the very many factors, whose interaction gives rise to the disorder we call toxæmia of pregnancy.

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EXPERIMENTAL KETOSIS IN PREGNANT EWES

A. T. PHILLIPSON

THE work to be described here is that concerned with the production of experimental ketosis in pregnant ewes for, as far as I am aware, this is the only one of the farm animals in which this condition is a serious source of loss to farmers; ketosis in dairy cows is not associated, in particular, with pregnancy. Another reason why the discussion will be confined to pregnant ewes is that only in these animals has experimental ketosis been produced.

The condition which may arise clinically in pregnant ewes in the later stages of gestation and which is accompanied—in the majority of cases—with ketosis is usually referred to as "pregnancy toxæmia." The signs and symptoms briefly are as follows: the ewe is found to be weak, often unable to stand, and shows no desire to eat food. Often the animal is apparently blind and other signs of deranged nervous co-ordination may appear. As the condition progresses the animal may assume a position of recumbency with the head held round to the flank in a manner reminiscent of "milk fever" in cattle. Analysis of the blood shows—in the large majority of cases—ketonæmia and hyoglycæmia. Acetone can be smelt in the breath and ketonuria is present. On post-mortem examination the two outstanding features are first, a grossly fatty liver, which on histological examination gives a picture of fatty infiltration with no signs of necrosis, and second, usually but not invariably, the presence of two or more fœtuses. Fatty infiltration of the tubules in the cortex in the kidney has been described.

Dryerre and Robertson (1941) found that an increase in the total liver lipides of normal Welsh ewes increased throughout

pregnancy and reached its peak by the last month of pregnancy ; on this score they suggest that mobilization of fat and fatty infiltration of the liver is a normal accompaniment of pregnancy in the ewe and is not peculiar to animals suffering from pregnancy toxæmia, especially as they found no correlation between multiple pregnancies and the degree of fatty infiltration. Snook (1939) on the other hand found a considerable increase in the fat content of the livers of ketonæmic ewes while the fat content in the livers of three pregnant ewes fed a fattening ration was within normal limits. The discrepancy in these results may be due to the speed with which body fat can be mobilized in healthy pregnant ewes and that even a twenty-four-hour fast may produce a greater degree of fatty infiltration in pregnant ewes than in non-pregnant animals.

A variety of conditions have been claimed to predispose to pregnancy ketosis in ewes ; these are overfatness combined with lack of exercise ; undernutrition—the precise opposite—especially in the later stages of pregnancy ; insufficient protein in the diet ; sudden changes in diet particularly in the later stages of pregnancy, and finally sudden changes in the weather, particularly snowstorms or other conditions likely to deprive sheep of their food.

This confusion has now largely been cleared up owing to experimental work designed to define the nutritional conditions which predispose to this condition. The first to produce experimental ketosis was Hopkirk (1934) in New Zealand, who placed pregnant ewes during the last few weeks of pregnancy on a ration of hay which was insufficient for their needs, and found that seven out of nine animals developed a condition which was apparently similar to the clinical entity. Five of the animals died, and two slowly recovered, one of those recovering having only one lamb.

The work of Fraser, Godden, Snook, and Thomson (1938, 1939) at the Rowett Research Institute, however, was performed on a far larger scale and represents the first experimental work to examine all the previously mentioned

hypotheses concerning the conditions predisposing to pregnancy toxæmia. This work was designed so that an exact nutritional history of a large number of pregnant ewes could be recorded and correlated to the onset of ketosis. The conditions were arranged to see the effect of :—

(1) Feeding ewes throughout the gestation period on a fattening ration with close confinement.
(2) Feeding ewes on a fattening ration in close confinement and suddenly reducing their food intake by a two-day fast. This was followed during the last month of pregnancy by a period of restricted feeding ; a period of full feed and a second fast.
(3) Feeding a maintenance ration throughout pregnancy with an enforced forty-eight hours fast in the terminal stages.
(4) Feeding a maintenance ration followed by liberal feeding in the last month of pregnancy.
(5) Feeding a maintenance ration low in protein and comparing it to a maintenance ration rich in protein.

The results of this work (see Tables I to III) were striking.

Table I

Group	Summarized Treatment	Daily Intake	
		Starch equiv. lb.	Protein equiv. lb.
1	Fed to overfatness	1.69	0.24
2	Fed to overfatness. Periods of fast . .	1.69	0.24
3	Undernourished. Period of fast . .	0.75	0.10
4	Undernourished	0.75	0.10
	Period of liberal feeding in last month of pregnancy	1.71	0.40
5	Low protein intake	0.80	0.086
6	Adequate protein intake	0.81	0.154

None of the ewes (Group I) receiving a fattening ration throughout pregnancy developed anything resembling preg-

nancy ketosis, in spite of lack of exercise, whereas ewes on the same ration but subjected to a sudden fast three weeks before they were due to lamb (Group II ; Table II) became very apathetic and weak and lost their appetite. Some of these animals became comatose and blindness developed. When given food again they showed little desire to eat but they did slowly pick up again. Blood analysis showed that blood sugar on an average had fallen by 25 per cent, but ketones were present in the blood in only two animals out of fifteen. During the following seven days, however, while maintained on a restricted diet, ketones appeared in the blood in nine out of the 15 ewes. The interesting thing in this group is that two ewes that showed least drop in blood sugar and no ketosis were the most severely affected, while the ewe with the greatest amount of ketones in the blood attracted no attention. After a week of restricted feeding the full ration was fed again and blood sugar returned to normal and ketones disappeared from the blood. A second fast in the last week of pregnancy, although producing a greater degree of ketosis and a greater fall in blood sugar, 50 per cent, had less effect on the ewes. Although the ewes were weak, they were more alert than in the earlier fast, and withstood it better.

The group of ewes (Group III) that received a maintenance ration followed by a forty-eight-hour fast fared better. Although blood sugar fell to very low levels in some ewes, and the level of ketones in the blood rose to a higher level than in the fat animals—they were present in the blood before the fast commenced—none of the ewes looked as ill as those that had been on the fattening ration. They became weak and had the general appearance of "weariness," and three developed other signs of pregnancy toxæmia, yet when food was given again they went to the troughs and ate some food although it was a little while before their appetite fully returned. These ewes in fact withstood the fast better than the fat ewes, and in both groups 75–80 per cent of the animals carried twins.

Table II

GROUP II—FED TO OVERFATNESS.

Periods of Fast.

Ewe No.	Blood Ketones—mg. per 100 ml.								Blood Sugar—mg. per 100 ml.							No. of Lambs
	1937 27/10	1938 28/1	15/2*	17/2	24/2	5/3*	7/3	12/3	1938 28/1	15/2*	17/2	24/2	5/3*	7/3	12/3	
61	0	0	0	0	23	0	5	L	50	58	44	44	63	27	L	2
51	0	0	0	0	32	L	L	L	50	56	39	37	L			2
92	0	0	0	Tr.	14	0	13	49	52	58	34	46	54	22	47	2
65	0	0	0	Tr.	27	0	13	0	37	40	30	30	48	26	56	2
28	0	0	0	9	24	5	L		42	42	30	36	43	L		2
88	0	0	0	0	0	0	0	0	46	53	53	48	53	36	53	1
97	0	0	0	0	0	0	Tr.	0	59	55	37	48	54	25	54	1
83	0	0	0	0	Tr.	L			46	52	38	47	L			2
99	0	0	0	0	12	0	9	0	50	62	44	54	53	27	54	2
96	0	0	0	0	0	0	7	L	48	50	48	45	63	28	L	1
63	0	0	Tr.	0	40	0	Tr.	0	42	46	30	28	42	25	43	2
98A	0	0	0	0	0	0	0	0	46	43	38	33	52	26	48	2
76	0	0	0	0	21	0	19	L	50	56	37	32	49	28	L	2
66	0	0	0	5	56	0	15	L	50	53	39	31	54	30	L	2
85x	0	0	0	0	0	D			54	55	58	52	D			(2)
Aver.									48	52	40	41	52	27	51	

* Period of fast commenced.

Table III

GROUP III—UNDERNOURISHED.

Period of Fast.

Ewe No.	Blood Ketones—mg. per 100 ml.						Blood Sugar—mg. per 100 ml.					No. of Lambs
	1937 29/10	1938 26/1	17/2	25/2*	27/2	9/3	1938 26/1	17/2	25/2*	27/2	9/3	
25	0	0	Tr.	13	27	9	38	47	37	26	43	2
70	0	0	0	0	25	19	36	38	40	15	33	1
48	0	0	12	29	lost	36	47	48	36	36	40	2
17	0	0	9	25	48	Tr.	40	42	32	24	42	2
26	0	0	9	15	35	Tr.	45	39	40	24	54	2
62	0	0	24	24	47	32	38	32	23	21	32	2
6	0	0	0	0	11	0	45	50	52	39	50	1
54	0	0	0	0	11	0	42	40	43	24	49	1
19	0	0	8	19	39	Tr.	42	39	32	16	50	2
58	0	0	14	29	55	20	40	39	33	21	46	2
37	0	0	19	25	43	28	34	19	28	14	39	2
75	0	0	0	Tr.	41	0	44	50	40	22	46	1
21	0	0	15	21	43	49	50	42	34	20	21	2
64	0	0	35	44	56	L	44	32	28	22	L	2
91	0	0	0	0	0	0	53	50	46	43	52	barren
Average							42	40	36	23	42	

Data for the barren ewe (No. 91) are excluded from the averages.

* Period of fast commenced.

The group of ewes (Group IV) that received a fattening ration for the last month of pregnancy thrived, and the small amount of ketones that had developed on the restricted ration disappeared. None developed pregnancy ketosis.

The two groups of ewes (Groups V and VI) receiving a maintenance ration through the whole of their pregnancy showed little difference irrespective of whether the food contained a little or a lot of protein. Animals in both groups became ketonæmic and some showed clinical signs while others showed none. No evidence was obtained to show that extra protein in ration in any way improved the lot of those ewes receiving it.

It was quite clear from these experiments that a condition simulating pregnancy ketosis by its clinical signs and symptoms could be produced :—

(1) By suddenly fasting fat ewes in the last few weeks of pregnancy ;
(2) By feeding an inadequate ration followed by a sudden fast ; and
(3) That supplementary feeding in the last month of pregnancy will prevent the onset of ketosis.

Further analysis in the following season enabled Fraser and his colleagues to show that supplementing a maintenance ration with starch alone, or with maize meal, would prevent the onset of ketosis, so that there is no doubt that this condition, as observed experimentally, is due to inadequate feeding as measured by calories. It is not due to overfatness, lack of exercise, or to insufficient protein alone.

These results have been largely confirmed by Groenwald *et al.*, 1941 ; Clark *et al.*, Clark, 1943, in South Africa. The dietary limitations to which their ewes were subjected seem to have been rather more severe than those just described ; thus ewes were fed on a production ration and switched abruptly on to a ration of veld hay at the beginning of the fifth month of pregnancy ; the result was a rapid fall in body

weight of approximately 15–20 lb. body weight or more in 14 days and the onset of severe ketonæmia. Two groups of ewes were given either an ounce of cane sugar or an ounce of meat meal as a supplement, but neither supplement was adequate in quantity to make up for the caloric deficit and consequently ewes in both groups developed ketosis. It is interesting, however, that a group of barren ewes that received the same treatment, changing from a production ration to a ration of veld hay with no supplement, also contained animals that showed signs of ketosis; the symptoms, however, were less severe than those seen in pregnant ewes, and took longer to develop, twenty-four to forty-eight days as opposed to three to seven days for pregnant ewes, which is an indication that the role played by the fœtus is that of placing greater demand on a ewe so that she is particularly susceptible in the last month of pregnancy.

The first question to ask of these experimental studies is whether the conditions produced are in fact clinical "pregnancy toxæmia." The clinical signs that are described by Fraser *et al.* and Groenwald *et al.* are consistent with those described from clinical cases in the field. The ketonæmia and hypoglycæmia found in experimental ketosis is also present in clinical cases. In addition the livers of animals suffering from experimental ketosis have a high fat content, and on histological examination show fatty infiltration (Snook, 1939; Groenwald *et al.*, 1941), as do those of clinical cases, although here we must recall that Dryerre and Robertson (1941) found that fatty infiltration of the liver appears in apparently normal pregnant ewes. In addition there is correlation between multiple pregnancy and experimental pregnancy ketosis; ketosis being more severe in ewes with two or more lambs. The two conditions, in fact, seem to be the same, and if this is so then clinical pregnancy toxæmia can be prevented by additional feeding during the last month of pregnancy and by avoiding as far as possible sudden checks to the food available to ewes.

The second point we must consider is whether the condition that develops in fat ewes subjected to a sudden fast is really the same as that seen in ewes on poor ration. In the first instance we have ewes that are not starving, and from their bodily condition would not appear to be in danger of dying of starvation, for they have ample body reserves with which to meet the sudden demand made upon them. In the second instance we have ewes already in a poor state of nutrition suddenly called upon to live on their body reserves and here one can reasonably assume that the condition is due to starvation.

With both groups of animals a fast in the last month of pregnancy must be much more severe than at other times, as the metabolism of the ewe is increased owing to the additional metabolism of the rapidly growing fœtus; if two fœtuses are present then presumably the increase will be greater, for although individual twins are smaller than singlets, yet together they weigh considerably more, and as such have together a total metabolism that is greater than one better developed lamb. Thus Philips (1928) gives the average birth weight of singlet lambs of Welsh ewes as being 8.9 and 8.4 lb. for male and female lambs, while the corresponding weights for individual twins were 8.0 and 7.1, or one ewe would bear on an average twins weighing together 16.0 or 14.2 lb. Barcroft (1946) gives figures for the oxygen consumption of the fœtus of the Welsh ewe at various stages of gestation and at 136 days the figure is 6.6 cc./kg./min., which is 9.5 litres per kg. per twenty-four hours. The weights of single and twin fœtuses of the Welsh ewe at 136 days from Barcroft's figures may be of the order of 3.5 and 3 kg. respectively. It is not possible to convert these figures precisely in Calories without a knowledge of the respiratory quotient, but if we assume that the metabolism of the fœtus at this stage is largely due to carbohydrate so that the caloric value of a litre of oxygen is approximately 5, then the heat produced by one 136-day fœtus per twenty-four hours is approximately 115.5 Calories and for twin fœtuses 198

Calories. Brody (1945) gives the resting metabolism of a 25 and 50 kg. ewe to be in the region of 1,240 and 1,575 Calories per day respectively. Welsh ewes weigh from 30–40 kg. so that we can expect their resting metabolism to be in the region of 1,380 Calories per day, and if we add to this the Calories produced by single and twin male fœtus at 136 days pregnancy, we find that the single fœtus is responsible for 10.7 per cent of the total Calories and the twins 17.1 per cent. There is still dispute whether the total metabolism of the mother is the sum of her own metabolism and the fœtal metabolism for there is some evidence to suggest that the mother's metabolism is itself increased slightly; however, these figures illustrate the extra demand the fœtus makes on the mother in the last fortnight before lambing and the extra burden imposed by twins. Bearing this in mind it seems that in ewes subjected to a sudden fast, the switch in metabolism must be more rapid in ewes bearing twins than in those bearing singlets or in non-pregnant ewes, to allow both mother and fœtus to maintain themselves, and this is probably the reason why ketosis—if we take this to imply an excessive utilization of body fat—develops rapidly. Here it is interesting to recall that of the fat ewes recorded by Fraser *et al.* (1938), those showing greatest distress when fasted were those with the least change in the blood picture; in fact one is tempted to suggest that the appearance of ketones in the blood is a sign that a rapid switch in metabolism has been accomplished successfully, and that severe "pregnancy toxæmia" appears in those animals which fail to accommodate themselves and so show relatively little change in the blood picture. Also we can suggest that the ewes on a poor ration were already attuned to the use of body fat and the effect of fasting accentuated fat metabolism so that the condition of the ewe was not so disturbed by the extension of a process already begun. If this hypothesis is correct then the two conditions are not the same, and future research can be directed towards discovering and studying the factors which limit the ability of the pregnant ewe to make a rapid change in metabolism.

There is plenty of evidence to show that β-hydroxy butyric acid is rapidly oxidized by many of the tissues and that its appearance in blood is indicative of increased production rather than inability to utilize it. Ketosis therefore is not necessarily the cause of the signs of the condition—weakness, inappetence, and coma, etc.—but is an accompaniment to the true crux of the metabolic disturbance.

It is clear that an additional supply of calories will prevent either condition appearing, but once it has occurred, glucose therapy, unless applied in the early stages, does not appear to be effective alone. The traditional method adopted by shepherds is to drive the ewes about and not let them rest, and that is said to be effective; working on the supposition that low blood glucose is the important factor Thompson and Thomson (personal communication) used adrenaline in the early stages with good results. Whether this response can be equalled by the injection of glucose is not so clear; several workers claim good results in the use of glucose, while others say that its use is disappointing. My own experience of glucose is extremely limited, but one case in particular was examined closely for several days, and administration of glucose was apparently responsible in tiding the ewe over the last week of pregnancy until she lambed; in spite of the fact that her blood sugar was less than 10 mg. per cent for three mornings in succession before glucose was given. Clark *et al.* (1943) claim good results with the use of glucose plus Vitamin B1. Other claims have been made at various times but no established remedy beyond glucose therapy has emerged. As, however, it is possible to produce pregnancy ketosis in two distinct ways, the opportunity exists of investigating further the critical change in metabolism, and of testing experimentally the effect of various methods of therapy without relying on clinical material with its inevitable inconveniences and limitations.

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THE INFLUENCE OF THE LEVEL OF CALCIUM IN THE DIET OF THE RAT DURING PREGNANCY AND LACTATION

(short contribution)

JOHN DUCKWORTH

STUDIES of the effect of the level of calcium in the diet of the rat were carried out over periods of three successive gestations and lactations, using 144 animals (Ellinger, Duckworth, Dalgarno and Quenouille, 1950).

The diet was composed of natural feeding stuffs, blood meal (dried at low temperatures) and dehydrated cooked cod flesh being used as sources of protein low in calcium. The diet of lowest calcium content contained 0.04 per cent calcium. Others were adjusted to contain 0.29, 0.54 and 0.79 per cent calcium.

When the diet contained only 0.04 per cent of calcium the withdrawals of minerals from the skeleton, over three gestation-lactation cycles, amounted to about 60 per cent.

In spite of this there was no detrimental effect on the health or reproductive capacity of the dams. There was no effect on the fertility of the animals and no effect upon litter size or the weights of new-born litters. The viability of the young was not affected. Calcium deficient mothers were not more prone to cannibalism or failure to lactate than calcium adequate animals. The growth of the young up to weaning was adversely affected, a reflection, probably, of milk production being reduced by inadequate milk supplies. Nevertheless the proportion of young successfully reared was not lower in calcium deficient litters than in normal litters.

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NEONATAL ATAXIA OF LAMBS

RUTH ALLCROFT

THIS disease of lambs has a wide geographical distribution throughout England, Wales and Scotland, and has been known for many years under a variety of names such as "swayback," "swingback," "bentback," "warfa," and others. It also occurs in other parts of the world and has been shown to be pathologically similar to "enzootic ataxia" of lambs in Australia, as described by Bennetts and his colleagues (Bennetts and Chapman, 1937; Bennetts and Beck, 1942), and to "renguerra" in Peru, described by Gaiger (1917).

Although the disease has a wide distribution throughout the country, the incidence varies from year to year on the same farms and in the same districts, but there are some areas, such as parts of Derbyshire, where it occurs year after year, the only variation being the percentage of lambs affected each year. Before prophylactic measures were taken the mortality in severely affected areas varied annually from 5 to 50 per cent of the lambs born, while in exceptionally bad years the losses sometimes reached 80 per cent.

Ewes of any age or breed may give birth to ataxic lambs, and ewes which produce affected lambs one year may produce normal lambs the next, but in our experience occurrence of the disease is broadly related to length of sojourn on "affected" farms.

Symptoms. There appear to be two types of the disease, (1) the common acute form in which the lambs are affected when born and (2) a "delayed" type which may develop as late as three months after birth. In both, however, the symptoms are essentially those of a spastic paralysis, particularly of the hind limbs, and vary only in degree of severity. All cases show incoordination of movement; severe cases are

unable to stand or walk; others may rise and walk with difficulty, while mild cases show only slight weakness of the hind quarters, particularly when made to move quickly.

Severely affected lambs usually die shortly after birth, but mild cases, usually of the delayed type which show only slight incoordination which does not progress, often survive, and when bred from later, may produce quite normal lambs. Mothers of affected lambs remain apparently healthy and show no clinical symptoms.

Pathology. Innes and Shearer (1940) carried out a detailed pathological study of the disease in this country, and showed that it is characterized by a diffuse symmetrical demyelination of the cerebrum, varying in extent from small foci in the centrum ovale to gross demyelination of the whole hemispheres with liquefaction and cavitation in extreme cases. Secondary degeneration of the motor tracts in the cord is always present.

Evidence at present indicates that demyelination occurs at a relatively late stage of the five months gestation period, probably within the last six weeks, i.e. after cerebral myelination has begun. Romanes (1947) has shown that the first myelin appears in the forebrain of the lamb at 96 days.

Ætiology. From 1932-37 many attempts were made to transmit the disease and to isolate a specific organism from tissues of affected animals, but all were negative. In 1937 Bennetts and Chapman in Australia first showed that the disease was related to a copper deficiency of the herbage. Later Bennetts and Beck (1942) showed that copper values of blood and liver of ataxic lambs and their mothers were extremely low and that the disease could be prevented by administration of copper to the ewe during the gestation period.

Subsequent work in Britain showed a similar low copper status of swayback lambs and ewes and it is now well known that the disease can be prevented by incorporating a little copper sulphate in licks or mineral mixtures for pregnant ewes. If the ewes do not voluntarily consume sufficient,

two substantial oral doses, one at eight weeks and the other at four weeks before lambing are adequate. Although not feasible in ordinary farming practice, Weybridge work has shown that a single intravenous injection of 20 mg. Cu as copper sulphate to the mother about six weeks before parturition, will also prevent the disease.

In so far as blood copper values are concerned a figure of about 1 mg. per litre may be regarded as a common normal for sheep and it is rare to find a ewe delivering a swayback lamb unless its blood copper is well below this. In Derbyshire, by far the greatest incidence of the disease occurs in lambs from mothers with blood copper values ranging between 0.1 and 0.6 mg. per litre. The relationship, however, is complicated by various factors such as the wide variation of blood copper levels in individual members of flocks on farms with no history of swayback. For example, Eden (1941) showed a tenfold variation in blood copper, from 0.2 to about 2.0 mg./litre with an average value of 0.8 mg./litre, in about 100 ewes on a farm in Northumberland observed for swayback for four years with negative results. The same ewes tended to remain high or low in successive years. The relationship therefore between low blood copper values in ewes and occurrence of the disease in their lambs is a "one-way correlation." An individual blood copper value is of no diagnostic significance and all that can be said is that if the blood copper status of a flock of ewes is low, a high incidence of swayback in their lambs is likely to occur.

Although swayback and enzootic ataxia of Australia correspond very closely, there is the important ætiological difference that in Australia the disease occurs on pastures low in copper, below 5 p.p.m. on a dry matter basis and commonly below 3 p.p.m., whereas in Britain it occurs irrespective of copper content and is prevalent in Derbyshire at levels of 7 to 15 p.p.m. or more. In Australia the disease has been attributed to a simple copper deficiency rectifiable by fertilizing the soil with copper salts. In Britain another factor seems to operate, which either depresses the availability of

the copper in the plant, or in some way interferes with copper metabolism in the animal itself.

The factor in the pastures which induces the disease in spite of normal or high copper content is unknown, but experimental work carried out at Weybridge about five years ago showed that it exists in transportable form. When 20 ewes, each with low blood copper and each with a past history of bearing swayback lambs, were transferred from an affected farm in Derbyshire to Weybridge soon after tupping and fed in stalls on a ration containing only one third of the copper in the natural "swayback" pasture, blood copper values rose to normal and no swayback appeared in their lambs. But when the experiment was repeated, substituting hay from the "swayback" farm for the Weybridge roughage, blood copper remained low and four of the 20 lambs born were affected, an incidence similar to that of controls on the farm.

There has been much speculation regarding the nature of the unknown factor. Lead has been suggested because pastures in some areas where the incidence of swayback is high, show a high lead content due to surface contamination from plumbiferous soils. The view has therefore been advanced that the complicating factor is a combination of high lead with low or moderate intake of copper. Observations at Weybridge showed that a daily dose of 50 mg. Pb as the acetate to hypocupræmic ewes did not increase the incidence of ataxia in the lambs nor did a high lead intake produce hypocupræmia in sheep even when given in quantities ranging from 100 to 400 mg. Pb daily for as long as a year.

Another suggestion is that a combination of moderately high molybdenum with low or moderate copper content of pastures causes a "conditioned" copper deficiency in sheep and cattle (Dick and Bull, 1945; Cunningham, 1946). Investigations at Weybridge have not so far confirmed these views and indicate that molybdenum content of pastures in Britain bears no relationship to incidence of swayback. Herbage samples from farms in Derbyshire where incidence of swayback was high showed normal molybdenum values of

0.6 to 1.8 p.p.m. on dry matter while on farms in the teart area of Somerset swayback is unknown in ewes grazing pastures with molybdenum contents ranging from 15 to 30 p.p.m. Further experimental work showed that administration of relatively large amounts of molybdenum over a period of fifteen months to sheep in which blood and liver copper values were known to be low (0.2 mg./litre and 15 p.p.m. on D.M. respectively) not only failed to maintain the initial low copper status but permitted rise of both blood and liver values to normal levels. At the conclusion of the experiment liver tissue had reached a mean value of 528 p.p.m. on a dry matter basis as compared with 512 p.p.m. for a normal control.

Since the unknown factor might also be organic, and compete for copper in enzyme systems in the same way as 2,3-dimercaptopropanol competes for metals when used as a detoxicating agent, large daily intramuscular injections of this compound were given to six normal ewes for periods of four to six weeks before lambing. This had no effect on the copper status of the mothers, and all lambs were born normal.

In conclusion it should be mentioned that during the last two or three years hypocupræmic disorders of bovines have been found widely distributed throughout England and Scotland (Allcroft, 1946; Jamieson and Allcroft, 1949; and Allcroft and Parker, 1950). In this condition, however, no demyelination disorder of calves has been observed and it is the growing and adult cattle which are affected. The clinical and pathological features are entirely different from those observed in hypocupræmic conditions in sheep. As in swayback the occurrence so far has been observed only on pastures of normal copper content and response to administration of copper is rapid. The disorder has been found on farms where swayback occurs in sheep and the evidence so far indicates operation of the same ætiological factor in these two pathologically diverse hypocupræmic diseases. It is interesting that a low copper status should be associated with cachexia in the cow without demyelination in the calf, yet

leave the adult ewe apparently healthy while affecting the lamb *in utero* so profoundly.

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OBSERVATIONS ON AND TREATMENT OF CLINICAL ACETONÆMIA IN CATTLE

A. MESSERVY

ACETONÆMIA is always associated with parturition and is sometimes accompanied by nervous symptoms. It is a post-parturient disease of high producing cows—not necessarily well fed—characterized by marked hypoglycæmia and acetonæmia, and is thought to be due to a deranged carbohydrate metabolism. The frequency with which it occurs on certain farms tends to point to some mismanagement or deficiency in soil.

It has been demonstrated that following parturition no reduction in the amount of blood sugar can be found in the normal cow, but there may be a tendency towards acetonæmia at the time of parturition. In marked ketosis, however, there is a pronounced drop in blood sugar and a substantial increase in blood ketones.

Ketone production by the liver from body fat is considered to be part of a normal reserve mechanism which is brought into play when the body lacks energy, because of a carbohydrate deficiency. There is no general agreement why the lack of carbohydrate occurs, and it is not surprising, therefore, that workers disagree on what constitutes rational treatment.

It has been suggested that hypoglycæmia is the essential and primary cause of acetonæmia, but in all cases where blood sugar determinations have been carried out, none have shown hypoglycæmia without acetonæmia.

Is it possible that there is a temporary imbalance between the various hormones secreted at the time of parturition? There is at this time a sudden increase in prolactin which is essential for lactation and the continued milk secretion. It may be, therefore, that the dairy cow with its greatly hypertrophied udder, and this applies particularly to the Jersey

on which all my observations have been made, requires an increased secretion of prolactin which in turn may affect the production by the pituitary of the diabetogenic factor, resulting in hypoglycæmia.

It is worth noting that in most cases of severe acetonæmia the serum calcium is normal.

In the normal cow the amount of acetone bodies in the blood is similar to that of other mammals, namely a few milligrams per cent. In a series of 83 cases of clinical acetonæmia the amount of acetone in milligrams per 100 c.c. of serum varied between 17 and 105, the average being 48.

The blood sugar in the lactating cow falls between 50–60 mg. per 100 c.c. of whole blood, which is low compared with the carnivore. In 50 cases of acetonæmia the average blood sugar was 34 mg. per 100 c.c. of whole blood.

Acetonæmia always occurs in high producing post-parturient cows, of any age, at any time of year, and in animals that have calved normally. Although a few cases have been encountered in which fœtal membranes have been retained, this cannot be regarded as an important factor.

Acetonæmia is frequently seen in the same cow at successive parturitions. It is almost certain that the milking of cows three times a day, thereby increasing production, and the failure to allow cows to dry off, have some influence on the condition. Acetonæmia has not been recognized during pregnancy. Age is not a significant factor; in a series of 132 cases of marked acetonæmia 80 fell between the ages of five and eight, the time when the cow has reached maturity and is milking heavily.

The time elapsing between parturition and the onset of the attack of acetonæmia ranged in 46 severe cases from 3–77 days, most cases arising between 14 and 42 days.

The appetite is diminished—in some cases of acetonæmia the cow will eat absolutely nothing. There may be a depraved appetite, the cow eating soiled bedding, and where they are tethered they are seen to eat the grass right down to the ground.

There is a marked loss in body weight. The rapidity with which this occurs is one of the most diagnostic features of the disease. It can be attributed to dehydration.

The drop in milk yield is not sudden, and sometimes is not marked in the early stages ; the drop does not appear to be related to the severity of the attack. Thus a cow was observed to be badly affected for one month, and was not eating as much in a week as a normal calf would eat in a day, and still it produced 40 lb. of milk per day.

Vomiting has been observed. In some cases an œdematous swelling develops under the jaw. Temperature, pulse and respiration are normal.

The animal gets tucked up and will stand in a characteristic attitude with arched back, and if made to move forward it is unable to do so in a straight line. Some animals will raise the hind legs high, then tilt over or fall or half fall, but they are always able to get up without assistance. The affected cow is dull and rumination is slow. Constipation is an early symptom, the fæces being covered with mucus, and there may later be very troublesome diarrhœa.

The characteristic odour of acetonæmia in the expired air and in the milk is the one invaluable symptom ; this smell is so marked that it can often be recognized on entering the cowshed.

Nervous symptoms may be observed, the cow staggering about, licking walls, licking themselves sore, or champing their jaws with increased salivation ; there may be apparent blindness. If nervous symptoms of this kind are present, the temperature may be elevated.

Urine tests are of no value in reaching a diagnosis. Rothera's test may be carried out on the milk. The average content of acetone in the milk in these cases is roughly half the content in the serum, but it would appear that the acetone content in the blood must be above 12 mg. per cent before any acetone is excreted in the milk.

The condition is rarely fatal ; if left untreated the mortality is probably less than 1 per cent, but in animals which recover

spontaneously there is a marked drop in their milk yield, a factor of great economic importance.

The post-mortem examinations, which have been carried out in only a very few cases, have revealed nothing beyond the marked odour of acetone when the peritoneal cavity is opened.

In the treatment of acetonæmia, glucose injections have been recognized to be of value for many years. Intravenous injections of glucose in doses of 160 gm. in 400 c.c. of distilled water repeated at intervals of three days for at least three injections constitute the only effective treatment. It alleviates the hypoglycæmia which accompanies ketosis and it depresses ketone formation. In addition, molasses may be fed *per os* but are of doubtful value. The liberal feeding of molasses before calving to cows known to develop acetonæmia at successive parturitions, is ineffective and may even be harmful.

Great emphasis is laid on the *repeated* intravenous injections of glucose. The first injection may relieve the symptoms temporarily, but the animal will certainly relapse. Clinically it has been found that over 80 per cent of animals thus treated are normal at the time of the third injection, which finding is supported by biochemical analysis of the blood at that time.

The affected cows are induced to drink large amounts of water to correct dehydration and to assist in excreting ketone bodies in the urine.

Much has been written about the diet in this condition, but practically little can be done as the animal is unwilling to eat foods which might be beneficial. Maize, crushed oats and boiled potatoes are useful. Grass is essential.

Conclusions

Post-parturient acetonæmia is closely associated with mammary hyperactivity, and is found especially in breeds with a high butterfat percentage.

Repeated intravenous injections of glucose, if given early, have a marked beneficial effect and appear to constitute the only rational treatment of the disorder.

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BIOCHEMICAL ASPECTS OF BOVINE PARTURIENT HYPOCALCÆMIA

A. ROBERTSON

BOVINE parturient hypocalcæmia or "milk fever" as it is often termed (although seldom febrile and has probably little to do with milk) has been known in this country for some 200 years but biochemical investigation has, of course, been largely limited to the last quarter of a century. It is interesting, however, in relation to the title of this symposium to recall that "toxæmia" has in the past hundred years or so been prominent amongst theories of its ætiology. Moreover, it was the belief that milk fever was due to absorption of toxins from the mammary acini which led Schmidt in 1897 to the discovery of the curative effects of the intramammary injections of potassium iodide solutions—soon to be replaced by water and eventually by air—a procedure which reduced the mortality from over 70 per cent to almost negligible proportions.

The next stimulus came with progress in endocrinology in the early 1920's when a number of workers in different countries began to speculate on the relationship of discoveries in that field to the problem of milk fever. One early theory was that of *hypoglycæmia*, based on the fact that the blood sugar in the normal pregnant cow was often low (*circ.* 40 mg./100 ml.) whilst large doses of insulin produced a coma said to be similar to that of milk fever. Moreover, inflation was found to produce a rise in blood sugar to which its curative effect was, therefore, ascribed (Widmark and Carlens, 1925; Maquire, 1926; Augur, 1928). This idea was soon refuted by the work of various individuals (Fish, 1927; Hayden, 1927; Schlotthauer, 1928; Hayden, 1929) who showed that milk fever was accompanied by a hyperglycæmia and that

the rise in blood sugar following inflation was largely due to the presence of lactose (Fish, 1928).

Meanwhile, another field was being rapidly developed following the pioneer work of Little and Wright (1925). Observing that the tetany of milk fever presented similar clinical signs to those associated with the lowered calcium content of the blood of parathyroidectomized animals, they investigated this point and showed that in 12 cases studied, the onset of milk fever was "accompanied by a greatly reduced concentration of calcium in the plasma, the severity of the case being proportional to the decrease in the calcium concentration; thus with mild symptoms reductions of 20 to 30 per cent were obtained whilst with more severe symptoms the fall was as much as 60 per cent of the normal." In this respect it may be interesting to note that in our studies to date my colleagues Marr and Moodie have recorded falls of as much as 47 per cent in the blood calcium of cows at normal calvings!

Little and Wright's (1925) observation was naturally followed up enthusiastically by a number of workers, prominent amongst whom were Dryerre and Greig who had already published some speculations on the role of the parathyroid in this condition, although regarding it largely as an example of guanidin poisoning. By 1928, however, they were able to publish ample confirmation of Little and Wright's work, showing that in some 20 normal cows sampled within the first forty-eight hours after calving, the blood calcium expressed as mg./100 ml. serum averaged 9.85 (8.14–10.7) whilst in 40 cases of milk fever the average was 5.18 (3.85–7.76). They confirmed, too, the calcium-elevating effect of inflation and noted in two normal cows the fact that the blood calcium fell at parturition which they ascribed to the effect of onset of lactation. They amplified this work in 1930 (Greig, 1930) when they also introduced treatment by calcium gluconate injections and in a paper to the International Veterinary Congress in that year Greig gave some striking illustrations of the dramatic effects of the new therapy. In

Holland at this time Sjollema and Seekles (1930), following the same trail, showed in milk fever a calcium ion value of 0.44 mg. per 100 ml. compared with a normal value of 1.65 mg. per 100 ml.

Meanwhile another aspect was being explored independently by Fish (1929) and by Sjollema (1929) who both noticed a drop in blood phosphates. Thus, Fish pointed out that both inorganic and acid soluble phosphorus fell in milk fever, the fall in inorganic phosphorus being to a level of about 2 mg. or less per 100 ml. Inflation, he said, produced an initial slight fall and then a gradual rise, the return to normal being much more rapid than in the case of blood calcium. This low blood phosphate he felt rather contradicted the hypoparathyroidism theory of Dryerre and Greig and he suggested that the low phosphate and high sugar levels indicated a possible disturbance in the hexosephosphate relationship which might have a bearing on the muscular paralysis observed.

Fish later drew attention to a slight fall (7 per cent) in serum proteins, a 10 per cent rise in N.P.N., and a 14 per cent rise in R.B.C's which he felt indicative of some degree of anhydræmia (Fish, 1930).

Palmer, Cunningham and Eccles (1930) in a study of normal cows, showed a decrease in inorganic phosphorus at parturition which might amount to as much as 3.2 mg. per 100 ml. plasma. They noted that the decrease set in before calving and reached its lowest point either just before or just after parturition.

About this time Seekles, Sjollema and Van der Kaay (1932) noticed a slight rise in blood magnesium in one of three cows at parturition and in a review article in 1932 Sjollema drew attention to the fact that the calcium-magnesium ratio in milk fever was about 2 compared with a normal ratio of about 6 and suggested that the loss of consciousness so often observed was possibly related to magnesium narcosis.

Between 1932 and 1934 there was a considerable amount of work done at the Rowett Institute by Godden and Allcroft on the blood changes in the normal cow at parturition. Thus

they noticed (1932) a slight fall in serum calcium just at or within twenty-four hours of calving, with a return to normal in four to five days. There was also a sharp fall in blood inorganic P just prior to calving (which they claimed was invariably indicative of the onset of parturition). Later they recorded a tendency for serum magnesium to rise just at or twenty-four to forty-eight hours prior to calving, but added that wide fluctuations made it difficult to assess the results (Allcroft and Godden, 1934). Further work by Godden and Duckworth (1935) suggested that the major part of the fall in both normal parturition and milk fever was due to a diminution in adsorbable calcium complexes. They also noted the rise in serum Mg in milk fever but suggested it was about the normal for parturition.

Allcroft and Green (1934) gave the following ranges from 139 normal cows: serum calcium 8.65–11.65; Mg 1.85–3.17; and noted in five cases of milk fever a tendency towards high magnesium though within the normal limits.

In 1938 Hayden took the phosphate studies a stage further with an estimation of various phosphate fractions, stating that inorganic, lipoid, acid-soluble and total P in pregnant cows showed little deviation from normal non-pregnant animals whilst in milk fever these various fractions all ran more or less parallel.

There was an interesting paper in 1939 in which Barker summarized the results of biochemical analysis at Weybridge of blood samples from some 300 cases of bovines showing metabolic disorders. About parturition, hypocalcæmia was a prominent feature, and he claimed that somewhere between 5 and 6 mg. per cent paresis supervened to be followed by narcosis, coma or convulsions depending on whether the blood magnesium was above, within or below the normal range of 1.8–3.2 mg. per 100 ml. This hypothesis, attractive in its simplicity, evoked a great deal of interest. An interesting summary of the biochemical evidence was published by Allcroft in 1947 but in so compressed a form that it is rather difficult to appraise.

Hibbs *et al.*, in 1946, carried out a survey of blood changes at parturition and in milk fever in cows fed large doses of Vitamin D and in untreated controls. They found the same changes in both groups, again more or less repeating the usual story.

My own attention was drawn to this subject in 1948 through a misfortune which befell a farmer friend of mine, viz. the loss of four valuable cows in succession which failed to get up following repeated large doses of calcium borogluconate, although otherwise apparently normal. In an attempt to find out what was going wrong, we decided to examine periodical blood samples from a number of cows approaching parturition and as already reported we were lucky enough to include two which developed milk fever (Robertson *et al.*, 1948). The intriguing feature in each case was the apparently almost complete absence of blood inorganic P during the disease and its rapid rise following inflation and coincident with recovery. In view of the fact that phosphates play an important part in the chemistry of muscle contraction, we began to wonder if hypophosphatæmia had been involved in the lack of response to calcium therapy. About this time there appeared a short article in the *Veterinary Record* (Barker, 1948) advocating the use of acid sodium phosphate injections in the treatment of the recumbent cow, a suggestion which seemed to fit in with our experience. Accordingly, we analysed a number of blood samples from cows with milk fever taken before and after treatment and after recovery and in a later article reported on some 28 cases (Robertson, 1949). They were a somewhat mixed bag, containing not only cases which could be classified under the headings Barker gave in 1939, but also included a fourth category which we classified as "alert," viz. animals which were quite bright in appearance and clinically normal in every way except for their inability to rise.

Our experience with these and a number of cases which did not respond so well to treatment led us to the conclusion that hypocalcæmia was not the only factor underlying the clinical

variations observed. We could not, moreover, support altogether the thesis that alterations in blood magnesium were the deciding factor; and incidentally the different types of syndrome observed did not correlate with blood calcium or inorganic phosphorus either. It looked to us, and subsequent experience has only tended to confirm this view, that there is some other factor, as yet unidentified, behind the very marked clinical variations which occur.

At that stage, I persuaded a couple of my younger colleagues to take up the problem and we started off with a detailed study of normal parturitions and of such cases of milk fever as have come our way. Most of the studies on normal calvings I have mentioned involved at the most daily sampling and we felt that a more detailed examination at the time of parturition was eminently desirable. We therefore arranged to take occasional samples for a week or two prior to the expected date of calving and then when parturition seemed imminent to take much more frequent samples—about six-hourly if possible—until about twenty-four hours after parturition and then daily for a few days thereafter.

The first discovery my colleagues made was that they did not really know when cows were due to calve! As a result our samplings about calving time are sometimes rather erratic, thus complicating statistical analysis of the results. We have, however, amply confirmed the results of previous workers in finding a fall in serum calcium and inorganic phosphorus and a rise in blood magnesium. We have, moreover, been able to show that the extent of the fall (and rise) in some 30 cases to date is largely influenced by the animal's previous calving history (Robertson, Marr and Moodie, unpublished results). Comparing the lowest level attained during the period twenty-four hours before to twenty-four hours after parturition with the average level attained prior to that period and expressing the fall as a percentage of that average, we obtain the results shown in Table 1.

Detailed study of the graphs, moreover, suggests some features not mentioned by previous workers, viz. a fairly

constant rise and secondary fall in Ca and inorganic P some two to three days later with a more or less reciprocal movement of blood magnesium.

A study of phosphate fractions tends to confirm that lipide P runs more or less parallel to inorganic P, at least in its primary fall, whilst the ester P which is very low in the cow is variable with no regular change.

There would appear, therefore, to be ample grounds for the belief that the milk fever syndrome, so far as biochemistry

Table I

VARIATION IN BLOOD CONSTITUENTS AT NORMAL CALVING.

Calvers	Calcium % Fall	Inorganic Phosphorus % Fall	Magnesium % Rise
1st	7 (1–18)	19 (16–23)	13 (4–26)
2nd	17 (7–22)	37 (22–53)	24 (14–34)
3rd and over .	25 (17–47)	46 (25–74)	34 (21–54)

is concerned at any rate, is largely an exaggeration of the normal picture, so that a knowledge of the cause of this normal variation might be valuable. It has often been suggested that drainage of calcium from the system via the milk with the onset of lactation was an important factor in initiating the milk fever syndrome and we felt that it would be a useful pointer to the validity of this conception if we were to study the effects of prepartum milking on the normal blood picture to see if the characteristic rhythm was upset in any way. Our first case gave us a very striking answer for although the animal had been milked for nearly a fortnight prior to calving she not only showed the characteristic blood changes at parturition but went on to develop milk fever as well. We have not had anything so spectacular with subsequent cases and they are at present too few to be dogmatic but my own belief is that we can dismiss the "drainage" theory of ætiology.

The other main possibility is the often advanced theory of hormonal upset and we are at the moment trying to find out

if any likely hormone or combination of hormones will produce the normal parturition blood picture, but to date we have been very limited in our animal material and have been mainly experimenting with dosage. Such tests as we have made, mainly with œstrogens and pituitary hormones, have yielded negative results. We have, however, just acquired a herd of some 30 dairy cattle, many of which are due to calve this spring, so we hope to make more rapid progress in the not far distant future.

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THE HUMAN PLACENTA IN TOXÆMIA OF PREGNANCY

NINIAN McI. FALKINER

THE problem of the ætiology of the toxæmias of pregnancy is still unsolved in spite of the vast amount of work that has been done. A meeting such as this may well prove a firm stepping stone towards the solution, for at this meeting the communications are based on facts and not concerned with gaining the acceptance of one particular theory.

My contact with the problem commenced in 1924 in the Rotunda Hospital, where Tweedy's theory was promulgated and formed a basis for the treatment of eclampsia.

Dietetic factors as a causal role in the development of the toxæmias of pregnancy cannot be regarded of prime importance, otherwise the incidence of eclampsia in the male would be quite high.

We have gradually seen the pathological changes in the kidney yielding in importance to those in the liver and then attempts have been made to show that the changes in the placenta were of ætiological significance.

I am convinced that the most significant change in pre-eclamptic toxæmia and eclampsia is the vascular spasm affecting all the arterioles and that the changes in the various organs such as liver and kidney are secondary to interference with their blood supply. I am also convinced that the changes in the placenta associated with eclamptic toxæmia, described so well by Young and Bartholomew and Colvin, are correct. I have never seen an equally careful type of investigation which disproves the association of placental changes with the toxæmias of pregnancy.

Bartholomew's ability to correlate the placenta with the clinical history in a high percentage of cases is very striking.

It is a very different thing when one comes to placing an ætiological significance upon placental changes and one is inclined to be sceptical when factors such as fœtal movement are dragged in.

So I would like to make it quite clear that my knowledge of physiology and biochemistry is such as to preclude my advancing any theories about histamine or guanidine being elaborated in the placenta, but I hope by a demonstration of the anatomy of the placenta followed by a series of pathological placentæ to show that placental changes do occur in toxæmia of pregnancy and are so marked as to make it quite clear that this occurrence is not purely a matter of chance. Those who have stated that their occurrence is a matter of chance have in my opinion not been fully conversant with either the anatomy or pathology of the placenta.

Anatomy of Placenta

The human placenta is described as hæmo-chorialis and there are certain anatomical features which may be stressed before showing any slides:—

(1) The villi are immersed in circulating maternal blood.
(2) The attachment of the placenta to the uterine wall is effected by a fusion between the proliferating plasmodium and the compressed decidua spongiosum.
(3) The vascular supply and drainage of the intervillous space pass through this basal plate.
(4) The circulation of blood through the intervillous space may be effected by three factors: (*i*) The *vis a tergo* derived from the pressure in the maternal arteries. (*ii*) The intermittent contractions of the uterus. (*iii*) The pulsation of the villous tree.

We know that the villus must be dependent for its nourishment on the maternal blood at the outset and it is likely that such conditions continue during the whole of pregnancy.

Therefore I am inclined to accept Young's contention that placental changes are more likely to be due to changes in the maternal circulation than changes in the fœtal circulation.

(The following slides and sections were then shown and described.)

Slide 1. Spanner's conception of the placenta :—

(i) General outline of placental structure.
(ii) Villous tree—attachment to basal plate.
(iii) Septs.
(iv) Uteroplacental arteries.
(v) Subchorial blood lake.
(vi) Circular sinus.
(vii) Uterine sinus.

Slide 2. Mucous membrane of uterus—reconstruction by Bartelmez.

Slide 3. Injected human uterus, showing venous plexus in endometrium.

Slides 4 and 5. Coil arterioles in premenstrual endometrium.

Slide 6. 15-day old human ovum embedded.

Slide 7. Anchoring villus.

Slide 8. Reconstruction of vessels in decidua.

Slide 9. Coil arteriole in decidua at six weeks.

Slide 10. Full time placenta *in situ*, specimen injected through uterine artery.

Slide 11. Section of placental site showing coil artery piercing basal plate.

Slide 12. Section of placental site showing injected coil artery.

Slide 13. Corrosion specimen of full term placenta.

Section 1. Placenta *in situ*, injected.

Section 2. Placenta prævia showing separation of placenta with breach in circular sinus.

Section 3. Central placenta prævia *in situ*.

Section 4. Ectopic placenta full term, showing absence of placental septs.

Section 5. Normal placenta.

Section 6. Placenta from case of ante- and intra-partum eclampsia.

Patient aged 42. Para VIII.

24th June, 1941, admitted to hospital. Relatively well until a week before admission, when she commenced having severe headaches. She was then 39 weeks pregnant. Eight hours before admission she had an eclamptic fit; these were repeated at more or less hourly intervals up to time of admission, by which time patient had had eight fits in all. She had never had any trouble with pregnancies or labours before; no history of rheumatic or scarlet fevers. On admission: Pulse 152/min. Temp. 99.6°. B.P. 154/108. Alb. abundant. Patient semi-conscious and very restless; marked œdema of face, hands, ankles, legs and lower abdomen. Uterus at term; vertex presenting: F.H.N.H. Uterine contractions palpable.

15.40 hours. Patient had ninth fit which lasted a minute. Became very cyanosed. Morph. gr. $\frac{1}{2}$.

16.45 hours. Patient had tenth fit; she became extremely cyanosed and ceased breathing. Oxygen and artificial respiration given, but patient did not recover from the fit. Mors.

The placenta in this case shows multiple infarcts and the condition, illustrated in Fig. 1, is a very acute infarction. Such a condition corresponds to the infarct that Bartholomew classifies as "E". The photograph illustrates the fact that the intervillous circulation would still exist in such a case while the general shape of the infarcted areas suggests that the whole cotyledon is involved.

Section 7. Placenta from case of ante-partum eclampsia.

Patient aged 35. Para IV.

Previous pregnancies: 1st—Normal.
2nd—Induction for albuminuria.
3rd—Normal.

27th Dec., 1940. Admitted at 30 weeks with history of eclamptic fit.

B.P. 130/90. Alb. abundant. Patient semi-conscious and had two more fits during that day.
28th Dec. Condition improved.
29th Dec. Induced by P.O.M. at 11.00 hrs. Delivered at 16.00 hrs.
The placenta (Fig. 2) shows an old infarction and an area of acute infarction.

Section 8. Placenta from case of nephritic toxæmia.
Patient aged 30. Para IV.
Previous pregnancies : 1st. Eclampsia, forceps.
2nd. Albuminuria, spontaneous.
3rd. Normal, spontaneous.
7th April, 1941, admitted at 30 weeks. B.P. 160/100. Alb. abundant, pre-retinitis.
7th May, labour induced. Baby alive, only weighed 2lb. 8 oz. and subsequently died. B.P. on discharge 180/100. Alb. trace.
The placenta (Fig. 3) shows old infarct and acute congestion of cotyledon.

Section 9. Placenta from case of chronic nephritis.
Patient aged 34. Para V.
Previous pregnancies : 1st ended as a three months' abortion.
2nd terminated at 34 weeks as a macerated fœtus.
3rd terminated at 24 weeks as a macerated fœtus.
4th terminated at 34th week by Cæsarean section, baby alive but died on sixth day.
7th April, 1938, admitted at 35 weeks, with dimness of vision which rapidly progressed to total blindness. Pulse and temp. normal. B.P. 128/93. Alb., trace. F.H.H.
The total blindness lasted for two hours.
9th April. Delivered by classical section of a living infant which survived.
13th April. Developed a left hæmianopia. Examination of the fundi showed they were normal. By 20th April visual symptoms had completely cleared up and the patient left hospital in good condition.
The placenta (Fig. 4) shows areas of old infarction. The loss of structure is well marked.

FIG. 1.

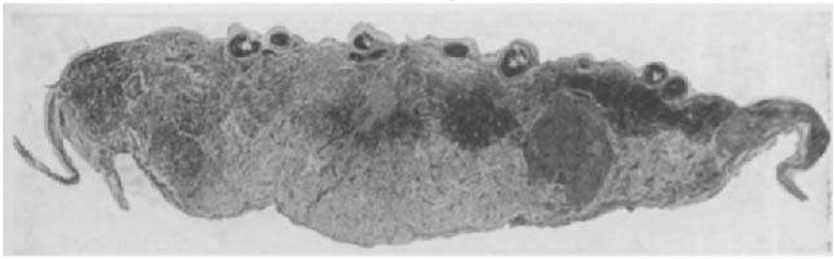

FIG. 2.

FIG. 3.

[*To face page* 130

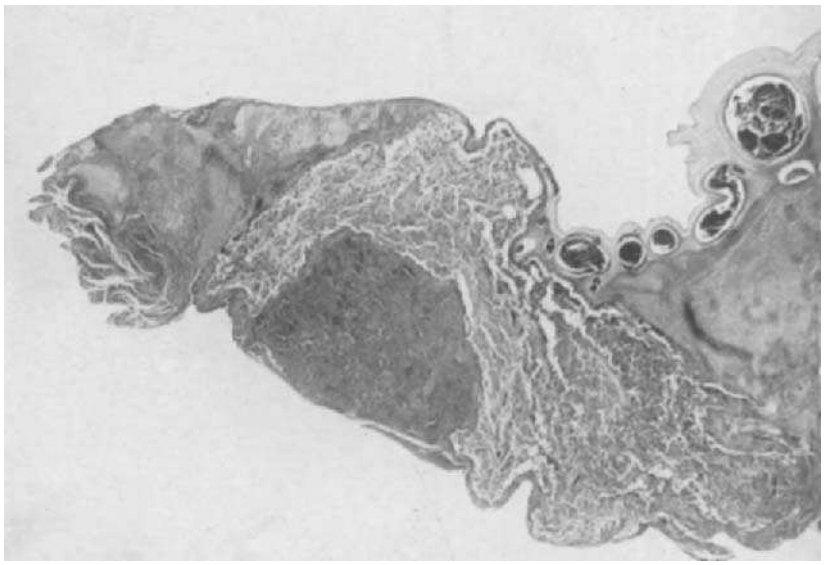

FIG. 4.

Section 10. Placenta from case of hypertension and albuminuria in a para II, which developed at the 26th week of pregnancy. B.P. 156/100. Alb., trace.
11th February, 1942. Optic fundus : pre-retinitis.
28th February. B.P. 220/130. Alb., abundant. Delivered by Cæsarean section. 18th day after delivery, B.P. 160/100. Alb., nil.
Placenta in this section shows two areas of infarction involving the cotyledon completely.

Section 11. Placenta from case of eclampsia.
Primigravida, aged 34.
Developed albuminuria at 28 weeks and two days later eclampsia.
19th February, 1947, admitted to hospital. B.P. 165/105. Optic fundus normal. Two further eclamptic fits.
23rd February. B.P. 205/100. Alb., trace. Delivered by classical section. Baby alive. Rapid recovery.
Subsequent pregnancy uncomplicated, delivered at full term of living baby.
Placenta shows infarct involving a whole cotyledon.

Section 12. Placenta from case of eclampsia.
Primigravida, aged 32.
11th February, 1947, admitted to hospital at 38 weeks, history of five fits. B.P. 170/90. Alb., abundant. No further fits.
12th February. B.P. 170/100. Alb., trace. Delivered by section, baby alive.
26th February. B.P. 165/105. Alb., nil.
Placenta shows the acute stage of infarction involving the whole organ.

Section 13. Placenta from case of acute yellow atrophy of the liver.
Patient aged 39, multipara.
Admitted with vomiting, jaundice, albuminuria, which had developed twenty-four hours previously.
Treated by induction of labour and intravenous glucose. Steady increase of jaundice. Twelve hours after induction no labour.
Delivered by section of living baby which died. Patient recovered.
Subsequent pregnancy normal.
Placenta shows widespread infarction.

The slides shown were prepared in the Zoological Laboratory, Trinity College, Dublin, by permission of Professor J. Brontë Gatenby. The expenses were defrayed by a grant from the Medical Research Council of Ireland.

Discussion

Classification of Toxæmias:—

Hyperemesis gravidarum, which will not be discussed.
Nephritic and hypertensive toxæmia.
Preeclampsia.
Eclampsia.
Acute yellow atrophy of the liver.
Bilateral cortical necrosis.
Accidental hæmorrhage.
Rupture of splenic or renal artery.

It would appear that women suffering from renal disease or the effects of renal disease and women with hypertension are more liable to the effects of the late toxæmias than women with normal renal and cardiovascular function. In such women intra-uterine death of the fœtus, premature labour, accidental hæmorrhage and the development of eclampsia and cerebral hæmorrhage are all to be feared.

The typical placental lesion is widespread infarction which apparently develops gradually and need not be associated with eclampsia.

The mechanism of this degenerative change is most probably a gradual failure of the maternal blood supply of the intervillous space—possibly due to thrombosis in the utero-placental coil arteries. In such cases separation of the placenta associated with accidental hæmorrhage may occur and be limited in its distribution : the retroplacental hæmatoma in such cases being due to a slow leakage from the intervillous space. I have delivered living babies under such conditions.

In preeclampsia and eclampsia the placental lesion is usually not an old infarction but the acute infarction described by both Young and Bartholomew. It is difficult to demonstrate because degenerative changes have not developed either because the placenta is delivered too soon after the onset or because the condition is capable of recovery.

The appearance of the cotyledon in eclampsia is generally one of congestion of the villous tree with partial obliteration of the intervillous space.

This might be due to an acute failure in the intervillous circulation due to spasm of the uteroplacental arteries.

In other words the placental changes in nephritic toxæmia are due to a gradual failure of circulation. In preeclampsia and eclampsia the vascular disorder is acute.

In the placenta obtained from the case of acute yellow atrophy the changes are well marked in spite of the fact that the patient was apparently well seventy-two hours before she was delivered, and although the appearance of the degeneration is so widespread, the placenta was capable of oxygenating the fœtus which was born alive although it succumbed rapidly.

In the two cases of bilateral cortical necrosis that I have seen, accidental hæmorrhage with fœtal death occurred simultaneously with the onset of renal failure. This would suggest that the vascular spasm in the cortex of the kidney was associated with a vascular spasm or rupture in the utero-placental arteries. I have no specimen of the placenta in such a case.

In cases of rupture of the splenic artery or renal artery in pregnancy the fœtus usually succumbs. It would be of great interest to know if this is due to the shock coincident with this grave internal hæmorrhage or whether it is due to some accompanying disturbance of placental circulation.

Accidental hæmorrhage in the acute cases which immediately endanger life is undoubtedly due to rupture of the uteroplacental arteries and in my opinion bears no direct relation to the toxæmias of pregnancy although we are aware

of its association with nephritic toxæmia, preeclampsia and eclampsia.

The predisposing cause is most probably a failure in development of the uteroplacental arteries which occurs in undernourished, overworked multiparæ of our large cities.

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STUDIES IN THE CIRCULATION OF NORMAL AND ABNORMAL PREGNANCY

R. J. KELLAR

In introducing this subject this afternoon, I would like to state that I act, as it were, as a spokesman for the group in Edinburgh who have been investigating certain problems in the circulation of pregnancy and toxæmia. Miss Burt and Miss Hamilton are both to say a word or two following this brief communication and many of the facts I have to offer are due to their work.

The Cardiac Output in Normal Pregnancy

In 1932 Grollman reviewed our knowledge on this subject although he apparently did not himself carry out any estimations. The results obtained before the use of the acetylene method can be summarized as follows: Linhard (1915) who with Krogh had introduced the nitrous oxide method noted the cardiac output in a woman before, during and after pregnancy and found that during pregnancy there was a considerable increase in the cardiac output. Weiss (1924) studied the cardiac output in eight women during the latter months of pregnancy and found an increase in cardiac output of the order of 45.85 per cent. Gammeltoft (1926) also confirmed the rise in cardiac output and in one case repeatedly studied showed that the maximum increase was at about the 34th week of pregnancy.

With the introduction of the acetylene method of Grollman, the subject was re-investigated by several observers and we can note the results obtained by Stander and his colleagues (1932). Briefly, they found that there was a steady increase in the cardiac output reaching its peak at or about term. The increase was of the order of 50 per cent. It was noted that

during the puerperium there was a rapid fall in the output. In 1938 Charles Burwell carried out repeated estimations on a small group of four trained patients and came to the same conclusions. It was found that, during the last four weeks of pregnancy there was a fall in the cardiac output and that this approached normal levels at term.

Until this last year, then, this was the position. Most investigators believed that there was a rise in cardiac output during pregnancy and that this was of the order of 50 per cent. It had been suggested that there was probably a return to normal before the onset of labour.

The introduction by Cournand of the auricular catheterization technique made it obvious that the whole question should be re-examined. The method, as you all know, involves the Fick principle, i.e. if you know the O_2 content of the arterial and venous blood and the amount of oxygen absorbed by the lungs in a given time, it is easy to calculate the cardiac output. In the past it had been impossible safely to obtain reliable venous samples. Direct cardiac puncture had been performed but appeared a little dangerous.

Dr. Hilary Hamilton (1949) has carried out the method on some 68 normal pregnant women and 24 normal non-pregnant women. She has now also carried out estimations in a number of patients with toxæmia. The following is a summary of the results obtained (Fig. 1). The cardiac output of the resting basal non-pregnant woman is of the order 4.5 litres per minute. At the tenth week of pregnancy the output begins to rise quite sharply and during the period 10th–13th weeks averages 5.14 litres. The maximum output is at the period 26th–29th weeks when it reaches 5.78 litres per minute. During the rest of pregnancy there is a gradual fall in the output and during the period 38th–40th weeks it has dropped to 4.60 litres per minute. During the early puerperium (4th–14th day) the output is normal.

It would seem, therefore, legitimate for us to assume that in pregnancy there is an increase in the cardiac output and cardiac work. At the peak load the heart is expelling about

25 per cent more than in the non-pregnant woman. The figure obtained is somewhat lower than that suggested by previous investigators but is no mean increase.

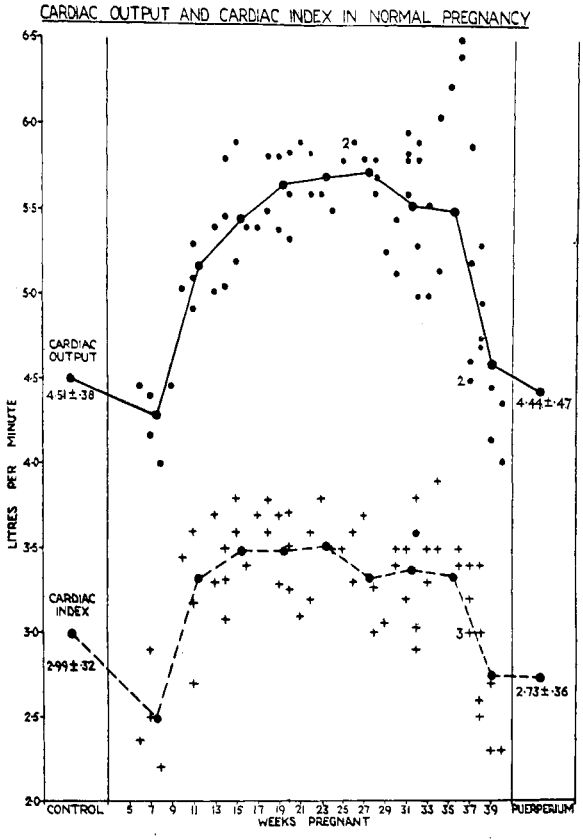

FIG. 1. Cardiac Output and Cardiac Index in Normal Pregnancy. (*Dr. H. Hamilton.*)

At the same time Palmer and Walker (1949) carried out a similar investigation and generally speaking obtained similar results except that they did not find any evidence of a terminal fall in cardiac output. Werkö (1948), however,

whom we welcome as a visitor amongst us, using the catheter technique did not find a constant rise in the cardiac output in normal pregnancy.

I do not intend to discuss the question of the terminal fall in cardiac output this afternoon. There is no doubt that it requires further study. You will note from the following

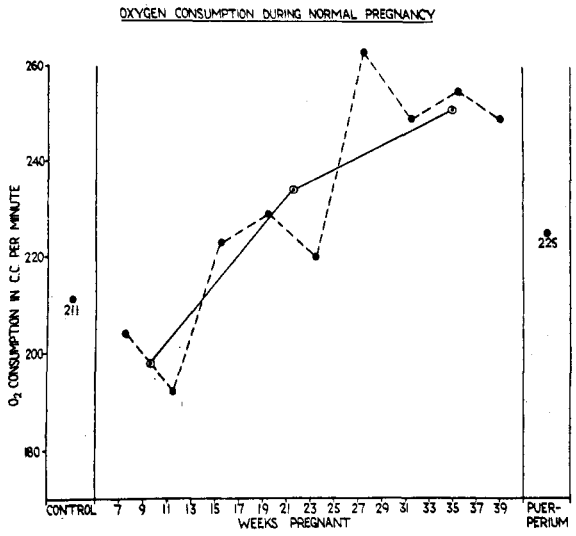

FIG. 2. Oxygen Consumption in Normal Pregnancy. (Same series as in Fig. 1.) (*Dr. H. Hamilton.*)

graphs that the O_2 consumption increases right up to term and that the oxygen A.V. difference does likewise, particularly in the last two to three weeks (Figs. 2 and 3).

Hamilton (1949) has published her preliminary results of the cardiac output in pregnancy toxæmia. In general the cardiac output rises in the pre-eclamptic to a level of over 6 litres a minute whereas in the pregnant hypertensive woman it remains within normal limits. These results must be regarded as provisional at present, for many more cases

require investigation. Werkö (1948) studied the cardiac output in a small series of pre-eclamptics but did not find any evidence of increased output. The matter is one of fundamental importance and it is to be hoped that the matter will be settled in the very near future.

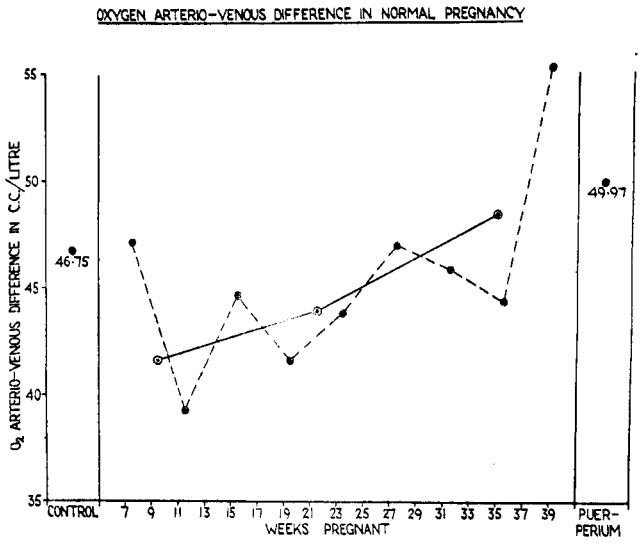

FIG. 8. Oxygen A/V Differences. (Same series.) (*Dr. H. Hamilton.*)

Blood Volume in Pregnancy

It is now some thirty-five years since Miller, Keith and Rowntree (1915) first demonstrated that there was a probable rise in the total blood volume in pregnancy. Since then several investigators have confirmed this, using various types of dye methods. As I was anxious to have certain facts confirmed in regard to blood volume in pre-eclampsia and hypertension I had the whole matter re-investigated by Rachel White (1949). She confirmed the results previously obtained that there is a rise in total blood volume of 25 per cent—a

figure which incidentally compares exactly with that obtained by Dieckmann and Wegner (1934). White investigated the blood volume in 25 cases of essential hypertension and 41 cases of pre-eclampsia. The results showed that blood volume in hypertension and pregnancy was essentially normal while the volumes obtained in pre-eclampsia were on the whole somewhat lower than normal. This result was in accordance with past work.

Rate of the Circulation

Our knowledge of circulation speed in pregnancy and pregnancy toxæmia is fragmentary. Cohen and Thomson's work (1939) has shown that generally speaking there is a speeding up of the circulation in normal pregnancy (arm to carotid). Spitzer (1937) had shown that in pre-eclampsia and eclampsia there was some slowing of the circulation.

There is some evidence that there is a lowered circulatory rate in the veins below the level of the liver. The pressure is certainly increased here. Payling Wright (1948) using sodium isotope (Na^{24}) has shown that the foot to groin time is lengthened, and Noble, working in my laboratory, and using a similar technique, has confirmed this and has found that the foot to heart time is also lengthened.

The circulation rate in pregnancy must surely bear some relation to the *blood viscosity.* It has long been stated that blood viscosity is lowered in pregnancy but the evidence on which this is based is not very convincing. Pellissier (1912) using the Hess viscometer carried out some direct measurements and showed that a fall in blood viscosity does occur in pregnancy. Cohen and Thomson using Nygaard's formula calculated viscosity from the hæmatocrit and found it lowered.

Hamilton has provided me with the following data derived from measurements on the Ostwald viscometer (Fig. 4). Although calculated on the results of 186 normal pregnant women the results should be regarded as provisional as many more estimations are required. The relative viscosity of

whole blood in the non-pregnant woman can be taken as 4.61. During pregnancy it falls to about 3.86 at twenty weeks and rises gradually until term. During the puerperium it returns to normal. Sixty-nine cases of pre-eclampsia

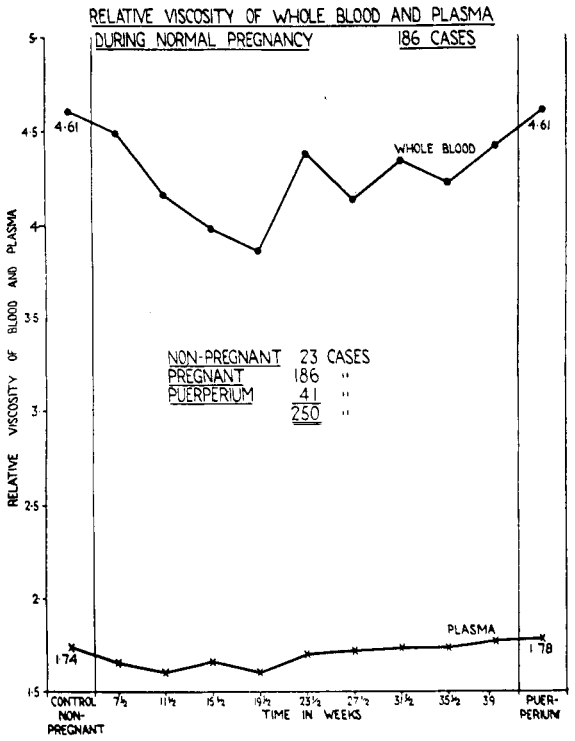

FIG. 4. Relative Viscosity of Whole Blood and Plasma during Normal Pregnancy. (*Dr. H. Hamilton.*)

occurring after the 29th week have been studied and so far do not appear to show any deviation from the normal pattern. Neither, apparently, do the hypertensives.

The slightest reduction in the viscousness of the blood must afford the heart considerable relief and probably explains the speeding up of the circulation on the arterial tree.

Now I am not going to spend much time on the subject of the *heart rate* in pregnancy but it is worth pointing out that our knowledge of the heart rate under basal conditions is woefully inadequate. There seems to be little doubt that under basal conditions the heart rate in pregnancy is about 82 contrasting with 65–70 in the non-pregnant control. Shortly after delivery the pulse rate slows. Burwell stated that this slowing to the non-pregnant level could be observed during a cæsarean section but in 200 cases which I had analysed I was not able to confirm this. I do not suppose that there is much alteration in pre-eclampsia and hypertension but as far as I know the matter has not been adequately investigated.

The *blood pressure* in pregnancy shows no tendency to rise but rather the reverse, and the well-known mid-pregnancy drop in blood pressure is found in many patients.

Venous pressures in pregnancy have now been fairly fully studied and the first-class researches of McLennan (1943) have shown that the cubital vein pressures are within normal limits in pregnancy and toxæmia. The venous pressures in the veins of the dorsum of the hand are unknown. The cardiac catheter has shown that if you avoid a uterine contraction the pressures in the right auricle are normal. The pressures in the femoral veins are of course greatly raised and if recorded during labour or cæsarean section are found to return to normal levels as soon as the fœtus is removed. As far as we know the venous pressures in pre-eclampsia and hypertension are within normal limits.

I have no personal data to offer on the subject of blood flow to individual organs but for the sake of completeness I should like to summarize the present position.

Hepatic Blood Flow

Bradley's methods have enabled us to measure with some accuracy the blood flow through the liver and also therefore the blood flow through the whole splanchnic area. Munnell and Taylor (1947) have found that the estimated hepatic

blood flow in normal and pregnant women remains the same, namely 1½ litre per 1.73 sq. metres of body surface. The liver does not apparently share in the increased turnover of blood in pregnancy. In six out of eight toxæmic cases the hepatic flow was raised and, in one at least, greatly increased. Further studies on hepatic flow are obviously required.

Cerebral Blood Flow

McCall (1949) has applied Keting's method of recording cerebral blood flow and shown that this is quite normal in pregnancy and pre-eclampsia, and in hypertension and pregnancy. Some reduction of flow is noted in eclamptics. This whole study of McCall's throws serious doubt on the conception of cerebral ischæmia as a factor in the genesis of eclampsia. Cerebral vascular resistance is of course increased in toxæmia, being greatest in the eclamptic.

Renal Blood Flow

All groups who have investigated the subject of renal blood flow in pregnancy have shown that it is well within the limits of the non-pregnant woman—namely 850–950 cc.—and that the glomerular filtration rate remains unaffected. In pre-eclampsia the renal blood flow may rise to levels as high as 1,200 c.c. but wide variations have been noted. The glomerular filtration rate falls. I am not competent to talk about the possibility of cortico-medullary renal shunts altering the renal blood flow mechanics.

Peripheral Blood Flow

There still persists an idea that there is a tendency to peripheral vaso-constriction in pregnancy. But the work of Abramson (1943) and more recently of Burt has surely dispelled this view for ever. Forearm and leg muscle blood flows are normal or increased in pregnancy. Burt (1949) has recently communicated her results of forearm muscle blood flows in normal pregnancy, pre-eclampsia and hypertension. In the control group the flow per 100 cc. per minute is 2.06,

in normal pregnancy 3.51 cc., in pre-eclampsia 4.47 and in hypertension 4.53—almost double that of the non-pregnant controls. On reflex vasodilatation a further increase in muscle blood flow occurs. Burt regards these figures as provisional and is at present further investigating this problem.

Skin Blood Flow

Burt (1949) has also shown that the pregnant woman is able to maintain skin vasodilatation of the hand at cool room

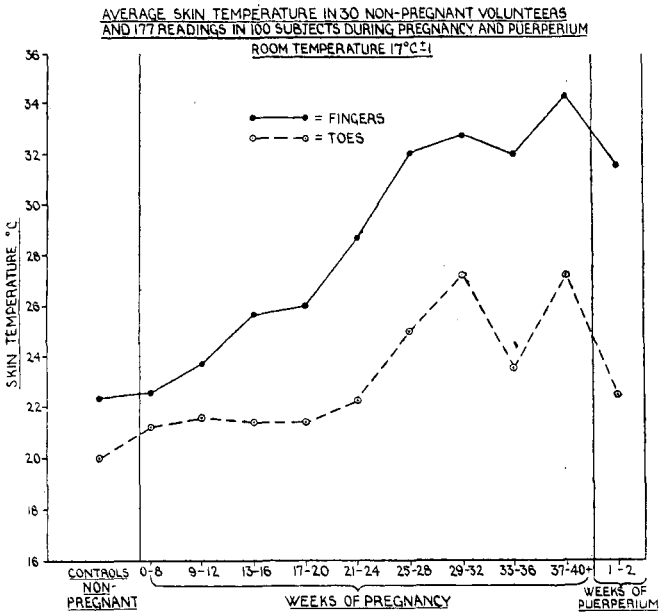

FIG. 5. Hand and Foot Temperatures throughout Pregnancy. (*Dr. C. C. Burt.*)
(*By permission of the Editor of The Lancet.*)

temperatures. The accompanying figure shows this effect (Fig. 5) very strikingly. When the hand blood flow is measured this effect is equally well shown.

Summary

In this short paper I have tried to summarize our present knowledge of the hæmodynamics of pregnancy and pregnancy toxæmia, and you will have observed that this is fragmentary and many problems require further study and experiment. The data available at present do not show evidence of any reduction of blood flow to the organs and tissues of the body in pre-eclampsia. In fact, the opposite would appear to be the case and so far every study appears to show a normal or an increased flow to the viscus or tissue studied. The uterine blood flow remains an enigma and at present we have no knowledge whatsoever on the rate of the blood flow through it either in normal pregnancy or in toxæmia.

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OXYGEN ARTERIO-VENOUS DIFFERENCE AND RIGHT AURICULAR PRESSURE DURING LABOUR

HILARY F. H. HAMILTON

PROFESSOR KELLAR has mentioned that in two series of cases investigated during pregnancy a fall in cardiac output occurs during the 37th–40th weeks. Burwell (1938) used the acetylene method and Hamilton (1949) the direct Fick. Other workers did not confirm this finding. Professor Kellar has also pointed out that in the cases of preeclampsia so far studied, changes in oxygen consumption and oxygen arterio-venous difference occur.

We decided that it would not only be of interest but also might help to explain these findings if cardiac catheterization was performed during normal labour. Such cases are at present being investigated. The object is primarily to record the changes, if any, in the oxygen arterio-venous difference and secondly to study the behaviour of the right auricular pressure during the first and second stage uterine contractions. The cardiac output cannot be calculated over short periods during labour by this method.

Ten normal women were chosen at random. The heart catheter was passed when the first stage of labour was well established, contractions occurring every three to four minutes. A sample of right auricular blood was taken every minute during two complete cycles. The right auricular pressure was observed over two similar cycles. In all these ten women similar results were obtained and may best be illustrated graphically. Fig. 1 shows the variations in oxygen arterio-venous difference during first stage contractions. The resting value is in the region of 55 cc./litre. During each of the three contractions shown the oxygen arterio-venous difference

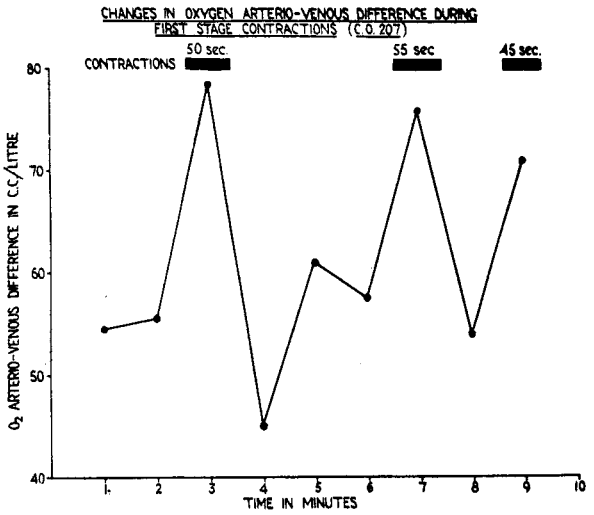

FIG. 1. Changes in Oxygen Arterio-Venous Difference during First Stage Contractions.

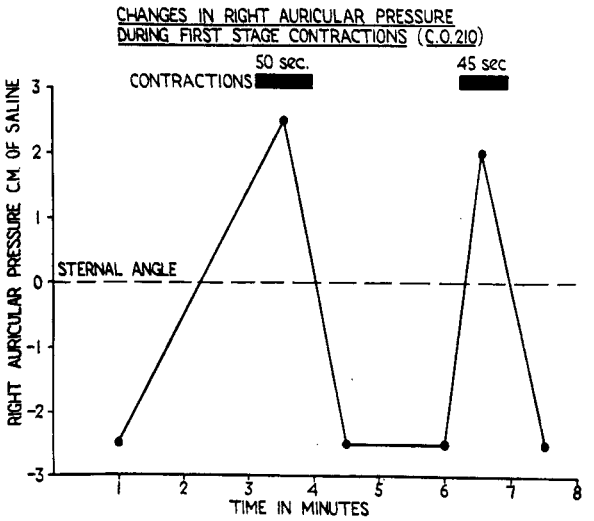

FIG. 2. Changes in Right Auricular Pressure during First Stage Contractions.

increased to 70–80 cc./litre. Immediately following the first contraction a fall to well below the base line occurred.

Fig. 2 shows typical changes in right auricular pressure during first stage contractions. In the resting period the right auricular pressure is within normal limits, 2.5 cm. saline below the sternal angle. By continuous observation of the manometer it was seen that the commencement of the rise in pressure coincided with the beginning of the contraction as palpated by a second observer and preceded the appreciation of pain by the patient. The second point on the graph represents the maximum pressure attained of 2.5 cm. saline above the sternal angle. The pressure took one minute to fall to its original level and the total variation was 5 cm. saline. It is worthy of note that although the patient felt the pains of uterine contraction she was not restless and the rise in right auricular pressure could not be accounted for by extraneous body movements. Changes of a similar order in right auricular pressure and oxygen arterio-venous difference were seen in all the ten cases.

Only one patient has so far been catheterized during the second stage (Fig. 3). She showed changes in oxygen arterio-venous difference of a similar range to those occurring in first stage contractions in spite of the fact that she was pushing well. In this case I obtained two samples during the first contraction. It was interesting to note that the highest oxygen arterio-venous difference was obtained at the beginning of the first contraction, the sample being taken during the first five to ten seconds. The arterio-venous difference was decreasing during the second half of the contraction when a sample was obtained between twenty-five and thirty-five seconds approximately. This suggests that during a contraction the right auricular blood is mixed with highly venous blood presumably squeezed out of the placenta and uterine veins. It also suggests that this influx is greatest at the commencement of a contraction.

Fig. 4 shows the changes in right auricular pressure in the same patient. A variation of 14 cm. saline occurred between

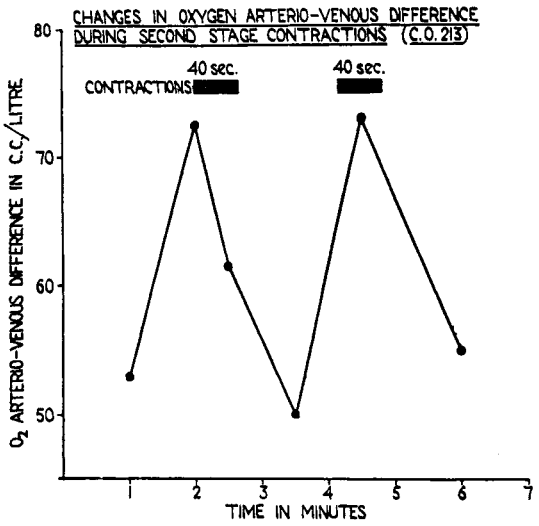

FIG. 3. Changes in Oxygen Arterio-Venous Difference during Second Stage Contractions.

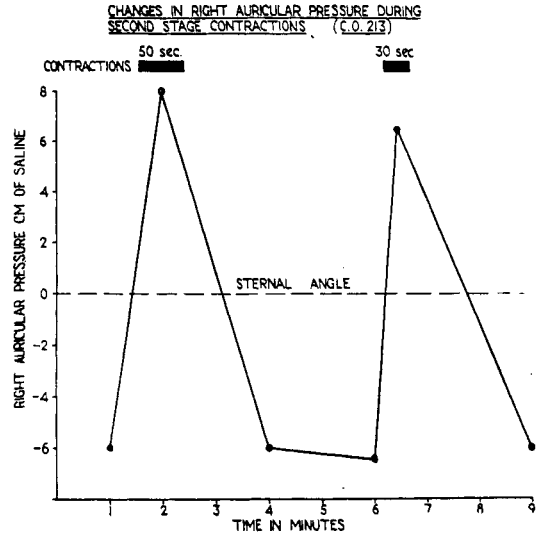

FIG. 4. Changes in Right Auricular Pressure during Second Stage Contractions.

the resting and contracting periods. The resting value being 6 cm. below and the maximum value 8 cm. above the sternal angle.

These studies are continuing and we hope to be able to extend them to cover the delivery and the third stage.

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FOREARM AND HAND BLOOD FLOW IN PREGNANCY

CATHERINE C. BURT

PROFESSOR KELLAR has mentioned our previous work (Burt, 1949) in which a gradually increasing peripheral dilatation in vessels to skin and to a lesser extent to muscle was demonstrated during normal pregnancy. Not only were the hands and feet warm with a high blood flow but they did not cool in an environment of 17°C. which was cold enough to cause vasoconstriction in the majority of non-pregnant subjects.

Method Used

During the investigation the skin temperature was recorded by copper constantan thermo-couples applied to the nail folds of the digits while blood flow was measured by venous occlusion plethysmography; the increase in volume in the enclosed part when the occlusion cuff is inflated gives a measure of the arterial in-flow during the first few seconds after occlusion. Blood flow measurements of hands give largely a measure of the blood flow to skin, while measurements of the forearm represent largely the supply to muscle.

At present we are continuing the studies of the resting skin temperature and blood flow to skin and muscle in normal pregnancy, but so far, measurements have been made in only a few cases. In the original work it was found that forearm blood flow was higher in pregnant than in non-pregnant subjects and higher in pre-eclamptic and hypertensive patients than in the normal pregnant subject.

Skin Blood Flow

It seems obvious that the skin temperature cannot rise much beyond that recorded in the final weeks of normal

pregnancy (34.2°C.) and we have found very little difference in this in patients with pre-eclamptic toxæmia and hypertension, but in the few cases so far examined the pre-eclamptic toxæmic patients have a resting hand blood flow which in eleven out of twelve cases was above that of the average hand blood flow recorded in 56 normal pregnant subjects

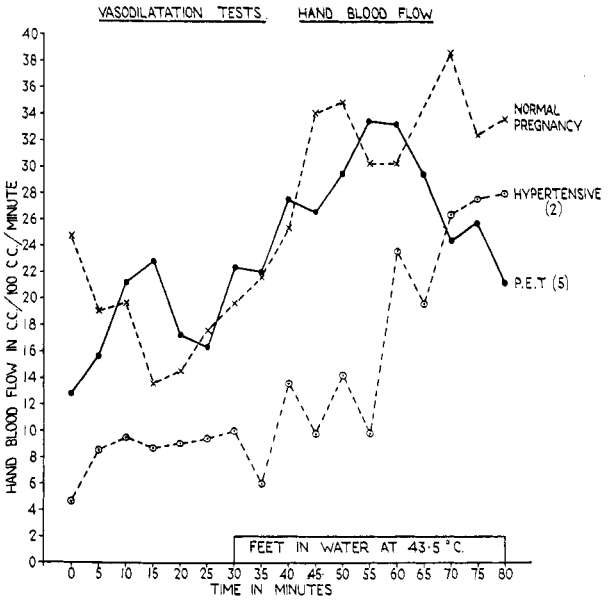

FIG. 1. Vasodilatation Tests: Hand Blood Flow.

(Fig. 1). Patients with essential hypertension may be more variable, but too few investigations have been done to draw any conclusions.

In Fig. 2 I have recorded the average hand blood flow in normal and hypertensive pregnant subjects and in patients with pre-eclamptic toxæmia during reflex vasodilatation tests. The numbers are too small for the differences to be significant, but the drop in hand blood flow in the pre-eclamptic toxæmic

group in the second half of the heating period may be related to the rise shown in the previous records of forearm blood flows and both may be due to increased adrenalin secretion caused by discomfort.

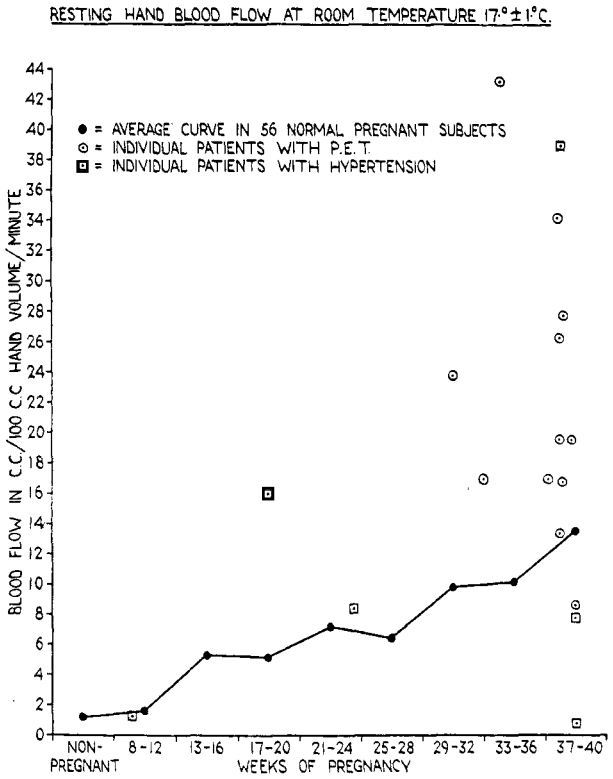

FIG. 2. Resting Hand Blood Flow at Room Temperature 17° ± 1°C.

My impression was that the patient with pre-eclamptic toxæmia was more intolerant to heating than the normal pregnant subject.

Muscle Blood Flow

When forearm blood flow was measured in the normal

pregnant subject and in the pre-eclamptic subject during induction of maximum reflex vasodilatation by heating the feet in water at 43.5°C., it was found that on the whole the

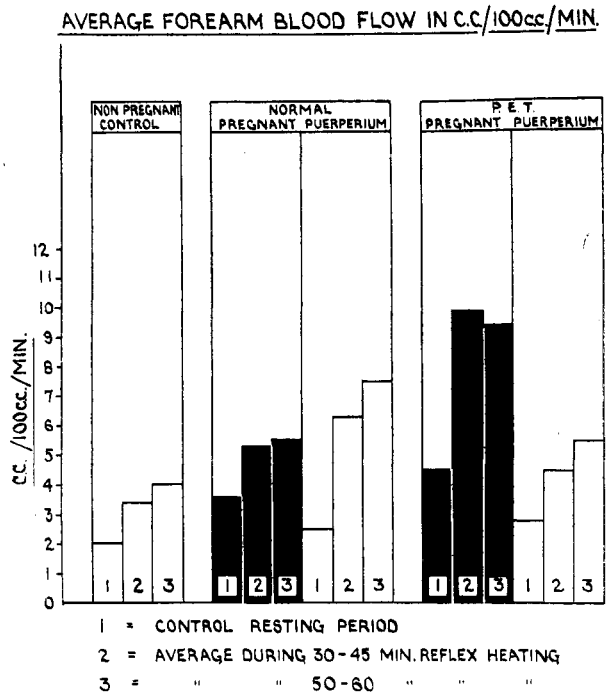

FIG. 3. Average Forearm Blood Flow—Non-pregnant controls, normal pregnant patients and patients suffering from pre-eclampsia. (*By permission of the Editor, Edin. Med. J.*)

forearm blood flow in the pre-eclamptic toxæmic patients rose to a height greater than that of the normal patients (Fig. 3).

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STUDIES IN THE PROBLEMS OF CIRCULATION IN PREGNANCY

(short contribution)

LARS WERKÖ

As Professor Kellar said, we have been studying the problems of circulation in pregnancy in Stockholm for a number of years. In estimating the cardiac output we have

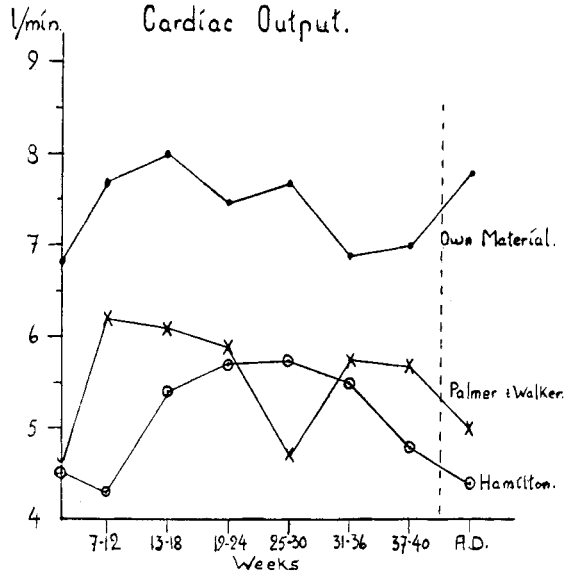

FIG. 1. Cardiac output determined according to Stewart and Hamilton (dye injection method) in 100 cases in different months of pregnancy, compared to the results of Hamilton and Palmer and Walker.

used a different method, the Hamilton dye injection method. For some reason we have obtained larger figures for cardiac output than Miss Hamilton or Palmer and Walker (Fig. 1). I do not know the reason for this.

We have made about 130 calculations in a little less than 100 cases of pregnancy. Some of the patients have been studied three or four times during pregnancy. You will see that you get an increase early in pregnancy of 1–2 litres in

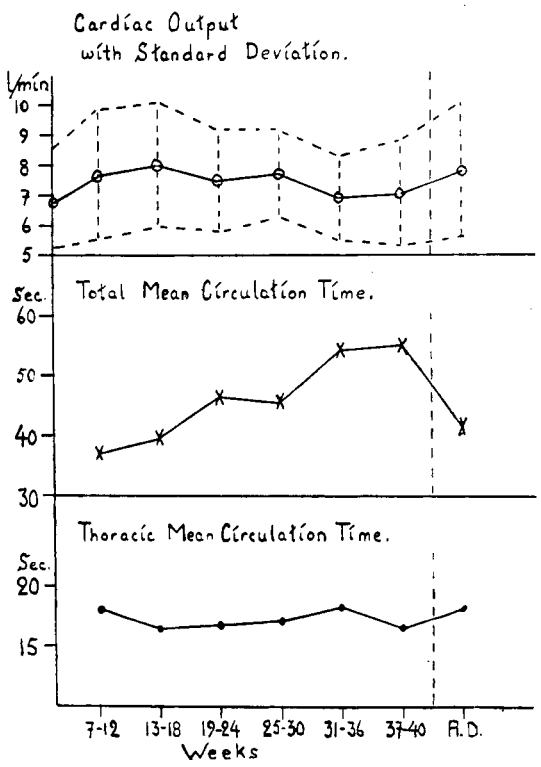

FIG. 2. Cardiac output total mean circulation time and thoracic mean circulation time in 100 cases in different months of pregnancy.

our own, English and Scottish material. We found the output lower in the later months of pregnancy, and immediately in the puerperium it rose again, but I don't know whether this rise is significant. We have calculated the total mean circulation time, by dividing the blood volume by the cardiac output,

and the thoracic mean circulation time, determined directly with the aid of intravenously injected dye, and our results are shown in Fig. 2. In the same cases we determined the hæmatocrit values and also the total blood volume at various

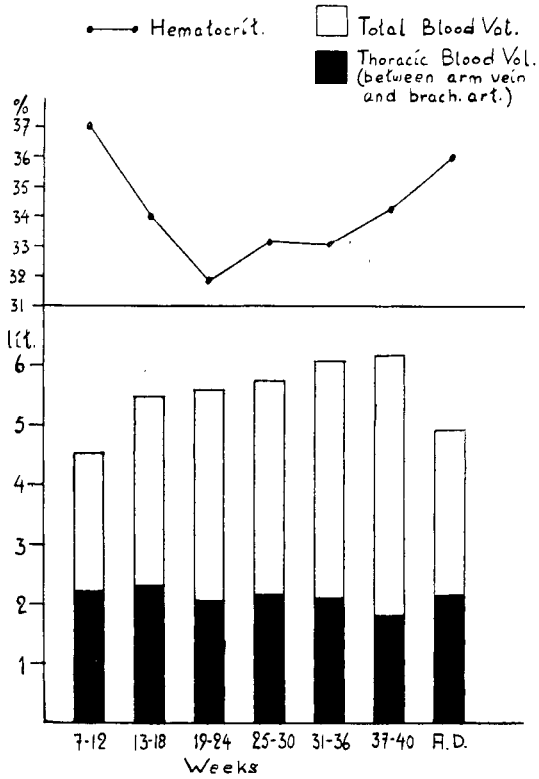

FIG. 3. Hæmatocrit and total blood volume and thoracic blood volume in the same cases as in Figs. 1 and 2.

stages of pregnancy, and after delivery. We also measured the thoracic blood volume, i.e. the amount of blood between the arm vein and the brachial artery, determined by the dye injection method (Fig. 3). The decrease of thoracic blood volume in the last month of pregnancy should be noted.

Fig. 4 shows the total circulation plasma protein and also the thoracic blood volume expressed as a percentage of the total blood volume, in different months of pregnancy in the same cases.

We also made a comparison between cardiac output, the

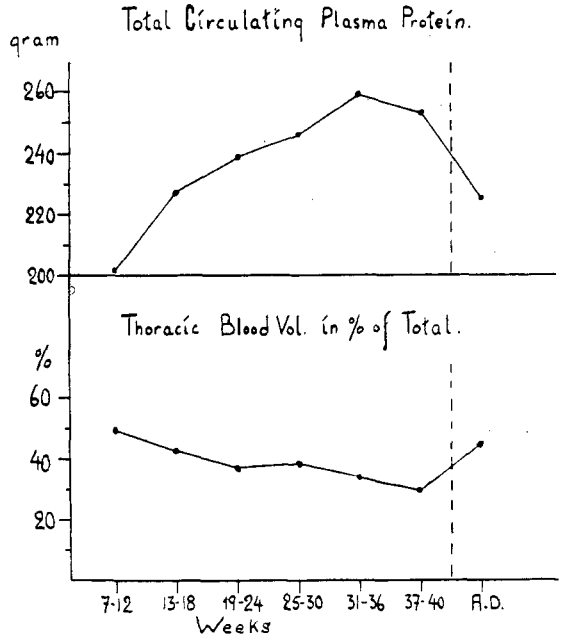

FIG. 4. Total circulating plasma protein and thoracic blood volume in the same cases as in Figs. 1, 2 and 3.

blood volume, the plasma protein and circulation times in groups of normal pregnant, preeclamptic, and hypertensive women. Fig. 5a shows the results obtained where the symptoms of preeclampsia or hypertension appeared between the 31st and 36th weeks, and in Fig. 5b there are the results in women where these symptoms began after the 37th week, in each case compared with a group of normal pregnant women

at the same stage of pregnancy. The marked differences in total blood volume and in total plasma protein in the pre-eclamptic women before the 36th week and after the 37th

	Nr. Cases	Blood Vol. Total ml.	Blood Vol. Thorac. ml.	Per cent of total	Hemato-crit. %	Circ. Plasma Protein Gm	C.O. L/min.	Circ. Time Total sec.	Circ. Time Thorac. sec.
Normal Pregn. 31-36 W.	20	6058	2100	34,8	33,1	259	6,91	54,1	18,3
Preeclampsia 31-36 W.	8	5090	1670	31,8	36,7	187	6,77	49,5	15,3
Hypertension 31-36 W.	8	5980	2180	36,2	36,8	250	7,88	45,1	16,9

FIG. 5a. Comparison between cardiac output, blood volume, plasma protein and circulation times in normal pregnancy and in pre-eclampsia and hypertension, starting between 31st and 36th weeks of pregnancy.

	Nr. Cases	Blood Vol. Total ml.	Blood Vol. Thorac. ml.	Per cent of total	Hemato-crit %	Circ. Plasma Protein gm.	C.O. L/min.	Circ. Time Total sec.	Circ. Time Thorac. sec.
Normal Pregn. 37-40 W.	20	6161	1800	29,7	34,3	253	7,06	55	16,6
Preeclampsia 37-40 W.	6	6230	2150	34,4	34,3	258	7,3	52,1	19,5
Hypertension 37-40 W.	11	6773	1980	29,3	35	280	7,37	61,8	17,6

FIG. 5b. Comparison between cardiac output, blood volume, plasma protein and circulation times in normal pregnancy and in pre-eclampsia and hypertension, starting after 37th week of pregnancy.

week should be particularly noted, the figures in the former group being significantly lower than in the normal or hypertensive women of the same period.

In another series of women we catheterized the patients, obtaining the blood pressures in the brachial artery, the pulmonary artery, the right ventricle and the right auricle. The pressures were recorded by the Tybjerg-Hansen-Warburg electrical manometer (Fig. 6). In late pregnancy we got

Blood Pressures in mm Hg during Pregnancy.

	Nr Cases	Brachial Artery		Pulmonary Artery		Right Ventricle		Right Aur
		S	D	S	D	S	D	M
Normal Women	16	130	76	20,2	7,1	22,6	3,7	2,5
Early Pregn. 10-19 W.	5	122	64	18,4	6,8	19	4,4	2
Late Pregn. 31-40 W.	11	112	71	15,0	5,8	15,5	0,1	0
Preeclampsia 31-40 W.	9	144	94	15,2	6,6	15,8	2,1	0
Hypertension 31-40 W.	2	150	100	17	5,5	19,5	0	-0,5

FIG. 6. Blood pressures in the systemic and pulmonary circulations in non-pregnant, pregnant, pre-eclamptic and hypertensive-pregnant women.

lower readings for the pressures in the lesser circulation than in normal women. There is no difference in the readings obtained in preeclampsia or hypertension from those in normal women.

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CIRCULATION IN PREGNANCY

(short contribution)

H. DE WATTEVILLE

As many others, we believe that some toxæmia symptoms could be very well explained by assuming the existence of a spasm of the small arteries. As a matter of fact, ophthalmological examination does reveal such alterations of vessels, but it seems quite obvious that local manifestations as well as the intensity of such a general disturbance may vary greatly, thus producing a great variety of different symptoms. We thought, therefore, that perhaps the *skin vessels*, which are readily affected, as you know, by humoral and nervous stimuli, might exhibit a local manifestation of abnormal toxæmic circulation.

Blood supply in the skin is rather well reflected by *skin temperature*, and any disturbances of skin circulation seem to be accentuated by the conditions of a *functional test after experimental stress*. In this test the *thermic reaction of the palm skin* after a cold bath is recorded; standardization of the starting point (two hours rest: a hot bath immediately preceding the cold one) reduces the inherent variation of the method to an acceptable minimum, and statistically significant effects can be observed in pathological states, or following therapeutic measures. Using this method, Burkhard and his co-workers (Zürich, Dermatologische Poliklinik) demonstrated that androgens and œstrogens increase peripheral blood circulation, and Zbinden (Maternité, Geneva) showed that the bad thermic skin reaction of ovariectomised women or of women suffering from ovarian disorders is ameliorated by the administration of chorionic gonadotrophin (L.H.).

A short time ago, we began to test the thermic skin reaction of normal and toxæmic patients, in pregnancy and the puerperium. Our very few data are in no sense conclusive. So far

it seems that there is no direct correlation between skin reaction and blood pressure or urinary albumen. Further investigations are necessary in order to decide whether our first impression that toxæmia may be associated with a bad thermic skin reaction, can or cannot be substantiated by statistically significant results.

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THROMBOPLASTIN COMPLICATIONS OF LATE PREGNANCY

CHARLES L. SCHNEIDER

It has long been considered logical to seek a mediator of toxæmia of pregnancy in the placenta or in the decidua. To this end experimental animals have been treated with appropriate extracts for half a century (Weichardt, 1909; Dienst, 1912; Young, 1914; Obata, 1919; Dieckmann, 1926-29; Smith and Smith, 1944; Schneider, 1946-47).

It has been shown that there is one and only one *immediately* potent pathologic factor in such extracts. This is thromboplastin (Schneider, 1947).

To appreciate and exploit this finding, with respect to investigating toxæmia of pregnancy, requires a reorientation in our thinking because thromboplastin is not a toxin in the usual sense of that term. The biochemical action of the thromboplastin remains the same as previously. It is concerned with blood coagulation. Instead of regarding it as a toxin, we must realize that it is a normal physiological agent, but that it can cause pathological manifestations. It can become pathologic because it can be translocated to, and act within a nonphysiologic environment, namely the circulating blood to which it may gain access.

The problem has now been studied from three main approaches :—

(1) By injecting extracts containing thromboplastin into experimental animals, intravascularly (cf. Schneider, 1947, 1950*a*).
(2) By causing a comparable "native extraction" of thromboplastin into the circulation to occur during pregnancy in animals by traumatizing the placentas (Schneider, 1950*b*).

(3) By studying collected clinical cases in order to evaluate whether a similar native extraction occurs in human pregnancy (Schneider, 1950*c*).

From the known actions of thromboplastin on coagulation *in vitro* predictions can be made as to reactions that will occur *in vivo* and also as to some reactions that will not occur. Nevertheless, these responses, particularly within the circulating coagulation system may be more complex than can be appreciated at the outset. Evaluation must, therefore, include experimental and observational approaches. It is necessary to address ourselves to experimental animals, despite the possibility of limitation of toxæmia of pregnancy to the human (cf. Editorial, 1948). Indeed, experiments with animals in the past decades of experimentation have given us many answers if we can but see in what manner these may fit together.

From the data of the diverse experiments already reported in the literature, it has become necessary to accumulate the pertinent information and to reconfirm this by animal experiments under suitable control. In several instances it has become necessary to extend these *in vivo* findings by new experiments.

The complications caused by placing thromboplastin in the circulation will be presented first; then complications of late human pregnancy will be considered in terms of these known reactions.

Before this, however, it will be well to refresh our knowledge concerning blood coagulation. In Fig. 1 is shown a simplified outline of blood coagulation as interpreted by present day investigators (Seegers, 1950). Prothrombin is considered to be present in the circulation and becomes activated to thrombin. This enzyme, thrombin, then acts upon the fibrinogen of the blood to deposit the fibrin clot. In the activation of prothrombin a number of factors are concerned. Among these are calcium, thromboplastin, accelerator globulin, factors derived from platelets, and perhaps other activators.

Let us focus attention on thromboplastin. The thromboplastin for this reaction is supplied from the fixed tissues, not from the circulation. It is the primary activator in the complex reaction leading to coagulation (Smith, Warner and Brinkhous, 1934). It is to be carefully noted that this agent is, therefore, not a variation of plasma fibrinogen in the sense of "tissue fibrinogen" as discussed by Mills (1921). It participates in the activation of prothrombin. It can initiate

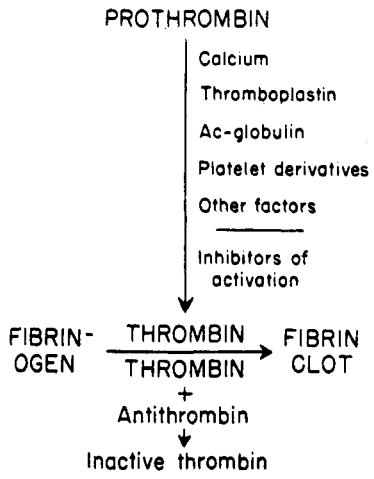

FIG. 1. Activators and stages of activation in the coagulation of the fibrinogen of the blood (Seegers, 1950).

the clotting mechanism. It does not enter the circulation by any physiological path; its normal locus of action is outside of the circulation. It is of such macro-molecular size that it can be centrifuged out of suspension with relative ease (Chargaff, Moore and Bendich, 1943). Our real knowledge of the properties and actions of thromboplastin and of its relation to blood coagulation is of recent origin (Seegers, 1950) and was not entirely known to investigators of toxæmia.

Let us now consider experiments concerned with the injection of thromboplastin. In a greater or lesser degree, any tissue may serve as a source of thromboplastin. Table I shows how much thromboplastin can be obtained from various sources. The placenta is one of the unusually rich sources; the decidua is even richer. Undoubtedly it was this thromboplastin activity that was encountered when investigators of toxæmia (Weichardt, 1909; Dienst, 1912; Obata, 1919; Dieckmann, 1926–29; Oettinger and Schwoerer, 1926; Sakurai, 1929; Schneider, 1946-50) injected placental extracts intravascularly.

Table 1

APPROXIMATE THROMBOPLASTIN YIELDS FROM DIFFERENT SOURCES. Determinations made with single stage clotting assay (cf. Schneider, 1947).

Source Material	Thromboplastin Units per gram of tissue
Amniotic fluid	1
Liver	10
Skeletal muscle	20
Kidney	50
Brain	50
Lung	200
Placenta:	
1st trimester	2,000
Term	200
Decidua:	
1st trimester	2,000
Term	1,500

These extracts are effective only when injected intravascularly (Schneider, 1946*a*). This is confirmed in Table II; there were no reactions when the material was injected subcutaneously, intramuscularly, or intraperitoneally. This was true even when the dose was ten times that which is fatal intravenously.

The extracts as ordinarily used were simple, crude, saline extracts of the tissues. It is well to avoid the use of abrasives

in the comminution of the tissues because of the influence of certain kinds of finely divided materials upon intravascular coagulation (cf. Lichtenstein, 1909). The extracts may be stored in the cold or preferably frozen. Even then they are likely to lose potency with storage.

Table II

Injection of thromboplastin is pathological only when given by the intravascular route. Even when ten minimum lethal doses are injected by other routes there is no effect. Eight to ten mice were used in each of the four test groups. The thromboplastin was extracted from decidual tissue which had been recovered from the maternal surface of a recently delivered placenta. These results confirm the similar experiment with placental extract (Schneider, 1946*a*).

Route of Injection	Thromboplastin Units Injected	Animals with Reactions	Animals Dying	Survivors with Liver Necrosis
Subcutaneous	10	0	0	0
Intramuscular	10	0	0	0
Intraperitoneal	10	0	0	0
Intravenous	1	all	½	⅛

That the "toxic" factor studied for many years and thromboplastin are identical follows (1) from recovery of both activities by sedimentation at high speed centrifugation (Schneider, 1947); (2) from the parallel inactivation of both activities by diverse physio-chemical and bio-chemical means (Schneider, 1947; Thomas, 1947*b*), and from the parallel pathologic effects (Schneider, 1947). There are several kinds of evidence that the action is that of intravascular coagulation (Oettinger and Schwoerer, 1926; Dieckmann, 1926–29; Sakurai, 1929; Thomas, 1947; Schneider, 1947-50). The activity can be determined in a mouse bio-assay (Obata, 1919; Schneider, 1946-47; Thomas, 1947*a*) in a simple, single-stage blood clotting assay (Schneider, 1947; Thomas, 1947*a*), or in a more refined two-stage analysis (McClaughry and Seegers, 1950). In the mouse assay the minimum lethal dose may be taken as the unit of activity (Schneider, 1946*a*, *d*).

Injection of Thromboplastin into Experimental Animals

When the extracts are injected intravenously, the response of the animals is prompt (Schneider, 1946*a*; Thomas, 1947*a*). The animals that undergo the more severe reactions may have convulsions or coma or both.* Usually these reactions are of short duration. They are followed within a few minutes either by death or by recovery.

If an animal dies, the respiratory movements stop before the cardiac pulsations stop. Death is, however, due to circulatory failure, not to respiratory failure, for it can be observed under the microscope that the peripheral circulation comes to a standstill before the respiratory movements cease (Schneider, 1947; Thomas, 1947*a*). The circulatory failure is a failure somewhere within the vasculature for, although the heart continues to pulsate actively, the blood in the peripheral circulation fails to move in the least. This may happen even if the dose has been a sublethal one, but with the sublethal doses, the blood soon begins to pulsate and then to flow again. Curious as are these intravascular phenomena following thromboplastin injection, they are in agreement with and are extended by the excellent work of Thomas (1947*a*, *b*) who has performed a similar study, for another purpose, using mouse brain as the source of the thromboplastin.

If the reaction proves to be sublethal, the animal promptly returns to normal activity. This recovery can occur even after convulsions and coma, and outwardly, at least, may be not only a prompt, but a complete, recovery.

Pathology: Fibrin Formed Intravascularly. In those animals that die at once, the gross findings at autopsy are essentially those of obstruction of the lesser circulation: there is distention of the liver, and dilatation of the chambers of the right heart. The basic lesion is microscopic, and characteristic (Fig. 2). It may be described as a disseminated,

*Note—It is not necessarily assumed that these immediate responses are the equivalent of the convulsions and coma of eclampsia.

INTRAVENOUS INJECTION OF THROMBOPLASTIN

Some resultant lesions in non-pregnant rabbits.

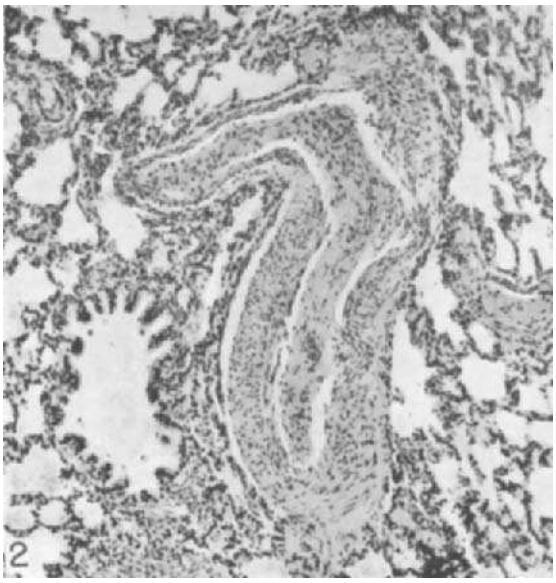

FIG. 2. Microscopic appearance of fibrin thrombo-emboli in the pulmonary arterial vasculature. Convulsions and prompt death followed injection of thromboplastin extract from a human placenta (Schneider, 1950*a*).

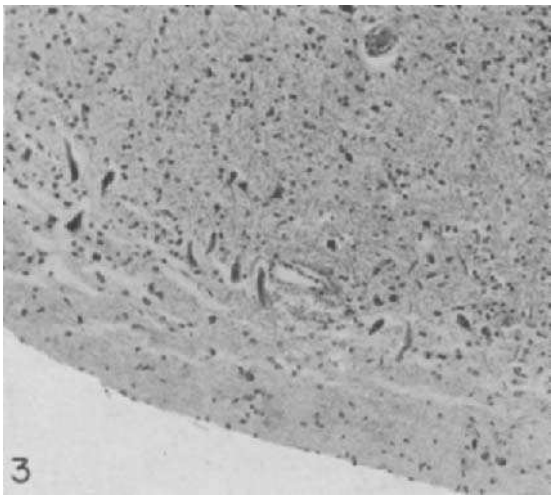

FIG. 3. Microscopic section of brain. Fibrin thrombo-embolus in a small artery; also a small perivascular hæmorrhage into the Virchow-Robin space about another small artery. Convulsions and death within a few minutes after injection of highly active (fifty units per cc.) thromboplastin extract from human placenta.

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INTRAVENOUS INJECTION OF THROMBOPLASTIN

Some resultant lesions in non-pregnant rabbits.

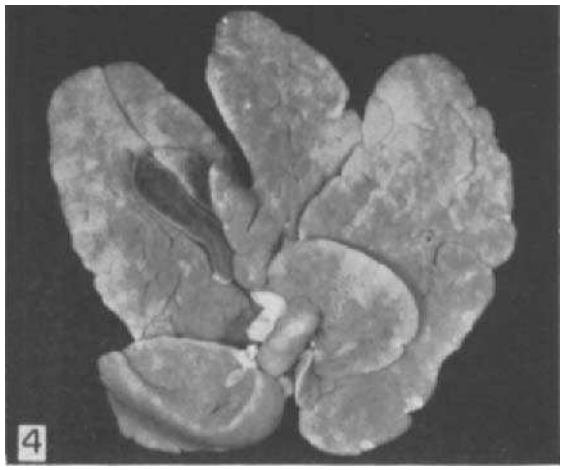


FIG. 4. Gross appearance of extensive liver lesions. The lesions tend to be most extensive at the borders of the lobes. The minute pattern of the lesions is reticular and follows the microscopically lobular structure of the liver. Sacrificed thirty-seven hours after injection of a dilute (one unit per cc.) thromboplastin extract from rabbit placenta.

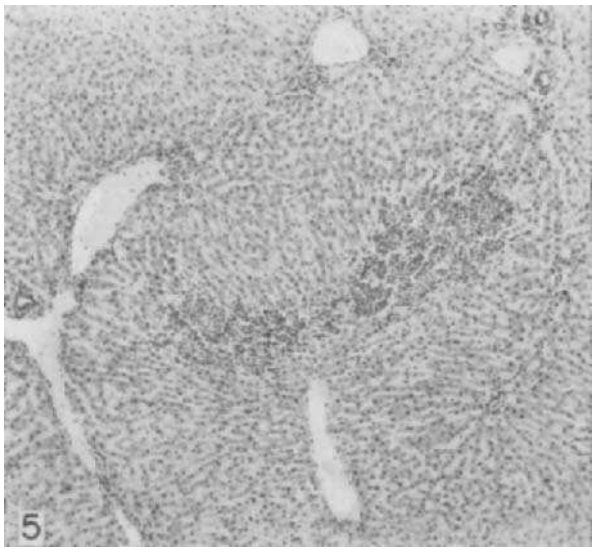


FIG. 5. Low power microscopic appearance of midzonal liver necrosis. Sacrificed sixteen hours after injection of dilute (one unit per cc.) thromboplastin containing fluid (human amniotic fluid which had been clarified by centrifugation) (Schneider, 1950*a*).

thrombo-embolism of the pulmonary arterial vasculature (Schneider, 1950*a*). These thrombo-emboli are not made up of mere coagulated, whole blood. Rather, their structure suggests that there has been a differential deposition of fibrin, under dynamic conditions. The appearance is such as to indicate that fibrin elements have been deposited by increments, under tension, from the flowing arterial circulation. The filaments of fibrin are oriented with the longitudinal axes of the vessels. Such few erythrocytes as are enmeshed within the thrombo-emboli are in longitudinal columns, which are one cell wide, or a few cells wide, within the fibrin matrix. By contrast, there are relatively many leucocytes embedded within these thrombo-emboli. Of these, some of the polymorphonuclear leucocytes provide additional evidence of the manner of deposition, for many of their nuclei may be seen greatly elongated as though under tension, parallel to the axes of the vessels.

These thrombo-emboli are widely distributed throughout the pulmonary vasculature of those animals which die of the injections. Anomalously, these pulmonary thrombo-emboli are rare or absent among the survivors. Even among the survivors that have undergone such severe reactions as almost to die, thrombi of any kind may be entirely lacking (cf. also Thomas, 1947*a*). It is only in those animals that die at once of the injections, that the pulmonary thrombo-emboli are a constant finding.*

Thrombo-embolism is not limited to the lesser circulation. The characteristic fibrin structures have been observed at least occasionally in different parts of the greater circulation, but they are most readily seen in the brain, in those animals which die of the injections. Fig. 3 shows a small thrombus in

* That thrombi may form and then quickly lyse *in vivo* is further indicated by the work of Green and Stoner (1947). that in the rat, following known, near-lethal doses of clotting agent, in combination with nucleotides, thrombi may be very extensive in surviving animals and yet disappear rapidly during the next twenty-four hours. In the same laboratory, Heard (unpublished work) has shown in the rabbit that under similar conditions, and after the intravenous injection of large numbers of blood clots, complete fibrinolysis occurs very rapidly.

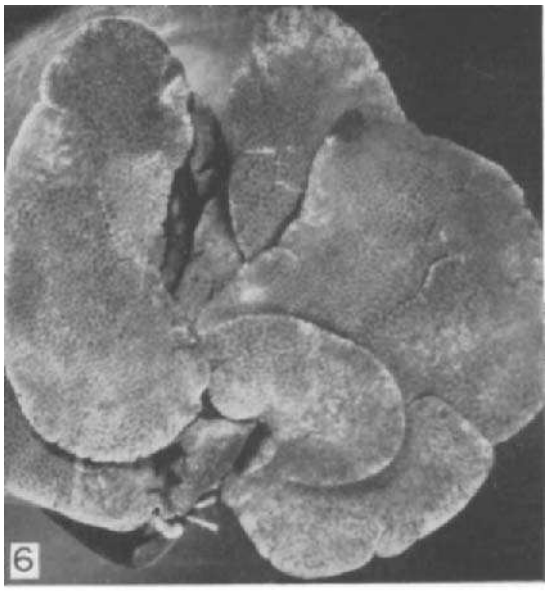
the brain of a rabbit dead of thromboplastin and also a perivascular hæmorrhage. Occasionally among the survivors also, there may be small perivascular hæmorrhages, sometimes with necrosis of the adjacent substance of the brain.

The production of localized central-nervous-system hæmorrhage and necrosis has been reported following injections of extracts of tissues other than the placenta (Hoefer, Putnam and Gray, 1938). Of the lesions following such injections it is not impossible that the large hæmorrhages found in the central nervous systems of repeatedly-injected dogs (Winternitz, Mylon and Katzenstein, 1940) may have been secondary to such small focal lesions.

Probably also belonging to this class of lesions caused by intravascular coagulation is the liver necrosis which has been reported (Dienst, 1912 ; Obata, 1919 ; Dieckmann, 1926-29 ; Schneider, 1950*b*). Fig. 4 shows a rabbit liver with extensive lesions (Schneider, 1950*a*). The lesions are most likely to occur within the survivors of severe reactions. The progress of these lesions can be studied. Fig. 5 shows the microscopic appearance of the liver necrosis. In the rabbit, if liver lesions are desired, it is best to dilute the thromboplastin extracts before injection. Also there are other species differences. The necrosis in the mouse is focal, i.e. without regard to the structure of the lobule of the liver (Schneider, 1946*a*). The liver necrosis in the rabbit is by contrast, strictly midzonal (Schneider, 1950*b*). Dieckmann (1941) concludes that the similar lesion in the dog may be influenced to be either midzonal or periportal. In the dog (Dieckmann, 1929) and in the mouse (Schneider, 1946*b*) there may be subcapsular hæmorrhages as well as necrosis of liver cells.

Deficiency of Fibrinogen. The experimental lesions described above appear to be the results of intravascular fibrin formation. However, animals that survive a just sublethal dose of thromboplastin may develop one or more complications from the resultant depletion of fibrinogen. First, there is lack of response to further injection (Schneider, 1946*d*). This apparent resistance or tolerance is achieved

Lesions in rabbits following experimental trauma to the placenta.



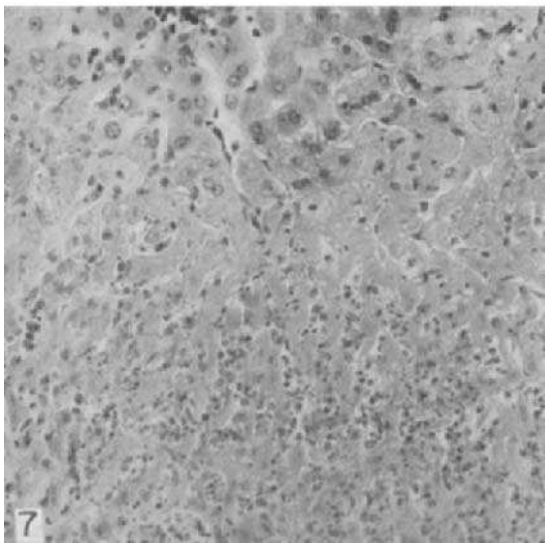


FIG. 6. Gross appearance of extensive liver lesions. The necrosis tends to be greatest at the peripheries of the larger lobes. The minute pattern of the lesions is reticular and follows the anatomically lobular structure of the liver. Sacrificed at fifty hours.

FIG. 7. High power microscopic appearance of mid-zonal liver necrosis. Sacrificed at twenty-eight hours. The midzonal portions of the hepatic cords, deep in the lesion, are compressed and narrow. There is an accumulation of leucocytes, the nuclei of which have stained deeply, but which are already fragmenting at this stage. At the borders of the lesions the hepatic cells are vacuolated and swollen; the intervening sinusoids are collapsed.

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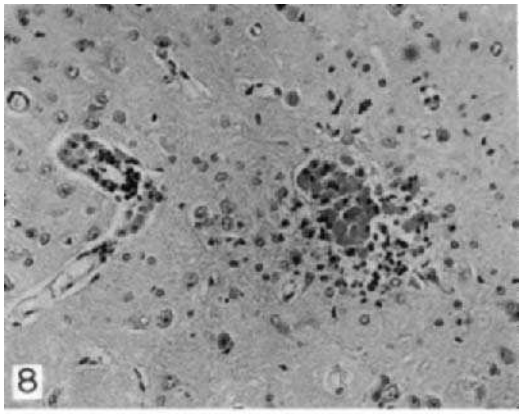
Lesions in rabbits following experimental trauma to the placenta.



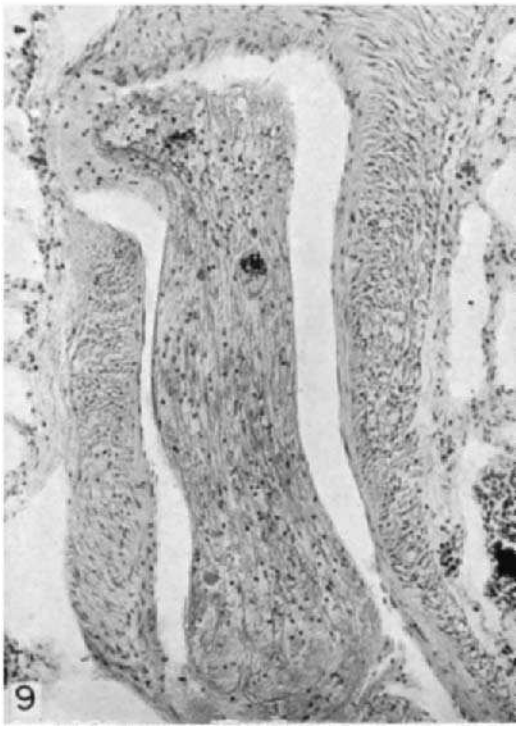


FIG. 8. High power microscopic appearance of perivascular hæmorrhages in the brain. Sacrificed at forty-five hours. The extravasated erythrocytes have been phagocytized and there is some local degeneration of the nervous tissue (Schneider, 1950*b*).

FIG. 9. Low power microscopic appearance of a thrombo-embolus in an animal that died promptly after trauma to several of her placentas. A giant cell, deported from the maternal placenta, can be seen not far above the middle of the thrombo-embolus: another can be seen less distinctly, high in the thrombo-embolus (Schneider, 1950*b*).

almost at once and persists for some hours. It can be so marked as to be, for practical purposes, absolute. This compares with the "negative phase" blood (Wooldridge, 1886) and is the result of intravascular defibrination (Mellanby, 1908).

Fulton and Page (1948) have shown not only that animals in this state of resistance are markedly deficient in fibrinogen, but that sensitivity to the thromboplastin extracts could be restored by artificially replenishing the plasma fibrinogen. Similarly, the sensitivity returns upon natural replenishment of the fibrinogen by the animal's own liver.

Manifestly, then, in these animals, the injection of thromboplastin has caused an intravascular defibrination.

There are certain implications of this deficiency state, for in it the coagulation mechanism itself has become deficient. Thereby an important portion of the hæmostatic mechanism has become defective. A hæmorrhagic tendency is occasionally found in the experimental animals (Schneider, 1950*a*).

Native Extraction of Thromboplastin into the Circulation in Experimental Animals

Because of the responses just described to the injection of thromboplastin extracts, it became of interest to know whether active materials could gain access to the circulation directly from the conceptus within the living maternal organism. To this end the placentas of several pregnant rabbits of appropriate stages of gestation were traumatized (Schneider, 1950*b*). This was accomplished at laparatomy, under conditions of surgical asepsis. The animals were studied at appropriate intervals. In these animals, anatomic traces of all of the thrombo-embolic lesions could be found. Areas of liver necrosis were readily obtained. The lesions are similar grossly (Fig. 6) and microscopically (Fig. 7) to those that are induced by injecting thromboplastin.

In Fig. 8 is shown a perivascular hæmorrhage which was also found in one of the animals.

One of the animals died as a result of placental trauma. In this animal there were disseminated pulmonary thrombo-emboli (Fig. 9). It was concluded that there had been a native extraction of thromboplastin from the traumatized placentas into the maternal circulation. Some of these thrombo-emboli contained formed elements. One of these which can be seen in Fig. 9 can be identified as having come from the maternal portion of the placenta. These served to implicate the maternal placenta as the source of the native extraction of thromboplastin (Schneider, 1950*b*).

Native Extraction of Thromboplastin into the Circulation During Human Pregnancy

Next it became of interest to determine whether a similar native extraction may occur in pregnant women (Schneider, 1950*c*).

Complete Placental Separation. This problem was approached by studying selected cases of defibrination of the kind that have been reported by Dieckmann (1936) and by Dam, Larsen and Plum (1941) to occur during premature separation of the placenta. The data presented in Table III

Table III

FIBRINOGEN DEPLETION DURING HUMAN PLACENTA ABRUPTIO, AND ITS RESTORATION THEREAFTER.

(Calculated from selected cases from: Schneider, 1950*c*; Dieckmann, 1936; Dam, Larson and Plum, 1941.)

Case Number	Lowest Fibrinogen during Placenta Abruptio	Total Calculated Fibrinogen including Transfusions	Total Observed Fibrinogen at 1–3 days	Therefore Fibrinogen Formed by Patient's Own Liver
1. V.S. (WH) . .	0.06	0.20	0.39	0.19
2. P.M. (HKH) .	0.09	0.22	0.52	0.30
3. (Calculated from Dieckmann) .	0.06	0.14	0.44	0.30
4. (Calculated from Dam *et al.*) .	0.12	0.14	0.32	0.18
5. (Calculated from Dam *et al.*) .	0.06	0.16	0.37	0.21

indicate that the defibrination had occurred as the result of an active process and not as the result of a liver dysfunction or of liver failure.

There was no reason to suppose that the fibrinogen levels of these patients may have been other than normal at the outset. Subsequent to the premature placental separation and to the accompanying defibrination, the fibrinogen was restored at least to the usual high levels of late pregnancy. This restoration occurred within a remarkably short time. Only a portion of this restoration could be accounted for on the basis of fibrinogen that had been supplied by intervening transfusions of blood. The remainder must have been supplied by the liver. The fibrinogen depletion, then, could not have been the result of liver failure. Alternatively, this must have been due to some active and extensive process of defibrination. Such an active defibrination could have resulted from a native extraction of thromboplastin from the conceptus into the maternal circulation.

In Fig. 10 there is diagrammatically presented a mechanism whereby a native extraction of thromboplastin from the decidua could have occurred.

This extraction process may continue so long as the retroplacental hæmatoma has not clotted. Even then it may be continued again by extension of the separation of the placenta to new areas, until at last the entire placenta had separated. Depending upon the circumstances of the given uteroplacental accident, such a native extraction might permit of extensive intravascular changes.

Partial Placental Separation. The problem arises whether a retroplacental hæmatoma such as that depicted in the diagram may actually occur. By the time of delivery of the placenta, the type of clot that is depicted schematically in this figure, could have long since become incorporated into the usual, massive, retroplacental clot of placenta abruptio, and thereby have long since lost its separate identity. However, since the work of Young (1914) such an incipient placenta abruptio or limited retroplacental hæmatoma has

been known to actually exist. In his Plates I and II, Young presented coloured drawings in which are included the very type of hæmatoma that I am considering. His interest was in relation to placental infarcts and the hæmatomas are described incidentally. In his Figs. 6, 7 and 9 he shows these

NATIVE EXTRACTION OF THROMBOPLASTIN IN HUMAN PREGNANCY
Schematic presentation of a hypothetical mechanism for native extraction of materials from the decidua, with maternal blood as the extracting vehicle, into the maternal circulation (Schneider, 1950*c*).

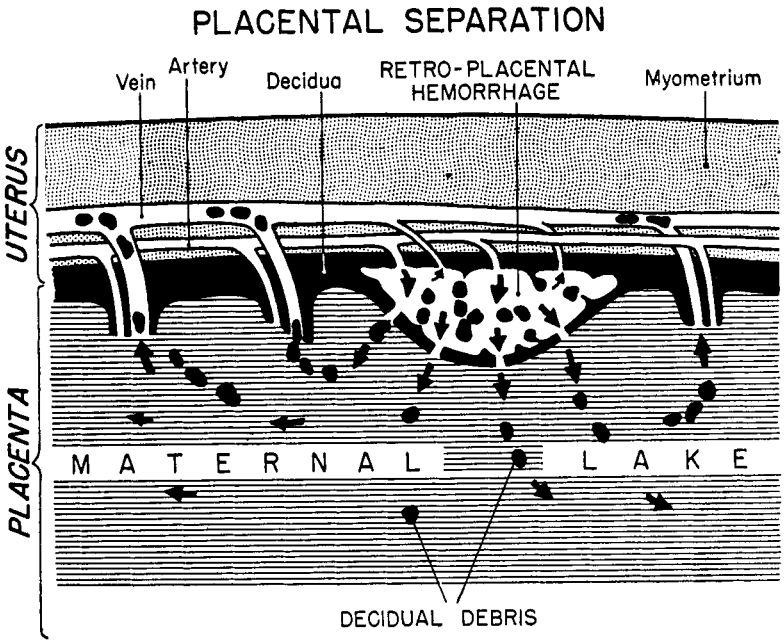


FIG. 10. A hæmatoma (retroplacental hæmorrhage) occurs within a separation in the decidua. Materials from the disrupted, fragmenting and friable decidua become mixed into the blood of the hæmatoma. Among these materials is thromboplastin. The mixture, including the thromboplastin, can then escape into the maternal circulation either through still functional passages into uterine vessels, or into the maternal lake; it may conceivably enter the maternal lake through open vascular channels or through disruptions in the fragile, split layer of decidua that serves to separate the hæmatoma from the maternal lake of the placenta. Once within the maternal lake the thromboplastin can be distributed into the general circulation by the usual pathways of its circulation (C. F. Spanner, 1935).

Retroplacental hæmatoma in a case of intrapartum eclampsia.

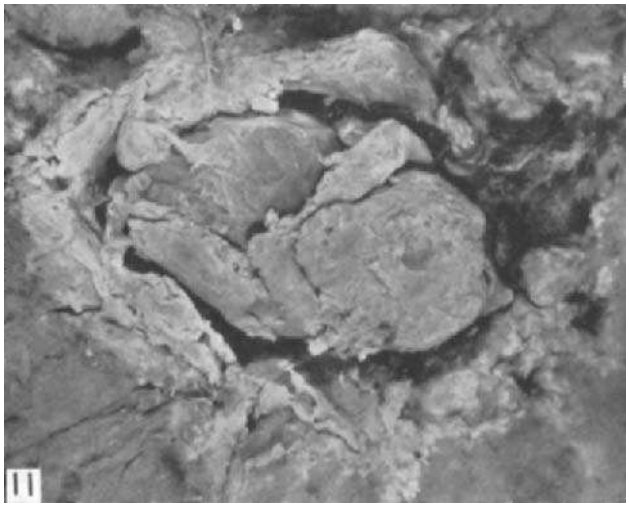


FIG. 11. Gross appearance, enlarged, of a recent retroplacental hæmatoma with the blood clot *in situ*. The apparent capsule at the surface of the lesion is the result of washing out of hæmoglobin from the surface portions of the clot during storage in saline.

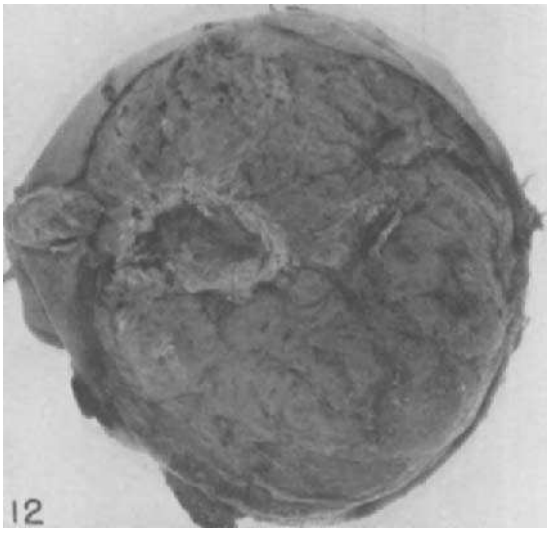


FIG. 12. Appearance of the hæmatoma of Fig. 11 in relationship to the entire placenta. The depression into the substance extends across one-fourth of the diameter of the placenta and to a depth of one-half of the thickness of the placenta. The blood clot has been lifted out of the depression in which it was found, so that the base of this depression in the placenta can be inspected; the blood clot itself is shown, inverted, at the margin of the placenta.

[*To face page* 174

Retroplacental hæmatoma in a case of intrapartum eclampsia.

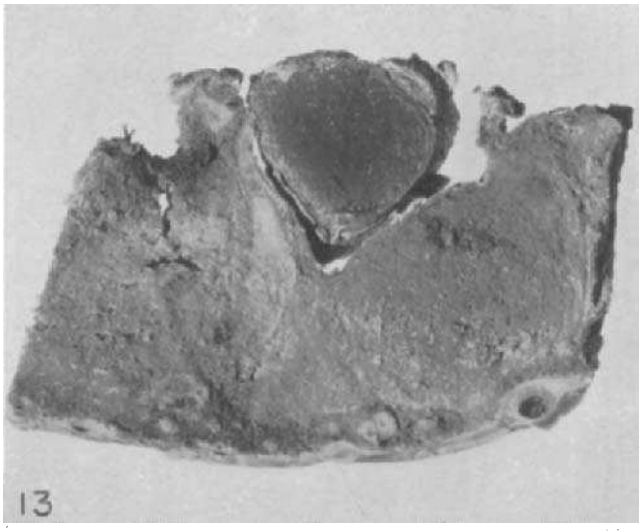


FIG. 13. Gross appearance of the same retroplacental hæmatoma as shown in Figs. 11 and 12, as seen in cut section. The clotted hæmatoma has compressed, or wedged apart, the underlying placenta to half thickness. There is a narrow, old, white infarct subtending one border of the hæmatoma.

retroplacental hæmatomas in the greater detail of cross sections. Similar retroplacental hæmatomas are shown elsewhere (cf. Dieckmann, opp. p. 310, 1941).

Because of the significance of these partial, retroplacental hæmatomas to native extraction into the maternal circulation from the decidua, some obstetrical cases have been studied in which these occurred (Schneider, 1950*c*).

Figs. 11–13 show the gross appearance of one of these hæmatomas. The previously shown diagrammatic retroplacental hæmatoma has here come to life. This patient had a complication which is sometimes associated with placenta abruptio. She had eclampsia. She survived.

Table IV

PARTIAL FIBRINOGEN DEPLETION DURING PARTIAL, PREMATURE SEPARATION OF THE PLACENTA, AND ITS RESTORATION.

Selected cases of intrapartum eclampsia (cf. Schneider, 1950*c*).

	Time, after Convulsion Began					
	Hours			Days		
	7	14	28	2	4	8
Case 1. A.A. (HKH) .		0.31	0.47	0.65	0.68	0.90
Case 2. J.A. (HKH) .	0.33	0.32	0.38	0.45	0.43	

Two more eclamptic patients with retroplacental hæmatomas were further studied. A summary of their fibrinogen levels is presented in Table IV. Each of the patients appears to have partially defibrinated her circulating blood. As with the cases of defibrination during placenta abruptio, these fibrinogen levels were also quickly restored not only to normal levels but to the high levels of severe toxæmia and of the postpartum interval. Since these patients had not received transfusions, in each case the woman's own liver must have accomplished the restoration of fibrinogen. Hence, in neither case, is it likely that liver dysfunction could have been the cause of the tendency for fibrinogen depletion. The

alternative is an active defibrination. It is concluded that the partial placental separations provided the mechanism for a native extraction of thromboplastin from the decidua into the maternal circulation, which was in turn, the cause of the defibrination.

Some of the placentas of the few eclamptic patients studied had more than one such retroplacental hæmatoma. Some but not all of these hæmatomas were subtended by grossly visible infarcts of the placenta. It must be added that, rarely, a similar retroplacental hæmatoma was encountered among the placentas of apparently normal pregnancies. More significantly, the frequency among cases of eclampsia was high (Young, 1914 ; Schneider, 1950*c*).

Conclusions

Pathologic findings similar to those which occur in experimental animals following injection of laboratory extracts of thromboplastin, or following native extractions of tissues of the conceptus, into the maternal circulation, also occur as complications of pregnancy in women.

Such complications of late human pregnancy may be associated with toxæmia of pregnancy in some cases and independent of it in others. Among them the zonal type of liver necrosis and cerebral hæmorrhage need only be mentioned. As is well known, the occurrence of one or of both of these pathologies in association with eclampsia is greater than chance (Dieckmann, 1941 ; Sheehan, 1950).

It should be emphasized in relation to the present work that obstetrical deaths due to massive cerebral hæmorrhage such as may occur even some days after delivery, have occurred with or without associated hypertension. The author has personally observed one such case wherein death occurred nine days postpartum, from a massive, intra- and extracerebral hæmorrhage which appeared to originate from a locus in an area of cerebral softening. Such a case, being free of hypertension, may be interpreted as having had thrombosis

and/or perivascular hæmorrhages at or near the time of delivery, with resultant local necrosis, and that this permitted the subsequent, massive, intracranial hæmorrhage.

However, a finding comparable to the most readily obtained of the experimental lesions, namely pulmonary thrombo-embolism, appears to have been reported in only one maternal death. In that case the "discrete thrombo-embolism of pulmonary vessels" was carefully noted by the pathologist, Dr. Rafael Dominguez; however, because of additional findings that were also reported it was necessary for Hemmings (1947) in reporting this case to include it under another pathology. It is possible that maternal deaths with the single diagnosis of disseminated pulmonary thrombo-embolism as a cause of death may be found at any time. This mixed case is mentioned now, in the hope that thrombo-embolism may be found in additional cases of obstetrical shock, in which death can not be otherwise adequately explained. It is possible that a figure shown by Schmorl (Fig. 5, 1893) depicts such a lesion.

It is not to be interpreted here, because one mechanism for the native extraction of thromboplastin into the maternal circulation from the conceptus has been demonstrated, that this is of necessity the only mechanism. On the contrary the demonstration of one path of entry from one source may be considered as lending support to the possibility that other plausible paths of entry, perhaps from other sources, may also exist. In considering other possible mechanisms, it is well to keep in mind the macromolecular size of thromboplastin, which puts limits upon its diffusability into the circulation from sources within or from without the body.

Among the more pertinent of such possible mechanisms, particularly for a gradually developing "toxæmia," would be that of repeated tearing off and deportation of placental fragments into the maternal circulation such as is described by Ceelen (1931). Such minute and perhaps chronically repeated release of active material into the circulation might well lead to a somewhat differently developing pathologic process than in response to the massive doses considered in

the present work. Gradual release of active material might lead to a less severe "toxæmia" than eclampsia, defibrination, or "obstetrical shock."

It is of interest to estimate the lethal dose of thromboplastin for a pregnant woman. There is an increased sensitivity of animals to thromboplastin during pregnancy. It can be calculated by extrapolation of the body weights during late pregnancy that the thromboplastin from approximately four grams of placenta (Schneider, 1946*e*) or of decidua could be lethal. This assumes, however, that the material would find its way into the circulation as though it were a single dose, quickly given. By contrast, an appreciable or even considerable time would have been required for its entry in the cases just described. Such prolonged administration, in the experimental animals, would have been likely to have led to defibrination, and consistently enough, at least from the results thus far, it seems that it was defibrination that was most likely to actually occur in human pregnancy.

Prophylactically or therapeutically, steps might be taken either to prevent the release of materials from the placenta or from the decidua, into the circulation, or to prevent their action once they had reached the circulation. One way to prevent further release of the materials into the circulation is to terminate the pregnancy; this is one of the classic methods of treatment of toxæmia. To prevent the action of the active material, the cautious use of heparin or of anti-thromboplastin has been suggested (Schneider, 1947). Maeck and Zilliacus (1948) have used heparin in ordinary doses, avoiding the crucial period of parturition, but with equivocal results. Page (1948) presents results with the use of heparin that are more suggestive that there may be merit in this anticoagulant therapy, at least in some cases of toxæmia of pregnancy.

In addition, Fulton and Page (1948*b*) have presented animal experiments from which it may be suggested that another substance, antitrypsin, may be effective against intravascular coagulation.

It cannot be overemphasized that quite aside from the dangers of maternal hæmorrhage that may follow upon the use of such anticoagulants, there may be similar or additional dangers for the fœtus as well. Because of hæmorrhage in the new-born, dicumarol is known to be unsafe in the pregnancy of dogs (Quick, 1946), of rabbits (Kraus, Perlow and Singer, 1949), and of man (Sydow, 1947 ; Sachs and Labate, 1949). Investigation of the other anticoagulants in animal pregnancy is apparently lacking. An as yet unconfirmed experiment of my own with pregnant rabbits suggests that even heparin may not be without its dangers to the subsequent development of the offspring. Further evaluation is urgently needed before definite recommendations in human pregnancy can be made.

Aside from the inherent dangers of the treatment itself, the value of anticoagulants against the peculiar thromboplastin complications of pregnancy may be limited. The limitation is the same as the limitation of anticoagulant prophylaxis elsewhere in medicine : for such prophylaxis it is necessary to predict the time at which the anticoagulant will be needed. As yet, this cannot always be done because many of the acute complications of late pregnancy, which may be considered as thromboplastin complications, cannot be accurately predicted clinically.

Summary

From fundamental studies of the blood clotting mechanism, some of the properties and the function of thromboplastin are well known. It has also been found that abnormal effects produced by it in the living organism are in many respects like certain pathologic states encountered in pregnancy. There is more than one available path for its entry from the conceptus into the maternal circulation and one of these has been demonstrated. Hence it is a plausible viewpoint that thromboplastin may be the fundamental cause or mediator of some of these disorders of late pregnancy. How many difficulties may be explained on this basis is not yet

known, nor is it known what may be resorted to for therapeutic purposes. For the moment we can at least turn our thoughts in that direction.

It is with heartfelt appreciation that the author takes this opportunity to thank Professor Walter H. Seegers of the Department of Physiology for his long and keen interest in these investigations; also Professor Charles S. Stevenson, of the Department of Obstetrics and Gynæcology for his enthusiasm and furtherance of the clinical correlation.

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TOXÆMIAS OF PREGNANCY: HUMAN AND VETERINARY
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ISCHÆMIA OF THE GRAVID UTERUS AS A PROBABLE FACTOR IN THE CAUSING OF TOXÆMIA

M. A. VAN BOUWDIJK BASTIAANSE
and J. L. MASTBOOM

IN the past years many theories as to the ætiology of toxæmia of pregnancy have been suggested. Although those who originated these theories considered that they had sufficient justification for them, they have always been refuted by new discoveries. I believe that our insight into the ætiology of toxæmia of pregnancy has progressed greatly in recent years. For the last twenty-five years Beker has given in various lectures and publications his opinion concerning the development of toxæmia of pregnancy. He believes that the cause of toxæmia is an abnormality in the hæmodynamic balance, which depends chiefly on the overcoming of a certain resistance in the wall of the uterus. The general blood circulation in pregnancy must also be provided with a certain "nutrition-reflex" originating from the uterus. When Beker spoke on this subject before the Netherlands Gynæcological Society in 1941, one of us (M.A.B.) was struck by the idea that due to an insufficient blood supply to the placenta, a type of mechanism might develop in the pregnant uterus similar to that in an ischæmic kidney, not only in cases in which the uterus wall is strongly stretched by its contents, but also in other cases of toxæmia. Without going into details, the findings in the ischæmic kidney were transferred to the ischæmic uterus. When the uterus is stretched to an extreme by its contents, the vessels are compressed and therefore less blood reaches the placenta.

An acceptable theory for the ætiology of eclampsia must first explain not only all the symptoms of toxæmia, but also

why and in what manner the toxæmia develops under certain conditions. Secondly an experimentally produced ischæmia of the placenta must cause a toxæmia in certain test-animals.

We believe that such a theory must explain:—

(1) The predisposing influence of *primiparity, multiple pregnancy* and *hydramnios.*
(2) The *increase in frequency,* the farther the pregnancy has progressed.
(3) The *rare recurrence* of eclampsia, whereas the toxæmia frequently recurs in cases of pre-existent vascular renal disease.
(4) The *difference in frequency* in various countries and populations and at different ages.
(5) The *earlier development* of toxæmia in pre-existent vascular renal disease.

The most important symptoms of toxæmia of pregnancy are: hypertension, œdema and albuminuria. Of these the hypertension is the most important. In the literature one sees occasionally that an eclampsia has developed without hypertension. In the large experience of our clinic we have never seen a case of eclampsia without hypertension. We have had patients who were sent in for eclampsia; however, on exhaustive examination it was never a real eclampsia and in most cases was an epilepsy.

The albuminuria and the œdema may in certain cases be absent. The height of the blood pressure alone is not proof of a toxæmia. It is very well possible that the hypertension existed before the woman became pregnant. A toxæmia only exists when during the pregnancy the blood pressure rises. In rare cases the rise can be so acute that the woman develops an eclamptic attack shortly after the beginning of the rise.

When must we speak of a hypertension? Browne believes that the upper limit of a normal blood pressure is 120/80 mm. If the pressure is higher than this, one may speak of a hypertension. We as well as many others such as Dieckmann

have placed the limit in pregnancy at 140/90 mm. Theoretically it is possible that a toxæmia will occur in cases in which the blood pressure has not attained this level. However, not the height of the blood pressure in itself but its rise is the most important symptom of toxæmia of pregnancy. When the blood pressure, which was 110 systolic before pregnancy, rises to for example 130 systolic, this is the result of some change in the organism which has caused the rise in the blood pressure. When this happens in a pregnant woman, then it is highly probable that a toxæmia of pregnancy exists. We have never seen an eclamptic attack with a systolic blood pressure lower than 140 mm.

When can an insufficient blood supply to the placenta occur? This may occur :—

(1) When the vessels to the placenta are more narrow than normal.
(2) If the blood supply to the placenta is normal but the placenta is larger than normal.

We believe that toxæmia could be caused by *any disturbance in the normal relation of the volume of blood carried to the placenta per unit of time and the quantity of placental tissue.* Toxæmia is then dependent on an *absolute or a relative insufficient blood supply to the placenta.*

In this way the toxæmia of late pregnancy is a sign of *insufficient adjustment of the mother's organism, especially her vascular system to the demands of pregnancy.* In cases of too high demands of pregnancy on a given state of the vascular system a sufficient blood supply to the placenta cannot longer be ensured: a toxæmia develops. In other words the toxæmia of late pregnancy is a disease of *insufficient adaptation.*

When we are asked as to when the blood supply is insufficient, the answer is: when the vessels of the uterus are decreased in number or when they are smaller in diameter than normal. The uterine vessels have a smaller diameter than normal :—

(*a*) When there is a congenital hypoplasia of the vascular system.
(*b*) When the uterine muscle is strongly stretched around its contents.
(*c*) If the hormone production which causes dilatation and hypertrophy of the vessels is insufficient
(*d*) If vessels cannot react normally to the physiological, hormonal stimulus which ensures a sufficient circulation in the intervillous spaces.

As regards the *infantile vascular system*, various communications can be found in the literature. Wettley found a hypoplastic vascular system in 25 per cent of the cases in a large group of fatal cases of eclampsia. Bartels collected 248 autopsy reports in cases of eclampsia from the literature. He found a hypoplastic vascular system in 44 per cent. In our clinic my assistant Lindeboom examined seven cases as to the calibre of the aorta and pulmonary arteries and in five cases these were definitely smaller than normal. The uterine vessels with an infantile vascular system will also be smaller in diameter than normal. During pregnancy these will increase in diameter due to the physiological hormonal stimulus originating from the placenta. This will probably not develop to the same extent as in women with a normally developed vascular system.

During the first pregnancy in a woman with a *normal* vascular system there exists also a *physiological relative hypoarterialization* of the uterus as compared with the vascular system of the uterus of a multipara, which is proved by the research of Horn and Beker, who showed that after the first pregnancy the uterine vessels remain markedly larger than before pregnancy. A *true* toxæmia in a multipara may thus only be expected when unusual factors as hydramnios or multiple pregnancy are present, which similarly obstruct the blood supply to the placenta.

As I already mentioned Beker suggested that the possible development of a toxæmia of pregnancy is greater when the

uterus is strongly stretched over its contents. We agree with him in this supposition. This will be the case in the *primipara* and in cases of *infantile* uterus which one may expect in a very young primipara, in an old primipara where the tissues in general, including the uterus, are probably less resilient and in cases with increased volume of the contents of the uterus as in *hydramnios* and *multiple pregnancy.* It is generally accepted that toxæmia occurs much more frequently in such cases.

Another support for our theory is the increase in frequency of toxæmia the longer the pregnancy has existed. After the fourth month, apart from its physiological hypertrophy, the uterus becomes larger due to stretching as a result of the rapid growth of its contents. When labour has developed, the blood supply to the placenta will be further obstructed so that we may expect a greater possibility of eclampsia which is indeed the case. We may also expect that women who had a completely normal blood pressure before the beginning of labour will show a rise in pressure during labour. This we have often observed and it has moreover been described in the literature.

Little is as yet known of the production of hormones by the placenta which would cause hypertrophy and dilatation of the vessels. The most important research along this line has been done by Smith and Smith. They state that the most important hormonal changes in the blood in toxæmia of pregnancy are a greatly increased gonadotrophin content and a low œstrogenic activity. These changes are identical with those occurring before and during labour which they believe shows that the premature development of senility of the placenta forms the basis for a toxæmia. Before and during menstruation they observed a decrease in the steroid content of the urine. This indicates a lack of œstrone and progesterone. They found that the euglobulin fraction of the menstrual blood contains a specific very toxic labile protein which causes the local vascular abnormalities in menstruation. They believe that a similar vascular abnormality

in toxæmia would be caused by the same toxic protein, which would also originate from tissue destruction as a result of decreased supply of hormones to the uterine contents. Smith and Smith presented the hypothesis that *tissue damage from any cause* releases a proteolytic enzyme which in its turn gives rise to a toxic labile protein of which the pathological action results in vasoconstriction, increased capillary permeability, œdema, hæmorrhage and necrosis. The research of Smith and Smith led to the assumption that a correlation exists between *the blood supply to the placenta and the production of steroid hormones. The adequate vascularization of the pregnant uterus is, according to them, as essential for a normal production and metabolism of œstrone and progesterone as an adequate supply of steroid hormones is for the normal development of the vascular system of the uterus.*

It seems to us that the vessels will be less able to react to the physiological hormonal stimuli which act to ensure an adequate circulation in the intervillous spaces, when *anatomical changes* in the vessel wall have developed. These changes in the vessels may be expected with every hypertension existing for some time, as in *arterio-sclerosis*, in *essential hypertension* and in the *hypertensive type of chronic nephritis*. It is a generally known fact that a toxæmia which is superimposed on a pre-existent vascular renal disease occurs earlier in pregnancy and accordingly is of longer duration. Since the frequency of hypertension, independent of pregnancy, increases with age, it may be expected that an early beginning toxæmia occurs more frequently in multiparæ than in primiparæ. This is indeed the case as shown by Fig. 1.

In pre-eclampsia more patients have the toxæmia superimposed on a pre-existing vascular renal disease than in eclampsia. Therefore, in toxæmias of a long duration there will be found more cases of pre-eclampsia than of eclampsia (Fig. 2).

In a pre-existing hypertension or a chronic nephritis in which a general constriction of the arterioles including those of the kidney is assumed, any extra supply of substances

which raise the vessel tone (in our view as a result of insufficient circulation in the intervillous spaces) will cause a decrease in blood circulation to the kidney. Therefore the

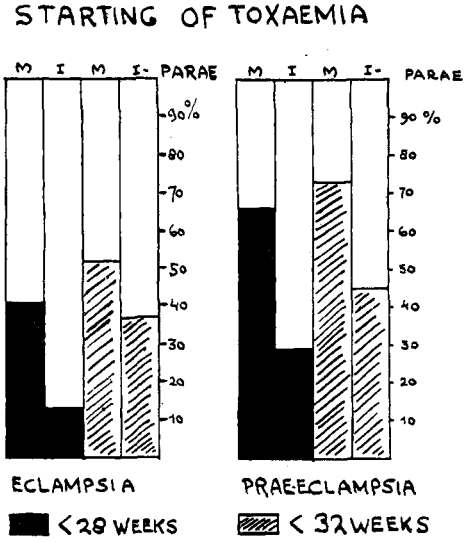

FIG. 1.

possibility for the development of a further hypertension of the *Goldblatt* type becomes greater. If the uterine vessels are already large before pregnancy then no vasopressor substances will be formed in the placenta even in cases of pre-existing vascular-renal disease and therefore no hypertension or progression thereof will develop. The blood pressure even can show a temporary fall in the same way that it does, although to a lesser extent, in a normal pregnancy,

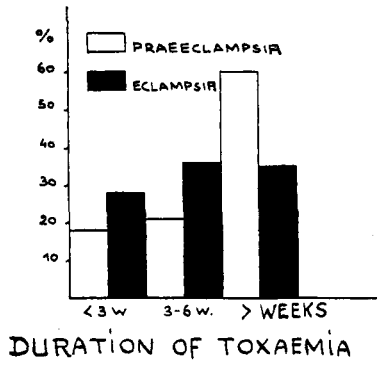

FIG. 2.

probably as a result of the decrease in the arteriolar tone, due to the progesterone action as well as possible changes in other hæmodynamic factors. In our patients we saw in somewhat less than 40 per cent a temporary but usually marked fall in the blood pressure in a pre-existing hypertension during pregnancy.

The importance of the age (Fig. 3) in the development of toxæmia could thus be explained as follows: the greater

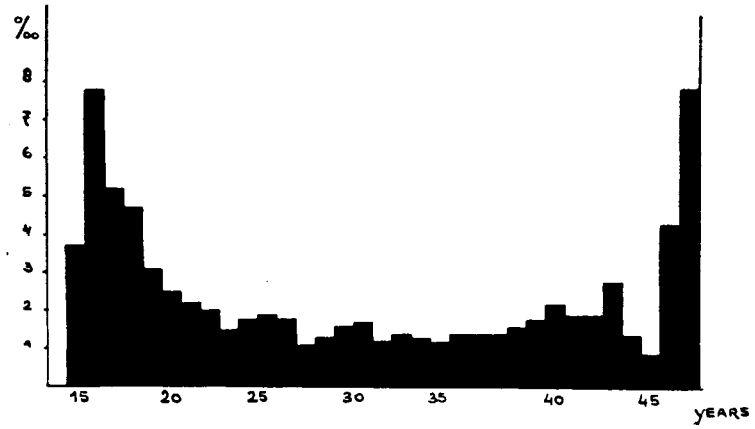

FIG. 3. Frequency of Eclampsia at Different Ages (Hauch and Lehmann).

frequency occurring below twenty years of age is caused by an insufficient development of the genital and vascular system, that is hypoplasia of the uterus and relative hypo-arterialization of the genital system; the greater frequency with more advanced age results from sclerotic changes of the uterine vessels and also from a decreased resiliency of the uterus itself.

When a toxæmia occurs superimposed on pre-existing vascular renal disease, there must be a great possibility that toxæmia will recur in subsequent pregnancies. The vessels will very probably still be insufficiently large to ensure an adequate blood supply to the placenta. The fact that the

toxæmia developed shows that the blood supply to the placenta was insufficient. In patients with pre-existing vascular-renal disease, who showed no toxæmia superimposed on this disease in previous pregnancies, there is a great possibility that also in subsequent pregnancies no toxæmia will develop. The non-occurrence of a toxæmia in a previous pregnancy showed that the vessels were capable of supplying sufficient blood.

In the second group of conditions in which a *relatively insufficient circulation in the intervillous spaces* can occur, we may place those in which a larger than normal placenta is present. This is amongst others the case in hydatiform mole and to a less extent in *hydrops fœtalis*, *multiple pregnancy* and *diabetes*. With regard to the relation of a molar pregnancy to toxæmia there is little to be found in the literature. It is however generally known that in molar pregnancy a hypertension and possibly albuminuria occurs much earlier and more frequently. Of 18 patients with a molar pregnancy who were treated in the University of Amsterdam Women's Clinic between 1938 and 1947, seven had a hypertension of at least 140/90 mm. and six of these had also albuminuria. These women had a completely normal blood pressure before pregnancy.

With regard to *hydrops fœtalis* with symptoms of toxæmia, a research by Kloosterman is of importance. He found a toxæmia in 23 out of 35 cases of *hydrops fœtalis* (65 per cent). He stated that the placental coefficient (the relation between placental weight and the weight of the child) in hydrops pregnancy combined with toxæmia was significantly higher than in cases without toxæmia (respectively 0.75 and 0.47). In this way he could demonstrate with more certainty than by the absolute placental weights, a definite *hyperplasia of the placenta* in hydrops pregnancies complicated by toxæmia.

Also in *diabetes* it is known that toxæmia occurs more frequently. Several factors may have an influence in this. Firstly the frequently larger placenta in these cases. Ten Berge found in a research on this subject that in diabetes

toxæmia occurs the more frequently the larger the placenta. I would like to call your attention to the fact that the frequency of toxæmia in the cases mentioned in Group (2) is also influenced by the presence of other toxæmia-predisposing factors such as primiparity, hydramnios, etc.

We believe that we can explain the greater part of the *symptoms of toxæmia* of pregnancy by spasm of the arterioles throughout the whole body. This spasm would occur due to the formation of substances in the ischæmic placenta which directly or by the intervention of other factors could cause a rise in blood pressure.

The *visual disturbances* as well as the frequent abnormalities in the retina could be caused by nutritional disturbances resulting from the spasm of the arterioles of the retina. The *albuminuria* may be caused by constriction of the renal arterioles, the *necrosis* and *hæmorrhages* in various organs such as in the liver by disturbances resulting from arteriolar spasm, the frequently *decreased weight of the fœtus* in toxæmia of longer duration by insufficient blood supply to the placenta due to constricted vessels in the uterus. The higher fœtal mortality can be explained in the same way as well as infarcts of the placenta.

Abruptio placentæ can be explained by a decreased resistance of the uterine vessels in pre-existing vascular renal disease exaggerated by nutritional disturbances as a result of the spasm.

The *oliguria* and possible *anuria* may be due to degenerative changes in the glomeruli and tubules by the inadequate oxygenation of tissue as a result of spasm of the renal arterioles, as well as to a possible hyperfunction of the tubules. These changes become accentuated when a large fall of the blood pressure occurs as a result of abruptio placentæ, in which case the blood pressure has become too low to force blood through the constricted arterioles.

The explanation of the resultant *œdema* is more difficult and is only partly explained by the increased hydrostatic pressure, the increased permeability of the vessel wall and

the hypoproteinæmia. We can only suspect but not prove the cause of œdema in the present state of our knowledge of sodium metabolism in pregnancy and of the physiology of the adrenals. It is possible that the higher sodium retention in patients with toxæmia is connected with the adrenal glands of which, in our view, the function is disturbed as a result of the hormonal dysharmony caused by an insufficient blood supply to the placenta.

Finally, there is evidence of an increased production of pituitary antidiuretic hormones as a result of this dysharmony.

Puerperal eclampsia is also difficult to explain. It does not seem impossible to us that puerperal eclampsia is associated with a *relative overfilling of the vascular system* in cases of mild or severe toxæmia, as a result of the emptying of the uterine vascular bed, especially when there is only a small blood loss during labour. As another factor of importance may be considered the well-known fact that during labour a relatively large volume of fluid is forced out of the vascular system into the surrounding tissues (Dieckmann, Albers). From the experiments of Dieckmann and others we know that the quantity of this fluid is much greater still in patients with toxæmia. When labour is over, the venous pressure will be decreased and the conditions will become such that the fluid will return from the tissues into the vascular system. In a non-toxæmic patient with a normal renal function, the kidney will see to it that the volume of circulating blood remains constant. On the contrary, when an oliguria exists, the kidney will be deficient in this function, so that the volume of circulating blood becomes too large. This might perhaps explain the frequently observed rise in blood pressure during the first days after labour. However, Dieckmann found that especially in cases of fatal eclampsia the blood volume does not increase. Therefore our suggestion must be wrong. It is, then, more probable that after labour the œdema fluid which was forced into the tissues during labour, diffuses still further into the surrounding tissues including the brain. This

might be the explanation of the development of eclamptic convulsions.

I have already mentioned that contrary to a toxæmia superimposed on pre-existing vascular-renal disease, a true toxæmia of pregnancy seldom occurs in multiparæ, and have also mentioned the earlier occurrence of the first form of toxæmia as compared with the latter.

How can we explain the *differences in frequency* in *various countries* and *populations* and in times of *adequate* and *inadequate nutrition* ? The difference between city- and country-patients can be explained by the difference in the relation between the number of primaparæ as compared to multiparæ. The decreased frequency of toxæmia in some populations, such as in the less well-to-do Indonesians, must be sought in the poorer state of the muscular system as a result of deficient nutrition and in the relatively large number of multiparæ. That the muscular layer of the arterioles is in a poorer condition in cases of a deficient as compared to a good nutrition can be demonstrated firstly by a research carried out by Sindram in our clinic, which showed that in the last war the average blood pressure in pregnancy was definitely lower than before the war. A similar research performed in our clinic in 2,400 non-pregnant patients supported the view that the blood pressure in non-pregnant women during the hunger-period was also markedly lower than in normal times. These findings have been confirmed in other clinics. Secondly, the uterine muscle itself also probably becomes weaker as a result of the poor nutrition. The work of De Snoo and Remmelts showed that probably the uterine muscle is weaker in malnutrition since they found in the less well-to-do women in Indonesia that postpartum hæmorrhage was more frequent than among the more prosperous women. In a recent research in our clinic by my assistant De Leeuw it was revealed that the number of postpartum hæmorrhages was greater during the war than previously, while the number increased with the duration of the war as the nutrition became increasingly poorer. The marked decrease in the frequency of toxæmia during the war

can then be explained as due to a better blood supply to the placenta as a result of a decreased tonus of the arterioles and the uterine muscle, caused by the malnutrition. An investigation on this subject showed that during the last war a progressive decrease in the frequency of toxæmia in Amsterdam took place which reached its lowest point during the hunger-winter of 1944–1945. In addition we may state that in this investigation careful attention was given to various types of pregnant women (percentage primiparæ) (Fig. 4).

Since all symptoms occurring with a toxæmia of pregnancy can be explained by assuming substances which either directly or indirectly can increase the blood pressure, which

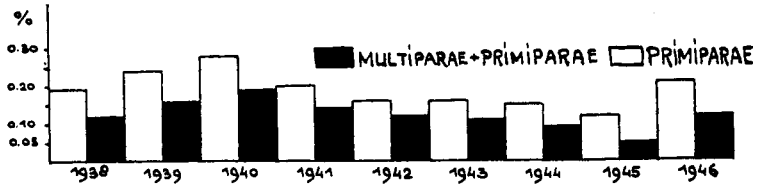

FIG. 4. Relative Frequency of Eclampsia at Amsterdam, 1938–1946.

substances would be formed in the placenta as a result of a decrease in the blood supply we thought that perhaps additional support for our hypothesis could be found by means of animal experiments. These experiments were performed in association with Prof. Ten Cate, head of the Department of Physical Physiology at the University of Amsterdam, and Dr. Horsten, assistant at that laboratory. We had already started these experiments during the war (Sindram, 1943). The only animals available at that time were rats, which proved to be too small, and we were obliged to wait until we could get larger animals. In the beginning we proposed to cause ischæmia of a pregnant uterus in a so-called chronic experiment. However, we met with such difficulties that up to now we have only been able to perform the so-called acute

experiment. We have drawn up a scheme for the chronic experiment and the preliminary steps have already been taken. In the acute experiment the blood pressure was measured by a mercury manometer connected to the carotid artery by means of a tube filled with magnesium sulphate.

Two groups of dogs were operated under intravenous or intraperitoneal anæsthesia. One group consisted of eight pregnant dogs with a pregnancy lasting from six to nine weeks (last term), whilst a second group consisting of eight non-pregnant dogs was used for control. Amongst the pregnant dogs the ischæmia of the gravid uterus was brought about by applying Goldblatt-clamps round the uterine arteries, having beforehand ligated the ovarian arteries which were very difficult to isolate and were entirely enveloped by fat. With two pregnant dogs the ischæmia was brought about by applying an aorta clamp made for this purpose immediately below the level of the renal arteries. Before proceeding to a partial closure of the clamps the manometer for blood pressure was connected with the carotid artery and we waited till the blood pressure had taken a constant level.

In the case of the eight non-pregnant dogs the ischæmia was brought about by the above-mentioned aorta clamp, which was immediately placed below the level of the renal arteries.

Discussion of the Results

(See Table I)

(*a*) *The Non-pregnant Dogs.* At a partial and even at a complete closure of the aorta clamp we did not see any special rise of blood pressure appear. Frequently a small rise was compensated again in few seconds. Sometimes even a small fall took place which was levelled up either via a short phase of over-compensation or not. When opening the clamp we always saw a strong fall in blood pressure, after which the blood pressure was again perfectly restored within some seconds. We thought we ought to attribute this to a sudden

Table I

SURVEY OF THE RESULTS.

Non-pregnant Dogs..

	Blood Pressure (mm. Hg.)		1° Duration of Clamping	B.P. after Clamping	2° Duration of Clamping	Particulars
	Before Clamping	After Clamping				
(1)	112	118	1'30"	114	2'30"	
(2)	100	110	2'15"	112	2'	
(3)	122	122	35"	125	38"	s. Fig. 5
(4)	130	132	2'20"	130	1'20"	s. Fig. 6
(5)	118	118	3'30"	120	2'20"	
(6)	126	130	3'10"	126	2'30"	
(7)	110	118	2'	112	3'10"	
(8)	122	130	2'40"	124	3'30"	

Pregnant Dogs.

	Blood Pressure (mm. Hg.)		Duration Ischæmia	Technics	Particulars
	Before Clamping	After Clamping			
(1)	124	145	7'30"	aa. uterinæ	
(2)	128	163	8'30"	aorta clamp	s. Fig. 7
(3)	112	141	7'	aa. uterinæ	
(4)	118	140	6'15"	aa. uterinæ	s. Fig. 8
(5)	110	146	12'15"	aorta clamp	
(6)	98	129	7'30"	aa. uterinæ	
(7)	122	155	6'	aa. uterinæ	
(8)	118	144	5'15"	aa. uterinæ	

strongly diminished supply of blood to the vessels lying proximal to the clamp (Figs. 5 and 6).

(*b*) *The Pregnant Dogs.* In the greater part of the cases (with the exception of Nos. 2 and 7) the ischæmia of the uterus of pregnant dogs was followed by a slow rise in blood pressure, in whatever way ischæmia was produced (Figs. 7 and 8). In cases 2 and 7, however, the rise seemed to fail to appear, for which reason we made the uterus again ischæmic after a preceding period of ischæmia of five to seven minutes. In both cases the rise in blood pressure then became evident.

Abolition of ischæmia by opening the clamps reduced the blood pressure again after a shorter or a longer time to the original value. We twice extirpated the uterus at the end of the experiment, and could ascertain that it was no longer

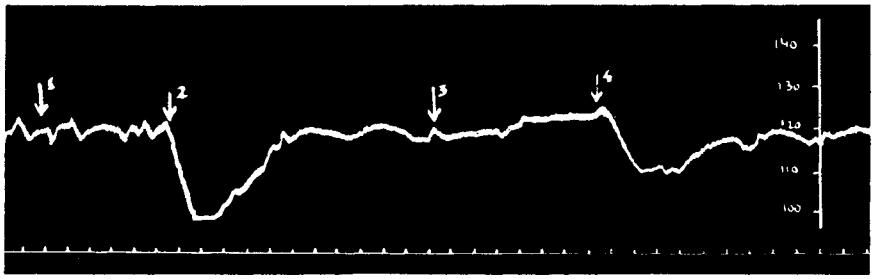

FIG. 5. Blood pressure of a non-pregnant dog (n.3). 1 and 3 (partial) closure of aorta clamp distal from the artt. renales ; 2 and 4 opening of aorta clamp. Time 10 sec.

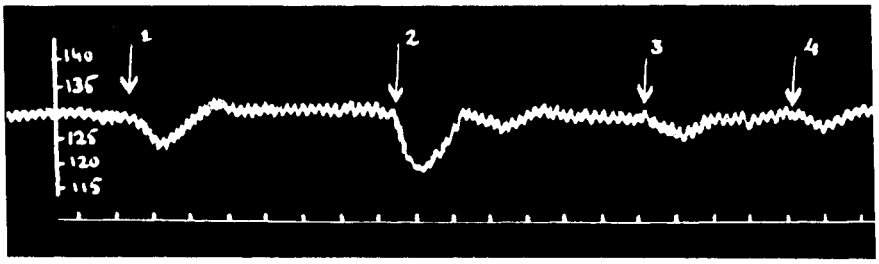

FIG. 6. Blood pressure of non-pregnant dog (n.4). 1 and 3 (partial) closure of aorta clamp distal from artt. renales; with 2 and 4 opening of aorta clamp. Time : 10 sec.

possible to bring about a rise in blood pressure by means of an aorta clamp below the renal arteries.

When judging such a rise in blood pressure one should ask oneself how far this rise might be a consequence of the altered hæmodynamic relations. Burwell compared the circulation in the human placenta with that in an arteriovenous fistula,

the closure of which is known to result in a slight rise in blood pressure which is however of a passing nature. After this the regulating mechanisms come again into operation and are responsible for the normal blood pressure keeping constant.

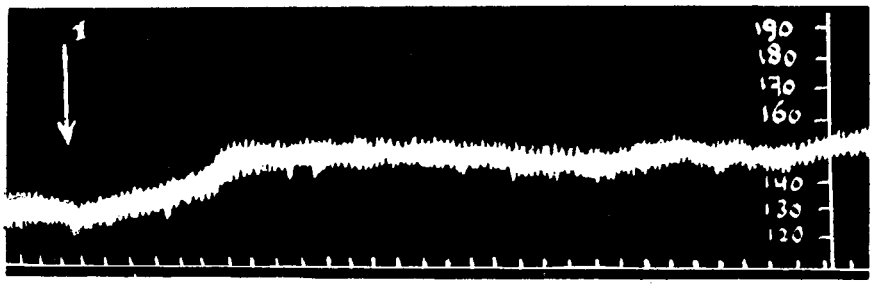

FIG. 7. Blood pressure of pregnant dog (n.2.) 1 partial closure of aorta clamp distal from artt. renales, after ligation of artt. ovaricæ. Time : 15 sec.

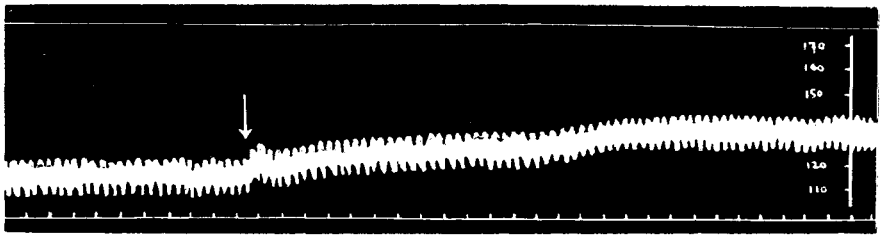

FIG. 8. Blood pressure of pregnant dog (n.4). 1 partial closure of clamps round artt. uterinæ, after ligation of artt. ovaricæ. Time : 10 sec.

In view of the endotheliochoreal structure of the placenta of dogs, little if any blood pressure raising effect of an artificial closure of an arteriovenous fistula may be feared. In our opinion only little influence on the blood pressure may be ascribed to similar artificial changes, considering the inclination of the organism to guarantee also in pregnancy the constancy of the blood pressure, in spite of radical changes in runway, minute volume, viscosity and blood volume.

After we decided to do these experiments it appeared that Ogden, Hildebrand and Page had performed similar experiments. They constricted the aorta distal to the origin of the renal artery and obtained the same results.

Mechanism of Hypertension by Ischæmia of the Pregnant Uterus

Many important questions arise with regard to the underlying mechanism of this form of increase in blood pressure. We can ask whether vasopressor substances are formed directly in the placenta. There is also the possibility that the *hypophysis*, *kidney* or *adrenal glands* are responsible for this production under the influence of a certain factor formed in the ischæmic placenta. We must however consider the possibility, mentioned by Browne, that a hypertension can develop without such an increased production by abnormal susceptibility of the arterial system for certain circulating hormones, in our opinion, under the influence of a factor formed in the ischæmic placenta.

We will now consider in a few words the importance of this hypothesis with regard to the *therapy*. It is evident that if the theory is true and if we were to succeed in increasing the blood supply to the pregnant uterus, we could prevent the occurrence of a toxæmia in predisposed patients or be able to cure an already existing toxæmia. We could do this by a substantial decrease in the tone of the muscles such as by a very drastic food-restriction, but we believe that it is practically impossible to attain a malnutrition as drastic as that occurring during the war. Although we believe that a marked decrease in food-intake has a beneficial effect, this alone will not be sufficient. We could also by means of other measures attempt to increase the blood supply to the uterus.

Smith and Smith recommend the administration of increasing amounts of stilbœstrol to prevent late toxæmia of pregnancy.

At present we are investigating in animals the value of attaching the omentum into or on the wall of the uterus in order to increase the uterine blood supply. The results of our experiments will be given at a later date.

Conclusion

Our conception of *absolute* or *relative insufficient blood supply to the placenta* is supported by the fact that our hypothesis fulfills all the requirements mentioned above.

We hope that further research along these lines may lead to improvement of the treatment of toxæmia in favour of our pregnant patients.

Summary

Several requirements are given which must be fulfilled by an acceptable theory for the origin of toxæmia.

A hypothesis is built up for the genesis of toxæmia :—

Toxæmia of pregnancy is caused by *any disturbance in the normal relation of the volume of blood carried to the placenta per unit of time and the quantity of placental tissue.*

The occurrence of toxæmia is related to an *absolutely or relatively insufficient blood supply to the placenta.*

Toxæmia of pregnancy is a sign of *insufficient adjustment of the mother's vascular system to the demands of pregnancy,* in other words a disease of *insufficient adaptation.*

The various ways in which an insufficient blood supply to the placenta can occur are discussed.

An explanation is given for all the symptoms of the eclampsia syndrome, including puerperal eclampsia.

A series of experiments in pregnant dogs is described in which an artificial ischæmia of the pregnant uterus caused hypertension. The mode of development of this form of hypertension is discussed.

Some suggestions for therapy are given in the light of the above-mentioned theory.

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FŒTAL MALFORMATIONS AND TOXÆMIA

(short contribution)

H. DE WATTEVILLE

MANY interesting communications have been made at the present congress, and I should like to express my gratitude for the fact that I was offered the opportunity to attend this distinguished gathering.

I believe that all of you will agree that, despite the whole score of new and relevant facts presented here, we have to face the conclusion that no general key to the explanation of that complex syndrome called toxæmia has been found yet. It seems very probable, however, that disorders of circulation are an integrating pathogenetic factor. In our toxæmia patients, the fundus oculi is examined regularly by an ophthalmologist, and in nearly all the cases, alterations of the vessels are to be seen. The most important one is a narrowing of the retinal arteries and a positive Gunn's sign, accompanied by œdema and hæmorrhage in severe cases. Furthermore, an increased arterial pressure in the retina can often be measured, not always paralleling the blood pressure of the arm vessels. Like the other toxæmia symptoms, these ocular alterations often regress completely during the puerperium, but in our experience they are very early and persistent symptoms.

I am in no better position than anybody else to offer a general explanation of all the facts, but I might perhaps add another puzzling observation. From the material of several German clinics, Witte, Berrens and Neuser had demonstrated that the number of fœtal malformations was higher in toxæmia cases.

At the Women's Hospital, Zürich, we had this observation controlled by Johanna Himmel, and to our surprise we obtained confirmation of the German authors' results. In

about 16,000 normal pregnancies of the period 1936–1945, there were 1.0 per cent of severe malformations, against 4.2 per cent in the 470 toxæmia cases of the same period. These differences are statistically highly significant. Another confirmation of the same relationship can be seen in Ehrat's results, demonstrating that the reverse is equally true; it showed that at the Women's Hospital, Zurich, 6.6 per cent of the mothers of malformed children had had toxæmia, while the average frequency of toxæmia in all pregnancies of the same period was only 3.0 per cent.

Since the determination of cellular development takes place during the first few weeks of intra-uterine life, it is quite unlikely that toxæmias, which occur only during the last months of pregnancy, could be responsible for malformations. Nor does it seem conceivable how reversely, a morphological malformation could cause toxæmic symptoms. On the other hand, we do know that there is a relationship between fœtal malformation and the *development of the trophoblast.*

In ectopic pregnancies, for instance, where the trophoblast is handicapped by unfavourable surroundings, fœtal malformations have been seen much more frequently than in normal nidation. We believe, therefore, that the correlation between malformations and toxæmias could perhaps be explained by *placental* anomalies, which, in turn, might be caused either by a poor biological quality of the fertilized ovum or by an environment failing to provide optimal conditions for its normal development. We should not forget that there is one common denominator to all varieties of toxæmia, they never occur without the presence of trophoblastic tissue.

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RELATION OF NUTRITION TO HEPATIC DISEASE AND TOXÆMIAS OF PREGNANCY

L. E. GLYNN

LESIONS of the liver have long been recognized as fairly common in fatal cases of pregnancy toxæmia. In recent years the dependence of the liver upon an adequate nutritional state for the maintenance of its structure and function has been repeatedly demonstrated. It is therefore not surprising that some nutritional defect should be suspected as underlying some of the manifestations of pregnancy toxæmia and especially those forms in which hepatic lesions are most conspicuous. It should be said at the outset that no close or direct relationship between dietary deficiency and toxæmia of pregnancy has yet been demonstrated either in experimental animals or man. Nevertheless the dominant part played by the liver in the body's metabolism implies that nutritional factors affecting the liver cannot be ignored and recent work, as will be shown later, offers some explanations of the failure to demonstrate a direct causal relationship between diet and toxæmia.

Two distinct lesions of the liver have been produced in experimental animals by dietetic means, namely fatty infiltration and its sequel diffuse hepatic fibrosis (Laennec's cirrhosis), and massive necrosis with its sequel of post-necrotic scarring and nodular hyperplasia (Himsworth and Glynn, 1944). The factors leading to fatty infiltration have been extensively investigated both here and in America. Attention was first directed to them by the observation that pancreatectomized dogs maintained by insulin develop severe fatty infiltration of the liver which could be prevented by a dietary supplement of lecithin. Best and Huntsman (1932) found that the fatty infiltration produced by feeding rats on a high

fat diet could also be prevented by lecithin and that the activity of lecithin resided entirely in the choline portion of the molecule. Channon and Wilkinson (1935) reported that an increase of casein in the diet would also prevent fatty infiltration. An analysis of the effect of the individual amino acids showed that whilst the majority were without significant effect, methionine and cystine appeared to be antagonistic to each other, the former preventing fatty infiltration and the latter favouring it. Substances such as methionine and choline which prevent the accumulation of liver fat are designated as lipotropic, those favouring its deposition as alipotropic (Best and Lucas, 1943). A common feature of these lipotropic agents is their possession of a labile methyl group (du Vigneaud, 1940), that is a methyl group capable of transference as a whole in the processes of endogenous syntheses. Thus by the use of isotopes, for purposes of identification, it has been shown that the methyl groups of choline and methionine are interchangeable and hence labile, whilst the methyl groups of creatine and creatinine are non-labile. Since the mammalian body is apparently incapable of synthesizing an adequate quantity of labile methyl groups it is essential that they be provided in the diet either as choline, methionine, etc., and amongst the evidence for their deficiency is a severe accumulation of fat within the liver. This accumulation of fat is the result of insufficient phospholipid synthesis, since the formation of phospholipid is an essential step in the metabolism and mobilization of liver fat (Perlman and Chaikoff, 1939).

Other members of the B vitamin complex also play a part in liver fat metabolism, but in most instances this is slight compared with the activity of choline. Both pyridoxine and inositol have weak lipotropic activity, whilst thiamine, biotin and pantothenic acid have been found in some circumstances to be alipotropic.

The second and even more striking hepatic lesion produced by dietary deficiency is massive hepatic necrosis (acute yellow atrophy). This was first produced in rats by Weichselbaum

(1935) using diets poor in thio-amino acids, but the lesions were considered to be hæmorrhages and not recognized as necroses. Györgi and Goldblatt (1939) were the first to recognize the necrotic nature of the lesions but they considered them to be more severe and acute manifestations of the cirrhosis that results from severe and prolonged fatty infiltration. Himsworth and Glynn (1944), however, were able to differentiate these two lesions quite conclusively and to produce each independently of the other. The diet necessary to produce these lesions must be deficient both in thio-amino acids and in vitamin E (Györgi, 1945), and since the body is capable of storing considerable quantities of this vitamin the deficient diet must be maintained for a sufficient length of time for the stores to become exhausted. Starting with animals in a state of considerable vitamin E depletion, massive hepatic necrosis may appear in as short a time as eleven days. At the other extreme it may be necessary to continue the deficient diet for 150 to 200 days if the animals start with a high reserve of the vitamin (Himsworth and Lindan, 1949).

The lesions produced are virtually identical with those of acute yellow atrophy in man. They do not show the regular zonal distribution that is characteristic of the lesions produced by carbon tetrachloride and chloroform, but the grossly irregular distribution seen for example in cases of TNT poisoning. Whilst some lobules may be completely necrotic, others may be completely unaffected, whilst still others may show centrilobular or periportal necroses, the former predominating. In the early stage of the lesions the necrotic cells are still visible *in situ* forming macroscopically yellow opaque firm masses. Within a few days, however, the cells are removed by a combination of autolysis and phagocytosis. The phagocytes appear to be derived partly from the Kupffer cells which are not usually involved in the necrosis, and partly from histiocytes in the portal tracts. The removal of the dead cells allows the previously compressed sinusoids to dilate and the area now acquires a dark red colour owing to this

sinusoidal congestion. This corresponds to the stage of so called "red atrophy." Animals surviving beyond this stage show nodules of hyperplastic liver cells, resulting from the proliferation of the surviving cells, alternating with depressed dark red areas consisting of vascular scar tissue and proliferating bile ducts, which correspond to the areas of complete liver cell destruction. From this description it is apparent that the lesion can be readily distinguished from that of eclampsia but has all the characteristics of acute yellow atrophy seen in pregnancy or otherwise.

A further close resemblance between the experimentally produced lesion and the natural disease in man is the striking tendency in both cases for the maximal necrosis to affect the left lobe. Himsworth and Glynn (1944) suggested that this is probably attributable to a peculiarity of the blood flow in the portal vein, as a result of which blood from the superior mesenteric vein passes to the right lobes, whilst blood from the spleen and left half of the colon passes to the left lobes. This streamline effect was first suggested by Sérégé (1902), subsequently demonstrated in dogs by Copher and Dick (1928) and confirmed in rats by Himsworth and Glynn. By injecting Indian ink into the spleen of normal anæsthetized rats it becomes readily apparent that those parts of the liver particularly involved in partial massive necrosis coincide remarkably with the areas supplied via the splenic vein. Since the products of protein digestion, including presumably the thio amino acids, are almost entirely absorbed from the small intestine via the superior mesenteric tributary of the portal vein, it is not surprising that hepatic lesions resulting from thio amino acid deficiency should favour those lobes supplied via the splenic tributary.

The Modifying Effect of Diet on the Susceptibility to Liver Poisons

Opie and Alford (1915) were the first to demonstrate the relationship of the nutritional state of an experimental animal to its susceptibility to an exogenous liver poison. They

showed that a high carbohydrate diet afforded considerable protection against the toxic effects of either chloroform or phosphorous, whilst meat was much less protective. This was the basis of the popular high carbohydrate regimen used in the treatment of liver disorders. A little later Davis and Whipple (1919) demonstrated the deleterious influence of starvation on the resistance of the liver to chloroform injury, and confirmed the findings of Opie and Alford with respect to the protective value of carbohydrate. Feeding of fat, however, still further increased susceptibility. A distinct protection was afforded by various protein foods such as beef, skim milk, or casein, but this effect was interpreted as resulting from the carbohydrate sparing action of these proteins. Despite the observation that depletion of the liver glycogen by thyroid administration did not unfavourably influence the resistance of the liver to chloroform, the conclusion was nevertheless drawn that resistance and glycogen content were closely correlated.

The significant part played by protein in modifying liver injury has only recently become appreciated. Goldschmidt, Vars and Ravdin (1939) found in the rat that protein diminished the extent of chloroform necrosis, and this has been amply confirmed on dogs by Miller, Ross and Whipple (1940). They found that liver injury in dogs lightly anæsthetized with chloroform was directly proportional to the degree of protein depletion. A single large protein meal given thirty-six hours before anæsthesia gave adequate protection. From the same laboratory Messinger and Hawkins (1940) reported similar results with arsphenamine. With a weekly dose of 0.03 grams per kilogram the injury produced in the dog's liver was closely dependent on the animal's diet. On a high protein diet the injury was trivial and promptly repaired. A high carbohydrate diet was also beneficial but not as uniformly protective as protein, and the liver injury was somewhat greater. Fat proved to be extremely inimical as the arsphenamine treated dog showed marked progressive jaundice and severe liver injury, sometimes fatal.

The elucidation of the mechanism of protection of the liver by high protein diets has been carried a stage further. Howlands and Richards (1909) had observed a marked increase in the neutral sulphur in the urine excreted by dogs following prolonged chloroform anæsthesia. This suggested to Miller, Ross and Whipple (1940) that the effect of protein depletion on susceptibility to chloroform may be due to deficiency of sulphur amino acids. In confirmation they found that this increased susceptibility could be completely neutralized by the administration of cystine or methionine in daily supplements of 2 to 10 grammes. Further they were able to show that protein depleted dogs are still more depleted in sulphur by estimating the N:S ratio in the liver, and that the hepatic deficiency in sulphur is rapidly made good following ingestion of cystine or methionine. The precise manner in which the sulphur-containing amino acids afford protection is still obscure, but is probably related to the detoxicating mechanism by which several aromatic and other organic compounds are excreted as mercapturic acids (Stekol, 1938).

The Hepatic Lesions in Toxæmia of Pregnancy

Lesions in the liver have been noted in fatal cases of hyperemesis gravidarum and of eclampsia but the lesions in each are distinct and in eclampsia are characteristic. In hyperemesis the lesions vary in intensity from fatty infiltration to centrilobular zonal necrosis. Neither the infiltration of fat nor the centrilobular zonal necrosis may be taken as evidence of the action of a toxic agent since both these lesions can result merely from severe dietary depletion of lipotropic factors (Handler and Dubin, 1946). In any well nourished individual starvation alone, such as is associated with intractable vomiting, results in severe fatty infiltration, and the latter, if of sufficient degree, can result in centrilobular necrosis, apparently as a result of impairment of the sinusoidal circulation by the fat distended liver cells (Glynn and Himsworth, 1948).

In eclampsia the hepatic lesions may be sufficiently extensive and irregular to bear a superficial resemblance to those of acute yellow atrophy and dietetically induced massive necrosis, but the unmistakable predilection for the periportal zones, the greater tendency to hæmorrhages and the characteristic hyaline thrombi indicate unequivocally that a different mechanism is involved and one on which our nutritional experiments at present throw little light.

Attention has already been drawn to the close similarity between the dietetically induced massive hepatic necrosis and acute yellow atrophy. Although this is a rare condition there is no doubt that its greater frequency in women is associated with pregnancy. Thus Thierfielder (quoted by Stander, 1945) found that of the 143 cases which he collected from the literature, 62 per cent occurred in pregnant women, and Hunter and Spriggs (1908) report that in 164 cases in women, 66 were either pregnant or suckling. Considering the nutritional priority that nature grants to the developing fœtus, it is not surprising that pregnancy tends to reveal states of latent malnutrition. A dietary level of thio amino acids barely sufficient for a non-pregnant woman would become grossly deficient in the presence of pregnancy. In view of the deficiency in the dietary protein in various parts of the world it is perhaps surprising that acute yellow atrophy does not occur more frequently. As discussed above, however, the dietetic deficiency necessary for the appearance of massive necrosis includes both thio amino acids and vitamin E, and if the body's stores of vitamin E are dangerously depleted pregnancy cannot be maintained. Development of a dietetically induced acute yellow atrophy in pregnancy therefore necessitates a nice balance between the amount of vitamin E necessary to maintain pregnancy and the amount required to maintain the integrity of the liver, too much preventing necrosis and too little preventing pregnancy. That this balance can be obtained experimentally has been verified (Glynn and Himsworth, 1945). Thus in rats maintained on a diet containing just sufficient thio amino acids to

prevent massive necrosis, pregnancy precipitated necrosis but, for the reasons stated above, this only occurred in a small proportion of the experimental animals.

Preeclampsia and Endocrine Imbalance

The theories that have been advanced to account for pre-eclamptic toxæmia are as innumerable as they are unsatisfactory. Amongst these theories are several that would implicate one or more of the endocrine organs, particularly the pituitary and suprarenal glands. Without, however, going so far as to incriminate any particular member of the "endocrine orchestra" it may be stated with assurance that several of the characteristic features of pregnancy toxæmia can be simulated by the administration of known hormones and that cases of preeclamptic toxæmia do show evidence of hormonal imbalance. Although many claims to have demonstrated such hormonal disturbances have not been confirmed, there is confirmation for example of Teel and Reid's (1939) observation that an anti-diuretic substance is present in the urine in preeclampsia and eclampsia but absent from the urine of normally pregnant women. Agreement is also fairly general with regard to abnormally low urinary œstrin and pregnanediol values in toxæmia and a tendency to high serum and urine values of chorionic gonadotrophin (Taylor, 1942; Browne, Henry and Venning, 1938). The hypertrophy of the adrenal cortex during pregnancy also directs attention to the remarkable properties of the range of steroids elaborated by this organ and the possible part they may play in the genesis of hypertension and œdema, and other characteristic manifestations of eclamptic toxæmia.

Granted that hormonal imbalance is a feature of pre-eclampsia and may indeed be responsible for several of its classical features, is there any evidence to suggest that this imbalance is mediated by hepatic dysfunction and if so is it in any way subject to modification by nutritional factors? Biskind (1946) in an article on the "Nutritional Therapy of Endocrine Disturbances" has adduced a considerable body of

evidence showing that hepatic function is of primary importance in maintaining a normal balance of hormonal activity and moreover that this important function of the liver is remarkably susceptible to nutritional deficiency. Thus Biskind and Mark (1939) showed that pellets of crystalline steroids implanted into the spleen of castrated rats of either sex exerted no œstrogenic or androgenic effects. The steroids tested included œstrone, œstradiol, œstradiol benzoate, testosterone, testosterone propionate and methyl testosterone. If the spleen had previously been grafted into the systemic circulation the specific effects of the hormones became apparent. Utilizing this same technique but with the spleen in its normal position, Biskind and Biskind (1941) were able to study the effect of certain dietary deficiencies on this hormone inactivating function of the liver. On a normal complete diet the castrated females remained in anœstrus. On a diet deficient in B vitamins the animals went into continuous œstrus which could be terminated by feeding with brewers yeast or supplementation of the diet with thiamine, riboflavine, pyridoxine and pantothenic acid. Subsequent investigations by several workers showed that amongst the B vitamins only thiamine and riboflavine are necessary for hepatic inactivation of œstrogen, but methionine is also required, indicating that an adequate dietary level of protein is also necessary (Györgi and Goldblatt, 1945). Androgen inactivation, unlike that of œstrogen, is independent of B vitamin intake and consequently B vitamin deficiency leads to a disturbance of the normal balance between these two groups of hormones in favour of the œstrogens. Since an excess of œstrogen produces hypertrophy of the adrenal cortex (Korenchevsky and Dennison, 1935), the same mechanism probably accounts for the hypertrophy observed in states of B deficiency. The part played by the liver in the inactivation of an anti-diuretic substance probably of pituitary origin is still more suggestive, since there already exists some evidence of its excess in toxæmia (Teel and Reid, 1939). Shay *et al.* (1945) have shown that water retention is

a feature of infective hepatitis in humans and have reported a similar retention of water in rats with fatty livers, and Ralli *et al.* (1945) have shown that water retention in human hepatitis is associated with excessive excretion of an anti-diuretic factor in the urine, from which it is concluded that the liver normally inactivates this factor but is incapable of doing so adequately when its function is impaired either by infection as in hepatitis or by nutritional defect as in Shay's experimental rats.

The hypothesis suggested here that an ætiological relationship exists between nutrition and preeclamptic toxæmia relies for its support on the establishment of three facts :—

(1) That endocrine imbalance is of primary importance in the genesis of the clinical picture.
(2) That the liver plays an important role in the maintenance of this balance by virtue of its power of inactivating certain hormones.
(3) That this function of the liver is easily affected by dietary changes.

But the *sine qua non* of this hypothesis is the establishment of an adequate correlation between nutritional state and the incidence of pregnancy toxæmia. Several experiments designed to establish this are referred to in Browne's review (1944) but to date the verdict is still not proven.

Summary

(1) Two distinct types of hepatic lesion have been produced in experimental animals by nutritional means :—

(*a*) Fatty infiltration and its sequel diffuse hepatic fibrosis.
(*b*) Massive acute necrosis (acute yellow atrophy) and its sequel nodular hyperplasia and post-necrotic scarring.

The former results from a dietary deficiency of labile methyl groups, the latter from a combined deficiency of thio amino acids and vitamin E.

(2) Dietary factors also play a dominant role in modifying the susceptibility of the liver to exogenous poisons such as chloroform, carbon tetrachloride, cinchophen and trinitrotoluene.

(3) The hepatic lesions in hyperemesis gravidarum and in acute yellow atrophy correspond to the two types of lesions produced dietetically in experimental animals. It is suggested that a similar nutritional fault underlies the production of these lesions in pregnancy.

(4) Evidence is presented indicating an endocrine imbalance in the genesis of preeclamptic toxæmia.

(5) The role of the liver in the normal control of hormonal balance is discussed and the part played by an adequate diet in the maintenance of this function is demonstrated.

(6) If nutritional deficiency is ætiologically related to the genesis of preeclampsia the relationship probably operates through this function of the liver in maintaining hormonal balance and the dependency of this function on an adequate diet.

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TOXÆMIAS OF PREGNANCY: HUMAN AND VETERINARY
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OBSERVATIONS ON THE PLACENTAL SEX HORMONES IN THE TOXÆMIAS OF PREGNANCY

IAN F. SOMMERVILLE

ATTEMPTS to associate endocrine dysfunction and the toxæmias of pregnancy have been the subject of many reports in the literature especially of the last fifteen years. Certain aspects of this wide subject have been discussed by other contributors to this symposium and my remarks will be confined to a consideration of the interrelationship which is thought to exist between certain of the placental sex hormones and the toxæmias. A large number of observations have been made on this subject but it may be stated at the outset that the data available still call for critical analysis and not for synthesis into a theory of ætiology. Accordingly, rather than indulge in premature speculation as to whether abnormal sex hormone production by the placenta contributes to, or is merely associated with, the pathology of the toxæmias, it will be my purpose to attempt to rationalize the evidence for this abnormality, to draw such interim conclusions as seem permissible, and to suggest where further experimental investigation appears to be indicated.

First, let us consider briefly the evidence for the secretion of the steroid hormones—œstrogen and progesterone—and of a distinct gonadotrophic factor—chorionic gonadotrophin (C.G.)—by placental tissue. In human subjects, ovariectomy after the third month of pregnancy is not necessarily followed by abortion and in cases where pregnancy continues, the metabolites of the steroid hormones continue to be excreted in the urine. The expulsion of the placenta appears to be associated with rapid withdrawal of these hormones from the body. In 1943 Seegar Jones and her co-workers (Jones,

Gey and Gey) demonstrated the elaboration of a gonadotrophic factor by placental tissue cultures, and equivocal evidence for œstrogen production by such cultures has been reported. Histochemical studies by Wislocki and Bennett (1943) indicate that the cytotrophoblast is the site of formation of the gonadotrophic factor and suggest that the syncytium may be the site of formation of the placental steroids.

Accepting the status of these hormones as placental secretions, it is obviously very relevant to our subject to enquire how accurately their placental output can be assessed in normal and toxæmic pregnancy. There is no direct method of assessment. Even if C.G., œstrogen and progesterone could each be determined with reasonable accuracy and facility in the serum of pregnant women, it could not be assumed that the blood levels so determined necessarily reflected the levels of placental secretion. For example, the fact that the high level of serum C.G. frequently found in the toxæmias appears to be accompanied by certain changes in œstrogen and progesterone metabolism and to be unaccompanied by hypertrophy of the cytotrophoblast, suggests to Smith and Smith—who have contributed so much to this subject—that a high serum C.G. indicates abnormal "utilization" of that hormone and not increased placental secretion. It seems probable that progesterone is present in only small amounts in the serum of pregnant women—or at any rate in amounts smaller than might be anticipated from our knowledge of the urinary level of its metabolites. It does not follow, however, that the placental production of that hormone is correspondingly small since the blood may possibly be an important tissue for the metabolic reduction of progesterone to its main metabolite, pregnanediol. Attempts to deduce placental progesterone secretion from blood progesterone levels may be further complicated if the hormone is present in the blood not only protein-bound (Hooker and Forbes, 1949), but also in some unknown conjugated form.

The deduction of placental output from the results of bioassay of serum levels is fraught with difficulty for similar

reasons. The total œstrogenic potency of a blood sample will depend upon the proportion of conjugated œstrogen present (and methods for the hydrolysis of such conjugates are far from perfect) and upon the proportion of the natural hormone, œstradiol, which has been converted into less active metabolites.

Histological examination of endocrine glands is a time-honoured method for determining their secretory activity. The low levels of excretion of the metabolites of œstrogen and progesterone found in many cases of toxæmias is ascribed by some workers (Smith and Smith, 1948) to degeneration of the syncytium and thus to diminished placental output rather than to increased "destruction" or renal retention. This degeneration is said to be more marked than that found in normal full-term placentæ but the toxæmic human placenta available for study is the final result of many pathologies and more vital evidence would be more convincing.

In view of these facts it is perhaps surprising to find in the literature many references to variations in the levels of production of these hormones by the placenta. Many such statements are based upon the assumption—which may be unwarranted—that a simple quantitative relationship exists between the amount of natural hormone produced, the blood level which it attains, and its excretion or the excretion of its metabolites in the urine. This assumption is open to experimental investigation and in fact studies of the intermediary metabolism of progesterone and œstrogen are yielding important information concerning the relationship between natural hormone and urinary metabolite and concerning the various factors which may influence that relationship (Stimmel, 1947 ; Heard, 1949 ; Marrian, 1949 ; Sommerville and Marrian, 1949, 1950). Our knowledge of steroid metabolism is very incomplete, however, and until further advances in this field have been made, interpretation of these serum and urinary levels must remain largely tentative.

There remains another way in which the placental output can be deduced from a study of the urinary excretion of the

metabolites of œstrogen and progesterone. If œstrogen and progesterone metabolisms are interdependent, then it may be that a study of the nature and level of the urinary excretion of the metabolites of either hormone will indicate whether the other is present in adequate or deficient amount. It is this idea of the interdependence of œstrogen and progesterone metabolism and in particular of the modifications in œstrogen metabolites which result from progesterone deficiency which forms the basis of the theory of Smith and Smith (1948). This evidence in relationship to the toxæmias must be discussed in more detail but first let us consider how the serum levels and urinary excretion of these hormones or their metabolites differ in normal and toxæmic pregnancy.

Chorionic Gonadotrophin

The serum C.G. (expressed in I.U. per litre) was first studied by Seegar Jones and her co-workers (1943). Other workers have obtained similar curves for the urinary excretion of this hormone (Browne and Venning, 1936 ; Smith and Smith, 1937 ; Taylor and Scadron, 1939 ; Venning, 1938 ; Loraine, 1949).

Gastineau, Albert and Randall (1948), calculating the renal clearance of C.G. at various stages of pregnancy, found no significant difference between renal clearance at the peak of excretion and at the plateau of the third trimester. These workers conclude that the wide fluctuation in normal pregnancy must depend upon the rate of formation or destruction of the hormone and not upon variations in its renal excretion.

In 1933, Smith and Smith reported excessive gonadotrophic activity of the blood and urine of patients with late pregnancy toxæmia. Since that time these workers have carried out repeated determination of serum C.G. on women during the third trimester. Their results are summarized in Table I. From these results Smith and Smith conclude that an abnormal rise in serum C.G. between the 24th and 36th week of gestation heralds complications, and especially pre-eclampsia, but that it gives no indication of the type or

severity of the complication, and furthermore that these complications may occur despite a normal serum level of C.G. The observation of high C.G. levels in blood and urine of toxæmic subjects has been confirmed by many workers

Table I

SERUM C.G. and LATE PREGNANCY COMPLICATIONS.

Smith & Smith, 1935-1948.

SERUM C.G.	No. of Cases.	Outcome of Pregnancy.
NORMAL. (no abnormal rise)	42	UNEVENTFUL
	19	TOXAEMIA : 10. PREM. DELIVERY. STILLBIRTH } 9
PROGRESSIVE RISE.	56	TOXAEMIA : 45 PREM. DELIVERY : 8 STILLBIRTH : 3.

although the correlation has not always been so clear-cut (Taylor and Scadron, 1939; Cohen, Wilson and Brennan, 1943; Watts and Adair, 1943).

White (1945) confirmed the association of high serum C.G. with the incidence of toxæmia in her diabetic series, but did not find a significant number of cases developing complications despite a normal serum level. My colleague, Dr. Loraine,

in collaboration with Dr. G. D. Matthew, has observed high serum and urinary C.G. in nine of 14 cases of severe pre-eclampsia. There was no correlation between the C.G. level and the progress of the pregnancies. In all but one case of mild pre-eclampsia, however, the urinary C.G. fell within normal limits. The observation by so many workers of normal C.G. levels in a proportion of cases with toxæmias is disappointing in view of the suggested use of assay of this hormone for prognostic purposes.

Progesterone

As we have seen, attempts to assess the level of placental production of progesterone are based upon a study of the urinary excretion of its main metabolite—pregnanediol. The excretion of urinary pregnanediol in normal pregnancy as determined by the method of Venning (1937, 1938) has been studied by Venning (1938) and by Bachman (1941). It is now recognized that the apparently purified final product of this method of determination—"sodium pregnanediol glucuronidate"—is contaminated by the sodium glucuronidates of substances other than pregnanediol (Strickler *et al.*, 1943; Mason and Kepler, 1945; Marrian and Gough, 1946). Methods have since been developed which appear to be reasonably specific for pregnanediol but such methods have not yet been widely applied to the study of normal and toxæmic pregnancy.

In 1938 Browne *et al.*, Smith and Smith, and Weil, reported low values for urinary pregnanediol glucuronide in toxæmic pregnancy. Bachman has studied the urinary excretion of this steroid in pre-eclampsia and chronic hypertensive disease of pregnancy and has found that abnormally low excretion was invariably associated with proteinuria. Control experiments showed that this was not due to technical failure to recover pregnanediol glucuronide from urine containing excess protein. Bachman suggests that these are associated and not directly related phenomena. The serum glucuronidase is high in pregnancy and higher still in pre-eclampsia

(McDonald and Odell, 1947), and it is interesting to speculate whether the presence of this glucuronide-splitting enzyme in proteinuric cases might not account for the low recoveries of conjugated pregnanediol. At any rate it will be interesting to observe whether the determination of pregnanediol by a method unaffected by the proportion of the steroid present in the urine in conjugated form reveals similarly low results. White (1947) has carried out such an investigation using the method of Astwood and Jones (1941) but has not reported her results in detail. Using a falling pregnanediol excretion and a rising serum C.G. as prognostic criteria in diabetic pregnancy, however, this worker has obtained striking results. In cases with normal findings there was a fœtal survival of 97 per cent, and an incidence of toxæmia of 2 per cent, whereas in cases with abnormal findings fœtal survival was only 52 per cent, pre-eclampsia followed in 50 per cent and premature delivery in 40 per cent.

It remains to be considered whether the abnormally low level of urinary pregnanediol excretion reported in the toxæmias is the result of renal retention, of abnormal metabolism or of low placental production of progesterone. Although results obtained by Cope (1940) suggest that pregnanediol glucuronide excretion may be low in chronic nephritic subjects receiving progesterone, it seems unlikely that renal retention accounts for the low urinary excretion in the majority of cases of late pregnancy toxæmia. The association of high serum and urinary C.G. and the apparent association of low serum and urinary œstrogen afford indirect evidence against the importance of the renal factor. As we have seen, Smith and Smith deduce the placental output of progesterone from a study of the urinary excretion of pregnanediol glucuronide and also of œstrogen metabolites. Using these criteria they have found evidence of progressive deficiency of progesterone in all of 50 cases studied by them prior to the development of toxæmia, premature delivery and intra-uterine death (1938, 1940, 1941, 1944, 1946). In addition the possibility must be considered that there is an

abnormality, of progesterone or pregnanediol metabolism in toxæmias, possibly associated with impaired liver function. Very preliminary results obtained by Professor Marrian and myself suggest the possibility that there may be an abnormality of progesterone metabolism in non-pregnant hypertensive subjects (Marrian, 1949).

Œstrogens

The excretion of œstriol and œstrone during normal pregnancy was first studied by Cohen, Marrian and Watson (1935). About 90 per cent of the œstrogen in the urine of pregnant women appears to be in the form of sodium œstriol glucuronidate. Œstradiol is present in very small amount (Bachman, 1941) and its excretion does not show the upward trend observed in the excretion of œstriol and œstrone. The apparent rise in the excretion of unconjugated œstrogens during labour has been reinvestigated recently by Dr. Clayton and Professor Marrian who find that it is due to hydrolysis of œstriol glucuronide by a glucuronidase present in contaminating liquor amnii and blood clots.

In 1933 low levels of total œstrogenic potency in the blood, urine and placentæ of patients with late pregnancy toxæmia were reported by Smith and Smith. Since then these workers have observed a progressive decrease of total œstrogen excretion, determined by biological or chemical methods, in their series of 50 cases previously referred to as exhibiting progesterone deficiency. Although normal and even high levels (Hain, 1940) have been reported in some cases of toxæmia, these observations of the Smiths have been generally confirmed (Taylor and Scadron, 1939; Watts and Adair, 1943).

The contention that progesterone deficiency is reflected by changes in œstrogen metabolism has been mentioned in my introductory remarks and in the previous section. This contention forms part of the general theory of Smith and Smith—progesterone deficiency being considered an important factor not only in the premature senility of the placenta

which in their opinion characterizes late pregnancy toxæmia, but also as a physiological mechanism for the control of the menstrual cycle and the duration of pregnancy. The change

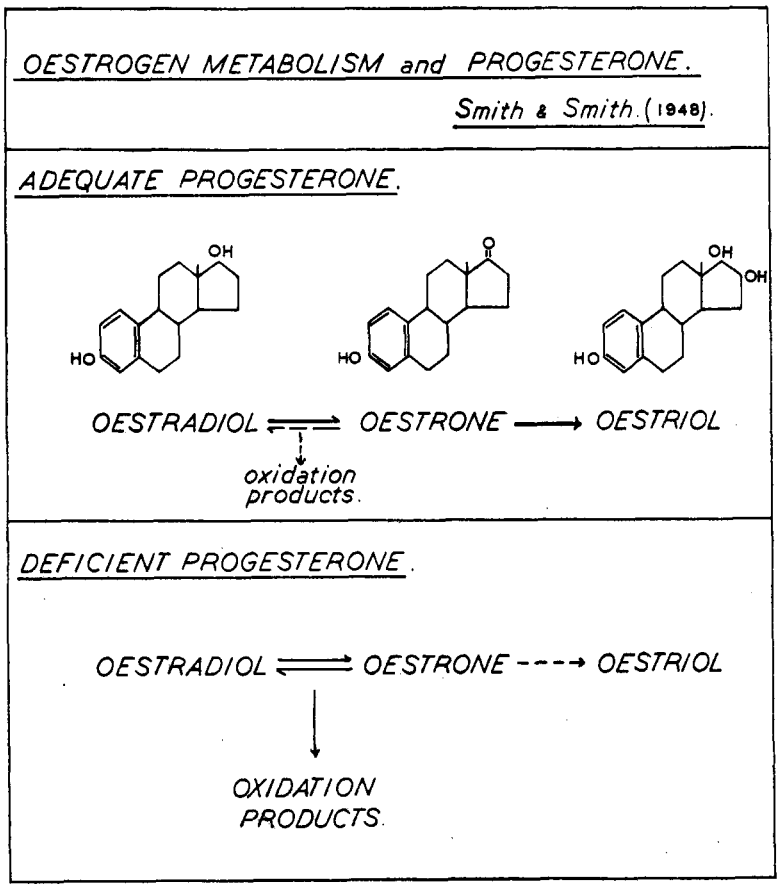

FIG. 1.

in the metabolic trend which they find in œstrogen metabolism under conditions of progesterone deficiency is shown in Fig. 1. Thus in toxæmias these workers find a lowered excretion of

œstriol, a lowered excretion of œstrone, and an increased excretion of œstradiol (1948). They further believe that in progesterone deficiency there is an increased formation of œstrogen "destruction" products—the destructive mechanism being "an oxidative one related largely to the reversible œstradiol to œstrone reaction."

These suggestions of Smith and Smith raise problems of great biochemical interest which cannot be discussed in this paper. It should be said, however, without discredit to their theory, that much of the evidence which they adduce is as yet circumstantial. The œstrogen inactivation products have not yet been isolated nor their oxidative derivation proved. Furthermore it is generally agreed that present methods for the quantitative determination of œstradiol, œstrone and œstriol are very unsatisfactory and possibly little significance can be attached to the variations which they report in the excretion of œstradiol and œstrone in this connection. The elaboration of new methods for the chemical determination of the separate œstrogen fractions and, as has been emphasized already, advances in our knowledge of œstrogen and progesterone metabolism, should lead to an assessment of the validity of this attractive hypothesis.

Smith and Smith (1944, 1946) have, however, sought confirmation for their belief that œstrogen destruction products stimulate placental steroid hormone production by a clinical trial with, as its object, the prevention of pre-eclampsia and other late pregnancy complications in pregnancies in which there appears to be incipient deficiency of progesterone and œstrogen. Accordingly they have investigated the effect of the administration of œstrogenic hormones to such cases and have determined the excretion of urinary pregnanediol glucuronide with a view to estimating the anticipated stimulation of progesterone secretion. Diethylstilbœstrol therapy was followed by a sharp rise in the excretion of pregnanediol glucuronide as determined by the method of Venning (1938) and withdrawal of the drug was followed by a precipitous fall. The data are not presented,

but Smith (1948) states that in this and other cases diethylstilbœstrol administration was accompanied by a fall in the elevated serum C.G. and that the serum C.G. rose again when the drug was discontinued. In view of doubts—previously referred to—concerning the purity of the pregnanediol glucuronide determined in these experiments, Professor Marrian and I decided to reinvestigate the problem using a method of pregnanediol determination which was thought to be reasonably specific for that steroid (Sommerville, Gough and Marrian, 1948). In this work—and in our study of the metabolism of progesterone—we benefited greatly from the whole-hearted co-operation of Professor R. J. Kellar, Professor D. M. Dunlop and their colleagues. Doses of diethylstilbœstrol greater than, less than and the same as those advocated by Smith and Smith were administered by mouth intermittently to normal and to diabetic pregnant women. The pregnanediol level was abnormally low in one of the diabetic cases. The effect was unequivocal—a sharp fall in the urinary excretion of pregnanediol followed the administration of diethylstilbœstrol in all cases and withdrawal of the drug was followed by a rapid return to control period levels or slightly higher. The urinary excretion of total œstrogens of endogenous origin determined by Dr. Clayton showed no change during the periods of diethylstilbœstrol administration (Sommerville, Marrian and Clayton, 1949). The urinary excretion of C.G.—determined by Dr. Loraine—was depressed by the administration, but the level rose again despite continued administration of large doses of the œstrogen (Loraine, 1949).

These results afford partial confirmation, therefore, of the Smiths' findings with regard to C.G., and extend them to urinary C.G., but afford clear-cut contradiction of their observations on urinary pregnanediol excretion. There can be little doubt that the reduction in pregnanediol excretion following treatment with diethylstilbœstrol is genuine, and it seems reasonable to suppose that the apparent rise in pregnanediol excretion reported by these workers was due

to the excretion of substances related to but not identical with sodium pregnanediol glucuronidate. If these other substances are metabolites of progesterone then it may still be argued that progesterone secretion is stimulated despite the depression of urinary pregnanediol excretion. On the other hand the possibility must be considered that the final product determined by these workers was contaminated by other glucuronides and even by the monoglucuronide of the diethylstilbœstrol administered.

Although these results are at variance with the experimental basis of the preventive therapy advocated by Smith and Smith, the efficacy or otherwise of that therapy may depend upon quite different and perhaps unsuspected factors. If this is so then the success or failure of clinical trials will not indicate the validity of their theory.

One may say in conclusion that observations which contribute to our knowledge of the association of placental sex hormone production and the toxæmias fall into two main groups. First, there are those studies concerned with the secretion, intermediary metabolism and excretion of these hormones, and secondly, and founded upon these fundamental studies, there are attempts to interpret the serum level and urinary excretion of these hormones, or of their metabolites, as objective criteria which, correlated with the clinical state of the patient, may be of value to the obstetrician in the assessment of prognosis and in the application of preventive and curative therapy. It is not impossible that such a correlation may on occasion be somewhat fortuitous but, as we have seen, it may yield new and potentially valuable information. It is certain, however, that the final interpretation of these associations will await a fuller understanding of reproductive physiology.

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ENDOCRINES AND TOXÆMIAS

(short contribution)

H. DE WATTEVILLE

AT the Maternité, Geneva, we have been making routine determinations of urinary pregnanediol for three years, using our method of weighing free crystallized pregnanediol obtained by chromatography of a neutral steroid fraction. Among our numerous determinations during pregnancy, there are 140 results in 25 toxæmia cases. None of those values is high, and only a few of them come near the lower limit of variation in our normal pregnancy cases. Many results vary between zero and 20 mg. per twenty-four hours. These findings confirm the results of other authors (e.g. Bachman *et al.*, Cope) demonstrating by different methods *low pregnanediol values in toxæmia.*

There are three possible explanations for this, as it seems, well established fact :—

(1) Incomplete pregnanediol *excretion* caused by renal insufficiency.
(2) Modified or inhibited progesterone *metabolism* due to liver or more general metabolic disorders ;
(3) Decreased progesterone *production* by an abnormal placenta.

In other cases (menopausal women) with disturbed renal function we have never found an appreciable decrease in pregnanediol excretion due to injected progesterone ; nor did we find that the lowest pregnanediol values were associated with the most severe manifestations of toxæmic symptoms *in the mother.* On the other hand, our experience keeps strengthening

the impression that consistently low pregnanediol values seem to be correlated with both *placental* damage and debility of the *child.* Therefore we tend to regard the pregnanediol deficit in toxæmia as evidence supporting the view that the placenta plays an important part in this mysterious disease of pregnancy.

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CHORIONIC GONADOTROPHIN IN PRE-ECLAMPSIA

(short contribution)

J. A. LORAINE

OBSERVATIONS of the C.G. levels in blood and urine have been made so far in 26 cases of pre-eclamptic toxæmia. The method of assay employed depends on the increase in prostatic weight in immature rats (Loraine, 1950). This method has been found both accurate and convenient for the assay of C.G. in blood and urine. Results are expressed in terms of the international standard for C.G. in I.U.'s per twenty-four hours in the urine and in I.U.'s per litre in the serum. A close quantitative relationship has been found between the urinary excretion and serum concentration levels when expressed in this way in both normally pregnant women and in cases of pre-eclampsia.

In the pre-eclamptic patients twenty-four-hour collections of urine have been made where possible on three consecutive days and one observation made on the serum during this seventy-two-hour collection period. Thus the renal clearance of C.G. in pre-eclampsia has been calculated. At the stage of pregnancy at which the estimations were made the normal C.G. levels in blood and urine lay between 4,000 and 11,000 I.U.'s. In a series of normally pregnant patients the mean renal clearance of C.G. was found to be 0.95 ± 0.032 ml./min. (S.E. of mean). The cases of pre-eclampsia were divided on a clinical basis by Dr. G. D. Matthew into mild and severe cases and urinary C.G., serum C.G. and the renal clearance were determined in both groups of patients.

Results

In the mild cases of pre-eclampsia the C.G. levels in blood and urine lay within normal limits (Fig. 1). The renal

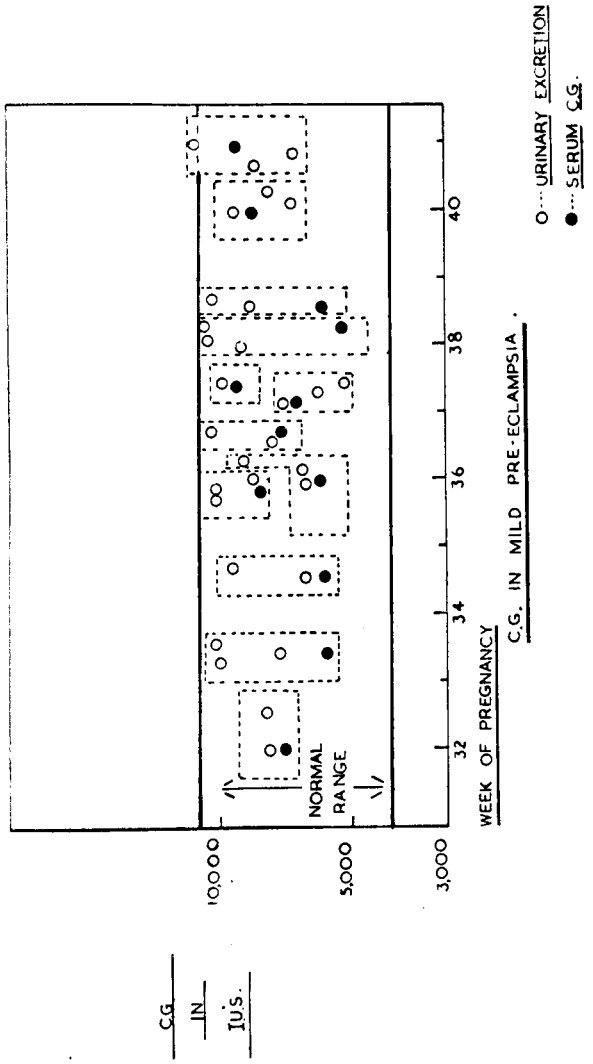
C.G. IN I.U.S.
10,000
5,000
3,000
NORMAL RANGE
32
34
36
38
40
WEEK OF PREGNANCY
C.G. IN MILD PRE-ECLAMPSIA.
O--- URINARY EXCRETION
●--- SERUM C.G.

Fig. 1.

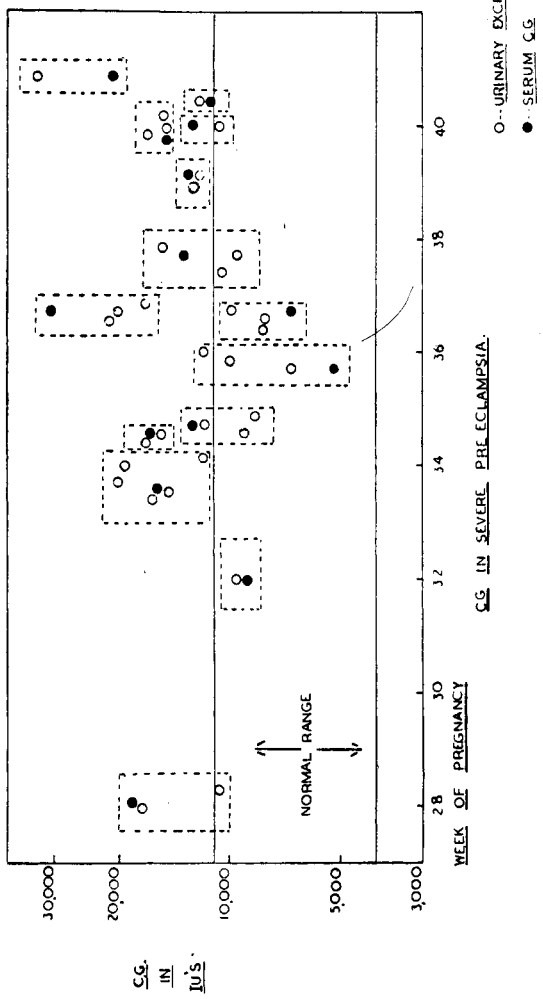
C.G. IN I.U.'S.
30,000
20,000
10,000
5,000
3,000
NORMAL RANGE
28
30
32
34
36
38
40
WEEK OF PREGNANCY
C.G. IN SEVERE PRE-ECLAMPSIA.
O--URINARY EXCRETION.
●--SERUM C.G.

FIG. 2.

clearance was 0.90 ± 0.041 ml./min. (S.E. of mean). This figure did not differ significantly from that in normal pregnancy.

In severe cases of pre-eclampsia nine out of the fourteen patients in this category consistently showed abnormally high C.G. readings in blood and urine (Fig. 2). The renal clearance of C.G. in this group was 0.73 ± 0.045 ml./min. (S.E. of mean). This was found to be significantly lower than the figure obtained in normally pregnant women ($P < 0.01$).

In a series of observations made on ten cases of essential hypertension in pregnancy the C.G. levels in the blood and urine lay within the normal range and the renal clearance did not differ significantly from that in normal pregnancy.

It should be emphasized that these results are of a provisional nature. The subject will be fully dealt with by Loraine and Matthew in a paper which is at present under preparation.

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THE MONO-AMINE OXIDASE ACTIVITY OF PLACENTA

R. H. S. THOMPSON

MUCH of what I am proposing to say about the experimental work which we have recently been carrying out at Guy's Hospital is still largely in the realms of biochemistry, and is therefore not directly or in any definite way applicable to the pathological problems presented by the toxæmias of pregnancy.

As, however, it is our belief that the pathology of pre-eclampsia is largely, in its earlier stages, the outcome of some biochemical lesion in the maternal organism—and I think it is safe to say that this is a belief which is shared by many other workers in this field—we feel that it is necessary as a start that we should be equipped with more knowledge than is at present available concerning the dynamic biochemistry of the placenta.

I want therefore to give you a brief account of some of the results which we have obtained in a study of certain of the enzyme-catalysed reactions performed by placental tissue. This work has been carried out by Dr. A. Tickner, Mr. R. W. R. Baker and myself in collaboration with Mr. J. B. Blaikley and the staff of the Department of Obstetrics and Gynæcology at Guy's Hospital.

When we first started thinking about this problem as a research project, we were much struck by the work which had been going on in Sweden, Scotland and elsewhere on the histaminolytic activity of placenta and of the serum of pregnant women. It seemed to us however that although these findings with regard to histaminase represent an important aspect of placental biochemistry, and one which may be of real

importance also in the pathogenesis of preeclampsia, an attack on a wider front of placental enzymic mechanisms should also be made. And, since hypertension is one of the outstanding signs of preeclampsia, our attention, like that of other workers, turned to a consideration of the biochemical mechanisms which have been implicated, in fact or in theory, in the problem of renal hypertension.

With this problem of hypertension before us we began with a study to determine whether placental tissue contained a mono-amine oxidase which, by virtue of its ability to inactivate certain pressor amines such as adrenaline and noradrenaline, might be of possible pathological interest.

Blaschko, Richter and Schlossman in 1937 had shown the presence of such an enzyme in kidney tissue, and it was also known from the work of Werle (1936), Holtz (1937) and others that under anaerobic conditions the kidney can produce pressor amines by decarboxylation of amino-acids such as tyrosine or dopa.

Further work, it will be remembered, soon led to the suggestion that, quite apart from the "Renin-hypertensin" mechanism, a further enzyme system, or rather a disorder of such a system, might also be playing a part in the production of certain types of renal hypertension. This work postulated the possibility of excessive production of pressor amines by the kidney or of a defect in the rate of inactivation of them by the mono-amine oxidase.

It must be remembered that many of the methods used for producing experimental renal hypertension involve a restriction of the renal circulation, so that, since mono-amine oxidase requires a supply of oxygen in order to inactivate amines, this restriction of renal circulation in experimental hypertension might inhibit the activity of the mono-amine oxidase in the kidney, and so make it possible for pressor amines to escape from the kidney and thus play a part in producing peripheral vaso-constriction.

These views, even as regards the problem of renal hypertension, are still largely theoretical, and are certainly not

accepted by all workers as representing a factual, participating role in the production of these types of hypertension.

Despite this, however, it was thought that in view of the findings with histaminase it would be well worth while to know something of the potentialities of the placenta with regard to the destruction of such vasoconstrictor substances as adrenaline and nor-adrenaline. In this connection it is of interest to note that the non-pregnant uterus of the sheep had already been shown by Bhagvat, Blaschko and Richter (1939) to have a high content of mono-amine oxidase, contrasting therefore with other muscular tissues which contain only slight amounts of this enzyme.

In our earliest experiments we extended this finding to the non-pregnant uterus of the rat and the rabbit, and showed that in both these species the uterus is rich in this enzyme. The enzymic activity was determined manometrically using the Warburg technique by measuring the extra oxygen consumption of the tissue homogenate brought about by the addition to the system of a suitable amine. In most of the experiments tyramine (0.01M) was used as the substrate since this compound does not show any appreciable rate of autoxidation, and is therefore technically a more satisfactory substrate than adrenaline for work of this kind. We have however also used adrenaline in a number of experiments, and have in fact found that this compound is oxidized even more rapidly than tyramine by homogenates of uterus or placenta. Using rats we showed that the high values of amine oxidase activity exhibited by the whole uterus early in pregnancy fell to a significantly lower level towards the end of pregnancy. This suggested to us that the enzyme in the uterus may be localized chiefly in the endometrium, and that the relatively greater mass of myometrium present late in pregnancy may be responsible for the lower activity per unit weight of the whole uterus at the end of the pregnancy. To test this point we have carried out estimations of enzyme activity in separated human endometrium and myometrium, and have found that the enzyme is in fact very largely concentrated

in the endometrium, the muscle layer showing only low values of activity (Table I).

Table I

LOCALIZATION OF MONO-AMINE OXIDASE IN HUMAN UTERUS.

State of Uterus	Enzymic Activity (μl./g./hr.)		
	Endometrium or Decidua Vera	Myometrium	Decidua Basalis
Non-pregnant	432	171	—
10 weeks pregnant	690	26	—
11 ,, ,,	507	129	453
14 ,, ,,	1071	—	—
17 ,, ,,	663	97	—
34 ,, ,,	—	15	320
40 ,, ,,	1125	—	—
40 ,, ,,	1016	—	—

We have also found a highly active amine oxidase in human and in rat, rabbit, guinea-pig and sheep placenta, and Luschinsky and Singher (1948) in America have also reported on the identification of this enzyme in human placenta. In a preliminary attempt to obtain some information about the localization of this enzyme in placental tissue we have compared the activities of acetone-dried preparations of both the maternal and the fœtal portions of sheep placenta. These preparations were very kindly provided by Professor A. St. G. Huggett. We found the activity to be almost entirely limited to the maternal portion (Table II).

Table II

MONO-AMINE OXIDASE ACTIVITY OF SHEEP PLACENTA SHOWING LOCALIZATION IN MATERNAL PORTION.

Site	Activity (μl./g. dry wt./hr.)
Whole placenta	157
Maternal portion	469
Fœtal portion	12

If this localization applies also to human placenta, and we have not yet fully tested this, the activity of the enzyme in those cellular areas in which it is present must be very high indeed, in view of the already high level of activity

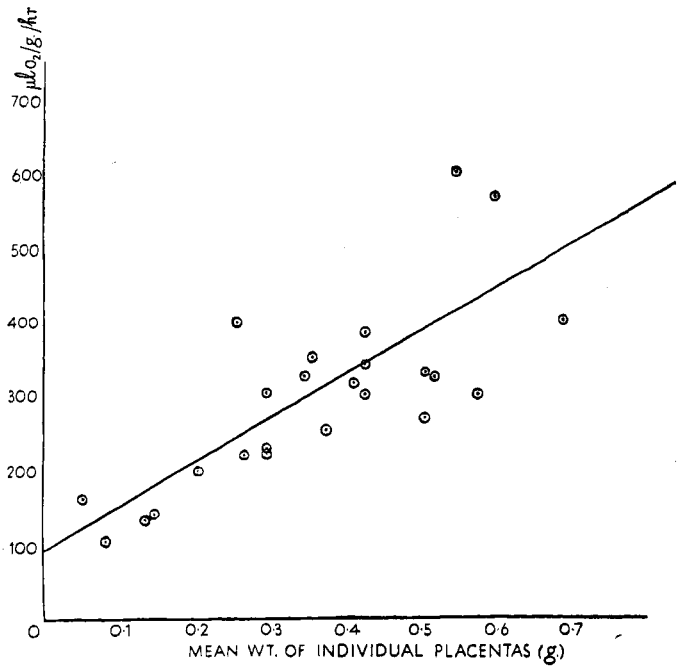

FIG. 1. Concentration of amine oxidase in pregnancy.

which we have found in homogenates made from samples of the whole thickness of the placenta.

In both the rat and in human placenta we have found that as pregnancy advances the concentration of amine oxidase in the placenta, expressed per gram of placental tissue, increases strikingly (Fig. 1). This increase in the concentration of the enzyme would suggest, although we have as yet no experimental evidence in support of this, that this amine

oxidase may exercise some function of increasing significance as pregnancy advances and the fœtus or fœtuses increase in size and differentiation.

One property of this enzyme which we have studied in some detail is its sensitivity to changes in the oxygen tension of the environment in which it is operating. This point, we felt, was of importance with regard to the pathological considerations which we had in mind in view of the postulated association between placental ischæmia and the development of preeclampsia.

By contrast with other oxidases, whose rate of action is not affected until very low oxygen tensions are reached, it had been shown by Kohn (1937) that the amine oxidase of pig liver is unusually sensitive to changes in oxygen tension, a relatively slight fall in the oxygen tension causing a profound inhibition of enzyme activity.

If, therefore, placental ischæmia exerts any causative action on the development of preeclampsia by its effect on the rate of inactivation of pressor amines it seemed important to know whether the amine oxidase in placenta is also sensitive to a fall in oxygen tension. On testing this we found that the placental enzyme behaves like the enzyme in liver, showing approximately 50 per cent inhibition of activity as the oxygen tension of the gas phase, with which the enzyme suspension is in equilibrium, is reduced from 20 per cent to 5 per cent, with an even more rapid rate of inhibition as the oxygen tension falls still lower. A fall of oxygen tension of only 5 per cent at these low levels causes a very significant inhibition of enzyme activity.

Arguing from these *in vitro* observations, it might be expected therefore that any interference with the normal oxygenation of the placental tissue would interfere with the action of this enzyme, but clearly to carry the argument further we are faced with the problem of the physiological significance of this placental amine oxidase, and at the moment we have little evidence with regard to this. In the case of the liver amine oxidase it is assumed by most workers

that it is concerned with the inactivation of toxic mono-amines such as tyramine and tryptamine absorbed from the gut where they are formed by bacterial action. On the other hand the enzyme has a wide distribution in the body and there is now considerable evidence in favour of the view first put forward by Professor J. H. Gaddum that it is concerned with the inactivation of adrenaline released at adrenergic nerve-endings.

Since, however, most histologists appear to agree that the placenta is a tissue devoid of nerve-fibres it would seem that this cannot be its action in this site. The possibility still remains that it may be concerned in the placenta with the inactivation of circulating adrenaline, or, alternatively, that the placenta may itself produce physiologically active amines which are then inactivated by this enzyme. In the case of the kidney, as I have already mentioned, it has been shown that certain amino-acid decarboxylases are present which, under anaerobic conditions, can form pressor amines, such as hydroxytyramine. We have searched for similar decarboxylating enzymes in placenta. Using a number of different amino-acids we have been unable to demonstrate any decarboxylation of any of them by placenta, while Page (1945) earlier on, using a biological method for the estimation of hydroxytyramine, had not been able to find any dopa-decarboxylase activity in human placenta.

In view of the effect of some of the steroid hormones on certain enzyme systems which have been described recently Dr. Tickner has embarked on some experiments to study the influence of œstrogenic and other steroid hormones on the activity of the placental mono-amine oxidase. Although this work is still in its early stages, he has found that under certain conditions the addition to the system of œstradiol, and also of stilbœstrol, brings about a marked activation of enzyme activity (see Thompson and Tickner, 1949*a*). Quite apart from any possible connection with preeclampsia these observations are clearly of biochemical importance, but in view of the profound alterations in endocrine balance in

pregnancy, any effect of the œstrogens on this or on other enzyme systems should certainly be studied with regard to any light which such observations may throw on the alterations in preeclampsia.

At present, therefore, we are not able to bring forward any clear-cut experimental evidence to explain the significance or the physiological function of this enzyme in the placenta. We have, however, established the presence of a highly active mono-amine oxidase in placenta which, whatever its function may be, is capable of inactivating vaso-constrictor amines, and which is itself inactivated by a fall of oxygen tension in its environment. Unfortunately we are not yet in a position to decide whether these observations which we have made bear any relation to the claims which have been put forward in the past of an increase in the blood tyramine concentration and of a hyperadrenalinæmia in eclamptic patients, but we do at any rate now know that the placenta contains this enzyme which, given an adequate supply of oxygen, can inactivate compounds containing a phenylethylamine grouping similar to that of adrenaline or nor-adrenaline by oxidatively deaminating the side-chain, and which, if for some reason exposed to conditions of lowered oxygen tension, would fail to inactivate these substances at the normal rate (Thompson and Tickner, 1949*b*).

I now want to turn for a few minutes to a consideration of another placental enzyme. It has been known for many years that the placenta contains acetyl choline and also a cholinesterase. The original finding of cholinesterase activity in fresh, unperfused placenta was not of course surprising in view of the large amount of blood contained in this tissue. Torda, however, in 1942, showed that perfused blood-free placenta was also able to hydrolyse acetyl choline at a considerable rate, but she made no attempt to characterize the type of cholinesterase. It will be remembered that the mammalian cholinesterases have been divided by Mendel into the two groups—"true cholinesterase," present in brain, skeletal muscle and red blood cells; and a "pseudo-cholinesterase,"

present in human plasma and capable of hydrolysing a somewhat wider range of esters than the so-called true enzyme. Mendel has also described selective synthetic substrates for the characterization of these enzymes, acetyl-β-methyl choline being hydrolysed by the true cholinesterase but not the pseudo, while benzoyl choline is hydrolysed by the "pseudo" but not the "true" enzyme. Nachmansohn and others have also attempted to correlate the true cholinesterase with nervous activity and to regard the pseudo-cholinesterase as largely unrelated to the physiological destruction of acetyl choline inside the body.

In view of this, we thought that it would be of interest to attempt to characterize the cholinesterase present in the placenta more fully. Using the synthetic, so-called "specific" substrates for the true and pseudo cholinesterases introduced by Mendel and his colleagues, Miss M. G. Ord and I have estimated the relative amounts of these two types of cholinesterase in fresh and in perfused placentas. In fresh placenta, as might be expected, we have found that both enzymes are present in roughly equivalent concentrations, but with perfused, blood-free placenta we found that while there is still an active true cholinesterase, the pseudo cholinesterase is present in negligible amounts. This finding is of interest when it is remembered that the tissue is devoid of any innervation; placenta, indeed, like the red blood cells, provides a second example of a nerve-free tissue which contains almost exclusively the true cholinesterase, hitherto associated with nervous activity.

Despite the absence of nerves from placenta therefore we have shown that this organ contains on the one hand a true cholinesterase capable of destroying the cholinergic transmitting substance, and on the other hand an amine oxidase capable of destroying adrenaline. It is tempting to speculate on the significance of the presence in this nerve-free organ of these two enzymes concerned with the destruction of physiological vaso-active substances, but before such speculations are likely to be profitable, more facts con-

cerning the physiology and biochemistry of the placenta are needed.

Before closing I would like to say a few words about some further work which we are now embarking on with a view to obtaining evidence as to the possible participation of adrenaline or of some related substance in the ætiology of pre-eclampsia.

It is, I believe, now widely recognized that the thyroid gland increases in size in the majority of pregnant women, and that this is associated with an increased activity of the gland; in support of this it has recently been shown by Heineman, Johnson and Man (1948) that the plasma protein-bound iodine level undergoes a significant increase in pregnancy. In this connection our attention was attracted to some recent work by Thibault (1949) in France, who has obtained further evidence in support of the old view that increased thyroid activity is associated with increased sensitivity to adrenaline. If this association is real, an exaggeration of the normal increase in thyroid activity in pregnancy might therefore predispose to vascular changes, either in the placenta or elsewhere, which might be of pathological importance. The evidence in the literature, however, on the level of thyroid activity in preeclampsia is strikingly inconsistent and even contradictory. Hoffmann and Anselmino, for example, have claimed that the amount of thyroid secretion in the blood is greatly increased in eclampsia, while Peters, Man and Heineman (1948) have more recently found no difference between their normal pregnant series and four cases of preeclampsia as regards the level of plasma protein-bound iodine.

We feel that it is desirable therefore to obtain more evidence on this point, and we are now hoping to determine the level of plasma protein-bound iodine in a larger series of pre-eclamptics.

With the time at my disposal I have been unable to do more than merely to describe very briefly some of our experimental findings, and to indicate some of the ideas that we are anxious

to put to the test. As I said when I began, most of what I have described is a long way from the problem of the pathology of eclampsia, and is indeed rather an incursion into the biochemistry of placental tissue. But it is, we feel, only by the slow accumulation of such knowledge that a logical approach to the problem may one day be made.

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TOXÆMIAS OF PREGNANCY: HUMAN AND VETERINARY
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HISTAMINASE IN NORMAL AND PATHOLOGICAL PREGNANCY

AXEL AHLMARK and LARS WERKÖ

ALREADY in 1915 Eustis showed that liver extract from a certain bird (Cathartes aura) destroyed histamine. He thought that this was due to an enzyme, as the histaminolytic effect was inhibited by boiling. This observation did not give rise to further studies. It was not until Best (1929) studied the stability of histamine in different tissues that the present interest in histamine and histaminase began. Best found that both the synthetic and the naturally occurring histamine was inactivated by lung tissue. He and McHenry (1930) proposed the name histaminase for "the substance or system, which produces a change in structure responsible for the loss of physiological activity of histamine."

The presence of high histaminolytic activity in the serum during pregnancy in man was first demonstrated by Marcou *et al.* (1938). Many observers have later confirmed and extended this observation. During the last ten years many Swedish investigators have contributed to the problem of histaminase in pregnancy, above all Ahlmark, Walentin, Wicksell, Willert and Swanberg. The latter in a not yet published work has conclusively demonstrated that the histaminase is produced in the maternal part of the placenta.

The Histamine-Histaminase Reaction

The exact chemical course of the inactivation of histamine is not known. The reaction is an oxidative de-amination, requiring the presence of oxygen. Kiese (1940) showed that one molecule of histamine required half a molecule of oxygen to be fully inactivated in the presence of a pure enzyme preparation. Zeller (1938) and Stephenson (1943) indirectly

demonstrated the production of hydrogen peroxide during this reaction. This was recently confirmed by Swedin in a polarographic study.

That ammonium was produced during the inactivation of histamine was shown by McHenry and Gavin (1932). They later demonstrated that the nitrogen ion originated from the amino group in the side chain and not from the imidazol ring. This is in accordance with the fact that histaminase also inactivated aliphatic amines like cadaverine, where the imidazol ring is not present. Swedin (1944), however, found that already in the first step of the histamine inactivation the imidazol group was destroyed, when he used electrophoretically purified histaminase. It thus seems possible that histamine may be inactivated by two or more enzyme systems.

The chemical nature of histaminase is not known. Zeller (1938) showed that it could be dialysed for weeks without losing its activity. He also found that it was completely inactivated by trypsin or pepsin. This strongly suggests a protein nature of the enzyme. Swedin (1944) showed that the enzyme effect is linked to a flavine-protein.

Many different methods have been used for the determination of the enzyme in blood or tissue extracts. Some methods are purely chemical, using for example the oxygen consumption or the ammonium production of the histamine-histaminase reaction. One widely used is the one designed by Zeller, where the amount of decoloration of indigo disulphonate is measured, produced when histamine is added to the sample. The most sensitive of all is the one described by Ahlmark. The principle of this method is as follows : after the addition of a known amount of histamine to the fluid whose histaminolytic power is to be estimated, the mixture is incubated for a definite time at a constant temperature. The fluid is then chemically treated and the remaining amount of histamine determined by assaying the sample on the surviving ileum of the guinea-pig against a standard solution of histamine. The histaminolytic power is expressed by the amount

of histamine base that is inactivated by 1 ml. fluid or 1 g. tissue in one hour under standardized conditions (γ/ml./hour).

Normally histaminase is present in many organs, in especially large amounts in the kidney and intestinal mucosa. Before 1944 the occurrence of histaminase in normal human plasma was studied by different investigators with different methods and varying results. The discrepancies are mostly due to unspecificity of the methods used or to their lacking exactness, as pointed out by Ahlmark. With the earlier mentioned biological method reproducible figures have been obtained. Using this method plasma from non-pregnant women in the child-bearing age has been found to contain a histaminolytic activity of only 0.002 microgram/ml./hour. This is at the lower margin of what can be assayed with this method. There is a rather large individual variation, some cases showing no activity at all, others three to four times the mean value. The histaminolytic power varies perhaps also a little during the menstrual cycle with lowest values between the menstruations. Values for males are of the same magnitude as for non-pregnant women.

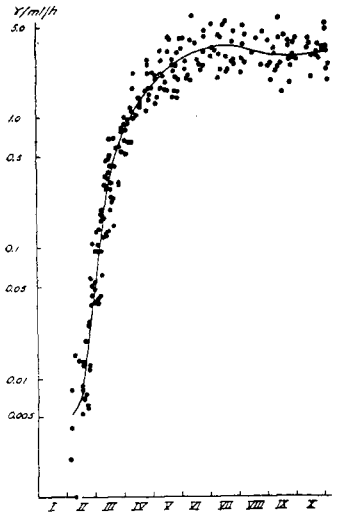

FIG. 1. Histaminase values obtained in different months of pregnancy.

During pregnancy the histaminolytic power of the serum increases more than a thousand times (highest value recorded 10.8 γ/ml./hour). Fig. 1 shows about 200 determinations from 45 pregnant women. It can be seen that the enzyme increases sharply from the end of the second month to the fifth

or sixth month. Fig. 2 shows the histaminase values from nine women where repeated determinations have been made. The increase during the eighth to the thirteenth week is so rapid that the change from one day to the other can be recorded by the method adopted. This is of importance for the diagnosis of disturbances in the course of the normal pregnancy.

During the latter half of pregnancy the histaminolytic

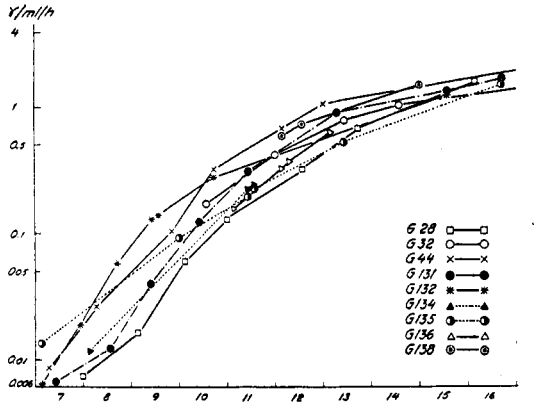

FIG. 2. Results of repeated determinations of histaminase in nine women during the 7th to 16th week of pregnancy.

power is quite constant. There is perhaps a slight decrease in the seventh month followed by a small increase.

After delivery the enzyme decreases about 45 to 50 per cent a day. Two to three weeks after delivery the values are the same as for non-pregnant women.

The histaminase values show regular changes even in different patients in the third and fourth months. A value of 0.18 γ/ml./hour for example occurs only between the 63rd and 75th days during normal pregnancy. Thus the histaminase values may be used to estimate the duration of pregnancy. In two cases out of three the length of pregnancy

can be determined within six days, which sometimes may be useful.

That histaminase occurred in the placenta was demonstrated by Danforth and Gosham (1937). Zeller and co-workers (1939) suggested a relation between this placental enzyme and the histaminolytic activity of blood, recently demonstrated by Marcou *et al.* The close correlation between the concentration of histaminase in the placenta and the blood is demonstrated in Fig. 3, showing values obtained in man by Ahlmark and Swanberg. The latter has studied the distribution of histaminase in the placenta. There was a higher concentration — sometimes more than 100 times—in the maternal part of the placenta than in the fœtal part. In later still unpublished studies Swanberg has demonstrated that the enzyme is really produced in the decidua and not only stored there. The histaminase is distributed in the maternal blood and not at all or only slightly in the fœtal circulation. Anrep and co-workers (1947) demonstrated a marked histaminolytic activity in blood from the umbilical cord. Swanberg could not confirm this. He shows that samples easily may be contaminated with amniotic fluid, that has a high histaminolytic activity.

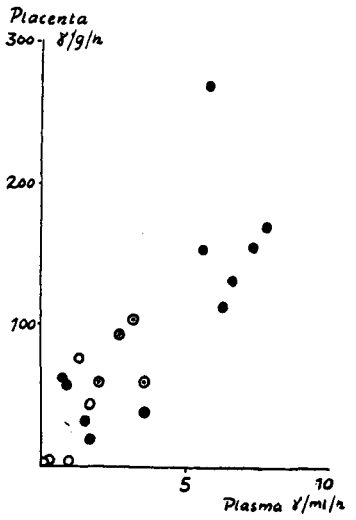

FIG. 3. The relation between the content of histaminase in placenta and in the plasma.

There have not been any studies of what starts and regulates the production of histaminase. Anrep *et al.* (1941) suggested that "it should be expected that the increase in the histaminolytic product in the blood would bear some relation to the production of gonadotropic or œstrogenic

compounds." A connection between vitamins and hormones and histaminase production has also been suggested by Swanberg.

The influence of the adrenocorticotropic hormone of the pituitary on the histaminolytic activity of serum in a case of rheumatoid arthritis is illustrated in Fig. 4 from a recent study by Berglund. Concomitant with a decrease in ESR

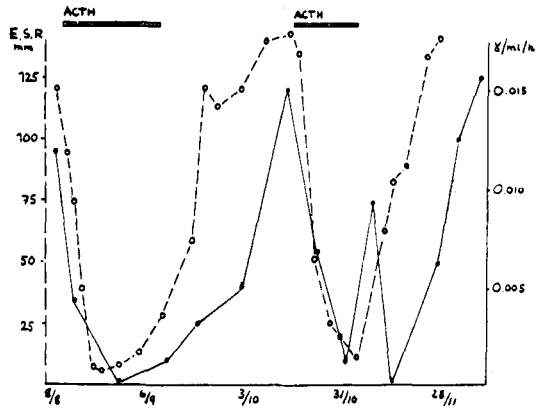

FIG. 4. The relation between the changes in sedimentation rate and histaminase in a case of rheumatoid arthritis treated with ACTH (from Berglund, 1949).

after the administration of ACTH there was a decrease in histaminase. Later the ESR and the histaminase rose paralleling each other. This effect, of course, is not comparable to the changes found in pregnancy but suggests a relation between hormones and the histaminase. More studies remain to be done to establish the exact interrelationship.

The physiological purpose of the increased histaminolytic activity during pregnancy is not known. It has been suggested that there is an increased production of histamine that has to be counterbalanced by increased histaminase. Different authors have demonstrated decreased sensitivity

to histamine injected intravenously or subcutaneously during pregnancy (Strauss and Castle, 1932; McElin and Horton, 1949). Wicksell (1949), studying the "triple response" to intradermally injected histamine, did not find any difference in reaction between non-pregnant and pregnant women. He concluded that his experiments did not give any evidence that histamine plays any role or that the histamine metabolism is in any way affected in normal pregnancy. Wicksell suggests that the histamine is present in the plasma in a form which is ultrafilterable but not attacked by histaminase. Ernest Page (1948) regards histaminase as only one of the many enzymes that are produced during pregnancy, all of which more or less directly are concerned with the vascular status. We also want to point out that the enzyme destroys other di-amines as well as histamine and thus not necessarily has to be produced as an anti-histamine.

The striking regularity in the histaminase values during normal pregnancy has stimulated interest in the changes in histaminase during pathological pregnancies. During the last few years the following states have been especially studied in different hospitals in Sweden:—

(1) Hæmorrhages in early pregnancy.
(2) Tubal pregnancy.
(3) Hydatid moles.
(4) Toxæmias of pregnancy.

Though we are not obstetricians, we will attempt to summarize the results of the different Swedish investigators and relate them to our own and others' work (Anrep *et al.*, Kapeller-Adler).

In hæmorrhages in pregnancy many thousand analyses have been done, making possible a fairly accurate estimation of the prognostic value of the method. Fig. 5 is taken from a paper by Walentin (1945). In the cases where the pregnancy continued and ended with the birth of a living child, the histaminase values were normal or just on the lower border

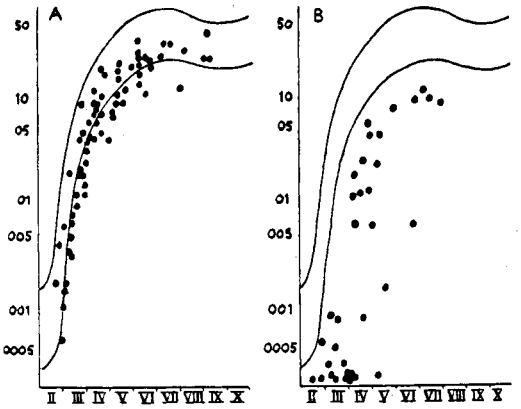

FIG. 5. Histaminase in cases with hæmorrhages in early pregnancy. A, with favourable outcome; B, ending in abortion.

of normal. In the cases ending in abortion, the histaminase content of serum was far below this border. Two examples are shown in Fig. 6. There are, however, exceptions to this, as later experiences have shown. Some cases ending in

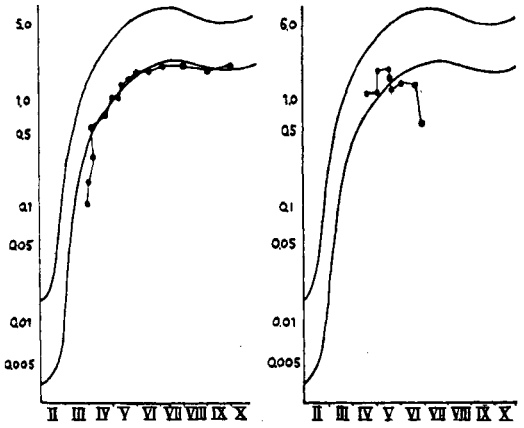

Fig. 6. Repeated determinations of histaminase in two cases with bleedings in pregnancy. The case to the left gave birth to a living child, that to the right ended in abortion (from Walentin, 1945).

abortion have shown rising histaminase values. Genell has demonstrated that in some cases the histaminase continued to increase even after the delivery of the fœtus. It has, however, been confirmed that cases with bleedings in the third or fourth months, with low or decreasing histaminase values, always have a bad prognosis. This fact makes the method of great value in deciding progesterone therapy in cases with threatened abortion. The economic consequences of this have caused some hospitals to use the histaminase determination as a routine procedure.

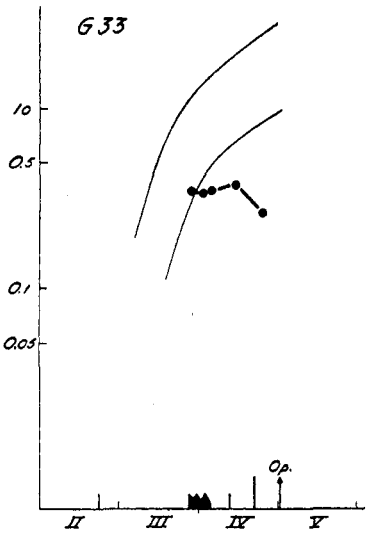

FIG. 7. Histaminase values in a case of tubal pregnancy.

The relation between the death of the fœtus and the histaminase values in late pregnancy is still a subject for investigation. Anrep, Barsoum and Ibrahim (1947) reported that death of the fœtus in the seventh to ninth month of pregnancy was correlated to a decrease in their "histaminolytic index." This has not been confirmed with the more sensitive methods used in Sweden. In some cases there may be a decrease in histaminase when the fœtus dies during the last months of pregnancy. In most of these cases, however, the histaminase is normal, or even increased (Swanberg, 1948). We do not believe that determination of histaminase has any prognostic value in the later part of pregnancy.

Only few cases with **tubal pregnancy** have been thoroughly studied regarding the histaminolytic power of plasma. Usually there is at first a normal increase; this eventually stops and even may decrease before rupture of the tubal pregnancy. This is illustrated in Fig. 7, showing a

case with small bleedings in the second and third months of pregnancy. The histaminase was normal until the 16th week, when it decreased about 50 per cent. The patient was treated as a threatened abortion. Six days after the last histaminase determination a tubal pregnancy ruptured. This was the first case to be followed with histaminase determinations. A

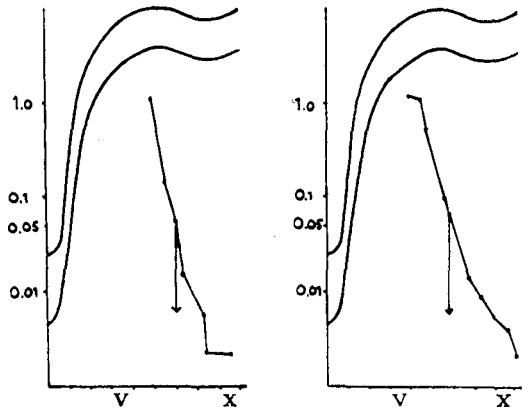

Fig. 8. Histaminase in two cases of hydatidiform mole. The arrow shows the birth of the mole (from Walentin, 1945).

patient with such a histaminase curve would nowadays be operated upon before the rupture.

In hydatid moles increasing experience is gained, giving clinically important information. The histaminase content of the plasma at first increases in a normal fashion until the mole begins bleeding. Then the increase stops and the histaminase value stays the same or may even decrease a little. After the delivery of the mole the histaminase rapidly resumes non-pregnant values. This is illustrated in Fig. 8. If the mole undergoes malignant changes the histaminase value con tinues to increase until the malignant growth is removed

Fig. 9 shows the histaminase values in a case of chorionepithelioma.

The determination of the histaminolytic power of the plasma may thus aid in the early diagnosis of chorionepithelioma.

Toxæmia of Pregnancy. The importance of the histidine-histamine metabolism during pregnancy and especially in toxæmia has been stressed especially by Westberg and Kapeller-Adler. Westberg showed (1941) that the amount of histidine in the urine was less in toxæmia of pregnancy than in normal pregnancy, where it is elevated. Kapeller-Adler and Adler (1942, 1943) demonstrated that histamine was present in the urine from patients with toxæmia. Kapeller-Adler (1944, 1949) has later shown that the activity of histaminase in the serum was less in patients with toxæmia than in normal pregnancy and that the enzyme reaction was weak or absent in cases with severe pre-eclampsia or eclampsia. Her results agreed partly with the earlier experience of Zeller (1941) and Werle and Effkemann (1940). Kapeller-Adler uses a modification of the colorimetric indigo disulphonate method by Zeller. Several Swedish investigators using the more sensitive, biological method have not been able to confirm these results. Fig. 10 gives a survey of the occurrence of histamine, histidine and histaminase in normal cases and in cases of toxæmia of pregnancy. Fig. 11 shows the histaminase values obtained in 20 cases of toxæmia of pregnancy. Some values are within normal limits, some extremely high and some low. There

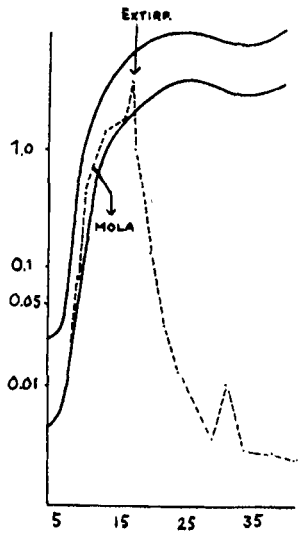

FIG. 9. Histaminase in a case of chorionepithelioma. The first arrow denotes the detection of the mole, the second shows the extirpation of the uterus with the tumour (from Willert, 1949).

was no correlation between the histaminase values and different symptoms of toxæmia, œdema, hypertension, eclampsia or proteinuria. The size of the fœtus was not

	Histidine-excretion in Urine	Histamine in Blood. Micro-grams per lit.		Histaminase in Plasma	
		In Red Cells	In Serum (approx.)	Biological method γ/ml/h	Chemical Method
Not pregnant . .	0	32	5	0.002–0.008	0
Healthy pregnant .	+	36	8	0.002– 6	+ +
Mild preeclamptic .	(+)	41	17	0.7 –10	+ +
Severe preeclamptic	0	21	25	0.7 –10	+ (+)
Puerperium . . .	0	43	10	0.002– 8	±

FIG. 10. Histidine excretion, histamine in plasma and histaminase in plasma in pregnancy. (*Partly after Kapeller-Adler.*)

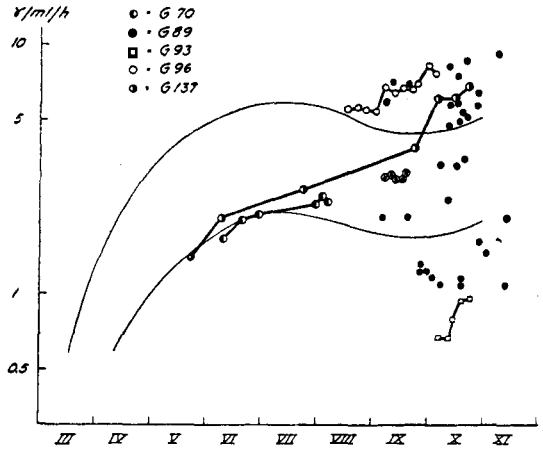

FIG. 11. Histaminase values in twenty cases of hypertensive toxæmia of pregnancy.

correlated to the enzyme values, nor the occurrence of intra-uterine death. The same lack of correlation is obvious in much larger material obtained in several hospitals in Stockholm and Malmö. Fig. 12 shows the values obtained

in a young woman with hypertension, developing a slight superimposed toxæmia; with increasing proteinuria, blood pressure and œdema, the histaminase values were constant. She was delivered of a living child, weighing five pounds.

It seems thus clear that the histaminolytic activity of the serum in toxæmia of pregnancy may be altered. There is, however, no definite correlation between the histaminase values and the severity of toxæmia. The changes in his-

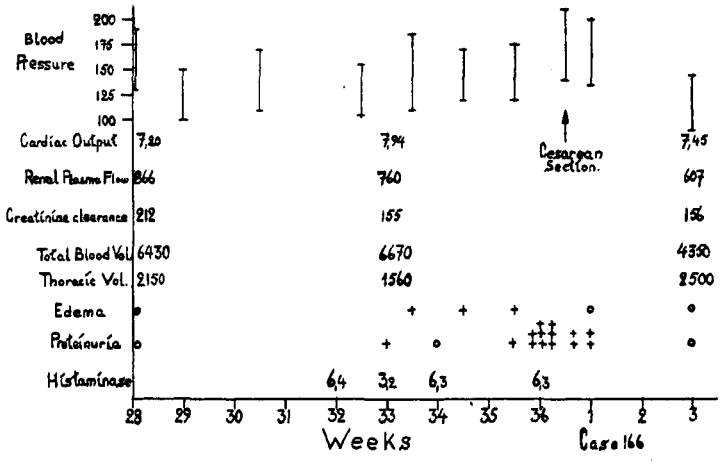

FIG. 12. Blood pressure, cardiac output, kidney function and histaminase in a case of hypertension with superimposed toxæmia.

taminase in toxæmia may well be secondary to toxæmic changes in the decidua. The irregularity of the values speaks in favour of such a concept. The altered hormone balance in toxæmia may also be a factor influencing the histaminase, according to Swanberg. The fact that histaminase values are normal in hydatid moles before bleeding, a state with a high toxæmia rate, and high or low in ordinary toxæmia, also suggests that the histaminase changes are secondary. On the other hand histaminase may well be of importance in the development of toxæmia, as it is not transferred to the fœtus, toxæmia being solely a maternal disease. Further

investigations are required to evaluate the importance of histaminase in this respect.

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HISTAMINASE IN NORMAL AND PATHOLOGICAL PREGNANCY

(short contribution)

R. KAPELLER-ADLER

DR. FALKINER said yesterday that we are here not so much to accept or to discard theories on the ætiology of pregnancy toxæmia but to gather facts. May I now be permitted to draw your attention to two biochemical facts characteristic only of human pregnancy and not to be found in pregnant animals. First of all there is to be mentioned histidinuria persisting throughout normal pregnancy, beginning soon after the embedding of the ovum and ceasing only after parturition or after the expulsion of the dead ovum. I have stressed the word *normal* pregnancy for in cases of severe pre-eclamptic toxæmia no histidine is excreted in the urine. So invariable is this finding that a missing histidine excretion in pregnancy may be used as a diagnostic sign of severe pre-eclamptic toxæmia. If the condition of the woman improves histidine reappears in the urine, only to disappear again on deterioration of the condition of the pregnant patient. Oral and intravenous applications of histidine to women suffering from severe toxæmia of pregnancy have revealed a tendency towards a histidine retention in the body of those women. There can be little doubt that under certain conditions the neutral compound histidine, so abundantly present throughout human pregnancy, can be converted into the potent substance histamine by an enzyme specific for this process, the histidine decarboxylase.

I have now to mention another biochemical fact, again characteristic only of human pregnancy. This is the histaminolytic power of the serum or plasma of normal human pregnancy, not to be encountered with in pregnant animals,

neither to be found in any other condition in man. The presence of histaminase in pregnancy serum must definitely have a certain significance. It probably represents a prophylactic measure in human pregnancy against a potential histamine intoxication.

Dr. Werkö has shown you results obtained when the histaminase activity in pregnancy plasma was investigated by means of a biological method. I have recently developed a simple chemical quantitative method, based on Zeller's qualitative indigo test, for the estimation of histaminase activity in biological media. I have used this method for the determination of histaminase in pregnancy serum and I should like to show you now the results obtained with this quantitative test.

The abscissa in Fig. 1 represents weeks of pregnancy, stages of labour and days of puerperium. The ordinate shows the histaminase activity expressed in terms of a new histaminase unit (permanganate unit) which, however, I am not going to discuss here today. The black spots represent cases of normal pregnancy, the crosses cases of toxæmic pregnancy, whereas the squares and the circles stand for cases of threatened abortion and twin pregnancy respectively. According to this figure histaminase appears in pregnancy serum in the third month of gestation, reaches its maximum between the 22nd and 26th week of pregnancy, somewhat declines in the 7th month of gestation, to remain more or less stationary until delivery. During labour and even more rapidly in the puerperium the histaminase activity in the serum tends to decrease. These results are similar to those shown by Dr. Werkö in cases of normal pregnancy. Abnormal results were obtained with the quantitative chemical test in three types of cases. Significantly decreased histaminase activity was seen in cases of pre-eclamptic toxæmia and significantly increased activity was encountered in cases of twin pregnancy. In some cases of threatened abortion the histaminase activity in the serum was found to be exceedingly low. All researchers in this field agree that the placenta is the site of formation of histaminase circulating in pregnancy serum.

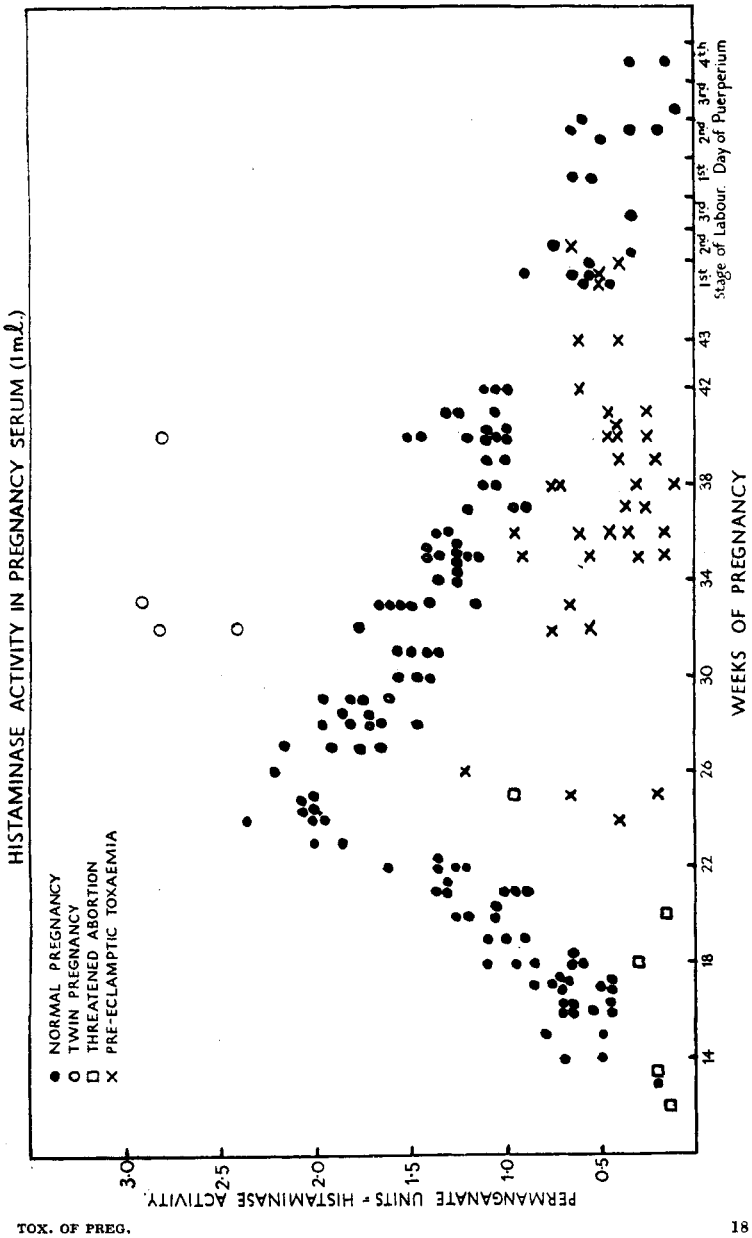
HISTAMINASE ACTIVITY IN PREGNANCY SERUM (1 ml.)
NORMAL PREGNANCY
TWIN PREGNANCY
THREATENED ABORTION
PRE-ECLAMPTIC TOXAEMIA
PERMANGANATE UNITS = HISTAMINASE ACTIVITY
0·5
1·0
1·5
2·0
2·5
3·0
14
18
22
26
30
34
38
42
43
1st 2nd 3rd 1st 2nd 3rd 4th
Stage of Labour Day of Puerperium
WEEKS OF PREGNANCY

FIG. 1.

Investigations on histaminase activity carried out with the new chemical quantitative test in normal placentæ and in placentæ from women who had suffered from severe pre-eclamptic toxæmia revealed a decreased histaminase content of the latter placentæ as compared with the histaminase activity in normal placentæ. Moreover, it should be borne in mind that any deficiency in the oxygen supply will further decrease the histaminase activity in the placenta and consequently also in the serum of toxæmic patients.

The histidine and histamine metabolism in normal and toxæmic pregnancy represents a vast problem, but my short time today permits me only to touch upon it. However, I hope I have succeeded in demonstrating today that the lack of histidinuria in severe toxæmia of pregnancy and the highly decreased histaminase activity in placenta and serum of the same condition, both deviations from well established phenomena in normal human pregnancy, must have some bearing on the problem of toxæmic pregnancy.

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SUMMARIES

FROM VETERINARY STANDPOINT

JOHN HAMMOND

THE various symptoms of the toxæmias described in the papers which have been presented on the veterinary side remind one of those of deficiency diseases in their acute form.

Making the survey from this point of view, one pictures the various tissues of the body struggling for the nutrients

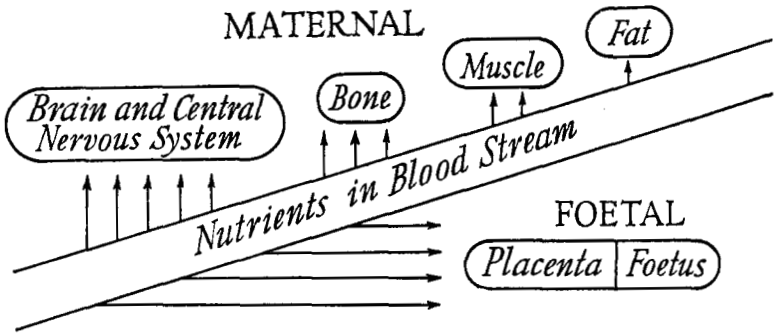

FIG. 1. Priority of Partition of Nutrients according to Metabolic Rate.

in the blood stream, the priority of each tissue being determined by the rate of its metabolism as shown in Fig. 1.

With a lower intake from the gut than is necessary to supply a specific nutrient to all the tissues requiring it, this substance is withdrawn from those tissues with the least priority and transported to those which have a higher priority, any metabolic transformation which is necessary being carried out in

the liver. The facts illustrated in Fig. 1 have been confirmed by direct experiment (Hammond, 1948).

Now let us consider how the conditions of the various toxæmias fit into such a system. Naturally, as Parry has stated, the kind of toxæmia which results from functioning of the mammary gland will differ from that of pregnancy according to the special nutrients (minerals or sugars) which are in greatest demand by the new tissue suddenly functioning and by the relative shortages of the reserves of these, or their availability in the body. With pregnancy toxæmia in the ewe there is ample evidence, supplied by Parry and Phillipson, to show that sugar is one of the major requirements of the fœtus during the later stages of pregnancy. If this is in short supply from the gut, the placenta has priority and the energy requirements of the body are called on from stored fat which is drawn off to the liver, where normally it would be burned up in a "flame of carbohydrate," but this being in short supply fat accumulates in the liver and gives rise to the symptoms of toxæmia. Wallace (1948) has shown that in low plane ewes just before birth of the lamb, this accumulation of fat in the liver is much greater when the ewe is fat at mid-pregnancy than when she is lean at this time, and that no fat accumulation takes place in the livers of ewes which are fully fed during the last two months of pregnancy. Since, as Phillipson has pointed out, the addition of starch to the ration prevents the onset of the toxæmia, there can be little doubt that this toxæmia is due to a deficiency of sugar in the blood stream. It will be obvious that the giving of glucose *after* the symptoms of toxæmia have occurred will have little effect, since the fat is already in the liver.

In the case of copper deficiency causing swayback in lambs, reported on by Allcroft, it would appear that the deficiency affects the offspring rather than the mother, because it is a case of priority of supply to the mother's brain over that to the placenta, an intermediary between the maternal blood stream and that of the fœtal brain tissues. The incidence of the disease in the lambs will also depend on how far the

brain requirements of the mothers have been met by previous food supplies.

The quantitative aspects of the subject, as distinct from the percentage composition, put before us by Duckworth, have a particular bearing on the mineral requirements of milking cattle.

As Messervy has pointed out, in milk fever the greatest incidence is found under conditions where milk production is highest, although in considering the many exceptions to this it should be remembered that nutrients are withdrawn from the blood stream before they appear in the milk. There may be recovery without treatment, but this is usually associated with a drop in milk yield. He also mentioned the depraved appetite reminiscent of phosphate deficiency and of ketosis such as occurs in the pregnancy toxæmia of sheep, which, as we have seen, is associated with carbohydrate deficiency.

As far as we know at present, sugar, calcium and phosphorus appear to be the chief substances concerned in deficiencies which may appear when the competition between the tissues of the mammary gland and that of the other body tissues takes place. Robertson's account of the various methods of treatment which have been evolved seem to bear this out. Cures may be effected by slowing down the rate of secretion of milk by pumping up the udder with air, etc., or by injections of calcium gluconate. The latter, however, does not touch the phosphate deficiency and so there are cases which respond to the former but not to the latter cure. Since the priority of the udder for nutrients is only just above that of bone, the main source of calcium and phosphorus, the lability of bone minerals also comes into play and this may be affected by the previous nutritional history of the animal or by the endocrine balance. Such causes may account for the apparently exceptional cases of milk fever which occur.

Since the previous nutritional history is important in determining the degree of deficiency in the tissues of the mother in the special substances required by the sudden

heavy demands which will be made on her by the fœtus in the later stages of pregnancy and with the onset of lactation, it would seem that the best thing we can do in the way of prevention (as distinct from cure) is to feed the mother with suitable substances before and not after the strain comes.

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FROM MEDICAL STANDPOINT

G. W. PICKERING

IT has always seemed to me that it was very unfortunate that toxæmia was the word chosen to characterize a number of obscure complications in pregnancy. The use of this term has given a spurious sense of unity to the conditions and implies that they are due to the action of a chemical substance, or toxin. Slowly we are beginning to distinguish these conditions one from another and to understand their pathology. Consider for example three conditions which have been included under the term toxæmias of pregnancy—Wernicke's encephalopathy, acute yellow atrophy and pre-eclamptic toxæmia. The first two are almost certainly deficiency diseases, quite different one from another. Pre-eclamptic toxæmia is almost certainly of different origin, but the pathogenesis remains obscure.

My remarks will be devoted entirely to so-called pre-eclamptic toxæmia. This is a condition occurring in the last few months of pregnancy and characterized by hypertension and almost always accompanied by albuminuria and œdema. In severe cases fits may occur and the condition is then known as eclampsia. The cause of these fits has not been made clear at this meeting. I would like to remind you that similar fits may occur in two other conditions not connected with pregnancy in which the hypertension is likewise of fairly recent origin and fairly severe, namely acute nephritis and malignant hypertension. The fits are commonly ascribed to œdema of the brain and there have been cases, for example one published by Blackman and Hamilton and one which I saw myself, in which evidence of a pressure cone was found post mortem. But Professor Sheehan tells me that he has not found any striking confirmation of the view that the fits in eclampsia

are due to œdema of the brain. Professor Kellar told us that the blood flow through the brain in eclampsia was normal; thus providing no evidence for ischæmia.

Hypertension is clearly the outward manifestation of a circulatory disturbance which may be the central, or merely one of the earliest and most constant, changes in this condition of pre-eclamptic toxæmia. Until recently the nature of the circulatory disturbance has been quite obscure. One of the most illuminating fruits of this meeting has been the evidence which Professor Kellar announced concerning the circulation to various parts of the body. It would seem that in pre-eclamptic toxæmia the cardiac output is increased. On Professor Kellar's figures the forearm blood flow is also a little increased. The blood flow through the liver, measured by the bromsulphaline method, is also normal or increased. That of the brain, by the nitrous oxide method of Kety and Schmidt, is normal, that of the kidney is normal, that of the uterus is not known. It is interesting to compare these figures with those for essential hypertension, in which condition the cardiac output is normal, the forearm blood flow is a little increased, the liver blood flow is normal, the brain blood flow is normal, and the kidney blood flow is reduced. Pre-eclamptic toxæmia would seem to be the only sort of hypertension accompanied by an increased cardiac output. Nevertheless it would seem probable that the cause of the hypertension is to be sought in vasoconstriction. From Professor Kellar's figures this would seem to be slight in degree and probably fairly widespread in distribution. Very relevant here is the question of retinal vascular spasm, for the occurrence of this would prove vasoconstriction and might give a clue to its cause and nature. I have observed the fundus oculi carefully in several cases of pre-eclamptic toxæmia and never seen a localized constriction of a retinal artery which disappeared after the blood pressure returned to normal. My ophthalmological friends who have looked at many cases of pregnancy toxæmia also used to tell me that they have never seen it. But recently Mr. Frank Juler has been looking at cases in Queen Charlotte's Hospital

with extreme care. He has shown me his preliminary report in which on the most careful inspection he finds minute irregularities in the arteries before parturition which are not seen on a subsequent occasion.

In view of the suggestions made at this meeting it is necessary to look at the evidence relating to the renal blood flow in pre-eclamptic toxæmia a little more closely. Chesley and his colleagues in 1940 found that the renal blood flow estimated by the diodone clearance method was normal. In 1941 Corcoran and Page investigated thirteen cases of toxæmias, seven of whom had eclamptic convulsions, by the inulin and diodone method. The renal blood flow was in the normal range except in one, where it was very low ; and filtration fraction was much reduced. In 1942 Wellen, Welch and Taylor investigated fourteen cases of hypertension all of whom had had œdema and albuminuria. They found the inulin clearance was normal, the diodone clearance above the mean normal in eight out of eleven. It fell after delivery in nine out of eleven even before the drop in the blood pressure. The filtration fraction was reduced. Since the diodone clearance was clearly normal or above normal there can be no generalized ischæmia of the cortex of the kidney. In human pre-eclamptic toxæmia, there can be therefore no cortico-medullary shunt in operation. Even Professor Brown's simple little hypothesis of the causation of albuminuria in pre-eclamptic toxæmia receives no support from these figures. Moreover there is no renal ischæmia to cause the release of renin, and the pattern of the renal circulation is quite unlike that produced by renin. It seems very unlikely, therefore, that the renal pressor substance has anything to do with pre-eclamptic toxæmia.

One of the most illuminating contributions at this meeting was that of Professor Sheehan describing the anatomical changes found in pre-eclamptic toxæmia. I have been wondering whether it was possible to explain these lesions on the basis of ischæmia, and I have come to the conclusion that it is not. Some years ago Scarff clamped the renal artery for some hours in the rabbit and then let it go. Subsequently the

kidneys were examined histologically. Scarff did not find the changes described by Professor Sheehan. I have examined many kidneys in the rabbit in which the renal artery has been constricted by Goldblatt's method for many weeks or months, and I have never seen these changes described by Professor Sheehan. The lesions in the liver have a periportal distribution, whereas one would expect that if ischæmia were the cause the necrosis would be central. And so it seems to me that these histological changes must have a cause other than simple ischæmia.

Unlike most other forms of hypertension the natural history of pre-eclamptic toxæmia provides one fact that is so important that we might almost call it a master fact, namely that the symptoms subside dramatically after parturition. Not only does the blood pressure fall, but the œdema, if present, disappears accompanied by a large diuresis. Obviously parturition is accompanied by a disappearance of the causative agent. The most probable sources of the agent or agents concerned would therefore appear to be the placenta, the fœtus or the ductless glands controlling pregnancy and parturition. The fœtus would seem very unlikely firstly because Brown and Dodds have shown that the new-born of a toxæmic mother has a normal blood pressure and secondly because pre-eclamptic toxæmia occurs in hydatidiform mole. Ham and Landis, confirming the work of others, have shown that the placenta of patients with toxæmia of pregnancy contains an antidiuretic substance which is not found at any rate with the same frequency in the placentæ of patients with normal blood pressures. This antidiuretic substance also appears in the urine, and it lessens after parturition. It is not unlikely therefore that the water retention may be due to secretion of this antidiuretic substance by the placenta. This meeting has drawn attention to the complexity of the hormones and enzymes found in the placenta. But there is as yet no clear evidence as to which of them, if any, is responsible for hypertension of pre-eclamptic toxæmia.

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FROM OBSTETRIC STANDPOINT

F. J. BROWNE

I AM afraid I am going to bring the discussion to a very low level. I am not a physician, nor a pathologist, nor physiologist, nor endocrinologist, nor biochemist but only an obstetrician who has been interested in toxæmias for many years.

First of all I should like to state some things that I am sure of in connection with eclampsia and pre-eclamptic toxæmia, and they are not very many. Toxæmia is four or five times as common in twin pregnancy as in single pregnancy; it seems to be more frequent in hydramnios; it is more frequent in hydatidiform mole and occurs much earlier, and eclampsia has been recorded in molar pregnancy as early as the 16th week; it is sometimes associated with concealed accidental hæmorrhage and with bilateral cortical necrosis of the kidneys; œdema when present may be gross, and form very rapidly; the vascular system is sensitized and this sensitization is not constitutional, but is acquired at some time between the 17th week of pregnancy and the time at which pre-eclamptic toxæmia develops; there is increased capillary permeability, as evidenced by the finding that the protein content of the œdema fluid is much greater than that of normal tissue fluid; and finally, eclamptic fits may begin for the first time three or four or even more days after delivery and when no remnant of placenta is retained in the uterus.

After listening to this discussion, I think we shall all agree that "toxæmia" in cattle is a different disease altogether from that in women. There is no hypertension, no œdema and there are no fits. I have the impression that it is due to some metabolic disturbance unlike anything occurring in human subjects. Here I may recall that many years ago in

Edinburgh, Russell Gregg and I attempted to cure eclampsia by blowing up the nipple, but we found it impossible because there are twelve tiny ducts opening in the human nipple instead of one large one in the cow.

Dr. Theobald is to be congratulated on his results. He has noticed that in pre-eclamptic toxæmia the stillbirth rate is higher if there is albuminuria. Is not the reason for this very simple ? If we accept the view that albuminuria is due to afferent arteriolar glomerular spasm causing anoxic injury of the glomerular capillaries so that they leak albumin, it is apparent that a similar spasm may occur simultaneously in the spiral arteries of the decidua, causing retro-placental hæmorrhage and fœtal death if the hæmorrhage is large enough. My own view is that this dangerous spasm occurs when the systolic blood pressure exceeds 160 mm. Hg.—often called the critical level of blood pressure in pregnancy. Dr. Theobald has for many years proclaimed the all-important role played by dietetic deficiencies in causing eclampsia, and there are many facts that lend support to this view. In Hong Kong, for example, eclampsia is many times more frequent in women suffering from beri-beri, which is thought to be due to a deficiency of vitamin B1. In passing I may say that I have been unable to reduce the incidence of pre-eclamptic toxæmia by giving vitamin B1, and Professor Dieckmann has told us that he has failed to do so even by giving B complex. This is all the more puzzling in view of the work of Calder (1944), who has caused hypertension, temporary and permanent, by feeding rats on a diet deficient in the heat stable fractions of B complex, as well as the thickening of the basement membrane of the glomerular capillaries which is characteristic of eclampsia. Professor Dieckmann's results are of the greatest interest. He can cause increase of hypertension and of albuminuria by injecting hypertensive saline. This suggests that the cause of hypertension and albuminuria might be salt and water retention. So far as my own clinical observations go, however, œdema does not always precede hypertension in the developing syndrome of pre-eclamptic

toxæmia. I have known the blood pressure rise from a normal level to 160 mm. Hg. systolic without any œdema either occult or manifest. This order of appearance of the signs of pre-eclamptic toxæmia may be observed by anyone in the ante-natal clinic. Dr. Falkiner has told us that those who deny that placental infarcts are more frequent in eclampsia are ignorant of placental anatomy and pathology! Well, I am not at all sure about this, and there are many papers in the literature denying any specially high incidence. I advise Dr. Falkiner to investigate this matter afresh and with an open mind.

Dr. Schneider has made an important contribution to our discussion. We know that fibrinous thrombi are often present in the portal tracts of the liver and indeed in every organ. Are they not, however, more likely to be formed in sites by the action of a vascular endothelial toxin that at the same time causes the increased capillary permeability? How is it possible to explain the hypertension, and the rapidly forming œdema by the presence of thromboplastin? Interesting as this work is, I cannot see that it is adequate.

Professor Kellar's team in Edinburgh is evidently doing work of fundamental importance. He has told us that there is no peripheral vaso-constriction. How then does he explain the hypertension? Mylius showed long ago (1927) that spasm of the retinal arterioles always occurs if the systolic blood pressure is above 150 mm. Hg. It is many years since I read his article, but if I remember correctly he gives coloured photographs of the condition.

Professor Bastiaanse's theory is certainly attractive. It might explain the greater frequency of eclampsia in twin pregnancy and in hydramnios, in both of which the uterus is over extended and the circulation in the placenta presumably reduced. This may be linked up with the work of Professor Thompson at Guy's Hospital, who finds an enzyme, amino oxidase, in the maternal part of the placenta which is inactive when the oxygen tension in the placenta is lowered. Is it possible that in the anæmic placenta there is the source of the

substance that sensitizes the vascular system in pre-eclamptic toxæmia ? It will be remembered that Shorr showed that such a sensitizing substance was produced in the anæmic renal cortex in cases of shock. It is clear that Bastiaanse's theory might well explain the hypertension, but can it explain œdema ? Does he think that the hypertension can cause capillary injury throughout the body generally ? Speaking only as an obstetrician, it would seem to me unlikely that it can do so because of the anastomosis between the vessels in the peripheral circulation. One great difficulty in accepting this theory of Bastiaanse is that it does not explain the onset of eclampsia three or four days after delivery when the uterus is not extended and the placenta is absent. That is a difficulty, however, that is common to all theories of eclampsia so far propounded, including the renal shunt of Trueta, Franklin, Sophian and others.

I am sorry that I did not hear the first half of Dr. Glynn's paper. I doubt, however, if there is any connection between acute yellow atrophy of the liver, including the massive hepatic necrosis caused by experimental diets deficient in protein and other protection nutrients, and the toxæmia of late pregnancy. Acute yellow atrophy does not, so far as I know, ever occur in eclampsia, and the areas of necrosis that do occur in the liver and in almost every organ throughout the body can be explained by vascular spasm. Byrom showed that it is possible to cause necrosis in the liver and kidneys by injecting vasopressin. In hyperemesis gravidarum it is a different matter, and then it is probable that the necrosis and fatty infiltration are due to loss of protection nutrients in the vomit.

It is rather strange that in all this discussion little or no reference has been made to the possible role of the adrenal cortex hormones in causing toxæmia. Yet there are some striking facts that are worth recalling. Some of the cortical hormones are closely allied chemically to the female sex hormones, and if injected into animals and humans can cause sodium retention, gross œdema, hypertension and albumin-

uria. Ferebee treated thirteen patients who had Addison's disease by desoxycorticosterone. It led to retention of salt and water, oliguria, a marked increase of interstitial fluid, and in two to four weeks the blood pressure rose to normal from the low levels characteristic of Addison's disease. In three of the patients it rose to 160/112 and 146/108. Ten of the thirteen developed clinical œdema varying from mild puffiness of the face and ankles, and anasarca. May it not be that increase in adrenocorticotropic hormone of the anterior pituitary accounts for the high incidence of toxæmia in diabetic pregnant women ? In hydatidiform mole there is a greatly increased output of chorionic gonadotrophin. Does this contain any adrenocorticotrophic hormone, such as might account for the increased incidence and early onset of toxæmia in this condition ?

We must all have been impressed during the last three days by the team work that is going on in this and other countries by groups of workers. Some of us have long felt that the problem of eclampsia is beyond the mere clinician, and that it will only be solved by such team work as this between physicians, physiologists, endocrinologists and chemists, together with an obstetrician to keep his colleagues in touch with the clinical aspects of the problem.

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