STUDIES IN TOXAEMIAS OF PREGNANCY.

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PREFACE.

The study on Toxaemias of Pregnancy, of which this thesis forms a part was commenced in India in 1939. During the years of war the investigation was temporarily suspended, but in 1947 the writer received a grant from the Government of India for the purpose of continuing the research at the research department of the Royal Maternity Hospital, Glasgow. The data on which this thesis is based were obtained wholly from the cases studied in this hospital. These results have not been combined with others obtained from a similar study in India inorder to maintain the uniformity of the series, although there has been a close agreement between the findings obtained here and those on a larger series of Indian patients living under different climatic, dietetic and environmental conditions.

There is hardly another subject in medicine in which so much literature has accumulated during the last seven decades. Every attempt has been made to compare the present findings with those of other observers, and any omissions in this respect is not due to negligence.

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TABLE OF CONTENTS.

Part 2.

Section 1.

Section 2.

APPENDIX

I N T R O D U C T I O N

1. Purpose of Investigation.
2. Materials for Investigation.
3. Methods of Investigation.

CHAPTER 1

PURPOSE OF INVESTIGATION

In no other branch of medicine there exists as many controversial theories and findings as in toxaemias of pregnancy. Even the very name for the condition has not been accepted unanimously. Pre-eclampsia, eclampsia, non-convulsive eclampsia, albuminuria of pregnancy, hypertensive toxaemia of pregnancy, and gestoses of the German authors all apparently refer to the same disease and merely express the uncertainty with which the condition is looked upon. As recently as 1941 De Lee (1) referring to the name "toxaemias of pregnancy" states that we have "become reconciled to its use as merely a name for a condition we do not understand".

However, the term "toxaemias of pregnancy" is generally used to designate a symptom complex, characterised by hypertension, albuminuria, oedema, and occasionally vomiting, headache and epigastric pain, affecting women during gestation. The condition sometimes undergoes spontaneous recovery after the termination of pregnancy, but not infrequently terminates in coma, convulsions or uterine haemorrhage. The clinical features often vary, but the principal characteristic is that the condition has never been known to occur at any time other than during pregnancy and in early puerperium. The obvious drawback of the nomenclature employed for this condition lies in the fact/

fact that it not only pre-supposes the existance of a toxin as the cause of the disease, but also conditions like essential hypertension and nephritis, which are but associated ailments in pregnancy have until recently been included in the same category. In 1937 the American Committee on maternal health appointed a commission to determine an acceptable classification for pregnancy toxaemias. The classification proposed by the Committee in 1939 (Mussey et al, 2, 1940) is elaborate but unfortunately still retains hypertensive and renal disease under "toxaemias" and yet fails to consider acute yellow atrophy as a separate entity. It is evident that even the present classification and conception of toxaemias is not entirely free from confusion. Nevertheless, it is difficult to see how this can be avoided until the nature of true toxaemias - pre-eclampsia and eclampsia - is properly understood. Indeed an author as recently as 1940 states that the term toxaemia of pregnancy has only served and still serves as a "diagnostic waste-basket" to cloak ignorance.

The disease was known in ancient times. Reference to a group of symptoms which would be known in the present days as manifestations of pregnancy toxaemias is found in the writings of Hippocrates and Galen. The very name eclampsia (GREEK λαμπω= flash) bears proof of it. But while the symptoms were well known and fairly well described, the cause for the condition, believed to be a retention of/

of various "humours" in the body has long been abandoned. A proper description of pregnancy toxaemias does not appear till the end of the seventeenth century, when Mauriceau (3, 1694) first provided an elaborate picture of the disease, to which only little can be added even to this day. But even in Mauriceau's time the belief of "corrupt humours" still persisted. The middle of the eighteenth century reveals an interesting observation on the aetiology of the condition in Burton's "New System of Midwifery" (London, 1751). This author claimed that the underlying causes were the stoppage of "menstrual flux" and the "bulk of the foetus, secondines and water"; the former caused "too great a distension of blood vessels" and the latter exerted an undue pressure on the abdominal viscera. It is interesting to note the similarity which exists between the comparatively modern Paramore's (4, 1932) theory of increased intra-abdominal pressure and the idea suggested by Burton nearly two centuries ago. It is even more interesting to compare Smith and Smith's (5, 1946) very recent theory of "menstrual" toxic eu-globulin being the cause of hypertension in toxaemias and the belief held by this ancient author.

The first suggestion of a state of altered composition of blood in toxaemias of pregnancy was made by Hamilton in his "Treatise of Midwifery" (Edinburgh, 1871) who believed that a state of hydraemic plethora was responsible for/

for the clinical symptoms. This author was the first to observe that a state of disturbed function of the "abdominal viscera", caused by "interruption of circulation" was the determining factor in exciting "nervous energy" responsible for convulsions. It is not difficult to see the resemblance of this idea to the theory of water retention suggested by Zangemiester (6, 1915) and that of the disturbed hepatic and renal functions which have been shown to exist in toxaemias by investigators of modern times.

The first suggestion of a toxaemic process being at work in this condition comes from John Burns of Glasgow (Principle of Midwifery, London, 1811) in the early part of the nineteenth century. He describes the disease as a "febrile state" and the fits of eclampsia as "a regular paroxysm of ague", and suggests that the origin is from "an incorrect state of the bowels". It is of great interest to see a century and a quarter after Burns, how this author went at length to devise means in order to prevent "fatal oppression of the brain or extravassation of blood within the skull", so that the "convulsion is mitigated". Throughout the nineteenth century there was little change in the idea as to the cause of pregnancy toxaemias. Over 50 years ago Jaggard is stated (de Lee, 1a. 1940) to have described toxaemia as a condition in which "the blood poisoned with excrementitous matters irritated the vascular centres and caused a sudden spasm of/

of the blood vessels of the kidney and brain". During the last half-a-century little has been added to our knowledge about the nature of pregnancy toxaemias, for only recently at the Ciba Foundation Symposium of toxaemia an eminent authority declared that pre-eclampsia and eclampsia are manifestations of a toxin in the circulation the nature of which is yet unidentified.

The story of the search for the cause of toxaemias of pregnancy is only one of contradictions and inconclusive evidences. A study of the physiology of pregnancy indicates that normal gestation is attended with considerable alteration of the normal metabolic functions of the body. From early days of investigation workers have looked for an explanation of clinical manifestations of the disease in the disturbed metabolic activities. This has been studied from every possible aspect during the last half a century. In fact, there is hardly a subject connected with toxaemias of pregnancy which has not already been investigated and there is scarcely a theory which has not been suggested in the past. But when the literature is carefully scrutinised an investigator invariably faces bewilderment at the contradictions in both the findings and their interpretations. Most of the earlier investigations were based on the study of a comparatively small number of cases. More recent observations are comparatively free from this criticism, but the discrepancies still exist in every direction.

Bunker and Mundell (10, 1924) observed that, if there is a retention of nitrogen in the blood in a case of toxaemia it suggests that nephritis is the predominant factor. Greenhill (11, 1943) in discussing this paper endorsed the statement from his experience in 50 cases of pre-eclampsia. Stander and co-workers (12, 1925) also found that the non-protein nitrogen level in toxaemia is within normal limits. On the other hand, Fahr and Williams (13, 1914) found evidence of nitrogenous retention in the blood of patients suffering from pregnancy toxaemia, and especially eclampsia. De-Wesselow and Wyatt (3, 1924), Bokelman (14, 1925), Hellmuth (15, 1923) and Cowe (16, 1930-31) arrived at similar conclusions. Obviously most of these observers failed to take the functional state of the kidneys and oliguria into consideration in evaluating the results. The literature on toxaemias of pregnancy is replete with terms like "renal insufficiency" and "renal derangement" apparently without sufficient significance. Yet, to understand the mechanism of true pregnancy toxaemias the functional status of the kidneys must be properly known.

Plasma protein concentration has been known to fall in pregnancy, toxaemia being associated with an ever further decrease of this component of the blood. Up to this point there is general agreement in the findings of different observers on the subject, but when one analyses the values

of the individual fractions one is faced with another field of controversy. Thus, the albumin: globulin ratio has been given variously as between 1.3 (Harden, 9, 1936) and 1.0 (Dieckmann, 7, 1934) by different investigators. Most observers agree that the globulin content remains unaltered or actually shows a compensatory increase, yet, Moller-Christensen (17, 1946) concludes from a recent elaborate study that serum globulin is actually diminished instead of increased as reported by other authors". Fibrinogen has been reported by Dieckmann (7a, 1929) to be increased in pregnancy toxaemias up to as much as 1.0 gms. in some cases, while Goetzee and Marrack's (13, 1924) report to the Royal Society of Medicine indicate that in most cases of toxaemia fibrinogen content of the plasma falls below normal.

The same state of confusion exists with regard to carbohydrate metabolism. To give only an instance, Titus (19, 1923), Siedentopf (20, 1933), and some other investigators observed that hypoglycaemia was the cause of eclamptic convulsions; Benthin (21, 1922), and Stander, Duncan and Sisson (12, 1925) on the other hand found that eclampsia was associated with hyperglycaemia. Again, Mays and McCord (22, 1935) after a detailed investigation stated that the blood sugar level and eclamptic convulsions were entirely unrelated.

Studies in fat metabolism, mineral equilibrium and acid-/

acid-base balance are similarly beset with contradictory and inconclusive statements.

There is a general agreement in the belief that toxaemia of pregnancy is associated with a disturbed state of metabolism, but very little is known so far as to how the disturbance in metabolism is brought about. The metabolism in normal pregnancy is different from that in non-pregnant persons. Pre-eclampsia and eclampsia are diseases characteristic of the pregnant state. The metabolic status in toxaemia can be understood only if they are studied in correlation with that of normal pregnancy. Isolated biochemical data obtained from a mixed group of patients, included, until recent years, under the common name of pregnancy toxaemia, are of considerable value in obtaining a panoramic view of the changes which occur in this condition. The difficulty in interpreting these data however lies in the fact that (1) Most series of cases make only a meagre distinction between true pre-eclampsia, and nephritis and essential hypertension complicating pregnancy; and (2) Hardly any attempt has been made to make a follow up study of the metabolic and the biochemical changes in relation to the nature and the course of the toxaemic condition. As a result of this it becomes very difficult for a student desirous of understanding the subject to determine the exact relationship existing between the clinical state of toxaemia and the disordered metabolism which/

which accompanies it. It was therefore felt that in investigation designed to overcome these difficulites may provide useful information and help in a better understanding of the nature of the toxaemia of pregnancy.

The present investigation has the following objects in view.

1. To study the general changes in the metabolism and the alteration of functions of particular organs with the hope of resolving some of the contradictory statements found in the literature on these subjects, and with a view to ascertain to what extent these changes are brought about by the toxaemic process per se.
2. To study the functional status of the liver in relation to the metabolic changes observed in toxaemia of pregnancy.
3. To determine the extent to which the vascular spasm in toxaemia is related to these changes.

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CHAPTER 2.

MATERIALS FOR INVESTIGATION

Most of the investigations on toxaemias of pregnancy appears to have been done on a heterogenous group of cases consisting of true pre-eclampsia essential hypertension and even some cases of nephritis. We felt that in order to be able to understand the nature of true pregnancy toxaemias cases must be selected in such a manner that all conditions which simulate pre-eclampsia but are caused by associated or intercurrent ailments must be eliminated from the series. This entailed a careful preliminary examination and a thorough search into past and personal history in every patient selected for this study. As a result, we had to abandon every patient where any doubt existed about the clinical condition.

No patient with a previous history of hypertension or where hypertension persisted after child birth has been included in our study. A case of essential hypertension developing symptoms which simulate pre-eclampsia is by no means infrequent. Not knowing to what extent essential hypertension per se, superimposed on pregnancy would bring about changes in the functions of the organs, we considered it best to keep these cases separate for a comparative study. Results obtained in a small number

of these cases are presented where relevant or interesting findings were observed.

Every effort was made to eliminate from this study cases of nephritis complicating pregnancy. Urea concentration, urea clearance and microscopic examination of the urine supplemented a careful inquiry into the history of every case, besides a post-natal examination in any patient where there has been reasons for doubt. Nephritis is by no means a common disease and our rather rigorous scrutiny left us with a small number of cases of true nephritis and pregnancy which will be presented in appropriate sections where comparison of values proved interesting.

On the same principle cases of accidental haemorrhage were eliminated from this series. Indeed, in most cases of accidental haemorrhage there is an associated toxaemia, but the onset of haemorrhage often adds the additional feature of shock. In course of our study however we came across a few cases of accidental haemorrhage who were considered interesting from a clinical point of view. We shall describe the findings in these cases where comparison with true toxaemias showed interesting deviations.

Our principal series consists only of cases of pre-eclampsia and eclampsia. No case of eclampsia which we/

we have not been able to follow up has been included for this study. This explains a comparatively small series of eclampsia which we have presented in this communication. Eclamptic patients were examined in the convulsive stage as often as feasible and on the first, second, fifth, twelfth and twenty-second day of convalescence.

Every case of pre-eclampsia was subjected to an investigation on the day of admission. Subsequent results showed that some of these cases were nephritis or essential hypertension. These were discarded. Cases of true pre-eclampsia were followed up every week until they were sufficiently improved to justify abandoning further investigations, or induced because of the severity of toxaemia or went into spontaneous labour. No patient who gave a doubtful previous history, or showed a maximum urea concentration of less than 2.5 per cent. or a urea clearance value of less than 90 per cent. was accepted for study. This explains why our series is not any larger.

The cases presented for this study were distributed as follows:-

1. Pre-eclampsia *- (a) 100 cases were studied and followed up for routine biochemical study.

(b) 15 studies were made on the effects of cholesterol finding.

(c)/

(c) 28 studies were done on the glycogen reserve capacity of the liver.

(d) 38 patients were tested for galactose tolerence capacity.

(e) 30 patients were examined in order to study the alkali reserve of the plasma and the state of compensation of the acidosis which has been reported to exist in toxaemias of pregnancy.

(f) Hepatic function as determined by bilirubin excretion test, estimation of plasma alkaline phosphatase, thymol turbidity and prothrombin response to Vitamin K was determined in 100 cases.

(g) In 27 patients an attempt was made to study the nature of hypertension in toxaemias of pregnancy.

2. Eclampsia - The series consisted of 13 cases. In general the system adopted was the same as for pre-eclampsia. The number of cases employed for individual items of investigation for obvious reasons varied in different instances. These will be detailed in their respective sections.

3. Comparative study of 5 cases of nephritis complicating pregnancy and 15 each of essential hypertension and accidental haemorrhage are presented where relevant findings have been observed.

4. Normal Pregnancy - Adequate control is necessary for all investigations. Elaborate studies in normal pregnancy have already been done by several investigators. But in order to avoid any change in metabolism, etc., which may occur due to different climatic, dietetic and environmental conditions, a control study in normal pregnancy was considered essential. Our normal cases consisted of 78 cases obtained from the antenatal clinic of the Glasgow Royal Maternity and Women's Hospital. These belonged to different periods of gestation. Thirty-none cases, however, were in the last trimester of pregnancy. The second series of normal cases consisted of 15 patients. These were selected in the early months of gestation and followed through pregnancy up to term. Examinations were done once a month. "Month" in all our subsequent descriptions refers to a lunar month or 4 weeks. The data obtained from our normal cases have at each stage been compared with most of the available data in the literature, and have been adhered to for the purpose of comparison with the results obtained in pregnancy toxaemias. The reason for this has already been described.

* In all our subsequent descriptions the terms "pregnancy toxaemia" and "toxaemia of pregnancy" refer only to true pre-eclampsia and eclampsia, other toxaemias will be mentioned specifically when so indicated.

CHAPTER 3

PROCEDURE OF INVESTIGATION

The details of the methods employed in this investigation are given in the appendix. The principles only will be discussed here.

Our investigation starts with a study of metabolism in toxaemias of pregnancy. Basal metabolic studies in terms of caloric output or respiratory quotient were not undertaken. We confined ourselves to a study of the methods whereby the essential elements, viz. protein, fat and carbohydrates are dealt with by the body in pregnancy toxaemias and in what respects they show deviation from normality.

1. Protein metabolism was studied in regard to -
    1. Nitrogen balance in a small limited number of cases and the manner in which it is affected by diets of varying protein content and the severity of the disease.
    2. Plasma protein concentration and maintenance.
    3. Urea synthesis and its relation to the amino acid content of the plasma in different stages of the disease.
2. Carbohydrate metabolism was studied with regard to -
    1. Blood sugar level and the course of toxaemias.
    2. The capacity for glucose mobilisation of the body/

body under the influence of adrenalin, with the object of trying to assess how much and in what way toxaemia might interfere with glocogen storage and mobilisation.

3. The capacity for glycogen storage under the influence of insulin after temporary induction of hyperglycaemia with intravenous injections of glucose.

3. Fat metabolism was studied with respect to -

1. Levels of plasma cholesterol in relation to the clinical course of toxaemia.
2. The ratio between total and ester cholesterol with a view to ascertain if the process of esterification was interfered with in any way.
3. The effect of ingestion of a moderate amount of cholesterol in order to observe if esterification at high levels of plasma cholesterol was of the same nature in toxaemias as in normal pregnancy.
4. Levels of phospholipids of the plasma in relation to the clinical course of the disease.

The next part of our investigation deals with some hepatic function tests. The tests are employed for this purpose consisted of -

1. Bilirubin excretion test.
2. Estimation of plasma alkaline phosphatase.
3. Thymol turbidity test.

4./

4. Galactose tolerence test.

and 5. Plasma prothrombin concentration and its response to Vitamin K.

Bromsulphalein test was not employed as it was considered that the excretory function of the liver could be estimated to an almost equal degree by the bilirubin excretion test. Moreover, it has the advantage of employing a substance which is a product of normal metabolism in the liver. The results of these hepatic functions were finally correlated with the results obtained from metabolic studies described above. As the liver constitutes the hub of the metabolic processes in the body it was considered that a comparison of results of both metabolic and functional efficiency tests might prove interesting.

The next part of the thesis consists of a clinical study of the nature of hypertension in toxaemia of pregnancy. The study is based on an analysis of the systolic and diastolic blood pressure readings in 430 cases of normal pregnancy and 346 cases of hypertensive toxaemia of pregnancy. The study is aimed at a clinical evaluation of the relationship of systolic and diastolic blood pressures and determination of the nature of compensation of the vascular spasm which is believed to exist in toxaemia of pregnancy. In an attempt to understand the mechanism involved in this vascular spasm tetraethylene ammonium bromine was injected intravenously in 27 cases of toxaemia in/

in order to remove the sympathetic influence. The results of these preliminary investigations of hypertension provided certain useful data, which are recorded.

PART I

STUDIES IN GENERAL METABOLISM

1. Protein Metabolism.
2. Carbohydrate Metabolism.
3. Fat Metabolism.

PART 1

STUDIES IN GENERAL METABOLISM

1. Protein Metabolism.
2. Carbohydrate Metabolism.
3. Fat Metabolism.

SECTION 1

PROTEIN METABOLISM

CHAPTER 1

NITROGEN BALANCE IN TOXAEMIAS OF PREGNANCY

Prior to 1930 the diet in toxaemias of pregnancy contained the minimal amount of proteins, especially those of animal origin. In recent years the attitude seems to have altered somewhat and it is now customary with many obstetricians to provide a diet rich in protein and especially proteins of first quality. This change in opinion has been caused by several interesting observations.

1. Continual loss of protein in the urine. The immediate effect of albuminuria is a fall in the protein concentration of the plasma, particularly that of albumin. Investigations (1, 2, 3, 4, 5) have shown that with an adequate protein intake regeneration of the proteins takes place fairly rapidly unless drainage on the plasma is constantly maintained over a period of time.

2. Several observers (6, 7, 8, 9, 10, 11) have demonstrated that protein starvation causes depletion of plasma protein, again mostly affecting plasma albumin, which can be restored only when the protein intake is increased (7, 11, 12, 13), either in the diet or by injection/

injection of protein hydrolysates (14).

3. It has been shown by numerous investigators (15, 16, 17, 18) that there is a fall of plasma proteins, especially of albumin in pregnancy toxaemia. It has also been suggested (19, 20) that the decrease in the plasma protein concentration is the cause of oedema, which is an important manifestation of toxaemia of pregnancy. Moreover, Harden (21, 21a) (1936, 1938) and Strauss (19, 1938) demonstrated that the manifestations of toxaemia of pregnancy could be alleviated if not cured with a diet adequately rich in protein.

4. The reports of investigations carried out by the Peoples League of Health (22, 1942) and the Toronto Experiment conducted by Ebbs, Tisdall and Scott (23, 1941) indicated that the incidence of toxaemia in expectant mothers can be reduced by about 4.6 per cent. on the over-all figures by instituting a regime of well-balanced diet adequately rich in protein, minerals and vitamins.

Thus, in recent years a good case has been constructed for advocating a high protein intake in toxaemias of pregnancy, if necessary by parenteral routes of administration. In fact, some investigators make an implicit suggestion that the cause of toxaemia may be linked with a dietetic protein deficiency. The basis of these conclusions however, is slender.

Sufficient/

Sufficient number of observations are on record to show that a state of positive nitrogen balance exists in normal pregnancy in order to provide for the growth of the foetus, placenta and uterus, the development of breasts, and the building of the reserve required for the purpose of lactation (24, 25, 26, 27). Unfortunately however equivalent data on toxaemia of pregnancy are comparatively meagre. The studies of Dodge and Frost (17, 1938) and Harden (21) show that patients with toxaemias of pregnancy suffer a negative nitrogen balance. But the difficulty in interpreting the values obtained by these authors lies in the fact that cases selected for study do not seem to have been selected with sufficient care in order to eliminate those which simulate pre-eclampsia. Further, correction for extra-metabolic nitrogen due to loss of oedema fluid does not appear to have been made before final results were calculated. As a result the exact state of nitrogen catabolism in true pregnancy toxaemias can be obtained only with difficulty from the data provided by these authors. Before toxaemias of pregnancy can be linked with a state of protein deficiency the nature of nitrogen equilibrium and the degree of negative balance should be known.

With this object in view we studied the nitrogen balance of three cases of true pregnancy toxaemia of almost/

almost equal severity in relation to the effects produced at different levels of protein consumption. In each case the investigation spread over a period of 14 days. The basal condition was studied during the first week by providing all of them with a uniform diet containing only a moderate amount of protein. During the second week the protein intake was raised in one patient, lowered in another, and maintained at the original level in the third case. The metabolic studies extended over a period of one week for each investigation, for it has been shown by Sontag and Potgieter (28, 1933) that unless a constant level of nitrogen intake is maintained for a minimum period of 3 days the variable factor of nitrogen excretion in the urine (especially if the diet consumed previously is of a different nitrogen content) interferes with the reliability of nitrogen balance studies. The diet employed for the purpose of this investigation was selected with the help of the dietician at the Glasgow Royal Maternity and Women's Hospital and the nitrogen intake was calculated from the protein values supplied by McCance and Widdowson (29, 1947).

Urine was collected in the wards as 24-hour specimens with toluene as preservative. All measurements and estimations were done in the laboratory. Faeces were similarly collected in weighed sealed pans containing

a/

a small quantity of strong sulphuric acid. From the time of collection up to the moment of estimation these specimens were kept in a refrigerator. The weight of the patients were taken every day at the same hour. In each instance the weight given for a certain day is that recorded in the next morning so that it indicated the change which took place during the preceding day of the balance study.

The methods of estimation have been described in the appendix. The total urinary nitrogen was estimated by Folin-Farmer micro-Kjeldahl method, a blank and a standard being put through at the same time with each test. The non-protein nitrogen in the urine was estimated by precipitating the protein with 10 per cent. trichloracetic acid and estimating the nitrogen in an aliquot part of the filtrate. The protein nitrogen in the urine was estimated from the difference. Faecal nitrogen was estimated by digestion with sulphuric acid aided by potassium persulphate, as suggested by Wong (30, 1923) and subsequent aeration and titration. During the period of investigation none of the patients received drugs containing nitrogen.

REPORT OF CASES

CASE 1

Mrs. Campbell, primigravida; age 30; duration of gestation 30 weeks; previous history revealed nothing of importance; health during pregnancy satisfactory until 1 week before admission, when she noticed some oedema of ankles. Two days later she developed frontal headache which was persistent. There was some oliguria for 12 days before she was admitted into the hospital on 3.6.48.

On admission: General nourishment satisfactory. There was appreciable oedema of the feet and legs. Colour, pulse and respiration were normal. General examination failed to detect any abnormality, except the blood pressure, which was raised to 160/110 m.m.Hg. Urine contained ++ albumin. The uterus was of the size of 30 weeks gestation; there was no obstetric abnormality. Urea clearance, 102.4 per cent. Plasma proteins, 5.90 gms. Blood urea, 23.8 mgms., Uric acid 4.1 mgms. Creatinine 1.21 mgms. and total blood N.P.N. 36.3 mgms. per 100 ml. Urine, sp.gr.1013, Albumin - 8.5 parts (Esbach), hyaline casts. No other abnormality was detected.

On 4.6.48 the patient was put on a diet consisting of 88.85 gms. of protein (of which 60.85 gms. were of animal origin), 295.4 gms. of carbohydrate and 73.7 gms. of/

of fat, yeilding a total caloric value of 2,202. The nitrogen balance study commenced on 7.6.43.

RESULTS

1. Control Period.

Table 1.

Date	Wt. K.G.	Cal-ories	N-intake			N-output			N-Bal-ance	Plas-ma NPN.	B.P.
			Total	Fae-ces	Net	Total	Pr. N.	NPN.			
7.6.43	72.5	2,202	14.20	1.71	12.49	13.72	1.71	12.01	-1.23	36.3	160/100
8.6.43	72.0	"	"	2.13	12.02	13.14	1.68	11.46	-1.12	36.0	160/100
9.6.43	70.7	"	"	1.33	12.37	13.91	1.41	12.50	-1.54	31.7	160/100
10.6.43	69.6	"	"	1.41	12.79	13.31	1.16	12.15	-0.52	30.0	155/100
11.6.43	69.0	"	"	2.0	12.20	12.72	1.16	11.56	-0.52	29.7	150/98
12.6.43	68.5	"	"	2.11	12.09	12.08	0.90	11.18	+0.01	28.0	150/98
13.6.43	68.3	"	"	2.10	12.10	13.34	0.91	12.43	-1.24	28.0	152/98
Loss In Weight = 4.2 KG.			99.40	12.84	86.56	92.22	3.93	83.29	Aver. daily balance = -0.66 gms. N.		

The above table indicates that during the period of study the net nitrogen-intake was 86.56 gms. The total nitrogen-output during the same period was 92.22 gms., and thus over a period of one week there was a nitrogen deficit of 4.66 gms. equivalent to 29.125 gms. of protein. However, the protein catabolism of the body, is expressed only by the output of metabolic non-protein nitrogen. In this case, this amounted to 83.29 gms. From this must be deducted the extra metabolic nitrogen which has been/

been lost from the body due to loss of oedema fluid and consequent loss of weight (31). Non-protein nitrogen is equally distributed between blood and tissues, the aqueous medium in either case being the solvent. This was assumed by Peters and Bulger (31, 1926) and confirmed by Butt, Snell and Keys (32, 1939) and by our own observations. The former authors state that under normal circumstances 70 per cent. of the body weight is composed of water, the concentration of water in the oedema fluid is at least 90 per cent. The loss in weight in a case of toxaemia of pregnancy in basal conditions is obviously due to the loss of the oedema fluid. In the present case the reduction in weight was 4.2 KGms. But this does not represent the net loss in weight for during a week between 28 and 32 weeks of gestation the foetus puts on 5 ounces (0.14 KG) (33). The actual loss in weight therefore, was (4.2+ 0.14) or 4.34 KGms. When this is taken into consideration along with the change in the plasma non-protein nitrogen level during the corresponding period, the amount of extra metabolic nitrogen can be calculated from the formula -

"Extrametabolic loss of nitrogen = 70 per cent. of the final weight X the change in non-protein nitrogen, plus, 90 per cent. of the change in weight X the initial non-protein nitrogen".

The actual calculation has been elaborately explained

by/

by Peters and Bulger (31, 1926) and is therefore omitted.

Applying this formula to our case the extra-metabolic loss of non-protein nitrogen amounts to

(0.7 X 68.3 X 0.073) + (0.9 X 4.34 X 0.363)

= 3.49 + 1.42 = 4.91 gms.

In other words, of the total non-protein nitrogen excretion of 82.29 gms. 4.91 gms. were due to the loss of nitrogen of extra metabolic origin (loss of oedema fluid). Therefore, the amount of nitrogen "catabolised" in the body equals 83.29 - 4.91, or, 78.38 gms. during the period of study. If to this is added the amount of nitrogen excreted in the urine as protein, we obtain the value which represents the net amount of nitrogen lost from the body during the period of observation. This equals 87.31 gms. of nitrogen. Compared with the net intake 86.06 gms. a negative balance of 1.25 gms. of nitrogen over a period of 7 days or 0.18 gms. of nitrogen daily is obtained. This represents the combined effect of protein catabolism and loss of protein in the urine on the assimated protein. It has been pointed out already that the total protein catabolism for the period of study is 78.38 gms. Therefore, if proteinuria did not exist the balance of nitrogen [(net nitrogen intake) - 78.38 (metabolic nitrogen/

nitrogen output] = 7.68 gms. of storage for whole period, or a positive balance of 1.10 gms. of nitrogen daily. This represents the actual state of equilibrium which exists between the net nitrogen consumption and total nitrogen catabolism in the case of pregnancy toxaemia studied above. If the state of nitrogen metabolism in pre-eclampsia is to be compared with normal pregnancy this constitutes an important point of comparison. For the study of only the total nitrogen output is likely to give an erroneous impression of the actual state of metabolism which exists in the body.

2. Period of Increased Protein Intake.

During the subsequent period of study the protein intake was increased from 65 to 108.5 gms. daily of which 93.2 gms. were first class proteins, with 179.25 gms. of carbohydrate and 90.6 gms. of fat. The total caloric yield of the diet was 1,971. The patient was put on this diet on 14.6.48 but in order to avoid the lag of nitrogen excretion the metabolic study did not commence till three days later. The following table provides the data (Table 2).

As a result of increasing the daily nitrogen intake by 3.16 gms. the gross daily balance changed from -0.65 to +0.49. In other words an active nitrogen retention of 1.14 gms. daily was obtained. The loss

of/

of weight during this period was 2.7 K.Gm. Taking the increase in weight of the baby during the period of investigation into account, the net loss of weight of the mother was 2.7 + 0.14 = 2.84KG. The loss of

Table 2

Date	Wt. KG.	Cal-ories	N-intake			N-output			N-Bal-ance	Plas-ma N.P.N.	B.P.
			Total	Faeces	Net	Total	Pr. N.	N.P.N.			
17.6.48	67.5	1,971	17.36	2.12	15.24	14.41	0.97	13.44	+0.83	29.4	155/98
18.6.48	67.0	"	"	2.04	15.32	14.10	0.94	13.16	+1.22	29.4	155/90
19.6.48	66.4	"	"	1.87	15.49	15.48	0.90	14.58	+0.01	30.1	155/90
20.6.48	66.0	"	"	2.09	15.27	14.65	0.90	13.75	+0.62	29.3	155/90
21.6.48	66.1	"	"	2.18	15.18	15.07	0.85	14.22	+0.11	27.6	155/90
22.6.48	65.3	"	"	1.91	15.45	15.39	0.70	14.69	+0.06	27.0	150/92
23.6.48	64.8	"	"	2.10	15.26	14.77	0.72	14.05	+0.49	26.3	150/90
Loss in Weight = 2.7 KG.			121.52	14.31	107.21	103.77	5.98	97.79	Average daily balance -0.49 gms N		

extrametabolic nitrogen during the same period amounted to (0.7 X 64.8 X 0.031) + (0.9 X 2.84 X 0.294) or 2.16 gms. Therefore, the total quantity of nitrogen catabolised in the body during the days of investigation was (97.79 - 2.16) or 95.62 gms., but the total nitrogen lost from the body, including that due to proteinuria was (103.77 - 2.16) = 101.61 gms. This, compared with the net assimilated nitrogen shows a balance of (107.21/

(107.21 - 101.61) or +5.60 gms., for a period of seven days or a daily positive balance of +0.80 gms. In other words, compared with the control period, an increase of daily nitrogen intake by 3.10 gms. improved the nitrogen balance by only (0.80 - (-0.18) or 0.98 gms.

If however, albuminuria were absent, the daily nitrogen balance during the period of increased protein intake would have been ($\overline{107.21 - 95.63}$ ÷ 7) or 1.65 gms. This compared with the control period shows gain of only 0.55 gms. It is of interest to note that the increase of assimilated nitrogen by 21.15 gms. during the period of study caused an increase in nitrogen catabolism by 17.25 gms. In the first week of study 91.1 per cent. of the assimilated nitrogen was catabolised in the body, during the second period of study when the protein intake was increased by 3.16 gms. daily the catabolic nitrogen amounted to 89.1 per cent. This indicates that only 18.5 per cent. of the net rise in assimilated nitrogen during the period of increased protein intake was used for the purpose of anabolism and storage. Moreover, a high protein diet did not in any way affect the rate of protein catabolism in the body.

The plasma proteins during the period of study were -

1./

1. At the beginning of the first period 5.90 gms. per 100 ml.
2. At the end of the first period 5.93 gms. per 100 ml.
3. At the beginning of the second period 5.94 gms. per 100 ml.
4. At the end of the second period 5.95 gms. per 100 ml.

CASE 2

Mrs. Donaldson, primigravida; age 30; duration of gestation 30 weeks. Admitted to hospital on 22.11.48 with oedema and headache. Previous and personal history revealed nothing of importance. For 8 days before admission the patient had swelling of the ankles which increased considerably during the 72 hours before admission. There was also a history of oliguria for 5 days before the oedema was noticed.

On examination general health was found satisfactory with no evidence of organic disease. Blood pressure on admission was 170/110, urine contained 8 parts of albumin, and oedema was present at the ankles and lower part of the legs. The uterus was of the size of a 30 weeks pregnancy and examination revealed no obstetric abnormality. Haemoglobin was 78 per cent. Urine sp.gr.1012. Albumin++ no other abnormality was detected. Microscopically it showed a few hyaline casts and white blood corpuscles. Urea clearance 109.6 per cent. Plasma proteins - 5.56 gms. Blood urea 17.5 mgms. per cent. N.P.N. 29mgms. per cent.

RESULTS/

RESULTS

1. Control Period

The patient was put on the diet already described (case 1, control period). The total nitrogen yeild of the diet was 14.20 gms. daily. The nitrogen balance study commenced on 24.11.48. The results obtained are given in Table 3.

Table 3

Date	Wt. KG.	Cal-ories	N-intake			N-output			N-Bal-ance	Plas-ma N.P.N.	B.P.
			Total	Fae-ces	Net	Total	Pr. N.	N.P.N.			
24.11.48	69.6	2,202	14.20	1.81	12.39	13.17	1.44	11.73	-0.78	29.7	165/100
25.11.48	69.5	"	"	1.79	12.41	13.37	1.47	11.90	-0.96	29.5	165/100
26.11.48	69.5	"	"	1.78	12.42	12.42	1.40	11.02	0	29.0	165/98
27.11.48	69.5	"	"	1.93	12.27	12.67	1.36	11.31	-0.40	30.1	168/100
28.11.48	69.1	"	"	2.10	12.10	12.09	1.30	10.79	+0.01	31.0	160/100
29.11.48	69.0	"	"	2.22	11.98	12.35	1.28	11.07	-0.37	31.4	160/100
30.11.48	69.0	"	"	1.94	12.26	12.38	1.28	11.10	-0.12	31.8	160/98
Loss in Weight = 0.6 KG.			99.40	13.57	85.83	88.45	9.53	78.92	Aver. daily balance = -0.52gmsN		

During this period of study there was an output of 88.45 gms. of nitrogen against a net intake of 85.83, giving a negative balance of 3.62 gms. of nitrogen for a period of 7 days or 0.517 gms. daily.

The loss in body weight for the same period was 0.6KGm. But taking the increase of the weight of the baby/

baby into consideration the net loss in weight was 0.6+ 0.14 = 0.74 gms. The extra metabolic loss of nitrogen during this period was (0.7 X 69.0 X 0.021)+ (0.9 X 0.74 X 0.297) or 1.17 gms. The amount of nitrogen catabolised in the body during the whole period, was therefore 78.92 - 1.17 = 77.75 gms. Thus, the amount of nitrogen available for storage was 85.83 - 77.75 or 8.08 gms. for the week, or 1.15 gms. daily. The corresponding figure in our first case was 1.10 gms. However, during the period of study 9.53 gms. of nitrogen was lost from the body as protein in the urine. The net loss of nitrogen thus amounted to 77.75+ 9.53 = 87.28 gms. This, against the net assimilated nitrogen leaves a negative balance of 1.45 gms. or 0.21 gms. daily. The protein loss in the present case was more than that in the first one, and consequently inspite of a slightly lower level of nitrogen catabolism the balance of nitrogen in the body was affected more adversely in the second patient.

2. Period of Diminished Protein Intake.

On 30.11.48 the patient was put on a diet consisting of 75.05 gms. of protein (43.2 gms. first class protein), 382.65 gms. of carbohydrate, and 68.1 gms. of fat and having a total caloric yield of 2,444. The mineral and vitamin contents were as far as possible kept identical.

The/

The metabolic study commenced on 3.12.48. The results are given in Table 4.

Table 4

Date	Wt. KG.	Calories	N-intake			N-output			N-Balance	Plasma N.P.N.	B.P.
			Total	Faeces	Net	Total	Pr. N.	N.P.N.			
3.12.48	69.1	2,444	12.0	1.40	10.60	11.30	1.26	10.04	-0.70	31.5	160/100
4.12.48	69.0	"	"	1.38	10.62	11.42	1.21	10.21	-0.80	31.0	160/95
5.12.48	69.0	"	"	1.44	10.56	11.44	1.14	10.30	-0.88	30.7	155/95
6.12.48	68.8	"	"	1.92	10.08	11.19	1.10	10.09	-1.11	30.6	150/95
7.12.48	68.4	"	"	1.57	10.43	11.67	0.93	10.74	-1.24	30.5	150/95
8.12.48	68.7	"	"	1.46	10.54	11.50	0.90	10.60	-0.96	29.3	150/90
9.12.48	68.1	"	"	1.71	10.29	11.31	0.82	10.49	-1.02	29.1	150/90
Loss in Weight = 1.0 KG.			84.0	10.83	73.12	79.83	7.36	72.47	Aver. daily balance = -0.945gms.N.		

During the second period of study the amount of nitrogen assimilated was 73.12 gms. The total nitrogen output for the same period was 79.83 gms. Consequently there was a nitrogen deficity of 6.71 gms. in 7 days, or 0.945 gms. daily. Thus as a result of decreasing the daily nitrogen intake by 2.20 gms., the nitrogen loss from the body increased by 0.43 gms. This however includes nitrogen lost as protein in the urine, as well as the extrametabolic nitrogen excreted during the period of study.

The loss in weight during the period of investigation was/

was 1.0 KG. Taking the increase in the weight of the foetus into consideration the total loss of weight equals 1.14 KG. The plasma non-protein nitrogen during the same time diminished from 31.5 to 29.1 mgms. So, the extrametabolic non-protein nitrogen excreted in the urine during this period was (0.7 X 68.1 X 0.024) + (0.9 X 1.14 X 0.315) or 1.47 gms. Thus, the net amount of nitrogen catabolised in the body was (72.47-1.47) = 71.0 gms. Consequently the result of reduction of the daily protein intake by 2.20 gms., caused the daily nitrogen catabolism to be reduced by (77.75 - 7.10 ÷ 7) or 0.96 gms. This obviously represents the nitrogen economy which this patient with pregnancy toxaemia was capable of making under conditions of deficient protein intake. If there was no loss of protein in the urine this economy in nitrogen break-down would have been able to provide a storage of only (73.12 - 71.0) = 1.12 gms. for the whole period of study or 0.16 gms. a day. The protein loss in the urine during this period was only 7.36 gms. of nitrogen, which was appreciably less than that in the preceding week. But when this is taken into account, as one must, in order to ascertain the net balance, it follows that inspite of a net intake of 7,312 gms. of nitrogen, (71.0+7.36) or 78.36 gms. were lost from the body. Thus, as a result of a reduction of the protein consumption a negative balance was established/

established at (78.36 - 73.12 ÷ 7) or 0.75 gms. daily, i.e., the nitrogen deficit had increased by 0.54 gms. per day. [illegible]. It should be noted, however that this was not associated with a great deterioration of the clinical condition. The plasma-protein values during this investigation were as follows -

1. At the beginning of the first period - 5.58 gms. per 100 ml.
2. At the end of the first period - 5.58 gms. per 100 ml.
3. At the beginning of the second period - 5.56gms. per 100 ml.
4. At the end of the second period - 5.57 gms. per 100 ml.

CASE 3

Mrs. Lawson, age 32, second gravida, duration of gestation 32 weeks, was admitted on 28.9.48 with oedema of ankles and feet and marked diminution in the quantity of urine. Past history revealed nothing of importance. The previous pregnancy and labour were normal, 3 years ago.

General examination showed no evidence of organic disease. The patient was well-built and there was marked swelling of the feet and legs. The size of the uterus indicated a gestation of 32-33 weeks, B.P.170/110, urine contained 11 parts albumin (Esbach), haemoglobin - 72 per cent. Plasma proteins 5.60 gms. Urea 20.5 mgms. N.P.N. 30.0mgms. Urea clearance 99.8 per cent. Urea concentration 3.14 per cent. maximum. Urine sp.gr.1012; pus cells were present, no casts. No other abnormality was/

was detected.

This patient was kept on the control diet (= 14.20 gms. N.) for a period of two weeks, metabolic studies being undertaken at the end of each period. The object of this was to determine how the balance of nitrogen adjusted itself with the alteration of the clinical condition. The results of the first period of study are given in Table 5.

Table 5

Date	Wt. KG.	Calories	N-intake		N-output				N-Balance	Plasma N.P.N.	B.P.
			Total	Faeces	Net	Total	Pr. N.	N.P.N.			
1.10.48	70.8	2,202	14.20	1.44	12.76	13.14	1.54	11.60	-0.38	30.2	170/110
2.10.48	70.5	"	"	1.57	12.63	13.31	1.50	11.81	-0.68	30.0	170/108
3.10.48	70.1	"	"	1.77	12.43	13.30	1.48	11.82	-0.87	30.1	165/108
4.10.48	70.0	"	"	1.59	12.61	13.39	1.45	11.94	-0.78	30.2	165/105
5.10.48	70.0	"	"	1.81	12.39	12.97	1.40	11.57	-0.58	30.0	165/102
6.10.48	69.8	"	"	1.79	12.41	13.05	1.32	11.73	-0.64	30.0	165/102
7.10.48	69.0	"	"	1.70	12.50	12.94	1.30	11.64	-0.44	29.8	164/102
Loss in Weight = 1.8 KG.			99.40	11.67	87.73	92.10	9.99	82.11	Aver. daily balance = 0.63 gms. N.		

During the first week the total nitrogen assimilated by the patient was 87.73 gms. while the total loss from the body was 92.10 gms. Thus, an apparent negative nitrogen balance of 0.63 gms. a day was present. The loss of weight during this period was 2.8 KG. (Between thirty/

thirty-second and thirty-sixth weeks the foetus gains 70% (33) or 0.20 $\hat{KG.}^{+1.8}_{\wedge}$ = 2.0 KG.) During the same period the non-protein nitrogen of the plasma dropped from 30.2 to 29.8 mgms. Thus the extrametabolic nitrogen amounted to (0.7 X 69.0 X 0.004) + (0.9 X 2 X 0.302) or 0.74 gms., and by subtraction the nitrogen catabolised in the body was 81.37 gms. The assimilated nitrogen thus exceeded the catabolic nitrogen by 6.36 gms. for the whole period of study or 0.91 gms. daily. Including the loss of nitrogen as protein in the urine the total nitrogen loss however exceeded the net nitrogen intake by 3.62 gms., thus giving a daily negative balance of 0.52 gms. of nitrogen. During this period there was only slight improvement in the clinical symptoms.

The second period of study was conducted during the following week. The results are submitted in Table 6.

Table 6/

Table 6

Date	Wt. KG.	Cal-ories	N-intake			N-output			N-Bal-ance	Plas-ma N.P.N.	B.P.
			Total	Fæ-ces	Net	Total	Pr. N.	N.P.N.			
8.10.48	69.0	2202	14.20	1.63	12.57	12.89	1.30	11.59	-0.32	29.8	162/100
9.10.48	68.4	"	"	1.60	12.60	12.92	1.30	11.62	-0.32	29.7	160/100
10.10.48	68.3	"	"	1.49	12.71	12.67	1.23	11.44	+0.04	29.6	160/95
11.10.48	67.8	"	"	1.55	12.65	13.05	1.17	11.88	-0.40	29.0	155/95
12.10.48	67.5	"	"	1.43	12.77	12.94	1.04	11.90	-0.17	29.0	155/90
13.10.48	67.0	"	"	1.57	12.63	12.72	1.00	11.72	-0.09	28.4	150/92
14.10.48	67.0	"	"	1.51	12.69	12.54	0.97	11.57	+0.15	28.2	150/90
Loss in Weight = 2 KG.			99.40	10.78	88.62	88.73	8.01	81.72	Aver. daily balance=-0.016gms.N.		

It will appear from the above table that during the second period there was an improvement in the apparent nitrogen balance which was now -0.016 gms. nitrogen per day. In other words, without any change in the nitrogen intake the deficit was compensated by 0.504 gms. of nitrogen daily. The only notable change which did occur during this period was an improvement in the clinical condition. The albuminuria became less, the blood pressure came down and the oedema improved. The extra-metabolic nitrogen lost during this period amounted to (0.7 X67.0 X0.016) (0.9 X 2.20* X 0.298) or 1.34 gms. The amount of nitrogen catabolised was, therefore 81.72 - 1.34 = 80.38 gms.

* The gain in weight of the baby was added to the recorded loss in weight.

Thus,/

Thus, if albuminuria had been absent 88.62 - 80.38 or 8.24 gms. of nitrogen for the whole period or 1.18 gms. of nitrogen daily would have been available for anabolism and storage. But the loss of 8.01 gms. of nitrogen as protein in the urine left only a meagre positive balance of 0.23 gms. for the whole period, or 0.03 gms. daily. On superficial examination this slight but notable improvement in nitrogen balance may be ascribed to the improvement in the clinical condition. Careful study however reveals that the factor which has been responsible for the change in the nitrogen balance is not so much the catabolic nitrogen, as that excreted in the urine as protein.

Plasma protein levels during the period of study were -

1. At the beginning of the first period 5.60 gms. per 100 ml.
2. At the end of the first period 5.60 gms. per 100 ml.
3. At the beginning of the second period 5.57 gms. per 100 ml.
4. At the end of the second period 5.56 gms. per 100 ml.

NITROGEN BALANCE IN NORMAL PREGNANCY AT DIFFERENT LEVELS OF PROTEIN INTAKE.

There is a general agreement that a high level of positive nitrogen balance exists in normal pregnancy. A comparative study of pregnancy toxaemias necessarly requires a knowledge of the level of nitrogen catabolism in the latter, for, if toxaemias of pregnancy are manifestations/

manifestations of disordered metabolism affecting the nitrogenous constituents of the body a comparative study of the nature and rate of nitrogen destruction in the body in pre-eclampsia is essential. It is with this object in view that one patient at 30 weeks of pregnancy was studied over a period of three weeks with levels of protein intake identical with those used for the study in toxaemia. The results are briefly discussed in this section.

Mrs. Harkins, primigravida, age 28 years, admitted for observation for contracted pelvis. There was no evidence of organic disease and general health was satisfactory. Haemoglobin 79 per cent. Plasma proteins 6.41gms. Blood urea 24.0mgms. Non-protein nitrogen 24.8 mgms. B.P. 118/72 mm.Hg. Urine clear. Urea clearance was 103.4 per cent. Maximum urea concentration 2.97 per cent. Weight 62.8 KGm.

In the first period of study the patient received the same diet as that given to toxaemias in the control period. The total daily nitrogen intake was 14.20 gms. The metabolic study was commenced on 3.7.48 and covered a period of five days. The results are given in Table 7.

Table 7/

Table 7

Date	Cal-ories	Food-N	Faecal N	Net N intake	Urine N Total	Urine N Pro-tein	Balance
3.7.48	2,202	14.20	1.43	12.77	8.94	-	+3.83
4.7.48	"	"	1.52	12.68	9.12	-	+3.56
5.7.48	"	"	1.64	12.56	9.06	-	+3.50
6.7.48	"	"	1.54	12.66	8.85	-	+3.81
7.7.48	"	"	1.50	12.70	8.77	-	+3.93
		71.00	7.63	63.37	44.74	-	Aver. daily balance = +3.73gms. N.

During the subsequent period of 9 days the nitrogen intake of the diet was increased to 17.36 gms. daily and the patient was put on a diet identical with that used in case 1. In order to avoid the lag in nitrogen excretion study of the balance, which covered a similar period of five days, did not start till four days after the commencement of the new dietary regime. The results are submitted in Table 8.

The increase of daily nitrogen intake by 3.16 gms. caused an increase of 2.51 gms. of nitrogen storage. Thus, 79.4 per cent. of the nitrogen added to the diet was being used for storage. Nitrogen catabolism increased only slightly to the extent of 0.2 gms. a day (6.2 per cent. of the basic level).

Table 8/

Table 8

Date	Calories	Food-N	Faecal N	Net N intake	Urine N Total	Urine N Protein	Balance
11.7.48	1,971	17.36	1.79	15.57	9.19	-	+6.38
12.7.48	"	"	1.81	15.55	9.24	-	+6.31
13.7.48	"	"	1.94	15.42	9.08	-	+6.34
14.7.48	"	"	2.06	15.30	9.28	-	+6.02
15.7.48	"	"	1.99	15.37	9.33	-	+5.97
		86.80	9.49	77.31	46.12	-	Aver. daily balance = +6.24gms. N.

During the subsequent period of 9 days the patient was put on a diet of which the nitrogen yield was only 12.0 gms. daily, and identical with that used for metabolic study for case 2. As in the previous case study of the nitrogen balance did not start until 4 days after the diet was commenced. The results are submitted in Table 9.

Reduction of the daily nitrogen intake by 2.20 gms. (from that of the control period) was followed by a decline in the amount of nitrogen stored by 1.16 gms. The protein catabolism was also lowered by 0.57 gms. of nitrogen per day (15 per cent. of the basic level).

Table 9/

TABLE 9

Date	Cal-ories	Food-N	Faecal N	Net N intake	Urine N Total	Urine N Pro-tein	Balance
19.7.48	2,444	12.0	1.26	10.74	8.14	-	+2.60
20.7.48	"	"	1.40	10.60	8.06	-	+2.54
21.7.48	"	"	1.31	10.69	8.11	-	+2.58
22.7.48	"	"	1.19	10.81	8.29	-	+2.52
23.7.48	"	"	1.22	10.78	8.17	-	+2.61
		60.0	6.38	53.62	40.77	-	Aver. daily balance = +2.57gms. N.

ANALYSIS OF DATA FROM NORMAL PREGNANCY

Comparison of these results obtained in normal pregnancy provides an interesting study. With medium levels of protein intake the stored nitrogen amounted to 29.4 per cent. of the nitrogen assimilated. When the protein of the diet was increased the nitrogen storage increased to 40.4 per cent. of the assimilated nitrogen. With reduction of the protein in the diet nitrogen storage dropped to 24.0 per cent. of the protein absorbed. Further analysis shows that by increasing the assimilated nitrogen by 22.2 per cent., the nitrogen storage was increased by 37.4 per cent. of the basic level. But decrease of the assimilated nitrogen by 15.3 per cent. caused/

caused an 18.4 per cent. drop in the stored nitrogen. These data indicate that protein storage during pregnancy is an active and vital process, which suffers when protein consumption is low but increases out of proportion at high levels of protein intake. It appears that high protein diet acts as an added stimulus for protein storage, and a low protein diet hinders the mechanism slightly more than the level of protein in the diet would indicate. This has a far reaching significance in antenatal obstetrics, but a discussion of this out of the scope of the present investigation.

COMMENTS

In 1874 Rosenstejn (34) declared that eclampsia was caused by cerebral oedema, which was due to a "too watery state" of the blood. This was agreed upon by Hamilton (35, 1881) and other subsequent authors belonging to the last and the earlier part of the present century. In recent years Strauss (19, 1938) pointed out the importance of low levels of plasma proteins in relation to oedema in pregnancy toxaemias and Boyd Harden (21, 1936) claimed to be able to reduce considerably the incidence of eclampsia by establishing what he named 'protein stabilisation'. The protein intake for a case of toxaemia is calculated by Harden in order to provide a small surplus over the total loss of protein and non-protein/

protein nitrogen in the urine. In this connection, he takes into consideration the starvation level of protein catabolism and the nitrogen requirements of the foetus. It is however interesting to note that Harden is able to obtain "protein stabilisation" with as little as 69 gms.of protein (11.1 gm.nitrogen) a day.

Nitrogen catabolism in normal pregnancy has been a subject of considerable study. In a normal individual the total nitrogen excretion is a fair measure of the amount of nitrogen catabolised in the body. Obviously the change in weight and the level of tissue and blood non-protein nitrogen have to be taken into consideration, but for short periods of metabolic study these seldom show any recognisable variation. The level of nitrogen elimination in the urine, representing the nitrogen metabolism, has been variously estimated from 10.08 (Long and Gephart,36, 1928) to 16.0 gms. (Folin, 27, 1905) of nitrogen in non-pregnant individuals. In pregnancy the level of excretion of the catabolic nitrogen has been found to be uniformly low. Rowe, Gullivan and Matthews (38, 1930) gives the average total nitrogen excretion as 8.03 gms. daily with a range of variation from 6.73 to 9.64 gms. The results obtained by us in our case of normal pregnancy are in close agreement with this finding as well as with those reported by other observers. Indeed, the level of nitrogen catabolism in/

in normal pregnancy is so low as to almost approach that seen in Benedict's (39, 1915) fasting man. Nevertheless this diminished catabolism is not due to starvation, but is caused by active protein storage, which creates a positive nitrogen balance in pregnant women. Hoffström (24, 1909) noted that the average daily retention was 1.8 gms. of nitrogen. Wilson (26, 1916) found that with a daily intake of 9 to 19 gms. of nitrogen a positive balance, sometimes amounting to 6 gms. a day could be observed. Hunscher et al (40,1933) from a collected review of the literature observed that 80 per cent. of the intakes extended from 10-18 gms. of nitrogen per day, while the retention came to the range of 1.5 to 2.7 gms. daily. That the actual amount of storage is dependent upon the biological value of the protein has been shown in a subsequent communication by Hunscher and co-workers (41, 1935). This is also amply supported in the case studied by us. During the period of low protein consumption 6.9 gms. of nitrogen were supplied as proteins of high biological value. The nitrogen storage during this period was 2.57 gms. per day. But when the consumption of first class proteins increased to 14.9 gms. of nitrogen per day, the nitrogen storage was raised to 6.24 gms. daily. Thus, with an increase in the first class protein consumption by 116 per cent., the nitrogen storage was raised by 143 per cent./

cent. The importance of this is enhanced when the higher carbohydrate and caloric value of the low protein diet are taken into consideration. The marked nitrogen retention which is seen during pregnancy is merely an expression of natures economy of the personal expenditure of the mother in order to provide for the foetus in utero and to ensure adequate lactation during puerperium. Both Coons and Bhent (42, 1930) and Rowe et al (38, 1930) showed that near term the level of nitrogen storage declines to some extent, although an appreciably large positive balance is still maintained.

Our study of nitrogen metabolism in toxaemias of pregnancy show a remarkable deviation from normal. There are three outstanding features in the metabolic study. Firstly, the position of gross nitrogen balance, secondly the level of nitrogen catabolism and thirdly, the protein which is lost in the urine without being of any use to either the mother or foetus.

For obvious reasons very severe cases of toxaemia are not suitable subjects for metabolic study. Our cases were selected from a group where the toxaemia was moderate. In order to obtain a correct idea of the level of nitrogen catabolism and balance the amount of extrametabolic nitrogen excreted must be taken into account. The fluctuations of plasma non-protein nitrogen could not obviously be due to impairment of renal function

for the urea clearance in all cases were normal or above normal value.

A superficial examination of the balance sheets of the three cases of toxaemia presented here all reveal a negative nitrogen balance varying from 0.52 to 0.65 gms. per day, with a dietary nitrogen content of 14.20 gms. of which 9.7 gms. were first class proteins.

With a correction for extra metabolic nitrogen the balance still remains negative at -0.18, -0.21 and -0.52 gms. of nitrogen per day respectively. The highest negative balance was observed in case 3, which also showed the most marked manifestations of toxaemia. On the face of these findings, the conclusion that a negative nitrogen balance exists in toxaemias of pregnancy appears to be reasonable. So far, our findings confirm those of Harden and other workers, but the state of nitrogen balance is not equivalent to what is shown on the balance chart but is considerably less than this value. It has been pointed out that normally, the amount of nitrogen storage which occurs in pregnancy is about 2 gms. per day with a protein intake of 10 to 18 gms. (40). Therefore, compared with normal pregnancy our cases of toxaemia had actually a deficit balance of about 2+(0.18, 0.21 and 0.52) gms. respectively per day. The state of gross nitrogen balance in pregnancy toxaemias is/

is thus of an extremely poor quality.

In the first case in our series this deficiency was made up by increasing the nitrogen intake by 3.16 gms. per day. As a result, the nitrogen equilibrium was established in this patient with a positive balance of 0.80 gms. In other words a net positive balance of 0.98 gms. was obtained following an increase of dietary nitrogen by 3.16 gms. per day. That is to say 31 per cent. of the added nitrogen was used for building up reserves for the body. Even with this improvement the state of nitrogen equilibrium was far below that found in normal pregnancy.

When the dietary protein intake was lowered (case 2), by 2.2 gms. equilibrium was established at -0.75 gms. of nitrogen per day. Thus, due to a loss of 2.2 gms. of nitrogen from diet the loss of nitrogen from the body increased by o.54 gms. only. This was possibly due to further economy on the part of nature in sparing proteins from destruction, and this was evidently helped by the raised carbohydrate and caloric value of the diet consumed.

The third case presents an interesting study. In the initial period of observation there was a negative nitrogen balance of 0.52 gms. per day. During the second period of observation inspite of the maintenance of the same dietary regime nitrogen equilibrium was established at a barely positive level of 0.03 gms. of nitrogen per day/

day. This was mostly brought about by a diminution of urinary loss of protein, for the change in nitrogen catabolism in the two periods of study showed but little change.

The amount of nitrogen catabolised in the body in our cases during the "control" period was 11.2, 11.1 and 11.6 gms. per day respectively. These values bear a fairly close relationship with the degree of severity of toxaemia at the time of investigation, although the margin of difference can hardly be regarded as striking. Compared with the level of protein catabolism in normal pregnancy these values show considerable augmentation. In fact they very nearly approach the level seen in the non-pregnant state. Such a circumstance may develop because of either (i) an increased active destruction of the proteins in the body in order to maintain the metabolic needs, or (ii) an inability on the part of the body to utilise the available nitrogen for storage purposes. As has already been mentioned, diminished protein catabolism in pregnancy is actually an active process. This is shown by a decline in the non-protein nitrogen level of the blood and urine during pregnancy. Increased protein catabolism has been observed in dehydration and infection. The "toxin" of pregnancy "toxaemias" has not yet been isolated, and it is

"water/

"water-logging" not dehydration which characterises pre-eclampsia. An active protein destruction should be amenable to increase of the carbohydrate, fat and caloric value of the diet, but in toxaemias of pregnancy these act as only poor protein sparers as judged by the level of nitrogen excretion. In fact, evidences available provide only a feeble support for the existence of a state of active protein destruction in the body in the pre-eclamptic states. On the contrary judging from the level of plasma proteins it appears that nitrogen synthesis is in some way affected in toxaemias of pregnancy.

The three cases presented here, as well as the discussion in the following chapter will show how little the plasma protein level in toxaemia is influenced by a high protein diet inspite of the presence a gross deficiency in the concentration of proteins in the plasma in this condition. Studies of Arnell and Coworkers (43, 1945) and of Dodge and Frost (17, 1938) also substantiate this. In this respect, a condition simulating toxaemia has been observed by Post and Patek (44, 1942) in cirrhosis of the liver. These authors found that with high levels of protein intake a positive nitrogen balance may be obtained but this was not associated with a rise in serum proteins. Reference to the

chapter/

chapter on plasma proteins will show that we failed to observe an increase of the protein level of the plasma with diet containing as much as 131 gms. of protein reinforced with 5 gms. of cystine daily. We therefore consider that the high level of nitrogen catabolism in toxaemia of pregnancy is due to a defect on the part of the body to anabolise proteins from the available nitrogen of the diet.

Further evidence of the existence of a state of augmented protein catabolism in pre-eclampsia is found when the effect of the change in the nitrogen content of the diet is studied. In the first patient when the dietary nitrogen was increased by 3.16 gms. per day, the daily rate of nitrogen catabolism also increased by 2.5 gms. Thus, an increase of dietary nitrogen intake by 22.2 per cent. was followed by an identical increase in the level of protein destruction in the body. In case 3, where, throughout both periods of study the nitrogen intake was maintained at the same level the rate of protein catabolism showed no appreciable change, being 11.6 gms. of nitrogen per day in the first week and 11.5 gms. during the second period of study. In the second case when the nitrogen intake was lowered by 6.45 per cent. during the second week the protein catabolism fell by 9.1 per cent. Undoubtedly this bigger drop in catabolism with low levels of protein intake

was/

was of a protective nature, aided probably by the higher carbohydrate content and caloric value of the diet. Such a condition has been known to develop even in normal non-pregnant subjects owing to the protein sparing effects of these agents. In the consideration of toxaemias of pregnancy however this is of little consequence. A diet low in protein, even when rich in carbohydrate value, has not been known to establish a positive balance in pregnancy. Foetal requirements of protein must be satisfied by the mother, otherwise there is naturally a drain on maternal protein reserve. Moreover, it has never yet been proved that the products of nitrogenous catabolism are harmful in pregnancy toxaemias. The excretory capacity of the nitrogenous waste products suffer but slightly, if at all, in true pre-eclampsia. If a positive nitrogen balance is to be desired in toxaemias of pregnancy it has to be established above the augmented level of nitrogen catabolism. That being so, the minimum nitrogen requirement for the mere maintenance of equilibium, as appears from these three cases, should be from 11 to 12 gms. of nitrogen per day. If a positive balance of at least 2 gms. per day is to be provided for the foetus, the lowest safe level of nitrogen intake appears to be about 14 gms. daily. This however does not include or make any provision for the protein lost in the urine.

The/

The amount of nitrogen lost as protein in the urine is a variable quantity not only in different patients, but also in the same patient in different stages of the disease. The protein lost in the urine is a complete waste for it fulfils no metabolic purpose. If proteinuria could be prevented a diet of a slightly low nitrogen value would not have a dangerous effect on the nitrogen balance, provided adequate caloric intake was ensured with additional carbohydrate and fat. This is shown in our second case, where inspite of the level of nitrogen intake being only 12 gms. per day, a nitrogen storage of 0.16 hms. daily would have been possible in absence of albuminuria. When the dietary nitrogen intake was 14 gms., the amount of surplus nitrogen over and above the level of catabolism was 1.10, 1.15 and 0.91 gms. daily in the first, second and third cases respectively, during the first week of study, inspite of toxaemia being of miderate severity. During the second period of study the excess nitrogen available for storage (but lost in the urine as protein) was 1.65, 1.12 and 1.18 gms. in the corresponding cases with an intake of 17.36, 12.0 and 14.20 gms. respectively.

Reference has already been made to the collective review made by Hunscher et al (40, 1933) who found that the average nitrogen retention in 80 per cent. of cases of normal pregnancy was 1.5 to 2.7 gms. per day. If in the/

the cases presented here the loss of protein in the urine was absent the state of nitrogen balance in spite of toxaemia would not have been considerably less than that in normal pregnancy. But the continual loss of protein in the urine in pre-eclampsia becomes a factor of immense significance in nitrogen metabolism.

It has been pointed out in the previous paragraph that in order to ensure a nitrogen retention of 2 gms. per day the minimum daily nitrogen intake should be no less than 14 gms. The average loss of protein in the urine in a moderately severe case of toxaemia is about 1.5 gms.per day. This however may show a considerable variation in individual cases. In order to replenish this nitrogen wastage the level of intake must be increased at least by a corresponding amount. Thus, the minimum nitrogen intake of a case of toxaemia of moderate severity losing not more than 1.5 gms. of protein nitrogen per day in the urine should be at least 15.5 gms. in order to ensure a storage of about 2 gms. of nitrogen daily. If the basic weight is regarded as 60 KG. (132 pounds) this offers 1.6 gms. of protein per Kilogram per day. This value is very near to that recommended by the League of Nations' Health Commission. Many authors (26) however have observed a nitrogen retention of about 6 gms.per day during pregnancy. Our observation in normal/

normal pregnancy show that with a nitrogen intake of 12 to 18 gms. per day, a daily nitrogen retention of 3-6 gms. may be ensured. In order to obtain the same nitrogen retention in toxaemia the intake should be raised to 18-19 gms. of nitrogen (112 to 118 gms. protein approximately), i.e. about 2 gms. of protein per kilogram of the body-weight per day. This may appear to be slightly higher than the League of Nations recommendations in normal pregnancy, but when one considers the slightly higher rate of protein catabolism and the loss of protein in the urine, this seems reasonable.

The results of our own investigation, as well as those of others referred to above, however clearly demonstrate that this high level of protein consumption can hardly be expected to bring about a gross alteration of the plasma protein level. If the aetiology of eclampsia is centred round hypoproteinaemia, mere establishment of a satisfactory nitrogen balance can not be expected to provide the remedy. Nevertheless, a high protein diet, with adequate positive protein balance corrects one of the important deficiencies in the metabolic chain and certainly deserves more consideration than it has hitherto received.

CONCLUSION

From the study of nitrogen balance in 3 cases of pre-/

pre-eclampsia [illegible], it was observed that in assessing the level of nitrogen catabolism, allowance should be made for the loss of extrametabolic nitrogen in the urine caused by loss of weight and diminution of oedema. The level of nitrogen catabolism in toxaemias of pregnancy appears to be higher than that in normal pregnancy. This is not due to an active increase in protein destruction but to the inability on the part of the body to utilise all the available nitrogen for protein synthesis.

In calculating the basic protein intake of a case of toxaemia, amount of nitrogen lost in the urine as protein should be taken into account, for the apparent negative balance in toxaemia is caused by proteinuria.

In order to maintain a positive nitrogen balance equivalent to that found in normal pregnancy, a toxaemic patient requires a higher level of protein intake, in order to cover not only the protein loss in the urine but also the increased rate of catabolism. The minimum satisfactory level is suggested at 15 to 16 gms. of nitrogen daily, equivalent to 95 to 100 gms. of protein per day. The optimum level is, however between 112 to 120 gms. of protein daily. It is also observed that in order to obtain a satisfactory positive balance the level of proteins of high biological value plays an important part. For the purpose of maintaining an adequate positive balance/

balance, the rate of protein catabolism must be kept at a low level. In this connection the value of adding sufficient carbohydrate in order to spare the proteins is indisputable.

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CHAPTER 2

PLASMA PROTEINS AND THEIR BEHAVIOUR

A. NORMAL PREGNANCY

Towards the end of the nineteenth century attention was drawn to "the watery state" of the blood in toxaemias of pregnancy (Hamilton, 1, 1872). Probably some of their cases of this apparent hydraemic plethora, were examples of what has recently been described by Scott and Govan (2, 1949) as "anaemia simulating toxaemia". But that the so called "watery state" of blood does exist in true toxaemia of pregnancy, apart from the condition just mentioned, has been demonstrated by many modern investigators and this led Zangemeister (3, 1917) to formulate the theory of cerebral oedema for eclampsia.

Study of plasma proteins in pregnancy and toxaemias have proved important, not only because its concentration in the blood offers an indirect evidence of the nutritional state of the mother, but also because the colloid osmotic pressure exerted by the proteins of the plasma has been believed by some investigators to be related to one of the important manifestations of toxaemia, viz. oedema. One of the most elaborate investigations on this subject is that of Dieckmann and Wegner (4, 1934). This author pointed out that serum proteins at term are from 0.3 to 15.0 per cent. (Average 7.0 per cent.) below those of/

of the first three months of pregnancy. In an attempt to correlate the serum protein content with the blood volume this author came to the conclusion that the fall in the protein concentration is not wholly due to haemodilution of pregnancy, for the amount of serum protein per kilogram remains constant. Most investigators agree that in pre-eclampsia there is a further fall in the plasma protein concentration. However, inspite of this general agreement in findings, there has been no attempt to ascertain the nature of the underlying process. It was therefore considered that a study of plasma proteins in pregnancy and toxaemias was essential.

Our investigations include, apart from a general study, the relation plasma proteins have with the different clinical manifestations of toxaemias of pregnancy, the course and progress of the disease, its behaviour under different dietary conditions.

1. Plasma Proteins in Normal Pregnancy.

Protein concentration of the plasma has been known to vary at different levels of nutrition. Although sufficient number of investigations have been done on plasma protein levels in normal pregnancy it was considered fit that the average protein concentration of the plasma in normal pregnant persons belonging to those districts from which our cases of toxaemia are derived should be known. It is with this object in view/

view that 93 cases of normal pregnancy were studied. These patients were obtained from the antenatal clinic of The Glasgow Royal Maternity and Women's Hospital. For descriptive purposes the cases are divided into two series. The first series consists of 78 cases at varying periods of gestation. The second series of 15 cases were selected in the early part of gestation and followed throughout pregnancy in order to study the variations in the level of plasma protein in individual cases as gestation proceeds. Any patient who showed any evidence of constitutional or functional disease either before or during the course of investigation was excluded from this series. No dietary restrictions were imposed on these patients. No patient with a haemoglobin concentration of less than 70 per cent. is included in this series.

FIRST SERIES

RESULTS

Total Plasma Protein - The average total plasma protein level in the 78 cases belonging to the first series was 6.63 gms. per 100 ml.; S.D. 0.42. This however does not depict the true state of affairs, for cases in advanced pregnancy showed appreciably lower values than those in early pregnancy.

As our investigation concerns toxaemia of pregnancy and as pre-eclampsia is a disease of the last trimester, 50 per cent. of our patients were selected from 28 to 40 weeks/

weeks of gestation. The earliest pregnancy studied in our series was one of nine weeks. Twenty cases from this series were re-examined six or more months after confinement and the values obtained at this examination were regarded as their basic plasma protein level. The frequency distribution of the total protein concentration of the plasma observed in these patients are given in Table 10.

In this series of cases the average plasma protein concentration was 6.63 gms. per cent., S.D. 0.42. This however does not indicate the mean value at any particular state of pregnancy. In general, there is a progressive decline of the protein content of the plasma as gestation proceeds. The lowest value was obtained in the ninth month (32-36 weeks) of gestation while during the last four weeks of pregnancy there was a slight increase. The difference between the individual values obtained at different months of pregnancy is not always statistically significant. Between the basic value and that obtained in the third months of pregnancy (8-12 weeks) the difference is not significant. During the subsequent four months the decline is consistent and significant at each stage. The beginning of the last trimester of gestation causes a further drop in plasma protein but it is of little significance at this stage. The maximum fall occurs during the following month but statistical significance/

Table 10

Gms./ 100 ml.	Basic	Lunar months of Gestation. 3	4	5	6	7	8	9	10	Total
5.60-5.80	-	-	-	-	-	-	-	1	-	1
5.80-6.0	-	-	-	-	-	-	1	2	1	4
6.0-6.20	-	-	-	-	-	1	1	2	2	6
6.20-6.40	-	-	-	1	2	1	3	3	2	12
6.40-6.60	-	-	1	2	2	2	5	4	3	19
6.60-6.80	-	-	1	2	2	2	2	2	2	13
6.80-7.0	2	1	1	2	1	1	1	1	2	10
7.0-7.20	3	1	2	1	1	-	-	-	-	5
7.20-7.40	5	2	2	-	-	-	-	-	-	4
7.40-7.60	8	2	1	-	-	-	-	-	-	3
7.60-7.80	2	1	-	-	-	-	-	-	-	1
Total	20	7	8	8	8	7	13	15	12	78
Average	7.39	7.34	7.01	6.72	6.63	6.54	6.45	6.39	6.50	6.63
Max.	7.73	7.67	7.59	7.16	7.15	7.0	6.82	6.82	6.95	7.67
Min.	6.82	6.81	6.44	6.24	6.21	6.06	5.83	5.62	5.91	5.62
S.D.	0.24	0.27	0.35	0.23	0.30	0.27	0.23	0.35	0.28	0.42
P.E.	0.16	0.13	0.23	0.19	0.20	0.18	0.15	0.23	0.19	0.28

significance disappears. During the last month of gestation the terminal rise is again just significant on statistical analysis. A critical examination of the table will indicate that the change in the average values is brought/

brought about by a deviation of the minimum values towards the left during the decline, while both the maximum values as well as their frequency show only a slight change. As a result from the second trimester onwards the scatter of individual values becomes greater. In the whole series of 73 cases, 69.2 per cent. of the values occupied a range between 6.20 to 7.0 gms. per cent., while the mean value lies in the range of 6.60 to 6.80. Compared with this mean range, 100 per cent. of the values in the third month of pregnancy were placed above the general mean. During the succeeding months of gestation the corresponding values were 75.0, 37.5, 25.0, 14.3, 7.7, 6.6 and 16.7 per cent. respectively. The lowest plasma protein level in this series was 5.62 gms. per 100 ml. in the ninth month of pregnancy. The maximum fall in the total protein concentration of the plasma amounted to 12.9 per cent. of the value in the third month of pregnancy and 13.5 per cent. of the basic level.

SECOND SERIES

This consisted of 15 cases examined first in the early months of pregnancy and then followed to term, examination being repeated once every month. Eleven patients in this series were first examined when they were 3 months (3 to 12 weeks) pregnant. The remaining 4 were first examined in the fourth month of pregnancy. The results obtained in these cases are presented in Table 11.

Table 11

No.	Total Plasma Protein, gms./100 ml. Lunar months of gestation 3	4	5	6	7	8	9	10	Average during Pregnancy	Average last Trimester	Fall in Protein% initial value
1	7.40	7.03	6.74	6.57	6.41	6.39	6.23	6.53	6.37	6.43	15.1
2	-	7.29	7.01	6.70	6.45	6.40	6.25	6.47	6.65	6.37	14.3
3	7.69	7.47	7.24	6.96	6.75	6.70	6.45	6.33	7.01	6.68	16.1
4	-	6.84	6.51	6.30	6.17	6.05	6.03	6.00	6.27	6.03	12.3
5	7.14	6.31	6.63	6.49	6.23	6.10	6.0	6.10	6.44	6.06	14.6
6	6.93	6.54	6.29	6.05	6.0	5.86	5.82	5.97	6.19	5.88	14.5
7	7.41	7.19	7.05	6.90	6.68	6.60	6.41	6.74	6.87	6.58	13.5
8	7.32	7.07	6.85	6.69	6.50	6.27	6.39	6.38	6.68	6.34	12.3
9	7.17	6.83	6.51	6.35	6.22	6.01	5.90	6.36	6.42	6.09	17.7
10	7.58	7.39	7.20	7.10	7.0	6.91	6.70	6.88	7.10	6.83	11.6
11	-	7.49	7.20	6.92	6.70	7.0	6.46	7.0	6.96	6.82	13.3
12	7.34	7.24	7.14	7.0	6.75	6.50	6.42	6.65	6.88	6.52	12.5
13	-	7.0	6.81	6.66	6.62	6.44	6.26	6.66	6.63	6.45	10.5
14	6.94	6.92	6.88	6.54	6.50	6.47	6.50	6.50	6.63	6.49	6.3
15	7.59	7.32	7.20	7.08	7.0	7.06	7.0	7.0	7.15	7.02	7.8
Aver	7.32	7.10	6.87	6.67	6.53	6.45	6.33	6.54	6.71	6.44	12.9
S.D.	0.26	0.26	0.33	0.32	0.30	0.37	0.26	0.33	0.31	0.37	3.12
P.E.	0.17	0.17	0.22	0.21	0.20	0.25	0.17	0.22	0.21	0.25	2.09

In both series there is an obvious general agreement in the values obtained at different periods of gestation. In/

In every instance in the present series there has been a fall in the concentration of plasma proteins as pregnancy advanced. Except in one case (No.4) the lowest level was reached in the ninth month of pregnancy (32-36 weeks), so that the average value obtained at this period of gestation was also the lowest in the series. The rate of decline is however neither constant nor uniform. In most of the cases the maximum rate of fall is noticed up to the end of the second trimester, whereas during the two succeeding months the diminution in the protein concentration becomes less, and at term there is actually a relative increase. The amount of this terminal rise varied in individual cases from 0.1 to 0.54 gms.per cent. In 4 cases in this series, however this increase of plasma protein concentration before labour was absent. The maximum drop in the protein level of the plasma, compared with the early pregnancy level was on an average 12.9 per cent.; S.D. 3.12, with a scatter between 6.8 to 17.7 per cent. The general average of the second series is in close agreement with that of the first. However, in order to compare normal pregnancy with toxaemia the average of the last trimester is important. It is of interest to note that this was identical (6.44 gms.per 100 ml.) in both series. In view of this, these two groups of cases, in all subsequent descriptions will be considered together.

B. Fibrinogen - Our results, based on 194 estimations on

93 patients were obtained by the estimation of the nitrogen content of the clot obtained from reconstituted oxalated plasma. These are presented in Table 12.

Table 12

Gms./ 100 ml.	Basic	Lunar months of gestation								Total	Total Last Trimester
		3	4	5	6	7	8	9	10		
0.2-0.25	3	2	3	-	-	-	-	-	-	5	-
0.26-0.30	8	5	6	6	3	1	-	-	-	21	-
0.31-0.35	7	9	10	7	5	4	5	1	-	41	6
0.36-0.40	2	2	4	8	12	14	11	7	2	60	20
0.41-0.45	-	-	-	2	3	3	9	15	2	34	26
0.46-0.50	-	-	-	-	-	-	3	5	16	24	24
0.51-0.55	-	-	-	-	-	-	-	2	7	9	9
Total	20	18	23	23	23	22	28	30	27	194	85
Average	0.30	0.31	0.32	0.34	0.37	0.39	0.40	0.43	0.47	0.39	0.43
S. D.	0.045	0.044	0.047	0.049	0.045	0.036	0.044	0.045	0.040	0.060	0.055
Max.	0.39	0.40	0.40	0.43	0.45	0.45	0.49	0.52	0.55	0.55	0.55
Min.	0.24	0.24	0.25	0.27	0.29	0.30	0.33	0.35	0.40	0.24	0.33

Compared with the basic value of our series the fibrinogen concentration during pregnancy is raised by 0.09 gm. per 100 ml. and this increase is statistically significant. It is gradual and progressive throughout gestation. Up to the sixteenth week the increase is slight and/

and hardly noticeable. During the following three months it is more marked and steady, while during the last trimester it is most evident and exceeds the accepted limit of normality (0.20 to 0.40 gms.per 100 ml.). The change in values between the seventh and eighth months in our series does not appear to be statistically significant although it is so at all other stages. It is however, interesting to note that comparison of Tables 10 and 12 do not show any close parellelism between decline of the total protein and increase in the fibrinogen content of the plasma, except that the pre-parturient rise in total protein is associated with a maximum plasma fibrinogen level. The net gain in fibrinogen in the last month of pregnancy exceeds that of any of the preceeding periods of gestation. While the total plasma protein drops by 13.5 per cent. of its basic value, the gain in fibrinogen amounts to 56.6 per cent. The mean for the whole series occupies the range of 0.36 to 0.40 gms.per cent. The distribution shows almost an equal frequency (35.1 per cent. below, and 34.5 per cent. above) both above and below this range. But when only the results of the last trimester are considered it is seen that 69.4 per cent. of the values are above the mean for the whole series while only 7.1 per cent. are below.it. This indicates a distinct deviation of the values to the right during the last three months of gestation, although a careful analysis of/

of the table reveals this tendency, even in earlier months. To sum up, the fibrogen shows a steady increase throughout pregnancy and at term the average value in our series was 0.43 gms. per 100 ml; S.D. 0.055. In our subsequent discussion of pregnancy toxaemias the values obtained will be compared with this figure.

C. Albumin: Globulin Ratio - There is a general agreement among all investigators that the fall in the plasma protein concentration in pregnancy is confined principally to serum albumin thus causing a drop in the albumin: globulin ratio. The protein fractions were estimated in all our cases. The frequency distribution of the albumin: globulin ratio is submitted in Table 13.

In all our estimations plasma albumin was estimated directly after precipitating the globulin with 40 per cent. sodium sulphite (method described in appendix), and the value for globulin was obtained by subtraction.

The average value for plasma albumin in 194 estimations in our series was 3.86 gms. per cent.; S.D. 0.30. The basic value in the 20 cases already referred to was 4.47 gms. per cent.; S.D. 0.10. There is thus a fall in the albumin content of the plasma of 0.61 gms. or 13.6 per cent. of the basic value. The average plasma globulin in these cases was 2.47 gms. per cent.; S.D. 0.05, a fall of 0.15 gms. per 100 ml. plasma or 5.7 per cent. of the basic value.

The/

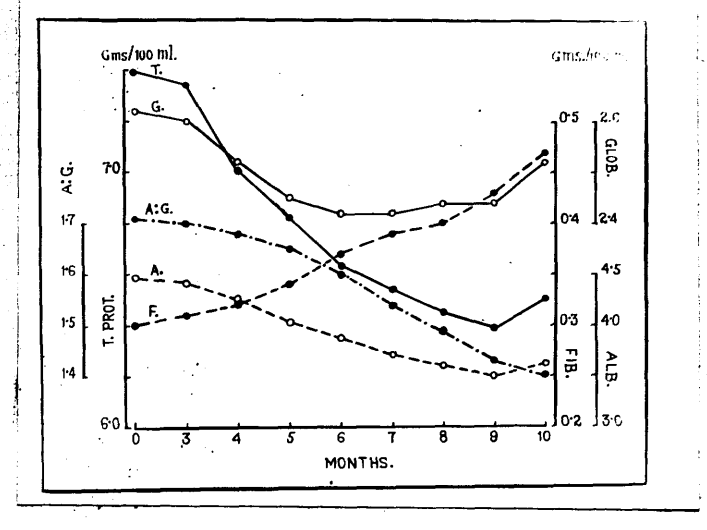

Figure 1. Plasma Proteins in Normal Pregnancy. The graph shows the variations in the concentration of the total protein, albumin, globulin and fibrinogen, and that of the albumin : globulin ratio in different months of pregnancy. The data are obtained from the cases in series 1.

The results obtained at the various stages of gestation indicate that there is a steady and progressive decline of the plasma albumin concentration as pregnancy advances. This becomes evident as early as the third month of gestation and continues steadily up to the middle of second trimester. After that the fall becomes slightly less marked but continues until the lowest point is reached between 32 and 36 weeks of pregnancy. As gestation advances to term there appears to be a slight but statistically insignificant rise in the pre-parturient period. At this stage the net fall in plasma albumin amounts to 21.7 per cent. of the basic, and 20.1 per cent. of the early pregnancy level.

The maximum fall in the globulin concentration of the plasma occurs in the earlier part of pregnancy. After the middle of the second trimester this decline in globulin concentration is arrested, and infact during the last three months of pregnancy there is a tendency for the plasma globulin to rise above the minimum level. The maximum concentration of globulin during pregnancy in our series was observed during the last four weeks of gestation and this amounted to an increase of 4.1 per cent. of the minimum value. At its lowest point the concentration plasma globulin was less by 7.6 per cent. of the basic, and 6.9 per cent. of the early pregnancy level.

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The rate of decline of the plasma albumin at all stages exceeds that of the globulin. As a result the albumin: globulin ratio is always less than normal. Even at the stage of pre-parturient rise the downward trend of the ratio is not arrested. Consequently, unlike the concentration of total protein and protein fractions, the albumin: globulin ratio was lowest, at term.

The average ratio of the albumin and globulin concentration of the plasma for the whole period of gestation was 1.55; S.D. 0.14, while that for the last trimester was 1.44; S.D. 0.10.

The decline in the albumin: globulin ratio is due principally to a fall in the concentration of the plasma albumin. The individual values for globulin also show a slight decrease from the basic level. This may produce an erroneous impression if the relative concentrations of the fractions are not considered. In the basic state the plasma proteins consisted of 60.5 per cent. albumin, 35.4 per cent. globulin, and 4.1 per cent. fibrinogen. At term they were made up of 54.1 per cent. albumin, 38.7 per cent. globulin and 7.2 per cent. fibrinogen. Thus, the composition of the protein at term is such that (compared with the basic state) it loses 10.5 per cent. of its quota of albumin, while those of globulin and fibrinogen increase by 9.3 and 75.6 per cent. respectively. Pregnancy therefore brings on not only a quantitative diminution, but also a qualitative change.

Table 13

A:G	Basic	Lunar months of gestation. 3	4	5	6	7	8	9	10	Total	Last Trimester
1.21-1.30	-	-	-	-	-	-	2	3	5	10	10
1.31-1.40	-	-	-	-	-	1	6	8	8	23	22
1.41-1.50	-	-	1	2	3	4	8	12	11	41	31
1.51-1.60	1	1	2	2	9	13	11	7	3	48	21
1.61-1.70	8	8	11	12	9	4	1	-	-	45	1
1.71-1.80	10	9	9	7	2	-	-	-	-	27	-
1.81-1.90	1	-	-	-	-	-	-	-	-	-	-
Total	20	18	23	23	23	22	28	30	27	194	85
Aver.	1.71	1.70	1.68	1.65	1.60	1.54	1.49	1.43	1.40	1.55	1.44
S.D.	0.07	0.06	0.07	0.08	0.08	0.07	0.10	0.09	0.09	0.14	0.10
Max.	1.82	1.80	1.80	1.78	1.73	1.69	1.66	1.60	1.55	1.80	1.66
Min.	1.55	1.54	1.49	1.44	1.42	1.39	1.30	1.26	1.24	1.24	1.24
Alb.*	4.47±0.07	4.42±0.07	4.23±0.08	4.04±0.08	3.87±0.09	3.72±0.08	3.61±0.09	3.50±0.09	3.53±0.09	3.82±0.20	3.54±0.15
Glob.*	2.62±0.03	2.60±0.02	2.52±0.04	2.45±0.02	2.42±0.03	2.42±0.04	2.44±0.03	2.44±0.02	2.52±0.04	2.47±0.03	2.46±0.03

* Gms. per 100 ml. plasma ± probable error.

COMMENTS

Most authorities (4,5,6,7,8,9,10) agree that there is a decrease in the concentration of plasma proteins during pregnancy. In a follow up study Plass and Mathews (7a, 1926) found that the plasma proteins commence to fall during the third lunar month, and sometimes earlier, and the decrease/

decrease gradually to a minimum at the ninth month of pregnancy. Thereafter there is a rise but the value at term is still below normal. Our findings confirm the above observation.

However, values for plasma proteins given by individual authors appear to vary considerably. Part of this may be due to environmental and dietetic conditions. Most of the available data have a range of values from 6 to 8.3 gms. per 100 ml. of plasma. Dieckmann and Wegner (4, 1934) observed that the average 'serum protein' concentration in pregnancy, based on 17 published reports was 6.5 gms. per 100 ml. The average value for "serum" protein in our series, viz. 6.24 gms. may appear to be slightly less, but it cannot be regarded as abnormal for in 2 of the reports reviewed by Dieckmann and Wegner the serum protein concentration was actually less than 6.20 gms. per 100 ml.

Very few follow up studies in which plasma protein concentration has been studied throughout the period of gestation, are found in the literature. The contribution made by Plass and Matthew has already been referred to. Dieckmann and Wegner found that the fall in the 'serum protein' concentration commences early in pregnancy and reaches a maximum at about thirty weeks. These authors stated that the decrease in the protein concentration of the plasma is only relative, for they found that the amount of total protein in the plasma at term was actually 13 per cent. more than that in early pregnancy.

Our study demonstrates that the decrease in the concentration of proteins per 100 ml. of plasma in the first trimester of gestation is only slight, although significant, and amounted to less than 1 per cent. of what we accepted as the basic value. During the second trimester the fall became appreciable and was equivalent to about 10 per cent. The third trimester brought on further change and plasma proteins were now a little over 12 per cent. less than that observed in the early months of pregnancy. The lowest level attained by the plasma proteins in our series, which was 12.9 per cent. below that in early pregnancy, appears to be less than that of some of the published reports. The average observed by Plass and Matthew (7a), Dieckmann and Wegner (4) and Reinhart (11, 1945) is little over 7 per cent. of the early pregnancy level. The greater fall noticed in our patients is apparently connected with the basic nutritional state of these patients, and the amount of protein reserve of the body at the commencement of gestation. It is obvious that inspite of a relative fall in plasma proteins during pregnancy there is actually more protein in the circulation than in the non-pregnant state. The investigations of Dieckmann and Wegner demonstrate this. Further evidence is found from the fact that inspite of an increase in the plasma volume during pregnancy by 25 per cent, the maximum fall in the protein concentration of the plasma during pregnancy has not been found by investigators (Dieckmann)/.

(Dieckmann) to exceed 15 per cent. The difference must necessarily have been made up by mobilising stored proteins. When the reserve of this store is low, the amount mobilised is also low, and consequently the fall in the relative concentration is greater. Scott and Govan (2a, 1949) working on anaemias in patients attending the same antenatal clinic found that the incidence of anaemia during pregnancy was higher than that reported by investigators from Edinburgh, Aberdeen and London. Scott (12) in an anaemia survey on patients attending the same clinic in 1946 and 1947 further observed that almost 50 per cent. of them had haemoglobin values which were either low normal or below normal levels. These investigations also suggest the existence of a state of low protein reserve in most of the patients seen in this hospital. Thus, a comparatively large drop in the concentration of plasma proteins in our series of cases is not an altogether unexpected finding.

The cause of this "physiological" drop in the concentration of plasma proteins has been rather inadequately explained. Plass and Bogert (7, 1924) suggested that the fall was caused by haemodilution and increase in plasma volume. It has already been pointed out that this explanation is unsatisfactory since the decline in the protein level is much less than the increase in the volume of circulating plasma. Dieckmann and Wegner (4, 1934) point out that the level of plasma protein observed is the expression of the balance/

balance between haemodilution and Nature's effort to compensate for the effects of increase in the volume of plasma, the compensation being of an inadequate nature. Comparison of haematocrit and plasma proteins undoubtedly support this assumption, but fails to indicate why the compensatory mechanism falls short of its requirements in every patient, irrespective of her nutritional status. Apart from the hydraemia referred to above, one outstanding feature of pregnancy is an increase in the nitrogen balance which often amounts to well over 12.5 gms. of protein (2 gm. nitrogen) per day. The mechanism responsible for this, is probably connected with the activity of the anterior pituitary, for Gaebler (13, 1933) succeeded in producing hydraemia and greatly increased nitrogen balance in experimental animals with injections of anterior pituitary extracts.

Michel (quoted by Eden and Holland (14, 1948) found that the daily protein requirement of the foetus is 6 gms. The growth of the uterus, placenta, and breasts require about 1.4 gm. of protein per day. The net daily storage thus appears to be about 5 gms. of protein or about 1400 gms. of protein for the whole period of gestation. For the plasma proteins to be maintained in the same concentration as before pregnancy the level requires to be raised by 25 per cent., which is the extent of haemodilution. On the basis of/

of average data, this requires an additional 35 to 40 gms. of protein in the circulation. Considering the amount of protein stored as reserve, this is indeed a small amount, and is less than 3 per cent. of the total storage. The amount of protein supplied to the plasma falls short of that required for maintaining the normal concentration by only about 10 gms. for the whole period of gestation, or 0.3 gms. of protein per day. Even if allowances are made for the early lactation period it is difficult to explain why Nature should be so reluctant to provide the plasma with an amount of protein which is almost negligible compared to the huge storage built up by the body.

Two important provisions must be made by the body on the advent of pregnancy. These are to provide for (1) an added area of sinusoidal circulation of a highly specialised type, and (2) a demand for increased provision of protein for the foetus and organs associated with pregnancy. As has been pointed out these call for an increase volume of circulatory fluid and a higher level of nitrogen storage, both of which demand an extreme economy in protein metabolism and storage. The position can be explained by giving an example.* A woman having a plasma volume of 2000 ml. becomes

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* The figures used in this calculation are based on the averages obtained in our series of cases already described. Data provided by Plass and Mathew, Dieckmann and Reinhart (America) and Coetzee and Marrack (London) were also subjected to similar analysis and produced almost identical results.

pregnant. At the commencement of pregnancy her plasma is found to contain 4.42, 2.60 and 0.31 gms. per cent. respectively of albumin, globulin and fibrinogen. The total amount of plasma protein in circulation thus amounts to 33.4 gms. of albumin, 52.0 gms. of globulin and 6.2 gms. of fibrinogen. By the end of the gestation the plasma volume has increased by 25 per cent. (Dieckmann), and her plasma now is found to contain 3.54, 2.46 and 0.43 gms. per cent. of albumin, globulin and fibrinogen respectively. The composition of the total circulatating protein at this stage is, therefore, 33.5 gms. of albumin, 61.5 gms. of globulin and 10.75 gms. of fibrinogen. Thus consequent upon pregnancy the total amount of protein of the plasma increases from 146.6 to 160.75 gms., a little under 10 per cent. of the early pregnancy level. When this is compared with an increase in plasma volume of 25 per cent., the natural conclusion is that protein regeneration during pregnancy is inadequate.

The position however requires further scrutiny. The immediate results of haemodilution are (1) alteration of the oncotic pressure of the plasma and (2) change in the physical character of the fluid in circulation involving viscosity and resistance to the flow of blood. From the physical point of view the proteins behave differently from the caystalloids present in the plasma, in as much as they cause a displacement of the water in which they are maintained as/

as a colloidal sol. The amount of water displaced depends upon the protein, and consequently varies with the size of the molecules of the different proteins.

The relative size of the molecules of plasma, albumin, globulin and fibrinogen is approximately 1:1.5:4.3. In terms of water displacement therefore, at the beginning of pregnancy the plasma contained an equivalent of (33.4 X 1 + 52.0 X 1.5 + 6.2 X 4.3) or 186.2 gms. of albumin. Towards the end of pregnancy the protein content of the plasma was equivalent to (83.5 X 1 + 61.5 X 1.5 + 10.75 X 4.3) or 232.15 gms. of albumun. In other words during pregnancy the plasma has been donated with an amount of protein whose mass is quantitatively equivalent to (232.15 - 186.2) or 45.95 gms. of albumin. On these data the "protein-mass" of the plasma increases by 24.9 per cent. of the early pregnancy level, which is identical with the increase in plasma volume.

It is thus evident that from the point of view of the physical character of the plasma Nature has infact established equilibrium in a most efficient manner.

However, the chemical character of the plasma is an entirely different matter. We shall again take the same example. In absence of regeneration of plasma proteins, the immediate effect of haemodilution would have been a lowering of the concentration of the plasma proteins to a level 25 per cent. below that of early pregnancy. In order to counteract/

counteract this, an increase in the total protein content of the plasma to 183.25 gms.would be necessary. In other words, there would be a demand for (183.3 - 146.6) or 36.7 gms.of protein to meet the deficit in the plasma. If the relative concentration of the protein fractions were to be maintained as before, this excess protein would have to consist of 22.1 gms.of albumin, 13.0 gms.of globulin and 1.55 gms.of fibrinogen. Instead of meeting this demand, Nature provides the plasma with only (160.75 - 146.6) 14.15 gms.of protein, which consists of 9.5 gms.of globulin 4.55 gms.of fibrinogen and a nominal amount of albumin. The inevitable result is a fall in the concentration of the total protein and albumin and a marked rise in fibrinogen, globulin varying only to a slight extent.

This peculiar behaviour of Nature with regard to plasma proteins raises two questions. One is connected with Nature's economy and the other with the manner in which albumin is utilised, stored and made in the body.

From the point of view of economy the immediate effect of the measure employed by nature is a net saving of 22.5 gms. of protein, which is not insignificant when the great needs of protein storage are taken into consideration. It is of further interest here to observe that of this amount nearly 99 per cent. is albumin which is vitally necessary, during the stage of active growth of tissues (foetus, uterus, placenta and breasts). Yet this saving is associated with no/

no disturbance of the physical character of the plasma. In this respect the economy appears to be on a sound basis. However, the physical character of the plasma does suffer with regard to the colloidal osmotic properties. The protein mass (by volume) does not suffer but the replacement of the smaller molecules of albumin by larges ones of globulin and fibrinogen tends to lessen the osmotic properties of this fluid.

The increase in plasma fibrinogen has usually been explained on the basis of chorionic villi from the placenta gaining entrance into maternal circulation (Dieckmann 4, 1934) and producing a foreign protein reaction. Fragments of chorionic villi have indeed been demonstrated in the maternal circulation, and such a foreign protein reaction is possible, yet the Abderhalden test for pregnancy which is based on this theory has never been known to give dependable results. It is also interesting to note that Goetzee and Marrack (9, 1924) observed that the change in plasma proteins during pregnancy does not simulate that seen in foreign protein reaction. It appears to us, that a simpler explanation for the increase in fibrinogen is possible on the physical basis mentioned above. It is difficult to disregard the fact that in presence of great demands for protein-saving in the body, Nature, by the measure adopted, can spare about 4.8 gms. of albumin for each gram of fibrinogen added to the plasma without altering the physical nature/

nature of the colloidal solution. At the same time, because of smaller molecular size a given bulk of tissue or cells, can be used to store about 4.8 times as much albumin as fibrinogen.

This economy of Nature is conserving albumin and maintaining the plasma protein "mass" with fibrinogen has another far reaching significance. If the loss of "protein mass" was not reconstituted it would have caused a relative increase in the amount of water in which this protein is kept as a colloidal solution. But proteins are not the only constituents of the plasma. The crystalloids and electrolytes have an important part to play. Infact, because of their colloidal nature, the plasma proteins exert even less than 1 per cent. of the total osmotic pressure of the plasma (osmotic pressure of plasma = 6.94 X 760 X 13.4 mm. water (Stirling) osmotic pressure of plasma protein = 357 mm. water, Drinker and Field). Thus, if there had been failure of restitution of the protein "mass" a marked increase of crystalloids and electrolytes would have been necessary in order to maintain the normal isotonicity of the plasma which Nature can ill afford to surrender. Most of these substances present in the plasma are as urgently needed for storage as protein itself. Thus, from the point of view of all out effort for economy the arrangement described appears to be the most satisfactory under the circumstances.

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It is needless to point out, that this system of economy is an example of an extreme measure and meets the requirements as long as no abnormal demands are made. The balance is just sufficient but very delicately placed. The economy is balanced just to meet the physical needs, but falls far behind the requirements necessary for maintaining the chemical identity of the plasma.

An answer to the second question is more difficult to obtain. It has been suggested by several authors, including Reinhart (11, 1945) in recent years, that the fall in the concentration of plasma albumin is due to a state of hepatic dysfunction present in "normal" pregnancy. Apart from the fact that conclusive proof in this direction is absent, it is difficult to see how a disturbed function of the liver could cause hypo-albuminaemia and at the same time increase the fibrinogen level. As far as is known the liver is the only site of fibrinogen production. Experimental study on the effects of hepatectomy on the plasma proteins reported by Warren and Rhoads (15, 1939) indicate that the fall in the plasma protein concentration after the removal of the liver is accompanied by an almost parallel drop in the fibrinogen level. It is however, possible that milder degrees of dysfunction could cause albumin to decrease before fibrinogen commences to fall. Experimental work of Foster and Whipple (47, 1921) demonstrates this.

There is however, another possibility which deserves

some/

some attention. When the plasma is depleted of proteins, e.g., in acute haemorrhage and plasmapheresis, or when plasma protein concentration is reduced by large infusions of saline (Foster and Whipple, 47, 1921) restoration of fibrinogen, globulin and albumin occur in that order. The relative increase of fibrinogen and globulin, while the albumin concentration is still low is understandable, if the necessity on the part of the body to restore the protein mass of the colloidal plasma solution is taken into account. Hydration and haemodilution is a physiological effect of pregnancy and Melnick and Cowgill (24, 1937) believe that pregnancy is to a great extent comparable to a state of internal plasmapheresis. This would also partly explain the behaviour of plasma proteins during gestation.

CHAPTER 3.

B. PLASMA PROTEINS IN PREGNANCY TOXAEMIAS

The results presented in this section are based on a study of 100 cases of pre-eclampsia and 18 cases of eclampsia.

1. PRE-ECLAMPSIA

1. Plasma Protein Concentration in Toxaemias of Pregnancy.

The average total plasma protein content in pre-eclampsia was 5.63 gms. per 100 ml.; S.D. 0.25. The series, however, consisted of cases of varying severity, and an analysis of the individual figures indicate that with increasing severity in toxaemia the concentration of plasma proteins tends to fall. We shall therefore discuss the mild and severe cases separately. Our criteria for the grouping of cases has already been indicated (pp. 34).

A. Mild Pre-eclampsia - On admission, 50 cases of mild pre-eclampsia in our series had an average total protein concentration of 5.77 gms. per 100 ml. of plasma; S.D. 0.16. Individual values occupied a range from 5.46 and 6.45 gms. In two thirds of the cases plasma protein concentration varied from 5.61 to 5.90 gms. Compared with normal pregnancy the decline in the total protein concentration of the plasma is significant, the fall amounting to 10.5 per cent. of the normal pregnancy level. In only one case in the present series the value just exceeded the average for/

for normal gestation. In the last trimester of normal pregnancy 52.5 per cent. of the values were placed between the minimum (5.62 gms. per cent.) and the average (6.44 gms. per cent.) for this series. In mild toxaemias 32 per cent. of the values occupied the same range. Sixteen per cent. of the values in toxaemia were lower than the minimum in the normal series. The frequency distribution is given in Table 14.

Fibrinogen content of the plasma in our series of mild toxaemias was 0.49 gms. per 100 ml.; S.D. 0.043, which is 60 mgms. per 100 ml. higher than that during the last trimester of normal pregnancy, and 20 mgms. per 100 ml. higher than the maximum average observed at any period of normal gestation. This increase of plasma fibrinogen in mild toxaemias is statistically significant. The range extends between 0.41 and 0.60 gms. Compared with the range observed during the last trimester of normal pregnancy (Table 12) both minimum and maximum values show a distinct shift to the right. In normal cases, 30.6 per cent. of the values were below the minimum observed in mild toxaemias, while 14 per cent. of toxaemias had higher fibrinogen level than the maximum obtained in normal pregnancy. The increase in fibrinogen in pre-eclampsia, even when it is mild, is further shown by the fact that in the present series 30 per cent. of the values were/

were placed between 0.45 and 0.54 gms. per 100 ml., whereas, in normal pregnancy only 44 per cent. of the values had the same distribution. The amount of this increase is found to be 63.1 per cent. of the basic and 16.2 per cent. of the normal pregnancy level in our series. The frequency distribution of plasma fibrinogen in toxaemia is given in Table 16.

The albumin: globulin ratio in this series averaged 1.28; S.D. 0.06, with a range of variation from 1.46 to 1.18. Compared with values obtained in normal pregnancy those found in mild pre-eclampsia show some amount of overlapping at the lower ranges of the values. Thus, in the group of toxaemias 84 per cent. of the ratios were between 1.21 and 1.40. In normal pregnancy 37.7 per cent. had a similar distribution. This of the values indicates that the albumin: globulin ratio tends to occupy the lower range of normal pregnancy values, without any marked tendency to fall below the minimum limit of that range. But the striking feature of the analysis is that, 49.5 per cent. of the values obtained during the last trimester of normal pregnancy were above the maximum observed in mild pre-eclampsias. The scatter of the values is small compared with that in normal pregnancy and 60 per cent. of it lies between 1.20 and 1.30. Eight per cent. of the values are placed below this level, which is also the lowest level seen in normal pregnancy,/

pregnancy, while in only 4 per cent. of cases the ratio exceeds 1.44, which represents the average for normal pregnancy in the last three months of gestation. The frequency distribution of the albumin; globulin ratio in mild toxaemias are presented in Table 17.

The fall in the albumin:globulin ratio is caused principally by the decline in the concentration of plasma albumin. It has already been seen that the fibrinogen level actually rises by 60 m.gms.per 100 ml. Inspite of this there is a decrease in the total protein of the plasma, 84.5 per cent. of this fall is due to a drop in the concentration of plasma albumin. The average value for albumin in our series is 2.95 gms.per 100 ml.; S.D. 0.15. Compared with normal pregnancy, this indicates a diminution by 16.6 per cent. The average globulin content in the present series was 2.30 gms.per 100 ml.; S.D.0.05. This represents a drop of 0.16 gms., or 7 per cent. of the normal pregnancy level. Compared with normal values, the rate of decline of plasma albumin in even mild toxaemias is more than twice that of globulin. The maximum values for plasma albumin and globulin in the present group of cases were 3.47 and 2.39 gms.per 100 ml. respectively. Both these are slightly lower than the lowest averages at any period of gestation (Table 13). The minimum values in this series, viz. 2.70 and 2.21 gms. per 100 ml. respectively are also appreciably lower than the minimum values observed in our series/

series of normal pregnancy (3.20 and 2.29 gms. for albumin and globulin respectively). Only 10 per cent. of cases of this group of toxaemias had a plasma albumin level of 3.20 gms. (minimum normal pregnancy level) or more, while in 72 per cent. the globulin level was at or above the low values observed in normal pregnancy. The change in the albumin: globulin ratio described above is, thus, mainly due to a fall in the concentration of plasma albumin.

B. Severe Pre-eclampsia - Fifty cases of severe pre-eclampsia in our series, on admission, had a plasma protein concentration of 5.49 gms. per cent.; S.D. 0.21. The coefficient of variation is 4.0, which compared with 2.3 in mild toxaemias indicates a wider scatter of the individual values. The maximum in this series was 5.90, which is the same as in milder group of toxaemias. The minimum values, however are much lower than those in the mild pre-eclampsia series. The lowest value for plasma protein in the present series was 4.82 gms. per 100 ml. (1 case), which is 17.2 per cent. less than the minimum in normal pregnancy. Comparison of the values in mild and severe pre-eclampsia reveals that just about 50 per cent. of severe pre-eclamptics had a plasma protein concentration of less than the minimum in mild pre-eclampsia while in 13 per cent. of mild pre-eclamptic patients the plasma protein was higher than the maximum among severe toxaemias. The highest frequency/

Table14

Frequency gms./100 ml.	Mild Toxaemia (50 cases)	Severe Toxaemia (50 cases)	Total (100 cases)
4.81-4.90	-	1	1
4.91-5.00	-	-	-
5.01-5.10	-	3	3
5.11-5.20	-	2	2
5.21-5.30	-	3	3
5.31-5.40	-	10	10
5.41-5.50	1	12	13
5.51-5.60	7	8	15
5.61-5.70	14	4	18
5.71-5.80	13	3	16
5.81-5.90	6	4	10
5.91-6.00	5	-	5
6.01-6.10	1	-	1
6.11-6.20	2	-	2
6.21-6.30	-	-	-
6.31-6.40	-	-	-
6.41-6.50	1	-	1
Average	5.77	5.49	5.63
S.D.	0.16	0.21	0.25
Maximum	6.45	5.90	6.45
Minimum	5.46	4.82	4.82

frequency in mild toxaemias was between 5.61 to 5.80 gms., and that for severe toxaemias was between 5.31 to 5.50 gms. per 100 ml. In 22 per cent. of the cases with severe toxaemia values encroached upon those of the lower range of normal pregnancy; in 33 per cent. similar overlapping with mild toxaemias was observed. Thus, it is evident that the plasma protein concentration gradually shifts to the left as toxaemia develops and increases in severity. This however does not show whether the diminished protein concentration is the cause or the effect of toxaemia or a mere coincidence. However, 4 of our cases of normal pregnancy who were followed through the total duration of gestation and developed pre-eclampsia in the course of investigation throw some light on the subject. The plasma proteins, blood pressure and oedema of these 4 patients are presented graphically in figure 3. Three out of these 4 patients show that, the first abnormal fall in plasma proteins does not become evident until after the blood pressure is raised, but subsequent to this, it bears no definite relation to the degree of hypertension present. Albuminuria and oedema had even less certain relationship to the decrease in the protein concentration. If hypertension is regarded as the first clinical evidence of toxaemia of pregnancy it is obvious that abnormal hypoproteinaemia does not commence until after the process of toxaemia has started. This provides a natural conclusion that the fall in the plasma protein/

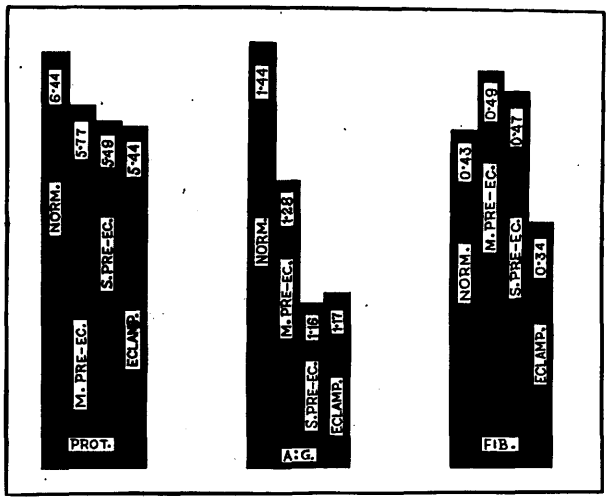

Figure 2. Total protein, albumin : globulin ratio and fibrinogen in normal pregnancy, pre-eclampsia and eclampsia. The values represent the averages in these conditions.

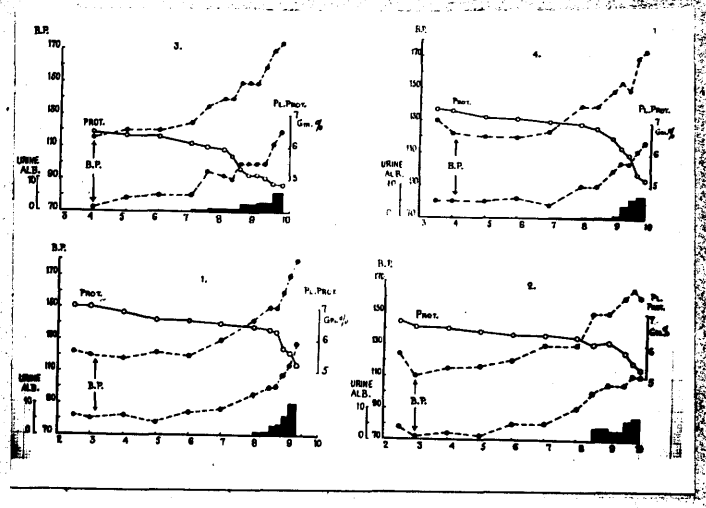

Fig. 3. Plasma proteins, albuminuria and blood - pressure in four patients, who during a follow-up developed signs of toxaemia.

protein is the effect of and brought about by pregnancy toxaemia. If this hypothesis is correct it would be reasonable to expect a spontaneous increase in the concentration of proteins with an improvement in the clinical state, and conversely a progressive fall as the condition deteriorated. It will be seen later that a follow-up study shows that such is the case. The frequency distribution of values for the total protein concentration in severe toxaemias is given in Table 14.

The average fibrinogen content of the plasma in severe toxaemia was 0.47 gms. per 100 ml.; S.D. 0.13. This is higher than that in normal pregnancy and the difference is significant. Compared with mild pre-eclampsia however, the difference is less striking and does not satisfy statistical scrutiny. The average value is indeed, less than that in the milder forms of toxaemia, but the scatter is extremely wide. This is shown by the coefficient of variation rising from 3.3 (mild pre-eclampsia) to 27.7 (severe pre-eclampsia). Both the maximum and minimum values for fibrinogen observed in the whole series of toxaemias were confined to the severe cases, the range being from 0.21 to 0.70. Thus, the maximum in this group was 150 m.gms. per 100 ml. higher and the minimum 120 m.gms. per 100 ml. lower than those seen in normal pregnancy. On closer analysis it is seen that exactly 50 per cent. of values in severe pre-eclampsia occupy the normal range,

30/

Table 15

Gms. per 100 ml.	Mild Toxaemia (50 cases)	Severe Toxaemia (50 cases)	Total (100 cases)
0.21-0.30	-	8	8
0.31-0.40	-	10	10
0.41-0.50	30	11	41
0.51-0.60	20	13	33
0.61-0.70	-	8	8
Average	0.49	0.47	0.48
S.D.	0.043	0.13	0.10
Maximum	0.60	0.70	0.70
Minimum	0.41	0.21	0.21

30 per cent. are placed above the maximum and 20 per cent. below the minimum normal values. It thus indicates, that while in milder degrees of toxaemias it is reasonable to expect a comparatively higher plasma fibrinogen level, as the toxaemia becomes severe the fibrinogen content becomes unpredictable. This is obviously the reason why some observers (11) maintain that fibrinogen increases in toxaemia while others find little change, or an actual diminution in its concentration (9). This point will receive further attention.

The albumin: globulin ratio in severe toxaemias in our series was, average 1.16; S.D.0.09. The values occupied a range of 1.0 to 1.32. The decrease in the albumin:/

Table 16

A:G. Ratio	Mild Toxaemia (50 cases)	Severe Toxaemia (50 cases)	Total (100 cases)
0.91-1.00	-	2	2
1.01-1.10	-	14	14
1.11-1.20	4	17	21
1.21-1.30	31	16	47
1.31-1.40	11	1	12
1.41-1.50	4	-	4
Average	1.28	1.16	1.22
S.D.	0.06	0.09	0.10
Maximum	1.46	1.32	1.46
Minimum	1.19	1.00	1.00
Albumin *	2.95 ± 0.10	2.69 ± 0.15	2.82 ± 0.16
Globulin *	2.30 ± 0.03	2.32 ± 0.01	2.31 ± 0.036

* Gms. per 100 ml. plasma : average probable error.

albumin: globulin ratio in these cases is statistically significant. In 66 per cent. of severe pre-eclamptic patients the values were less than the normal minimum and in 50 per cent. they were less than the minimum values in mild pre-eclampsia. When both series of toxaemias are taken together and compared with normal pregnancy it appears that the albumin:globulin ratio falls with the onset of toxaemia and becomes still less as the severity increases.

The/

The decreasing ratio seems to follow directly the course of the plasma albumin concentration. Between mild and severe cases of toxaemia the albumin level falls by 260 m. gms. per 100 ml. of plasma which is equivalent to 8.8 per cent. of the value obtained in mild pre-eclampsia. When compared with normal pregnancy the fall in the plasma albumin concentration amounts to 350 mgms. per 100 ml. or 24 per cent. of the normal pregnancy level during the last trimester.

The average value for globulin during severe pre-eclampsia appears to be slightly higher than that in the milder form of the disease, but this difference is not significant. It will be fair to conclude that plasma globulin level does not show an appreciable alteration when toxaemia assumes moderate severity (compared with milder forms). The fall in the albumin:globulin ratio which occurs in severe toxaemias is therefore entirely due to a decrease in the concentration of the plasma albumin. That the fluctuation of the plasma albumin plays the important part in the alteration of the ratio is further shown by the fact that as toxaemia becomes severe the range of values for plasma albumin increases. The co-efficient of variation changes from 5.1 in mild toxaemias to 8.5 in the severe cases, while the individual values in the latter condition were scattered between 3.43 and 2.29 gms. per 100 ml. Compared with this the co-efficient of variation for plasma globulin show/

show a remarkable decrease (1.3 in mild and 0.4 in severe toxaemias), which indicates a condensation of the values around the mean. It follows, therefore, that the factor, or factors which normally maintain the albumin level of the plasma is in some way affected by the process of toxaemia, while compensation, if there is any, is of a very poor nature. The labile state of albumin and fibrinogen deserves adequate consideration.

11. Plasma Proteins and the Clinical state of Toxaemia.

If the concentration of plasma proteins in toxaemia of pregnancy is directly related to the underlying cause, it would be natural to expect an improvement or deterioration in the protein content of the plasma with a corresponding variation in the clinical course of the disease. An attempt was made to study this problem by weekly follow-up of all cases in our series and comparing the plasma protein level with other clinical features of the ailment. During our investigation 49 patients showed clinical improvement. In 51 patients the condition deteriorated to such an extent that in 36 labour had to be induced. Our findings with regard to the total protein and albumin:globulin ratio in these cases are given below.

a. Cases showing improvement (49 cases) - The total plasma protein concentration in these cases on admission was 5.66 gms. per 100 ml.; S.D. 0.19. In the following week, inspite of the improvement in the clinical condition, the total protein/

Table 17

		1	2	3	4 weeks
Total Protein (49 cases)	Average	5.66	5.54	5.67	5.75
	S.D.	0.19	0.25	0.30	0.32
	Range	5.90-5.07	5.31-4.94	6.20-5.26	6.16-5.40
A.:G. Ratio (49 cases)	Average	1.22	1.26	1.29	1.32
	S.D.	0.10	0.10	0.09	0.08
	Range	1.43-1.05	1.47-1.05	1.49-1.13	1.43-1.20
Haema-tocrit (30 cases)	Average	38.1	34.4	34.0	35.1
	S.D.	2.2	3.5	2.7	2.1
	Range	36.0-41.1	30.1-39.1	31.0-37.0	32.0-37.5

protein concentration decreased to 5.54 gms. per 100 ml.; S.D. 0.25. During the two subsequent weeks the hypoproteinaemia was corrected spontaneously, and the concentration of protein increased to 5.67 gms.; S.D. 0.30 in the third week, and then to 5.75 gms. per cent.; S.D. 0.32 in the fourth week of investigation (Table 17). This variation in the level of plasma proteins does not show uniform statistical significance. The decline in the concentration during the first week is striking but is of bare statistical significance. The interest however lies in the fact that this drop in the plasma protein level affected not only the average value but also the minimum and maximum values of the series. On analysis of individual cases/

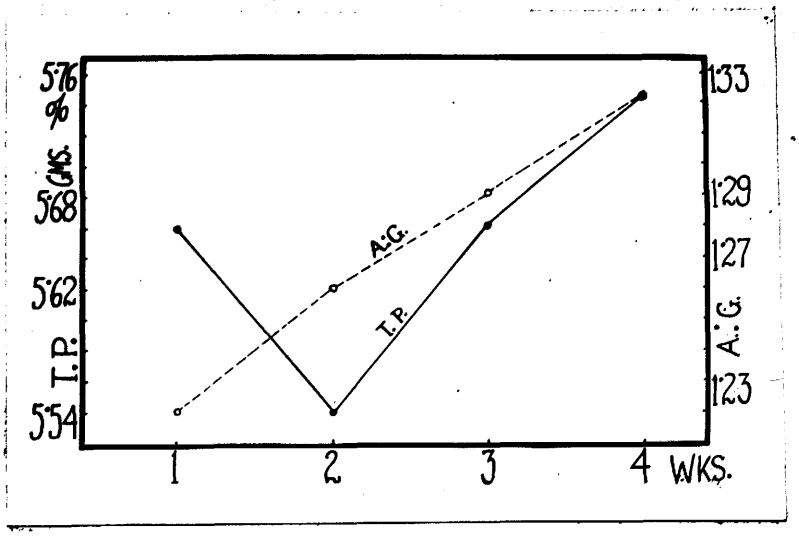

Fig. 4. Plasma proteins in relation to the clinical course of toxaemia. The graph shows the behaviour of the total protein and the A : G ratio where the clinical condition improved during the investigation

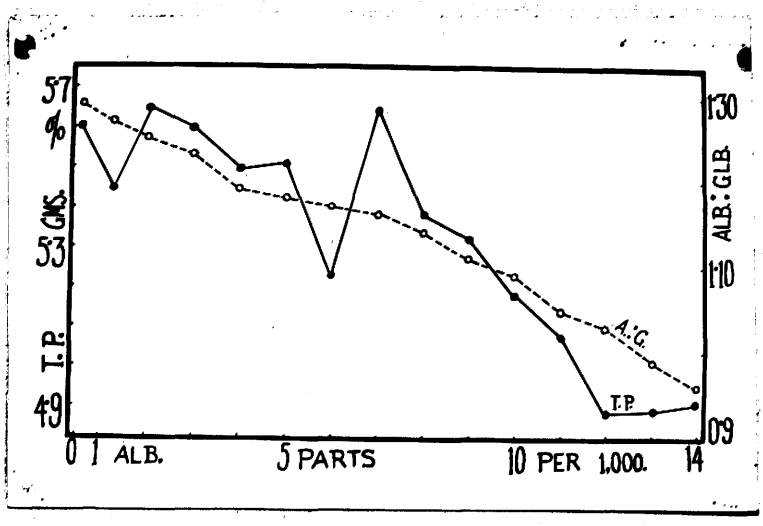

Fig. 5. Plasma proteins and the A.G. ratio in relation to the albuminuria of pre-eclampsia.

cases it was found that the protein concentration, during the second week was less than that at the time of admission in 61 per cent. of cases. The extent of this fall varied from 0.02 to 0.26 gms. per 100 ml., the average being 0.12 gms.; S.D. 0.03. This is equivalent to a 2.1 per cent. depreciation below the admission level. During this period however the clinical improvement was of an appreciable nature. The fall in the plasma protein level inspite of improvement in toxaemia required investigation. One of the possibilities was that this decrease was merely apparent, being caused by haemodilution. This point was investigated in the last 30 cases in the present series. It was found from haematocrit study that simultaneous with the clinical improvement the haematocrit reading became less, indicating a relative increase in plasma volume. During the period under consideration the relative haemodilution amounted to 6.0 per cent. of the admission level. This, compared with the fall in the plasma protein concentration, referred to above, suggests an actual increase in the protein content of the plasma inspite of the apparent diminution of the concentration per 100 ml. That, such is really the case is shown by the subsequent behaviour of the protein level. The rise during the third and fourth weeks of investigation is steady and considerable, and satisfies statistical analysis. The haematocrit during this period shows no appreciable change. It thus appears that an improvement of/

of the state of toxaemia is attended with active regeneration of the proteins of the plasma, although normal pregnancy level was not regained even when considerable clinical improvement occurred.

Another evidence of the regeneration of plasma proteins is found in the increase of the albumin:globulin ratio. Inspite of the fall in the plasma protein concentration during the first week the ratio increased from 1.22 to 1.26, and during the subsequent period this improvement was steadily maintained. The increase in the ratio was brought about at all stages by an active increase in the albumin content of the plasma for the plasma globulin (apart from a slight fall due to haemodilution in the first week) showed no recognisable change (Figure 4[redacted]).

b. Cases where Toxaemia persisted and Deteriorated (51 cases)
The total protein concentration of the plasma in this group of cases on admission was 5.57 gms. per 100 ml.; S.D. 0.24. This is slightly lower than the corresponding value in the cases showing improvement. Unlike the cases where improvement occurred, a fair number, in the deteriorated group, could not be followed-up for the intended period of four weeks, as in the majority of them, pregnancy had to be artificially terminated. However, taking the whole series together as the toxaemia became worse both the total protein concentration and the albumin:globulin ratio showed a progressive and marked deterioration. [redacted]

Fourth/

[redacted] Out of the 51 cases, in this series, only 26 patients could be followed-up for the whole period. Their plasma-protein concentration and albumin:globulin ratio are presented in Table 18.

Table 18

		1	2	3	4 weeks
Total Plasma Protein	Average	5.60	5.52	5.39	5.15
	S.D.	0.22	0.26	.029	0.31
	Range	6.16-5.29	6.14-5.22	5.83-4.82	5.73-4.60
A.:G. Ratio	Average	1.26	1.23	1.21	1.17
	S.D.	0.10	0.09	0.08	0.09
	Range	1.46-1.06	1.43-1.06	1.32-1.05	1.29-1.04
Haema-tocrit (14 cases)	Average	33.6	39.4	40.9	42.2
	S.D.	1.9	2.3	2.4	2.8
	Range	41.5-35.0	42.3-35.4	44.0-35.5	45.7-37.0

Both the overall values shown in figure and those obtained from a complete follow-up study (Table 18) indicate that with increasing severity or persistence of the toxaemic state the concentration of the plasma proteins and albumin:globulin ratio are both adversely affected. This is manifested as a fall in the albumin content of the plasma; the globulin level remains practically unaltered, which accounts for a progressive diminution of the albumin-globulin/

globulin ratio. It will be seen later however that although the decline in the level of plasma albumin is the principal cause of the drop in the concentration of the total protein, it is not the only factor concerned in the process, for in very severe toxaemia plasma fibrinogen also diminishes.

In understanding the extent of the fall in the total protein and albumin concentration haematocrit studies are indispensible. The importance of this was realised only when the investigation was already in progress, and the results obtained in only 14 cases in this series have been presented here, but they provide sufficiently conclusive evidence for the purpose.

It will be seen that during the whole period of study there was a steady increase in the packed-cell volume, which suggests a progressive haemoconcentration. In most of these cases, with increasing severity of toxaemia oedema also became worse. The haemoconcentration was apparently due to a loss of fluid from the plasma to the extravascular spaces. Capillary endothelium however acts as a semipermeable membrane. Consequently uncomplicated haemoconcentration would be expected to cause a relative increase in the protein concentration of the plasma, and thereby mask the effects of hypoproteinaemia. The fact that, inspite of haemoconcentration the plasma-proteins decreased as toxaemia persisted, imparts considerable importance to this finding.

During/

During the whole period of study the plasma volume diminished by 3.6 per cent. In absence of an active hypoproteinaemia this should have raised the protein concentration from 5.60 to 5.94 gms. per 100 ml. The estimated protein content in the fourth week of study was 5.15 gms. per 100 ml. which indicates a net fall of 14.1 per cent. of the original value obtained at the time of admission.

It is thus evident that the clinical course of toxaemia has a profound effect on the protein concentration of the plasma, especially on that of the albumin fraction. The protein content increases when toxaemia improves and decreases when it becomes worse. Acute infectious diseases have long been known to cause a state of hypoproteinaemia, but in the majority of these conditions (e.g. pneumonia, enteric fever) there is an active loss of protein from the plasma. In toxaemia of pregnancy also a somewhat similar condition exists in the form of albuminuria. It is therefore necessary to investigate how the loss of albumin in the urine affects the plasma protein level in pre-eclamptic toxaemia.

111. Plasma Proteins and Albuminuria.

For the purposes of this investigation we have studied the results obtained from 304 estimations done on 100 cases of pre-eclampsia of varying severity at different stages of the illness. If the level of protein in the plasma is dependent upon its loss in the urine, it would be reasonable to/

to expect plasma protein concentration to follow closely the degree of albuminuria present. The results obtained in our cases are presented in Table 19 and in figure 6. In order to provide comparison the plasma protein concentration in 15 cases of essential hypertension complicating pregnancy (36-40 weeks gestation) but without any albuminuria are also presented.

Table 19

Aver. (Esbach)	Plasma Protein		Albumin: Globulin		Aver. (Esbach)	Plasma Protein		Albumin: Globulin	
	Aver.	S.D.	Aver.	S.D.		Aver.	S.D.	Aver.	S.D.
0 *	5.60	0.21	1.39	0.08	7.1 - 8	5.39	0.30	1.14	0.05
Tr. - 1	5.44	0.24	1.27	0.08	8.1 - 9	5.33	0.32	1.11	0.09
1.1 - 2	5.65	0.19	1.25	0.09	9.1 -10	5.19	0.27	1.09	0.10
2.1 - 3	5.60	0.23	1.23	0.07	10.1-11	5.08	0.31	1.05	1.10
3.1 - 4	5.50	0.20	1.19	0.10	11.1-12	4.85	0.34	1.03	0.06
4.1 - 5	5.52	0.22	1.18	0.08	12.1-13	4.89	0.29	0.99	0.05
5.1 - 6	5.23	0.30	1.17	0.06	13.1-14	4.90	0.33	0.96	0.06
6.1 - 7	5.65	0.21	1.16	0.07	-	-	-	-	-

* Values obtained in hypertension without albuminuria.

COMMENTS

The first point of interest in this table is that both the total protein concentration and albumin:globulin ratio in hypertension complicated with pregnancy bears close resemblance to the average values observed in our series of pre-eclampsia/

pre-eclampsia, superficially this suggests some similarity between true pregnancy toxaemia and essential hypertension complicating gestation.

The total protein concentration of the plasma in pre-eclampsia shows a general tendency to deterioration as albuminuria increases. However, this downward slope of the curve is interfered with by occasional ascents when albuminuria is mild or moderate. With more marked albuminuria (0.3 gms. per cent. or more) the fall in the total protein concentration is more evident. Apart from this general behaviour neither the extent nor the gradient of fall satisfies statistical analysis.

The behaviour of the albumin:globulin ratio is still more misleading, for at each stage the values show a downward trend, but the difference between the consecutive values is not statistically significant. If however the values in the above table are telescoped together into 4 groups the differences become statistically significant. This is apparently due to the fact that while albuminuria per se is not directly responsible obviously the deterioration of the plasma protein and albumin concentration is not so much related to albuminuria as to the severity of the toxaemic process itself. It will be evident that the descending slope of the albumin:globulin ratio is not present in the graph depicting the total protein concentration. This is to some extent because the fibrinogen content/

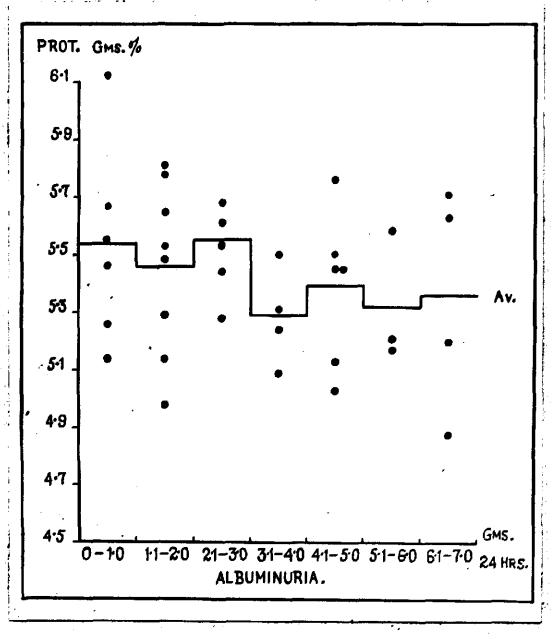

Fig. 6. A scatter diagram showing the relation of the concentration of plasma proteins to varying degrees of albuminuria.

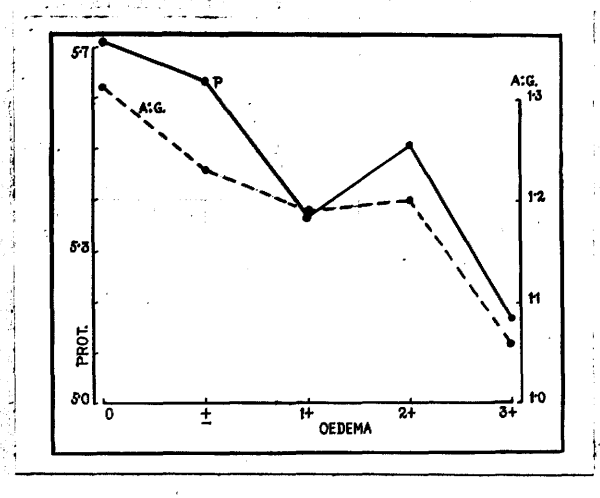

Fig. 7. Diagram showing the concentration of plasma proteins and the albumin : globulin ratio in relation to oedema.

Considerable literature has accumulated in recent years on the relation between hypoproteinaemia and oedema of pregnancy toxaemia. Some investigators (3, 8) have stated that the fall in the protein concentration of the plasma is responsible for oedema. Others including Harden (16, 1936) claim that they have been able to reduce the incidence of eclampsia by raising the protein content of the plasma with the help of high protein diet and establishing a positive nitrogen balance. However, Dieckmann (4a, 1941), Tillman (17, 1939) and several other authors point out that plasma protein level has no significant effect on oedema. It thus appears, that the subject is not free from contradictory findings and deserves investigation.

For this analysis, we have arranged our values for plasma protein into 2 groups and shall present them separately.

Group 1. This consists of the results of 100 estimations on our cases of pre-eclampsia, observed at the time of admission, and before compulsory bed-rest was imposed upon them. The results are presented in Table 20.

These figures suggest that with increase in the degree of oedema the plasma protein concentration tends to decline. The average values satisfy statistical analysis, the minimum and the maximum values also shift to the left as oedema increases. The scatter of values in each group however/

however increases considerably and steadily as oedema becomes worse. The difficulty of evaluation of these results lies in the fact that when the patient is ambulent, oedema, especially of the extremities is always more marked because of associated alterations in venous pressure caused by gravity; the effect which hypoproteinaemia alone has on oedema thereby becomes to some extent masked.

Table 20

Oedema	Average	S.D.	Maximum	Minimum
±	6.23	0.15	6.45	6.10
1+	5.71	0.18	6.19	5.48
2+	5.59	0.19	6.0	5.07
3+	5.37	0.27	5.76	4.82

Group 2. This consists of 304 estimations in our series of 100 cases of pre-eclampsia. The period of study covered from one to four weeks during which period all patients were kept at rest in bed. No discrimination was made between clinically improved and deteriorated cases. The most satisfactory method of evaluating oedema is to watch the change in body-weight under basal conditions. This however, was not practicable, so we shall present our results in relation to the traditional, though somewhat crude form of classification. These are presented in Table 21 and figure 8. In this connection, values for plasma protein from 26 patients/

patients having some degree of hypertension and albuminuria but no evident oedema and diagnosed in the antenatal clinic as toxaemia have been used as control (indicated by "0" in the table and figure).

Table 21

	Total Plasma Protein Gms./100 Ml.			A.:G. Ratio		
Oedema	Aver.	S.D.	Max.-Min.	Aver.	S.D.	Max.-Min.
0	5.71	0.22	6.20-5.41	1.31	0.04	1.40-1.24
±	5.63	0.24	6.16-5.20	1.23	0.06	1.34-1.14
1+	5.37	0.27	6.0 -5.10	1.19	0.09	1.32-1.10
2+	5.51	0.33	6.14-4.95	1.20	0.07	1.29-1.10
3+	5.17	0.30	5.76-4.82	1.06	0.11	1.26-0.94

COMMENTS

Both the total protein concentration and the ratio of albumin to globulin are lower in the oedematous than in the non-oedematous hypertensive cases, and the difference in values at this stage is apparently significant. But when the oedematous patients are classified according to the severity of oedema statistical significance becomes less evident. The lowest values were obtained in patients with generalised oedema, but apart from oedema these patients also suffered from very severe toxaemia for which pregnancy had to be artificially terminated in most instances. In patients with lesser degrees of oedema the downward trend/

trend of the curve described above disappears, and is even reversed. The toxaemic process in these cases was not of an hyperacute nature. If hypoproteinaemia was aetiologically responsible for oedema, it is evident that the tendency to decline would have been evenly maintained in this zone of the curve. It is probably more reasonable to believe that, both hypoproteinaemia and oedema are controlled by the common factor of underlying toxaemia than to accept that oedema in pre-eclampsia is caused only by a falling concentration of the protein (principally albumin) of the plasma.

V. Plasma Proteins and Blood Pressure.

It has been pointed out that available evidence indicates that the fall of plasma protein in pre-eclampsia is caused by the underlying process of toxaemia. The nature of this toxaemia is yet unknown, but in recent years it has been more or less accepted that hypertension is its most important manifestation. That being so it would be expected that the behaviour of the plasma proteins should in some respects follow the course of blood pressure. The analysis which is presented here is based on 304 estimations, done on 100 cases of pre-eclampsia.

It has already been seen that the concentration of the "serum" proteins in toxaemia follows closely that of albumin, for the globulin content vaires to no appreciable degree./

degree. The albumin:globulin ratio fairly indicates the nature of this change. Plasma fibrinogen however has been found to show an erratic response. This often obscures the real state of concentration of albumin, when total "plasma" protein concentration is examined. It is for this reason that the present analysis will be based on the albumin:globulin ratio and the fibrinogen content of the plasma in relation to different levels of blood pressure. Because of careful supervision at the antenatal clinics most of the hospital admissions come within the range of 150 to 160 mm.Hg. systolic and 100 to 110 mm.Hg.diastolic. Comparatively fewer cases have been noticed at very high levels of blood pressure. The results obtained are presented in Tables 22 and 23 and in figures 8 and 9.

Table 22

B.P. mm. Hg.	A.:G	S.D.	Fibrin-ogen gms./ 100 ml.	S.D.	B.P. mm. Hg.	A.:G	S.D.	Fibrin-ogen gms./ 100 ml.	S.D.
146-150	1.24	0.05	0.46	0.04	176-180	1.10	0.06	0.36	0.13
151-155	1.23	0.06	0.40	0.09	181-185	1.22	0.10	0.24	0.05
156-160	1.17	0.03	0.47	0.14	186-190	1.03	0.05	0.17	0.03
161-165	1.15	0.09	0.47	0.13	190-195	1.05	0.05	0.20	0.04
166-170	1.07	0.03	0.49	0.07	196-200	1.01	0.02	0.29	0.05
171-175	1.13	0.06	0.35	0.10	201-210	1.22	0.03	0.44	0.10

Table 23 shows the relation of the albumin:globulin ratio and plasma fibrinogen values to various levels of systolic/

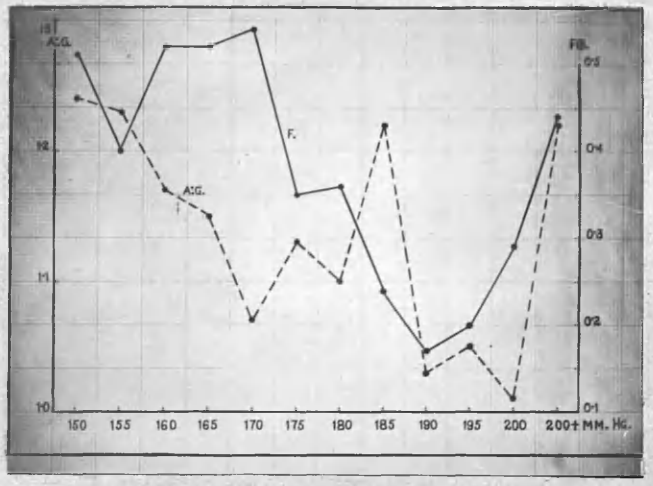

Fig. 8. Fibrinogen and albumin : globulin ratio in relation to the systolic blood pressure in pre-eclampsia.

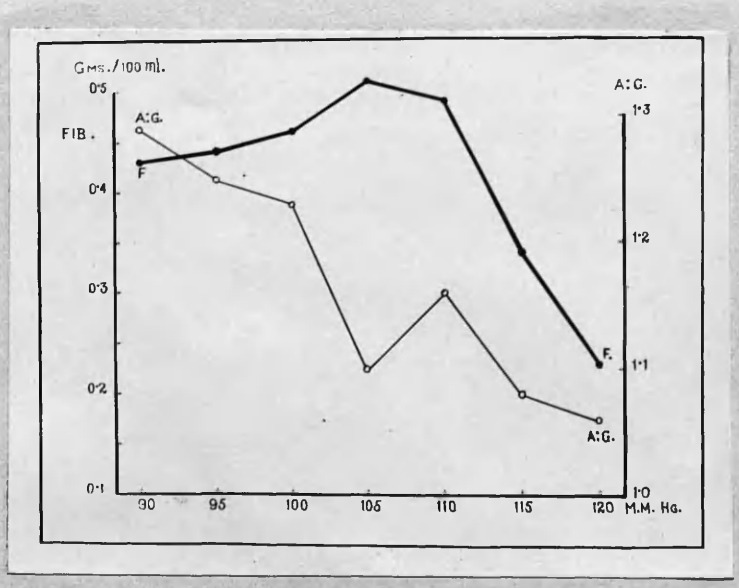

Fig. 9. Fibrinogen and albumin : globulin ratio in relation to the diastolic blood pressure in pre-eclampsia.

systolic blood pressure. It is interesting to note that apart from a very general tendency to decline (which however is not significant at all stages) there exists no relationship between the systolic blood pressure and the behaviour of the albumin:globulin ratio, or that of fibrinogen. Neither the albumin nor the fibrinogen content of the plasma seems to be affected by the height of blood pressure alone in pregnancy toxaemia. The lowest albumin:globulin ratio (0.90) was found with equal frequency with blood pressures of 130, 190 and 200 mm. of Hg. (systolic). Similarly the ratio of 1.03 was found in one patient with a blood pressure of 160, and another with a pressure of 200 mm. Hg. Yet one patient with a systolic blood pressure of 210 mm. Hg. had an albumin:globulin ratio of 1.27, which was a frequent finding in the blood-pressure group of 150 to 160 mm. Hg. Nevertheless, some of the high values for the ratio ranging between 1.32 to 1.42 were found only at the lower ranges of systolic blood pressure.

The behaviour of fibrinogen is even more atypical than that of the albumin:globulin ratio. At no stage is any correlation found to exist between the systolic blood-pressure and the concentration of plasma fibrinogen. The highest value for this constituent of the plasma in our series, viz. 0.74 gms. per 100 ml. was found in a patient with a systolic blood pressure of only 160 mm. Hg. Yet, less/

less than 0.20 gms. of fibrinogen per 100 ml. was seen with a blood pressure as high as 210 and as low as 160 mm.Hg. As the standard deviations would indicate, the scatter of values at different levels of blood pressure varied only slightly. In view of these findings it is impossible to believe that the level of systolic blood pressure in pre-eclampsia can have any effect, harmful or otherwise, on the concentration of the plasma proteins or on that of its individual fractions. Moreover it follows that, if toxaemia affects the plasma protein level, as it is likely to do, the measure of the intensity of toxaemia apparently does not lie in the level attained by the systolic blood pressure alone.

Table 23

B. P. mm. Hg.		90	95	100	105	110	115	120
A.:G	Aver.	1.29	1.25	1.23	1.10	1.16	1.03	1.06
	S. D.	0.10	0.09	0.09	0.10	0.09	0.10	0.13
	Max.-Min.	1.49-1.12	1.45-1.09	1.46-1.03	1.16-1.02	1.32-1.00	1.23-1.00	1.27-0.90
Fib-rin-ogen	Aver.	0.43	0.44	0.46	0.51	0.49	0.34	0.38
	S. D.	0.04	0.05	0.06	0.08	0.13	0.11	0.15
	Max.-Min.	0.50-0.39	0.53-0.36	0.63-0.23	0.55-0.39	0.74-0.24	0.43-0.19	0.58-0.13

The diastolic blood pressure however gives a slightly different impression from what has just been described (Table 23). The albumin:globulin ratio shows an even down-

ward/

downward tendency with increase of pressure, apart from a sudden depression at the level of 105 mm.Hg. There were however only 3 cases in this group, and the maximum value obtained here was the lowest in the whole series. The maximum values at lower ranges of pressure show hardly any significant alteration, and closely approach the normal figures. At higher levels of pressure these drop considerably below normal but still remain within a narrow range. The minimum values throughout the series however show a progressive deterioration. The difference at each stage appears to be statistically significant. The gradient of fall is small at lower levels of diastolic pressure but above 110 mm.Hg. the decline is rapid and marked.

The manner in which fibrinogen reacts reveals several interesting features. As the diastolic pressure rises above normal the fibrinogen content of the plasma tends to increase. It will appear (c.f. Table 12) that at 90 mm.Hg. pressure the average plasma fibrinogen level equals that in the last trimester of normal gestation, and shows almost similar distribution of values. As the blood pressure increases the concentration of fibrinogen also rises until the maximum is attained between at 105-110 mm.Hg. This change is brought about by a larger number of higher values in each group. The minimum values obtained show considerable lack of uniformity. Above 110 mm.Hg. diastolic pressure the fibrinogen level declines rapidly. The gradient of descent/

descent is much greater than that of the rise. Highest values for fibrinogen (0.70 - 0.74 gms. 100 ml.) in our series were obtained when the diastolic blood pressure was 110 mm. Hg. The lowest value for plasma fibrinogen was observed in a patient with a diastolic pressure of 120 mm. Hg. However, the co-efficient of variation of the values increases with increase in pressure and the fluctuation of the average are not uniformly significant at all stages.

COMMENTS

The relation between raised diastolic blood pressure and the behaviour of plasma protein is interesting. However, these findings alone do not justify the conclusion that the level of proteins in the plasma is directly related to the diastolic pressure. It is possible that vascular spasm affecting the organs (notably the liver) entrusted with formation of plasma proteins is the cause of changes described above. Diastolic blood pressure is merely an expression of the degree of vascular spasm present, and it is only in this respect that the significance of diastolic pressure can be evaluated in its relation to the levels plasma proteins.

VI. Plasma Proteins and Protein Intake.

In recent years considerable attention has been drawn to the effects of high protein diet on toxaemia of pregnancy. The investigations of the Peoples League of Health (13,1942) and/

and the Toronto experiment conducted by Ebbs, Tisdall and Scott (19, 1941) point out that the incidence of pre-eclampsia could be appreciably reduced if expectant mothers are provided with an adequate dietary with optimum intake of proteins. Strauss (3a, 1937) believes that most of the manifestations of toxaemia are caused by lowered plasma protein concentration, which again is related to the level of dietary proteins. Harden, McEllroy and Huggins (16a, 1935) observed that a negative nitrogen balance in toxaemia of pregnancy could be corrected by an increased protein intake. Harden (16, 1937) in a subsequent communication states that he had been able to considerably reduce the incidence of eclampsia by establishing protein stabilisation. However, Arnell, Goldman and Bertucci (20, 1945) in a discussion on protein deficiency in pregnancy state that the relation between protein intake and plasma protein concentration is only of a general nature. They found that the average values for plasma proteins were lower in the low protein group, but the highest plasma protein value obtained by them was also in this group. P.F. Williams (21, 1945) in discussing this paper also stated that he was "unable to make any positive correlation between the intake of protein and the severity of toxaemia". In view of the contradictory nature of these observations a study of the problem was considered useful.

All/

All our cases of pre-eclampsia were derived from the three units of the Glasgow Royal Maternity and Women's Hospital. The composition of the diet varied in each unit but the total caloric consumption was about the same. The result are analysed below (Figure 10).

Unit A.

Diet - Carbohydrate 236 gms.
Fat 73 gms.
Proteins 102 gms.
(71 gms. first class protein).
Calories 2,254.

There were 42 patients in this unit, 24 were cases of mild pre-eclampsia and 18 had severe toxaemic manifestations. The values obtained are presented in Table 24.

Table 24

	Severe Pre-eclampsia			Mild Pre-eclampsia			Total		
	Aver.	S. D.	Min-Max.	Aver.	S. D.	Min.-Max	Aver.	S. D.	Min.-Max.
Total Protein	5.49	0.17	5.17-5.82	5.72	0.14	5.53-6.16	5.62	0.21	5.17-6.16
Fibrinogen	0.46	0.13	0.28-0.70	0.49	0.03	0.41-0.54	0.48	0.09	0.28-0.70
A.:G.	1.18	0.08	1.06-1.28	1.23	0.06	1.20-1.46	1.23	0.10	1.06-1.46
Albumin	2.72	0.14	2.41-3.00	2.93	0.17	2.76-3.40	2.84	0.19	2.41-3.40
Globulin	2.31	0.02	2.27-2.33	2.30	0.04	2.21-2.35	2.30	0.03	2.21-2.35

Of the 42 cases in this series 14 or 33.3 per cent. showed clinical improvement. In 17 or 40.5 per cent. the condition/

condition deteriorated, and in 26.2 per cent. (11 cases) the toxaemia persisted without appreciable aggravation.

Unit B.

Diet - Carbohydrate 180 gms.
Fat 116 gms.
Protein 131 gms.
(115 gms. first class protein)
Calories 2,238.

Thirty-three cases of pre-eclampsia were studied from this unit, 18 of whom were cases of severe toxaemia and 15 had mild pre-eclamptic symptoms. The results of investigation are presented in Table 25.

Table 25.

	Severe Pre-eclampsia			Mild Pre-eclampsia			Total		
	Aver.	S.D.	Min-Max.	Aver.	S.D.	Min.-Max.	Aver.	S.D.	Min.-Max.
Total Protein	0.52	0.22	5.07-5.90	5.36	0.24	5.56-6.45	5.68	0.23	5.07-6.45
Fibrinogen	0.53	0.12	0.27-0.67	0.53	0.03	0.47-0.59	0.53	0.06	0.27-0.67
A.:G.	1.16	0.09	1.02-1.32	1.30	0.07	1.13-1.45	1.22	0.04	1.02-1.45
Albumin	2.68	0.24	2.36-3.48	3.01	0.21	2.71-3.47	2.83	0.19	2.36-3.48
Globulin	2.31	0.24	2.29-2.34	2.32	0.03	2.27-2.35	2.32	0.02	2.27-2.35

Under this dietary regime 11 or 33.3 per cent. of patients showed clinical improvement. In 16 patients or 48.5 per cent. the condition deteriorated and in the remaining 7 cases (21.2 per cent.) the state of toxaemia persisted almost unchanged.

Unit/

Unit C.

Diet - Carbohydrate 382.65 gms.
Fat 68.1 gms.
Protein 75.05 gms.
(43.2 gms. first class protein)
Calories 2,444.

There were 25 cases in this series. Of these 14 had severe pre-eclampsia and 11 were suffering from mild toxaemia. The results are presented in Table 26.

Table 26

	Severe Pre-eclampsia			Mild Pre-eclampsia			Total		
	Aver.	S.D.	Min.-Max.	Aver.	S.D.	Min.-Max.	Aver.	S.D.	Min.-Max.
Total Protein	5.33	0.18	4.82-5.58	5.63	0.09	546-5.74	5.49	0.22	4.82-5.74
Fibrinogen	0.39	0.11	0.21-0.60	0.46	0.07	0.41-0.60	0.42	0.05	0.21-0.60
A.G.	1.16	0.10	1.0-1.25	1.26	0.07	1.19-1.31	1.21	0.03	1.0-1.31
Albumin	2.68	0.20	2.29-2.91	2.33	0.10	2.19-3.17	2.77	0.24	2.29-3.17
Globulin	2.31	0.02	2.28-2.34	2.29	0.05	2.19-2.35	2.30	0.04	2.19-2.35

With the low protein diet described above 8 patients or 32.0 per cent. showed clinical improvement. In 7 patients or 28.0 per cent. the toxaemia was aggravated and in the remaining 10 cases or 40 per cent. the condition persisted without any appreciable change.

COMMENTS

It will be evident from the cases presented here that the protein content of the diet per se, has very little effect/

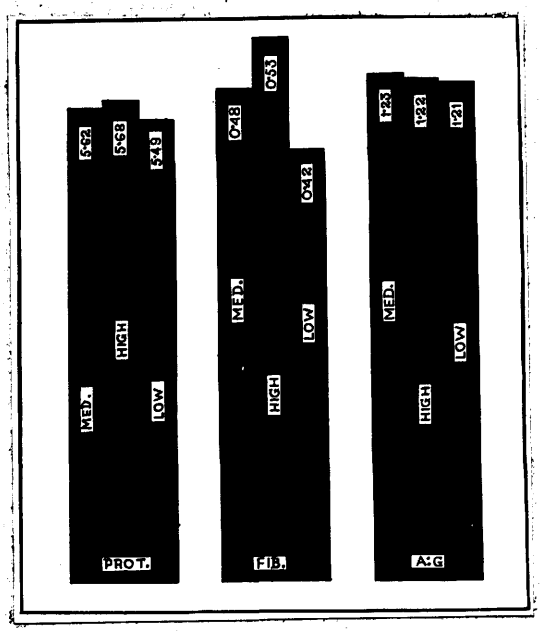

Fig. 10. Total plasma protein, fibrinogen and albumin : globulin ratio in pre-eclampsia at different levels of diatery protein intake.

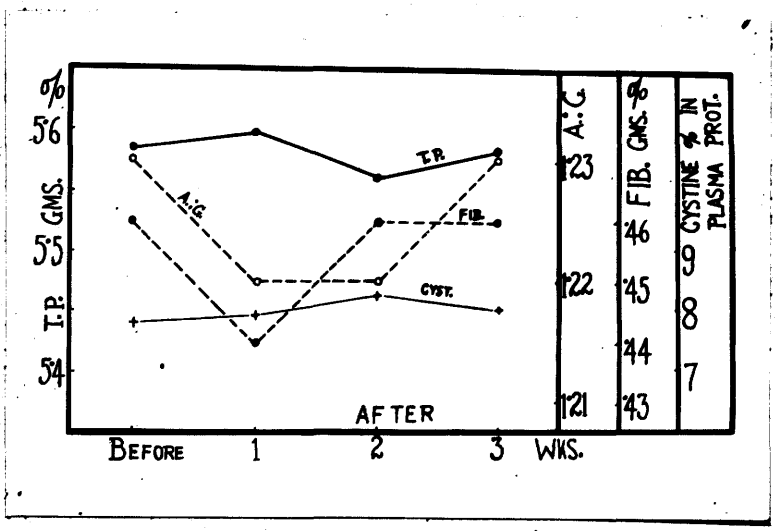

Fig. 11. Total protein, fibrinogen, alb. : glob. ratio and the cystine content of plasma proteins in pre-eclamptic patients whose diet was reinforced with 5 Gm. of cystine daily.

effect on the immediate course and prognosis of the disease. It will also appear from this analysis that irrespective of the amount of protein consumed in the diet (which varied from 72 to 131 gms. total protein, and 43 to 115 gms. of protein of high biological value) in approximately two-thirds of the patients the toxaemia either persisted or actively deteriorated. In 13 per cent. of patients receiving high-protein diet, 20 per cent. of those having low protein diet and 21 per cent. of cases with medium protein consumption the toxaemia assumed such severity as to need artificial termination of pregnancy.

The relation between the level of dietary protein intake and that of the protein concentration of the plasma appears to be as indefinite as the gross clinical results obtained in our series. The total protein content of the plasma appears to be slightly higher in the high protein group than in those who receive a diet comparatively poorer in protein. It has already been pointed out that fibrinogen behaves in a rather erratic fashion in toxaemias of pregnancy, being unusually high in some cases and abnormally low in others. Moreover, it is the serum albumin which not only constitutes the most important fraction, but also is the first to suffer in pregnancy toxaemia. The effect of high-protein diet is, therefore, to be judged by the level of serum albumin and albumin:globulin ratio. These do not show any significant variation among the group of cases presented above. It is true/

true that both the minimum and maximum values in the "high-protein" group are to some extent higher than the corresponding values for albumin and albumin:globulin ratio in the "low-protein" cases, but when one considers that the level of protein intake in the former group of patients was 1.75 times higher than that in the latter, the slight difference in values noticed loses its importance. In this respect comparisons of values obtained in Units A and B are extremely striking, for inspite of a difference of intake of 44 gms. of first class proteins daily the values for both plasma albumin and albumin:globulin ratio were almost identical.

When the mild and severe pre-eclampsias are examined separately further evidence is obtained to show that the level of protein consumption is not the only factor which affects the plasma protein concentration. Indeed, in mild toxaemias the average values for plasma albumin and that of the ratio are highest in the "high-protein", lowest in the "low-protein" and intermediate in the "medium-protein" intake group. Unfortunately however, the difference in the values are not of sufficient statistical significance. In severe toxaemias both plasma albumin and albumin:globulin ratio were identical in both Units B (131 gms. protein) and C (75.5 gms. protein). This suggests that when toxaemia attains a certain degree of severity inspite of high levels of protein consumption the plasma protein concentration falls,/

falls, apparently due to interference with the mechanisms involved in the process of regeneration of proteins in the circulation. This has also been noticed in connection with the nitrogen balance studies described in the preceding chapter. These facts however do not provide arguments against the employment of a high protein diet in pre-eclampsia. Restoration of a positive balance of nitrogen and building up the protein reserves of the body, which play an essential role in pregnancy, are two very important functions of a diet rich in protein. Such a diet however need not be expected to immediately rebuild the plasma protein level until these essential demands have been fulfilled and the process of toxaemia is under control.

One interesting facts deserves mention in connection with high-protein diet. An analysis of the figures presented above will show that a distinct effect of increased protein consumption is an elevation of the plasma fibrinogen. This is to some extent responsible for a raised level of total protein concentration of the plasma, but from the physiological point of view this is of little benifit, for fibrinogen plays an insignificant role in the oncotic properties of plasma proteins. The effect of high protein diet in raising the fibrinogen content of the plasma is interesting in relation to Dieckmann's (46, 1929) experiments on the effects of tissue fibrinogen in the production of hepatic lesions of eclampsia in experimental animals.

We/

We shall have occasion to discuss this subject in a subsequent section.

The cause for this lack of response of serum albumin to high protein diet in pregnancy toxaemia is as yet imperfectly understood. There may be two possible explanations for it. (1) Conditions which are associated with recognised toxaemia, bacterial or otherwise have been known to be associated with increased tissue destruction, one of the evidences for which is a high level of excretion of products of nucleoprotein metabolism. The plasma proteins are called upon to meet the loss suffered by the tissues. Experiments of Fink et al (22, 1944) and several other investigators have demonstrated that there is a free exchange of proteins between plasma and tissues. In toxaemias of pregnancy, especially eclampsia the level of uric acid in the plasma rises. This has been suggested by Stander (17a, 1932) to be due to haemorrhage taking place in the liver, and by itself is not sufficient evidence for assuming the existence of active tissue destruction in pre-eclampsia. Plasma uric acid shows hardly any change from normality in the early stages of the disease and in mild pre-eclampsia. At this stage the nitrogen excretion in the urine also does not show any increase above normal levels, if proteinuria can be excluded. Infact, the available data of almost all investigators on the subject show that the/

the biochemistry of blood and urine show little deviation from normality at an early stage of toxaemia when plasma proteins commence to fall below the normal pregnancy level.

It is however worthy of note that Poo, Lew and Addis (23, 1939) demonstrated that during pregnancy the rate of protein anabolism is considerably augmented. In pregnant rats this accounts for a 23 per cent. increase in the protein assigned to the liver, much of which constitutes the reserve protein of the body. Melnick and Cowgill (24, 1937) found by means of plasmapheresis in pregnant dogs, that when the reserve proteins are exhausted there is a marked impairment of regeneration of plasma proteins. If toxaemia of pregnancy is associated with a depletion of the reserve proteins of the body and a consequent secondary fall in the plasma protein concentration, high intake of dietary protein would be expected to build up the protein reserve before the plasma proteins show an appreciable increase. The nitrogen balance studies described in the previous chapter show that inspite of high levels of protein consumption, a sufficiently high state of positive nitrogen balance is difficult to obtain in pre-eclampsia. These facts makes the second explanation for the decrease in the plasma protein concentration more plausible, viz. (2) The capacity of the body to anabolise large amounts of protein suffers in toxaemias of pregnancy. Normal pregnancy is associated/

associated with a positive nitrogen balance, which sometimes amounts to as much as 2.7 gms. of nitrogen (= 16.9 gms. protein) per day. (Hunscher et al, 25, 1933). In toxaemias of pregnancy such high levels of positive balance are seldom obtained. A detailed study of the mechanism of protein synthesis in pre-eclampsia is expected to provide an answer to this problem. It was not possible for us to use dietary or injectable proteins with an attached tracer nitrogen, so we undertook to investigate the subject in an indirect manner.

Sulphydril compounds in the proteins are comparatively easily detected, and the sulphur contained in the amino-acids having such sulphydril radicals can be quantitatively measured. L-cystine is an essential amino acid, which together with choline exerts a lipotropic effect on the liver, and it has been claimed by Krohn and Borwolff (26, 1937) and Maksimova (27, 1937) that cystine possesses a protein sparing effect when the diet is low in protein. It is on these grounds that 14 patients in our series were given 5 gms. of cystine daily for three weeks in addition to the diet they consumed.

Sulphur was estimated in the plasma proteins before cystine was administered and then at weekly intervals for 3 weeks. The method of estimation employed is described in the appendix. For the sake of simplicity, the sulphur content of the proteins is expressed as "combined" cystine per/

per 100 ml. of plasma. The results are presented in Table 27 and figure 12.

Table 27

	Before	1	2	3 weeks
Total Protein	5.58 ± 0.03*	5.60 ± 0.08	5.57 ± 0.09	5.60 ± 0.11
	5.36 - 5.86	5.23 - 5.75	5.03 - 5.99	4.90 - 6.16
Fibrinogen	0.46 ± 0.03	0.45 ± 0.07	0.46 ± 0.06	0.46 ± 0.09
	0.41 - 0.51	0.26 - 0.59	0.24 - 0.56	0.13 - 0.54
A.:G. Ratio	1.23 ± 0.02	1.22 ± 0.02	1.22 ± 0.02	1.23 ± 0.03
	1.18 - 1.29	1.11 - 1.32	1.03 - 1.37	1.05 - 1.38
Cystine	0.77 ± 0.03	0.78 ± 0.03	0.82 ± 0.05	0.79 ± 0.08
	0.69 - 0.81	0.73 - 0.82	0.75 - 0.89	0.71 - 0.90

* Mean ± standard deviation.

The data presented above show that, cystine is a poor basis for regeneration of plasma proteins. It is interesting, in this connection, to note that Morse and Schmidt (28,1944) failed to maintain a positive nitrogen balance in pregnant rats by adding even d-l-methionine to a 33 per cent. nitrogen diet.

COMMENTS

In the series of cases presented above, additional cystine not only failed to increase the concentration of plasma proteins, but also proved ineffective in increasing the content of sulphur containing amino-acids in the proteins of the plasma. Three cases of normal pregnancy were given 5 gms. of cystine daily for one week (in addition to the ordinary diet). All showed a slight increase in the content of/

of plasma albumin at the end of the period of investigation. This amounted to 0.14, 0.20 and 0.29 gms. per 100 ml. respectively. Simultaneously, there was an increase in the sulphur content of the plasma proteins in each case, the average being 0.04 gms. per 100 ml. plasma. The sulphur content of the plasma proteins appears to be fairly constant in normal pregnancy. This constancy is affected to a great extent in toxaemias and could not be restored in our cases with additional cystine. It is difficult to believe that all of the cystine given to these patients was put aside for storage, for the excretion of sulphur in the urine during the period of study increased from 3.6 ± 0.2 to 3.98 ± 0.3 gms. per day. These findings together with the results of the nitrogen balance already described suggest that the process of protein synthesis is not as efficient in toxaemias as in normal pregnancy.

In this connection it is interesting to recall the experiments done by Whipple and his co-workers (29, 1934). These authors found that regeneration of plasma proteins in a normally nourished dog occurs with great rapidity when these are removed from the circulation. But if the animals are depleted of proteins by the removal of plasma proteins and/or haemoglobin over a prolonged period, regeneration is greatly retarded. Normal pregnancy is associated with a decrease of about 17 per cent. in the concentration of plasma proteins and about 15 per cent. in haemoglobin. Milnick and Cowgill (24, 1937) observed that pregnancy

is/

is akin to a state of internal plasmapheresis. Under these circumstances when toxaemia develops and gives rise to further depletion of plasma proteins a condition is created which can to some extent be compared with the experiments described by Whipple. As a consequence the regeneration of the proteins of the plasma is retarded and falls below the mark it is expected to attain in presence of high dietary protein consumption.

VII. Effects of Raising the Plasma Protein Level by by infusions of Concentrated Human Plasma Protein.

Elman (30, 1937) pointed out that intravenous infusions of protein hydrolysates caused an increase in nitrogen storage, and regeneration of plasma proteins in wasted subjects. This observation has been confirmed by other subsequent workers (31, 32). Recently Seeley (33, 1944) demonstrated that in cases of acute protein depletion intravenous injections of concentrated plasma restored normal conditions. Arnell and co-workers (20, 1945) claim that massive "nutritional" oedema in pregnancy, simulating toxaemia can be successfully treated by this method of therapy. Occasionally one comes across a sporadic case-report where toxaemia has been successfully treated by infusions of plasma. These reports are essentially of a clinical nature and lack in the data necessary to understand the manner in which such improvement is brought about. It was therefore considered necessary to investigate the physiological/

physiological basis of this treatment.

Nine cases of genuine pre-eclampsia were studied for this purpose. Each of them received a high protein diet (vide supra, Unit B). The fluid intake was limited to 1.5 litres a day, and none of them received any treatment apart from routine sedation with phenobarbitone gr. ¼ t.i.d. until the test was over.

The quantity of plasma protein injected in each case varied from 24 to 32 gms. The concentration was adjusted in order to make the solution 2½ to 4 times more concentrated than normal plasma. The actual quantity of protein administered was determined by estimation of the total protein content of the final solution. The method employed for this purpose was essentially similar to that used for the determination of plasma proteins.

The investigation covered a period of 7 days starting from the day when the infusion was given. The basic values were obtained from samples of blood collected immediately before the infusion.. The investigations carried out consisted of the study of changes in plasma protein concentration, albumin:globulin ratio, fibrinogen, urea, amino acid nitrogen, plasma volume, urinary output, oedema, blood pressure and albuminuria. For obvious reasons blood volume measurements with Evans blue (T 1824) could not be repeated every day. The plasma volume was estimated by injection of the dye before the test started and at the conclusion

of/

of the experiment. In the intervening period the volume of plasma was calculated from the initial results obtained and the data derived from haematocrit estimation. It was assumed that during the short period of investigation the total red-cell-mass would not change to such an extent as to introduce a large error on the values for plasma volume.

The interesting feature of this study was the uniformity with which every patient reacted to the treatment. The details of results obtained in each case are given in the appendix. Only one typical case will be described here. The average values obtained from all cases are presented in figure 12.

Mrs. D. primigravida, age 29. Past history revealed nothing of importance. Ante-natal history normal until 2 weeks before admission, when she noticed some swelling of the ankles. Examination on 9.7.43 for the first time showed slight hypertension, B.P. 144/92 mm.Hg. There was slight oedema of ankles but no albuminuria. One week later, the blood pressure increased to 160/105, oedema was marked, and the urine contained albumin ++. The patient was admitted on 16.7.43.

On 17.7.43 the general condition was about the same. B.P. 155/105 mm.Hg. Urine contained 10 parts (Esbach) albumin, oedema was gross (3+). Blood urea 21 mgms.per cent. Urea clearance 114 per cent. of maximum normal. Maximum urinary urea concentration 3.9 per cent. Weight 69.5 kilograms.

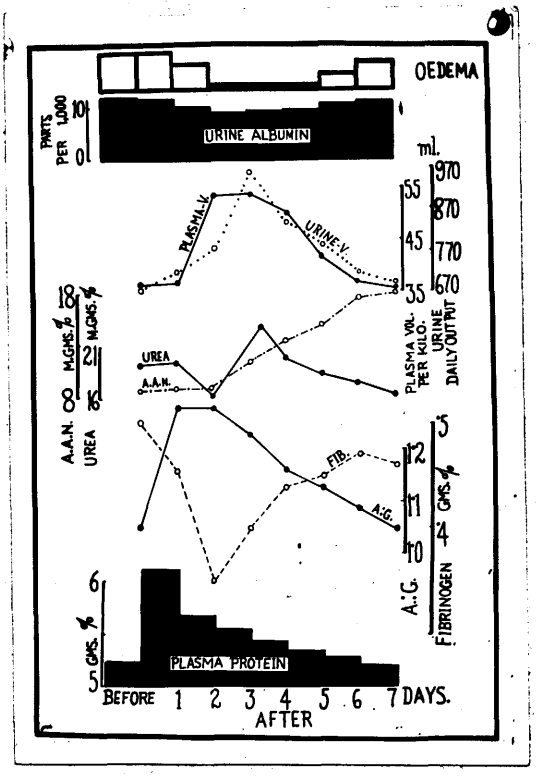

Fig. 12. Effects of injection of concentrated human plasma protein in toxaemia.

The infusion of plasma protein was given on 19.7.48. The results of investigation obtained during the period of study are presented in Table 28.

Table 28

	Before Infusion	After Infusion (Days)						
		1	2	3	4	5	6	7
Plasma Protein gms.%	5.27	6.12	5.74	5.60	5.43	5.39	5.30	5.25
Fibrinogen gms.%	0.49	0.46	0.34	0.39	0.44	0.46	0.43	0.47
A.:G.Ratio	1.04	1.29	1.29	1.25	1.16	1.13	1.09	1.05
Urea mgms.%	19.0	19.3	17.0	24.7	20.8	13.6	17.9	17.0
A.A.N. mgms.%	3.1	3.6	3.7	10.7	13.5	15.0	13.0	13.3
Plasma vol. ml./K.G.	36.0	36.2	51.4	52.0	49.7	42.3	33.0	36.3
Diuresis ml./24 hrs.	674	720	733	969	333	800	706	636
Albuminuria (Esbach)	11	10.5	9	7	7.5	8	10	11
Oedema				-	-	-		
B.P.	160/ 105	160/ 103	160/ 100	160/ 100	158/ 100	162/ 100	163/ 103	170/ 110

The first specimen of blood was examined 8 hours after the infusion containing 23.7 gms. of protein dissolved in 200 ml. of distilled water.

COMMENTS

The immediate effect of the injection was an increase in the concentration of plasma proteins by 0.85 gms. per

100/

100 ml. The level which the plasma proteins were expected to attain as a result of the infusion is $\left(\frac{5.27 \times 36.0 \times 69.5}{100} + 23.7\right) \div \left(\frac{36.0 \times 69.5 + 200}{100}\right)$ or 5.94 gms. The estimated level of plasma proteins is slightly higher than the calculated value and exceeds the margin of error of the method of estimation employed for the purpose. This increase is difficult to explain unless it is assumed that the injected protein provided some stimulus to the release of reserve proteins in the circulation. Confirmatory evidence in this direction is not available at present. But in all of the 9 cases studied by us, it was observed that the rise in plasma proteins concentration after infusion was higher than the calculated increase.

However, this increase was not maintained for more than a very short period, for only 32 hours after the infusion the plasma protein level had dropped below that of the previous day and was actually less than the calculated value by 0.20 gms. per 100 ml. Thereafter the decline was steadily maintained until the pre-infusion level was reached between the sixth and seventh day after the injection. However, this response of plasma proteins is only apparent, and does not represent the reactions of the body to the added amount of plasma infused.

On the second day the concentration of plasma proteins was 5.74 gms. per 100 ml. The plasma volume on that day increased to 51.4 ml. per kilogram. The total amount of plasma/

plasma protein in the circulation was therefore (51.5 X 69.5 X 5.74 ÷ 100) 199.0 gms. By a similar calculation it is found that the total protein of the plasma on the previous day amounted to 160.5 gms. In other words during the previous 24 hours 33.5 gms. of protein must have been added to the circulating blood. During this period of study the plasma volume increased by 35 per cent. while the total plasma protein content was raised by 24 per cent. This explains the apparent drop in the relative concentration and simultaneously indicates that plasma transfusion has a stimulating effect (at least temporary) on the regeneration of plasma proteins.

A study of the albumin:globulin ratio throws further light on the subject. Before the commencement of the experiment the total albumin and globulin content of the plasma were 61.1 and 58.6 gms. respectively. The ratio was 1.04. The infused plasma was estimated to contain 16.5 gms. of albumin and 10.7 gms. of globulin. Thus, as a result of the infusion the plasma should have contained a total of 77.2 gms. of albumin and 69.3 gms. of globulin, giving a total of 146.5 gms. Eight hours after the infusion however the plasma contained 80.1 gms. of albumin and 62.3 gms. of globulin, (Total 142.4 gms.). The albumin:globulin ratio changed to 1.29.

This/

This analysis indicates that within a short time after the extra protein was added to the circulation and re-adjustment occurred which entailed a storage of 4.1 gms. of protein. This was however not a simple quantitative removal of the protein fractions from the circulation but consisted of a selective process which apparently involved a "give and take" between the plasma and tissues of the body. For, in the process of withdrawal of 4.1 gms. of protein from the circulation, the plasma evidently donated 7 gms. of globulin to the tissues and received in return 2.9 gms. of albumin. This process of readjustment is attended with an increase in the plasma albumin concentration of 0.75 gms. per 100 ml. with its osmotic advantages. Moreover, by this measure, an overloading of the circulation with large-molecubed globulins is prevented, while these are utilised for building up the depleted store of reserve proteins. Thus the advantage of the mechanism becomes obvious.

Further interesting events are noticed during the following 24 hours. It has already been pointed out that due to the haemodilution and consequent increase in plasma volume, the actual content of proteins in the plasma is masked, so that inspite of a true increase of these elements their relative concentration falls. The total amount of protein circulating in the plasma on the second day of study was 199.0 gms., of which 108.1 gms. were albumin and 84.1gms. consisted/

consisted of globulin. The ratio was still maintained at 1.29. Thus, during the preceding 24 hours the plasma was donated with 49.3 gms. of protein of which albumin and globulin consisted of 28.0 and 21.3 gms. respectively (ratio = 1.23). It may be mentioned here that in this process 4.7 gms. of fibrinogen was removed from the circulation. This shows the great rapidity with which regeneration of plasma proteins may occur if suitable conditions prevail.

Scrutiny of the results of the subsequent days however show that the stimulus provided by the infusion is of a very tranitory nature. On the third day not only the relative concentration of plasma proteins shows a further fall, but also the actual content of proteins in the plasma shows some deterioration.

Plasma was found to contain 198.6 gms. of protein. (Weight = 68.2 kilogram) of which albumin and globulin were 102.7 and 82.1 gms. respectively. The ratio declined to 1.25. Thus, compared with the preceding day the plasma albumin diminished by 6.0 gms. This was accompanied by a loss of 2.0 gms. of globulin and a gain of 7.0 gms. of fibrinogen. The labile nature of the plasma fibrinogen is clearly demonstrated in these experiments. However, even at this stage the plasma contained 78.9 gms. of "non-fibrinogen" protein more than that in the pre-infusion period and 56.2 gms. more than that caused by the infusion itself.

The/

The corresponding increase for plasma albumin was 41.6 and 22.6 gms. respectively. This shows that the fall in the total protein content of the plasma was confined principally to the albumin fraction, and to a much less extent to plasma globulins, while the fibrinogen content was actually increased.

On the following day further deterioration of the condition was observed. The protein concentration of the plasma had dropped by 0.12 gms. per 100 ml., and the total protein content had declined to 185.7 gms. (= loss of 12.9 gms.). Simultaneously the fibrinogen content had increased to 14.9 gms. (= +1.1 gms.) while the level of albumin had fallen to 91.2 gms. (= loss of 11.5 gms.) and that of globulin to 79.6 gms. (= loss of 2.5 gms.). Thus, the decrease in plasma proteins was no longer relative but absolute. Nevertheless four days after the infusion the status of plasma proteins was still better than that before the injection of plasma proteins.

The fifth, sixth and seventh days of the study showed little difference in the nature of the change which commenced on the third and was established on the fourth day after the infusion of concentrated human plasma. The progressive drop in the relative concentration is obvious from the table presented above. The absolute content of the plasma proteins also shows a similar behaviour. Thus the total protein content of the plasma on these three days

were/

were 156.2, 133.3 and 131.4 gms. respectively. It will be evident that on the last day of the investigation, inspite of the concentration per 100 ml. being less than that in the pre-infusion state, the actual protein content of the plasma was slightly higher. This progressive loss of the protein from the plasma affected chiefly the albumin fraction, the estimated content of which was 75.9, 65.6 and 62.0 gms. respectively. The decrease in the absolute concentration of the globulin was slight and followed the changes in plasma volume, as a result of which the relative concentration remained fairly constant.

The behaviour of urea and amino acid nitrogen will be described in the appropriate section.

The alteration in oedema was the most striking change in the clinical condition of the patient. Before concentrated plasma was administered the oedema was marked and almost generalised. Between 24 and 32 hours of the plasma infusion it started diminishing and this was accompanied by an appreciable diuresis. By the third day, there was only a trace of oedema and this condition persisted during the following two days. On the sixth day pitting oedema had reappeared and continued to increase. The cause of this improvement in oedema appears to be directly connected with the increase in the protein concentration of the plasma. This is evident from the alteration observed in the plasma volume almost concurrent with the subsidence of oedema. It is/

is interesting to note that diuresis was not much in evidence until the withdrawal of the oedema fluid in the circulation had progressed considerably. These factors will receive further attention in connection with the investigation of oedema. It is interesting to note that apart from improvement in oedema and some accompanying diuresis infusion of concentrated plasma showed no demonstrable effect on blood pressure or albuminuria. Concentrated infusions of human plasma seem to have a temporary effect on the plasma protein level, but appears to have no influence on the factors which initiate or maintain the state of toxaemia.

2. ECLAMPSIA

The values for plasma protein obtained in 13 cases of eclampsia in our series are given below -

Total plasma protein 5.44 gms. per 100 ml.; S.D. 0.28
Maximum - 6.20 gms.; Minimum - 4.97 gms.

Fibrinogen 0.34 gms. per 100 ml.; S.D. 0.20
Maximum - 0.76 gms.; Minimum - 0.16 gms.

Serum Albumin 2.75 gms. per 100 ml.; S.D. 0.39
Maximum - 3.16 gms.; Minimum - 2.13 gms.

Serum globulin 2.35 gms. per 100 ml.; S.D. 0.06
Maximum - 2.56 gms.; Minimum - 2.30 gms.

Albumin:globulin ratio 1.17; S.D. 0.12
Maximum - 1.40; Minimum 0.94.

These average values show only slight variation from those in severe pre-eclampsia. However, the scatter of values in eclampsia is considerably wider than that in non-convulsive toxaemia, as a result both the minimum and

maximum/

maximum values tend to exceed the limits seen in the latter condition. For the same reason the co-efficient of variation is also greater than that in pre-eclampsia. The difference in values between eclampsia and pre-eclampsia is not statistically significant.

Nevertheless, this does not represent the actual nature of the changes taking place in the plasma proteins in eclampsia. This was revealed during haematocrit studies which were undertaken in order to ascertain the cause of this unusual variation of values.

In 15 cases of eclampsia belonging to this series the average packed cell volume was 41.96; S.D. 2.43, with a range of 40.1 to 49.0. This shows an increase of 4.9 per cent. of the average haematocrit in severe pre-eclampsia, and a little over 10 per cent. over that in normal pregnancy. Against this increased haemoconcentration, the rise in plasma globulin by 0.03 gms. per 100 ml. (c.f. severe pre-eclampsia) shows that the globulin concentration has increased by only 1.3 per cent. Thus, inspite of a relatively higher value of globulin per 100 ml. plasma, there has been an actual decrease in the total globulin content of the plasma. The albumin:globulin ratio in eclampsia remains practically the same as that in severe pre-eclampsia, which means that there has been a proportionately bigger fall (1.16 to 1.17) of the albumin content. Again, if the haemoconcentration is taken into account this assumes considerable significance.

Fibrinogen, however shows an important deviation from that observed in pre-eclampsia. The average value is considerably less, but because the scatter of values is much wider, the difference between pre-eclampsia and eclampsia does not appear to be statistically significant. The highest value (0.76 gms. per 100 ml.) was higher than any we found in non-convulsive toxaemia, and the lowest value was nearly as low. In 22.2 per cent. of cases the level of plasma fibrinogen was less than that regarded as the normal minimum in the non-pregnant state. In 27.8 per cent. it was higher than the average for pre-eclampsia. The change in the plasma concentration of fibrinogen therefore is to some extent unpredictable in eclampsia. It is of interest to note that Coetzee and Marrack (9, 1924) also observed a similar behaviour of plasma fibrinogen in eclampsia. Dieckmann's average (4a, 1941) is however higher than normal, although he mentions 2 cases where the plasma fibrinogen dropped to zero during the course of the disease. Further estimations of fibrinogen done in our laboratory (after this series was compiled) confirms our belief that in a sufficiently large series of cases the average fibrinogen in eclampsia will appear to be less than normal. In this respect we have the support of the cases presented by Coetzee to the Royal Society of Medicine.

DISCUSSION

All investigators agree that the plasma protein concentration/

concentration in toxaemia is lower than that in normal pregnancy. One of the earliest communications on this subject in this country is that of Coetzee and Marrack (9, 1924), who observed that in toxaemia of pregnancy the change consisted of a uniforn fall of plasma albumin, "rather low" concentration of globulin and a variable behaviour of fibrinogen. They also noticed that in eclampsia the changes were more striking. Investigations of Plass and Bogert (7, 1924), Eufinger (34, 1928), Eastman(6, 1930), Strauss, (3a, 1937), Reinhart (11, 1945) and Moller-Christensen (35, 1946) also confirm that in toxaemia of pregnancy the protein concentration of the plasma suffers an appreciable deterioration mostly with regard to the fraction of albumin. The findings described by us in the preceding pages agree with these observations.

Two points which require investigation are the nature and the cause of the fall in the protein concentration in the plasma. It has been pointed out in connection with normal pregnancy that the loss of the protein concentration of the plasma in normal cases affects the chemical composition of the proteins, while the physical effects of haemodilution are compensated by mobilising larger molecules of fibrinogen. It may be of interest to see how this physical compensation is affected in toxaemia.

In order to study this, it is necessary to take into account the haemoconcentration which is always present in toxaemia/

toxaemia of pregnancy. This varies considerably with the degree of oedema present, but in a mixed group of pre-eclampsias we observed that compared with normal pregnancy the plasma volume, on an average, falls by 3-4 per cent. in mild pre-eclampsia, 6.0 per cent. in severe pre-eclampsia and about 10 per cent. in eclampsia. On this basis we shall analyse our data in the same manner as we have done in normal pregnancy.

The plasma volume in pregnancy in the example given before was regarded as 2,500 ml. With mild toxaemia the plasma volume drops to 2425 ml., which gives the protein composition of the plasma as, total 133.5 gms., albumin 71.5 gms., globulin 55.1 gms., and fibrinogen 11.9 gms. In terms of the protein mass expressed as albumin this is equivalent to 212.5 gms. Had the fall in plasma volume in this case been of a physiological nature and not due to toxaemia, loss of water from the plasma would call for a readjustment of the level of the proteins in order to maintain the same phase of dispersion of the colloid*.

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* This assumption is not based on a theoretical foundation. Experimental work of Lyons, Jacobson and Meerkin (36, 1945) has shown that normally the protein concentration of the plasma is not allowed to alter with a change in the plasma volume, for protein is added to the plasma when the volume increases and withdrawn from it, when it falls.

With a 3 per cent. loss of fluid this would cause the protein content/

content to change from 232.15 to 225.15 gms. (vide supra) equivalent of albumin. Thus, the "protein mass" in toxaemia is deficient by an amount which is equivalent to that of (225.15 - 212.5) or 12.65 gms. of albumin. This represents a decrease of 5.6 per cent. of the normal pregnancy level.

When toxaemia is severe, the protein mass (based on average figures already described) consists of 63.1 gms. albumin, 54.1 gms. globulin and 11.1 gms. of fibrinogen (total = 133.3 gms.). Expressed as albumin this is equivalent to 197.4 gms. The protein mass of the plasma is thus deficient from normal cases by (232.15-(232.15X0.06)-197.4) or 20.85 gms. equivalent of albumin, which represents a decrease of the colloidal mass by 9.55 per cent. of the normal pregnancy level.

The change in eclampsia is even more striking. After making correction for the blood volume, the proteins of the plasma are found to consist of 61.3 gms. of albumin, 53.0 gms. of globulin and 7.65 gms. of fibrinogen, total 122.45 gms, which is, equivalent to the mass of 177.9 gms. of albumin. Therefore compared with normal pregnancy the protein mass decreases by (232.15 - (232.15 X 0.1) - 177.9) or 31.0 gms., i.e. 14.85 per cent. of the normal pregnancy level.

These figures show clearly that the delicate equilibrium of the physical mass of the proteins of the plasma which is maintained in normal pregnancy is lost with the onset of toxaemia. The failure of compensation appears to be/

be a gradual event, and becomes more marked as toxaemia becomes severe, and attains considerable magnitude in eclampsia.

The chemical composition of the protein also shows alteration from the state observed in normal pregnancy. When the normal values for the protein fractions, corrected for the decrease of the plasma water, is compared with those in toxaemia it is seen that the relative proportions of the different fractions are affected as follows:-

Albumin decreases by 16.3% in mild pre-eclampsia, 24.2 per cent. in severe pre-eclampsia and 29.0 per cent. in eclampsia.

Globulin decreases by 7.7 per cent. in mild pre-eclampsia, 5.7 per cent. in severe pre-eclampsia and 3.3 per cent. in eclampsia.

Fibrinogen increases by 10.1 per cent. in mild pre-eclampsia, 10.0 per cent. in severe pre-eclampsia and decreases by 20.9 per cent. in eclampsia.

The albumin content of the plasma is the first to suffer, and the magnitude of its fall is also the highest. In this respect our findings are in close agreement with those of other investigators. These authors, however, have described the results based on comparison of the albumin concentration per 100 ml. of plasma, and have observed a decline in the albumin content of about 30 (Eastman) to 33 (Reinhert) per cent. It is obvious that the net albumin content of a colloidal solution like plasma can not be strictly comparable unless corrections are made for the volume of water in which they are maintained as a solution.

The/

The data presented above indicates that there is an absolute decrease in the albumin fraction of the plasma proteins, which becomes more marked as the toxaemia increases in severity, and in this respect the change in the relative concentration indicates the nature of the change in the total albumin content.

Several interesting hypotheses have been made regarding the cause of this fall in plasma albumin, none of which are sufficiently convincing. It has been pointed out in connection with normal pregnancy that one of chief causes of the decline in the albumin concentration is demand for protein storage. It is possible that the exaggerated fall in toxaemias is due to some interference with this storage mechanism. Studies in nitrogen balance presented in the previous chapter indicate that even if the protein lost in the urine is not taken into consideration the amount of stored protein is far less than that in normal pregnancy. It has also been seen that by considerably augmenting the level of protein intake the amount of positive balance in toxaemia can not be raised to the expected level. These facts tend to suggest that the mechanism of protein storage is defective in pregnancy toxaemia. That this is not merely due to increased protein catabolism is shown by the fact that high protein diet restores neither the normal positive nitrogen balance of pregnancy nor raises the protein level of the plasma/

plasma. This has been seen not only in the cases studied by us but also by Arnell and co-workers (20,1945) and Williams (21, 1945). Some light is thrown on the subject by the results obtained with infusion of concentrated plasma proteins. It has been noticed that artificially raising the protein concentration of the plasma acts as a stimulus to increased formation of plasma proteins. This is best manifested on the second, and third days after the infusion. But the effect is of a short duration. It is possible that by continually maintaining a high plasma protein level with repeated injections of concentrated plasma (we believe, on the above findings that injections should be repeated every third day), the vicious circle which interfers with protein synthesis and storage may be corrected. In this connection, it is of interest to point out an experimental observation made by Elman and Heifetz (30a, 1941). These authors found that if hypoproteinaemia persists for any length of time, it causes impairment of liver functions. Goettsch et al (37, 1942) confirmed this finding and stated that this hepatic dysfunction is a reversible process and can be corrected by improving the level of plasma proteins. It is possible that prolonged physiological hypoalbuminaemia, in presence of a low nutritional status during pregnancy, makes the liver more susceptible to the strain, imposed upon it by the onset of toxaemia, as a result of which further fall in protein

concentration/

concentration occurs.

Hepatic functional derangement has long been held responsible for many of the manifestations of toxaemia of pregnancy, including a fall in the plasma protein concentration, and especially that of the albumin. This finds support in the behaviour of plasma proteins in organic diseases of the liver, e.g. cirrhosis, hepatitis or malignant growths. In these conditions also the plasma protein concentration decreases below normal level, chiefly due to a loss of serum albumin, while fibrinogen and globulin often show a relative increase. In this respect the similarity between these conditions and pregnancy toxaemia is obvious. Hepatic function tests in pre-eclampsia have been reported by several investigators (38,39,40,41) to give sub-normal results. Our own observations (to be described later) confirm this. It is possible that the disturbance of hepatic function in pregnancy toxaemia brings about the change in plasma proteins, particularly that of albumin. Nevertheless, it must be admitted that such a hypothesis merely begs a number of questions, the answers to which are not free from contradictions.

The marked decrease in the plasma albumin concentration which occurs in toxaemia is not associated with a complete breakdown of the compensatory mechanism. This is particularly observed with regard to fibrinogen. Attention has already/

already been drawn to the process where a decrease of the albumin content of the plasma is made up by an increase in the fibrinogen, the mass of which is practically equivalent to that of the albumin lost. From the data presented above it will be evident that while the reduction in albumin is considerable there is in fact a rise in fibrinogen. An analysis of the behaviour of fibrinogen is interesting. In the example given above the net amount of fibrinogen in the plasma is 11.9 gms., in mild pre-eclampsia the plasma contains an additional (11.9 -(10.75-10.75X0.03)) 1.5 gms. of fibrinogen. This indicates a 10.1 per cent. increase over the normal pregnancy level. However, the deficit of (33.5 - 33.5X 0.03 - 71.5) 14.4 gms. of albumin required (14.4 ÷ 4.8), 3 gms. of fibrinogen for the restoration of the protein mass. Thus, inspite of a 10.1 per cent. increase, the amount of fibrinogen added to the circulation supplies only 50 per cent. of the amount needed. It follows therefore, that in toxaemias of pregnancy there is a defective production of fibrinogen as well. The calculation presented above does not take into account the readjustment necessary for the decrease of globulin. If this is considered the compasatory increase in fibrinogen appears to be extremely inadequate.

In severe pre-eclampsia the increase in fibrinogen is still 10.0 per cent. of the pregnancy level, but when the deficiency/

deficiency of albumin is taken into account it appears that the plasma has been supplied with only 19.9 per cent. of the fibrinogen required to restore the balance upset up a further decrease of albumin. Thus in severe toxaemia the regeneration of fibrinogen is even less than that in mild pre-eclampsia.

Eclampsia is found to cause a complete breakdown of all compensatory efforts. It will appear from the data presented above that compared with normal pregnancy there is actually a deficiency of fibrinogen in the plasma amounting to $(\overline{10.75 - (10.75 \times 0.1)} - 7.65)$ 2.03 gms. The loss of albumin in eclampsia requires $(\overline{38.5 - (38.5 \times 0.1) - 61.8} \div 4.8)$ 3.74 gms. of fibrinogen. In other words the net deficit is (3.74 -(-2.03), 5.77 gms. This shows that the plasma contains an amount of fibrinogen which is 155.0 per cent. less than the amount required for physical compensation.

The behaviour of fibrinogen seems to offer support to the belief that the cause of the decrease in the plasma protein concentration in pre-eclampsia and eclampsia is connected with hepatic dysfunction. We have observed (vide infra) that the efficiency of the liver suffers progressively as toxaemia attains severity. As far as is known the liver is the only site of formation of fibrinogen, and it will be evident from the analysis that the production of fibrinogen in pregnancy toxaemia becomes less at each successive stage as/

as the condition deteriorates. In this connection it is interesting to recall the alterations of plasma fibrinogen in relation to blood pressure. It has been observed that the concentration per 100 ml. increases up to a diastolic pressure level of 105-110 mm.Hg., after which there is a sudden and rapid fall. High diastolic pressure in pregnancy toxaemia is indicative of vascular spasm, with the attendent risks of a deficient supply of oxygen. It has been shown experimentally by Engel, Harrison and Long (42, 1944) that the liver cells can not resist prolonged anoxaemia. It seems reasonable to conclude that persistent vasospasm, associated with toxaemia imposes a strain on the normal activities of the liver, one of the functions of which is the manufacture of plasma protein, especially that of albumin and fibrinogen. This would explain the changes in plasma albumin and fibrinogen just described.

Globulin also reacts in a very interesting manner, but its behaviour is less typical. Its relative concentration remains almost the same in mild and severe pre-eclampsia, and actually shows a very slight increase in eclampsia. Similar findings have been recorded by other investigators also. In view of the progressive haemoconcentration this led the previous investigators to believe that there is an actual increase in the globulin content of the plasma in pregnancy toxaemia. Moller-Christensen and Thygesen (35, 1946) are the only authors to suggest a true decrease of/

of plasma globulin in severe toxaemia. If the data presented above are applied to the example used for illustrating our agument it appears that the total globulin present in the plasma amounts to 55.1, 54.5 and 53 gms. in mild pre-eclampsia, severe pre-eclampsia and eclampsia respectively. If the globulin content of normal pregnancy, viz. 61.5 gms. is adjusted to the decrease in the plasma water the expected globulin level should in the conditions mentioned above, be 59.7, 57.3 and 55.4 gms. respectively. Therefore, there is an actual decrease in the plasma globulin in pregnancy toxaemia, a finding which agrees with that of the last-named authors. The extent of this decrease amounts to 7.7, 5.7 and 3.3 per cent. respectively, of the quantity expected to be present. In other words, toxaemia brings about a fall in the globulin content of the plasma, which tends to get less as the disease increases in severity. Such a condition is possible only if there are sites of globulin formation other than the liver. The investigations of Madden, Whipple and co-workers (29a, 1940) suggest the existence of such extrahepatic sources of globulin formation. Hawk, Oser and Summerson (43, 1947) also state that "indeed there is considerable evidence that parts of the body other than the liver are concerned with plasma globulin formation".

In view of the facts just mentioned it seems reasonable to conclude that the initial fall of plasma globulin is associated/

associated with a defective function of the liver, which also brings about a decrease of plasma albumin and only an inadequate supply of fibrinogen. As toxaemia increases the hepatic efficiency further suffers. As a result, other extra hepatic compensatory mechanisms of the body are called upon to act in order to maintain the level of the colloids of the plasma. This explains the slight apparent improvement in the status of plasma globulin while that of fibrinogen and albumin continues to deteriorate.

The balance of the chemical composition of plasma proteins is sacrificed even in normal pregnancy. In toxaemia it is worse, The physical equilibrium which is just delicately maintained in normal gestation is completely upset in toxaemia. As a result in pre-eclampsia, and eclampsia the plasma proteins are affected both qualitatively and quantitatively with no evidence of compensation in either direction.

In this connection, an observation made by Smith and Smith (44, 1947) appears interesting. These authors stated that in toxaemias of pregnancy there is an increase in the plasma of the euglobulin which possesses toxic fibrinolytic property. These authors suggested that this euglobulin is likely to be the cause of the clinical manifestations of toxaemia. Considering, that extrahepatic sites of formation of globulin are called upon to supply the needs in severe pre-eclampsia and eclampsia an abnormal quality of these proteins/

proteins may not be an unexpected phenomenon. We estimated the euglobulin content of the plasma in 11 cases of severe pre-eclampsia and 3 cases of eclampsia, by precipating it with 13.5 per cent. sodium sulphate at 37°C. The values obtained ranged between 4.3 to 11.0 per cent. of the total protein with an average of 7.1; S.D. 2.1. Normally euglobulin constitutes about 3 per cent. (Hawk) of the total protein. In 6 cases of normal pregnancy the average euglobulin content of the total protein was 4.4 per cent. (range, 2.9 to 7.1). Eufinger (34a, 1923) observed that euglobulin is normally raised during pregnancy. The series studied by us is small and does not provide a satisfactory conclusion. If further investigation confirms these findings the assumption made above would be reasonable. However an increase of euglobulin does not necessarily provide an evidence for the toxic quality ascribed to it. We have not observed any fibrinolytic property of this supposed by toxic euglobulin obtained from cases of severe pre-eclampsia and eclampsia. Nevertheless, proteins particularly globulins have important physical functions to perform. There is a state of lipaemia of the blood during pregnancy, which increases in toxaemia. Several investigators, including Eufinger (34a) have observed that part of this increased lipoid (especially cholesterol) is bound to the proteins in the plasma, and euglobulin plays a major part in this respect. A relative increase in euglobulin would be an

essential/

essential compensatory phenomenon in view of rapidly diminishing concentration of all fractions of plasma proteins Because of its hydrophobic properties, cholesterol, in increased concentration has been known to affect (Overton, 45, 1901) the permeability of cell membranes. Investigations of Hermann (46, 1923) and other workers have shown that with the physiological hypercholesteraemia in pregnancy, the percentage of cholesterol bound to proteins increases from 20 per cent. (normal, non-pregnant) to 40 per cent. When further increase of lipoids occurs in toxaemia, associated with a decrease in plasma proteins a compensatory increase of euglobulin derived from extra hepatic sources appears to be a natural event. The increase in euglobulin in toxaemia observed by Smith and Smith, and by us in the small series of cases described above may be explained on a physico-chemical basis without imparting a hypothetical toxic property to these proteins.

CONCLUSION

The study of plasma proteins in pregnancy show that there is a pregressive decline in their concentration in the plasma, which reaches a maximum in the ninth month (32-36 weeks) of gestation. This affects principally the plasma albumin. The relative concentration of globulin shows only little change, while that of fibrinogen is actually raised.

When the increase in blood volume which occurs in

pregnancy is taken into account it is found that there is a net increase of about 10 per cent. in the total protein content of the plasma. This increase is confined to fibrinogen and globulin and is hardly at all shared by albumin. It appears that in the compensatory mechanism adopted, consequent upon the haemodilution, the chemical integrity and composition of proteins are sacrificed. In their place readjustment of only the "protein mass" occurs, in which the large molecules of fibrinogen are made to fill up the deficiency created by the lack of plasma albumin. This only fulfills the purpose of maintaining the "water of displacement" in the plasma at the same level, besides providing an increased quantity of larger colloidal particles which have some important adsorptive functions to perform. The cause of the decrease of plasma albumin appears to be connected with (1) the mechanism of protein storage during pregnancy and (2) the status of the protein reserve of the body before conception.

Toxaemia causes a further fall in protein concentration of the plasma. Initially the change is of a similar nature as in normal pregnancy but more marked, viz. a greater fall in albumin and a more notable increase in fibrinogen. The changes progress with the toxaemic process, and becomes most evident where the toxaemia is most severe and in eclampsia. At this stage, the decrease in albumin continues, and the compensatory process which consisted of an increase in fibrinogen/

fibrinogen starts to fail. In very severe cases and especially in eclampsia the compensation totally breaks down.

Plasma globulin also shares the initial loss, but in a compensatory mechanism, in which, probably the extra-hepatic sources are called upon, this deficiency is, to a small extent, made up. However, this additional supply of globulin does not prove to be wholly adequate.

The change in plasma proteins in toxaemia may be related to the state of increased vascular spasm which exists in this condition. It seems likely that the spasm affects the hepatic vessels and thereby undermines the capacity of this organ to make good the deficiency in the blood. The decrease in plasma proteins was not found to be directly related to either albuminuria or oedema. However, in severe toxaemia these clinical manifestations are marked, and the plasma proteins are also low. Apart from this no direct correlation was observed in our investigation.

High protein diet, and/or additional dietary amino acids was not found to stimulate regeneration of plasma proteins. This shows that once the toxaemia is established, the cause of the reduced plasma protein concentration is linked not so much with dietary protein intake, as with the mechanism of regeneration of proteins in the body. However, a high protein diet may have a benificial effect in the "prevention" of toxaemia by improving the status of plasma/

plasma proteins before the onset of the disease. At the same time infusions of concentrated plasma were found to have a stimulating effect on the regeneration of proteins. The effect was however temporary and was most-marked up to the third day after the infusion. It is possible that repeated infusions may bring on a lasting improvement of the process involving protein regeneration and storage.

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CHAPTER 4

AMINO ACIDS AND UREA SYNTHESIS

Since Lever's (1, 1843) discovery of albuminuria in eclamptic patients there has been a persistent idea that eclampsia is due to an underlying renal defect. As a result, a voluminous literature has accumulated around the subject of the behaviour of the various nitrogeneous constituents of the blood and urine. Recent work has demonstrated however, that pregnancy toxaemia is not always associated with an organic renal defect. As a result of this change in the outlook it became possible to separate nephritis from pre-eclampsia and it was soon demonstrated that there was no retention of urea in the blood of a patient suffering from the latter condition. In an excellent discussion on the subject Bunker and Mundel (2, 1924) stated "If in a case of toxaemia the blood showed decided nitrogen retention it is strongly suggestive that nephritis is the predominating factor in the toxaemia". However, high urea and non-protein nitrogen values are sometimes seen in pre-eclampsia and eclampsia, apart from any evidence of nephritis. In recent years the generally accepted view is that such nitrogenous retention in pregnancy toxaemia is dependent upon oliguria of functional origin.

Thus, so far as being indicators of renal efficiency, blood urea and non-protein nitrogen in toxaemia have lost much/

much of their significance. Little investigation however has been made of the precursors of these constituents, the amino acids. A few indirect observations have been made. Thus de Wisselow and Wyatt (3, 1924) state "Even in patients in whom this latter function (excretion of water and chlorides) is definitely impaired, and in whom the response to the urea concentration test is on the low side, urea does not appear, however, to accumulate readily in the blood". The authors explain this by mentioning the "possibility" of a diminished production of urea. It has already been seen that protein synthesis is somewhat adversely affected in pregnancy toxaemia. If the circulating amino acids are not utilised for protein synthesis in the body one would expect increased urea production and excretion, provided the process of deamination followed a normal course. McIllroy (4, 1936) states that in severe toxaemia and eclampsia urea excretion is slightly diminished. Most authorities (Cruickshank et al, 5, 1927) observe that in absence of gross oliguria urea excretion remains unaltered in pregnancy toxaemia. In view of these findings it is possible that the level of urea production in the body and consequently deamination is reduced in toxaemia. It was therefore considered that this point required further investigation.

Urea nitrogen normally constitutes about 50 per cent of the non-protein nitrogen in the plasma (U.N. : A.A.N. = 0,45, Mosenthall/

* Very recently Smith (58, 1949) by employing chromatographic method for the estimation of urinary amino acids has observed that in pre-eclampsia amino acid excretion may be inreased in some cases and decreased in others. The author however, was unable to follow-up his cases and provide a satisfactory explanation for his findings.

Mosenthall and Hillar, 6, 1917), but urea is formed in the body as the end-result of deamination of amino acids. Consequently for our present investigation we shall confine ourselves to the urea and amino acid nitrogen content of the blood.

Normally, amino acids are utilised for protein synthesis the surplus being converted into urea. The ratio of unconverted amino acids and urea was therefore considered important in order to assess the rapidity with which urea synthesis occurs in the body. This ratio will naturally depend on the rate of excretion of both these substances in the urine. McIlroy (4, 1936) observed that in severe toxaemia amino acid excretion is increased. Under the circumstances the ratio of Urea N: Amino acid nitrogen may be expected to provide information about the state of deamination until active urea retention occurs. *

In view of the fact that numerous investigators have reported their findings on the changes of the non-protein nitrogenous fractions of the blood during normal pregnancy, we shall present here only a brief summary of the values observed by us in our series of normal cases.

1. NORMAL PREGNANCY

Urea

The results presented here are based on 194 estimations done on 93 cases of normal pregnancy. As described before, they consisted of two series of cases, but, as there was no essential/

essential difference in the nature of results obtained these have been presented together in Table 29 and figure 14.

Table 29

Lunar Months		3	4	5	6	7	8	9	10	Total	Last Trimester
Urea mgms.%	Aver.	30.35	27.45	26.0	25.14	25.0	25.95	26.40	27.19	27.10	26.51
	S.D.	1.23	2.10	1.86	1.92	2.31	2.07	1.74	1.60	1.56	1.50
A.A.N. mgms.%	Aver.	6.20	5.70	5.45	5.40	5.60	6.19	6.45	6.50	5.90	6.38
	S.D.	0.35	0.36	0.33	0.33	0.29	0.47	0.49	0.36	0.54	0.46
U.N. A.A.N.	Aver.	2.30	2.30	2.29	2.21	2.12	2.00	1.95	1.99	2.15	1.98
	S.D.	0.15	0.15	0.14	0.13	0.15	0.16	0.18	0.13	0.16	0.14
No. of Tests		18	23	23	23	22	28	30	27	194	85

COMMENTS

Individual values for blood urea during pregnancy given by different investigators vary considerably. A collective review of some of the values given by different authors is submitted below for a comparative analysis.

1. Fahr & Williams (7,1914)	10	cases	10.0 mgms.	U.N./100ml.
2. Slemons & Morris (8, 1916)	35	"	10.4 "	"
3. Folin (9,1917)	100	"	4-9 "	"
4. Killian & Sherwin(10.1921)	5	"	10.4 "	"
5. Caldwell & Lyle (11,1921)	150	"	11.5 "	"
6. de Wisselow & Wyatt(3,1922)	-		<9.3 "	"
7. Hellmuth (12,1923)	8	"	7.7 "	"
8. Bunker & Mundell (2,1924)	52	"	12.5 "	"
9. Stander, Duncan & Sisson (13,1925)	-		13.26 "	"
10. Cruickshank, Hewitt and Couper,(5, 1927)	42	"	11.0 "	"
11. Williams & Wills (14,1929)	30	"	9.1 "	"
12. Hurwitz & Ohler (15,1932)	4	"	6.8 "	"
13. Dieckmann (16,1935)	23	"	12.2 "	"
14. Cadden & Ferris (17,1936)	-		7.1 "	"
15. Gibberd (18,1943)	-		<11.7 "	"

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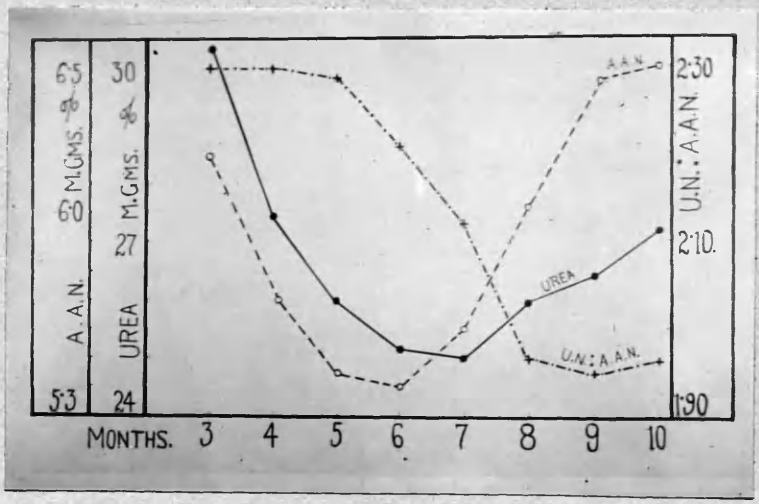

Fig. 13. Plasma urea, amino acid nitrogen and the U.N. : A.AN. ratio in normal pregnancy. The diagram shows the change in different months of gestation.

Inspite of a wide variation of the values obtained by individual authors, a decrease in the urea content of the plasma during pregnancy is evident from the data presented above. MacKay and MacKay (19, 1927) from an elaborate compilation observe that in a great majority of normal individuals the values for blood urea fall between 18 to 38 mgms. per cent. of urea or 8 to 18 mgms. per cent. of urea nitrogen. The average during pregnancy from the data presented above together with those from our series is 23.7 mgms. per cent. of urea or 11.2 mgms. per cent. of urea nitrogen. This is slightly less than that observed in non-pregnant individuals. The difficulty of correlating all the data found in the literature lies in the fact that the values provided do not take into consideration (1) the amount of dietary protein, (2) variation in technique, (3) inadequate data as to the use of whole blood or plasma. Urea diffuses freely through the water of the body and consequently its concentration per unit of water is the same in the blood-cells and plasma. But the volume of packed red cells decreases during pregnancy by about 15 per cent. (Dieckmann) consequently inspite of the fairly constant ratio of 1:0.8 of urea between plasma and red blood cells, the concentration of urea in the plasma in a pregnant women is likely to be slightly different from that in the whole blood.

A close analysis of the data (making allowance for this factor, where indicated) shows that the urea concentration/

concentration of the plasma actually decreases during pregnancy. We found that this decrease is progressive up to the end of the second trimester of gestation, after which a slight increase in the level of plasma urea occurs. A similar observation was made by Cadden and Ferris (17,1936), Pillman Williams (14, 1929) and by several other investigators. The cause of this decrease in the level of the plasma urea is not quite clearly understood. Cadden and Ferris suggested that it is due to haemodilution. The extent of the fall in urea is however more than the degree of haemodilution. In the series presented by Williams and Wills (14) blood urea decreased 35.8 per cent. of the basic level. The values supplied by Cadden and Ferris themselves show a decrease of 57 per cent. In the 15 cases where a follow-up study was undertaken by us plasma urea diminished by 30 per cent. of the value observed in early pregnancy. It is thus obvious, that some active factor apart from haemodilution is responsible for the change in blood urea which occurs during pregnancy.

It is generally assumed that the decrease in blood urea is related to an increase in protein storage and a consequent fall in protein catabolism during gestation. But the fall in blood urea, is usually greater than the reduction of metabolism of proteins in the body. Both MacKay and MacKay (19,1927) and Priestley and Hindmarsh (21,1925) found/

found that in normal subjects, the ratio of gms. of nitrogen metabolised per day: mgms. of urea nitrogen per 100 ml. of blood is approximately 1:1. The reduction of the average daily nitrogen metabolism amounts to 2 to 3 gms., which could account for a corresponding decrease of urea nitrogen in the blood. Available data however indicate that the fall is actually greater than this and is of a progressive character.

There is yet another factor which requires consideration. Nice (22, 1935) and Hurwitz and Ohler (11, 1932) observed that extremely low blood urea values were found when the level of renal clearance was unusually high, viz. between 120 and 200 per cent. of the average normal. Unfortunately there is no universal agreement about the level of urea clearance observed in normal pregnancy. Some of the values found in the literature are given below.

1.	Stander, Ashton & Cadden, (13a, 1932)	Urea clearance	100	per cent.
2.	Hurwitz and Ohler (15,1932)	"	127	"
3.	Cantarow & Ricchuiti (23, 1933)	"	72	"
4.	Cadden & McLane (24,1934)	"	123	"
5.	Nice (22,1935)	"	153	"
6.	Elden & Cooney (25, 1935)	"	85	"
7.	Dieckmann (20a, 1935)	"	102	"
8.	Chesley et al (26, 1939)	"	107	"

With the exception of two, all authors quoted above found that the urea clearance in pregnancy is 100 per cent. or the more. This increased clearance of urea by the kidneys during pregnancy would probably explain partly the comparatively/

comparatively low value of plasma urea during gestation. It is needless to emphasise, however, that of the three factors discussed above, increase renal clearance is by far the least important.

It is interesting to note in this connection that Fraenkel-Conrat and co-workers (27,1943) demonstrated that purified gonadotrophic and growth promoting extracts of anterior pituitary diminish the arginase activity of the liver in both hypophysectomised and normal rats. Increased concentration of gonadotrophins in the blood and urine of pregnant women forms the basis of tests employed for the diagnosis of pregnancy. In view of these facts it seems reasonable to believe that the alteration in blood urea in pregnancy is brought about by an active process which involves diminished production and also by the passive factor of haemodilution. If the renal clearance is more than normal this would cause further reduction of the level of urea in the plasma. In absence of increased clearance, blood urea would still be expected to remain below the normal limit for the non-pregnant state, an abnormal rise being possible only when the renal clearance is unusually low.

Amino-Acid Nitrogen

Unlike urea, the status of amino-acid nitrogen of the blood during pregnancy is less certain. Most methods of estimation measures the aliphatic mono-amino acids excluding the/

the diaminoacids (e.g. lysin, arginin) and the aromatic and heterocyclie amines (e.g. histidin and prolin). Since pre-eclampsia and eclampsia have been regarded as manifestations of "toxaemia" and Kapeller-Adler's (28,1949) repeated observations on increased concentration of histamine in eclampsia estimation of amino-nitrogen assumes some importance. One of the earliest reports on the subjects is that of Morse (29, 1917), who found "no marked difference in amino acid levels between normal non-pregnant and normal pregnant women". However this author recorded values as high as 14 mgms. per cent. during pregnancy. Subsequent investigators fall into two groups. Loose and Van Slyke (30,1917), Hellmuth (12,1923), Schlossman (31, 1925), Plass and Matthew (32,1925) and Pommerenke (33,1936) are of the opinion that there is no change in the amino-acid content of the blood during pregnancy. Folin and Bergland (34,1922), Wu (35,1922), Frey (36,1924), Runge and Juhl (37,1927), Herold (38,1935) and Botella-Llusia (39,1936) maintain that the level of amino acid in the blood is higher during pregnancy than in the non-pregnant state. In a very recent study on a small series of cases Bonsness (40,1947) revives the controversy and states that the amino acid level of the plasma actually falls during pregnancy.

In view of such diversity of findings we propose to present our figures for plasma amino-acid nitrogen in some detail./

detail. The results obtained by us in 194 estimations (largest series so far reported) are submitted in Table 30.

Table 30

Amino Acid Level mgms./100 ml	No. of cases per lunar month of gestation								Total	Last 3 months
	3	4	5	6	7	8	9	10		
4.61 - 4.80	-	-	1	2	1	-	-	-	4	-
4.81 - 5.0	-	1	2	3	2	1	-	-	9	1
5.01 - 5.20	1	2	3	3	4	-	-	-	13	-
5.21 - 5.40	-	4	5	5	4	3	4	1	27	8
5.41 - 5.60	1	3	5	6	4	2	1	-	22	3
5.61 - 5.80	3	6	3	2	4	4	6	1	29	11
5.81 - 6.0	2	3	3	2	2	3	1	-	16	4
6.01 - 6.20	5	2	1	-	1	4	1	4	18	9
6.21 - 6.40	5	2	-	-	-	4	2	5	18	11
6.41 - 6.60	-	-	-	-	-	5	9	8	22	22
6.61 - 6.80	1	-	-	-	-	2	6	8	16	16
Maximum	6.40	6.40	6.20	6.0	6.19	6.61	6.72	6.79	6.79	6.79
Minimum	5.07	4.91	4.69	4.61	4.70	4.83	5.35	5.19	4.61	4.83
Average	6.20	5.70	5.45	5.40	5.60	6.19	6.45	6.50	5.90	6.38
Probable Error	0.23	0.24	0.22	0.22	0.19	0.31	0.33	0.24	0.36	0.31

COMMENTS

It will be evident from the table that individual values vary to some extent during pregnancy within a range of 5.0 to 6.7, although by repeated examination on the same patient/

patient it was found that the amino acid content of the plasma showed little variation from day to day. It is therefore obvious that the change noticed in the series presented above is caused by the state of pregnancy.

Like urea the amino acid concentration also drops during the first half of gestation. The maximum fall amounts to 12.9 per cent. of the early pregnancy level. From the middle of the second trimester the values increase gradually until the maximum is attained at term. At this stage it shows only a 4.8 increase over the average of early pregnancy. It is therefore evident that the value of amino acid nitrogen observed during pregnancy may appear to be unaltered, increased or diminished depending upon the stage of pregnancy when the test is performed.

It is however clear, that the general tendency is for the amino acid nitrogen to increase as gestation advances. The initial fall is apparently due to haemodilution, which, to some extent masks the effect of the increased content of amino acids in the plasma. This explains why the decrease of the amino acid level seen in the first half of gestation amounts to only 12.9 per cent. inspite of an increase in the plasma volume by 25 per cent. But this haemodilution continues up to the thirty-sixth week, while the amino acid nitrogen actually increases in the plasma during the latter half of gestation.

This increase of plasma amino acids during pregnancy is/

is not easy to explain. Neither the state of positive nitrogen balance which exists in pregnancy, nor a supposedly increased demand made by the foetus offer an adequate explanation. Urinary excretion of amino acids is not altered, for, there is no change in the percentage of "undetermined" nitrogen excreted in the urine during pregnancy. Whenevery

Whenevery the amino acid level of the blood is raised by ingestion of proteins or amino acids or by intravenous injection of amino acids deamination is accelerated. Van Slyke, Cullen and McLean (41, 1915) demonstrated that the liver increased the production of urea even before the tissues have received their supply of amino acids. Bolton and Wright (42, 1937) observed a similar condition in cats even after 48 hours of starvation. Yet the production of urea during pregnancy is diminished while the amino acid level of plasma is relatively high. The amino acid content of the cord-blood (foetus) is only slightly higher than that of the mother, the difference observed by us being 1.65 mgms. per 100 ml.; S.D. 0.30, in a series of 30 cases. Plass and Matthew (43, 1925) in a similar study found that the amino acid nitrogen content of foetal and maternal blood was 8.2 and 6.1 mgms. per 100 ml. respectively. This might provide an explanation for the behaviour of the plasma amino acid during pregnancy, but further facts must be available before a satisfactory explanation can be offered.

The/

The result of the progressive decrease of urea and a relative though small increase of amino acid nitrogen causes the U.N.: A.A.N. ratio to fall as pregnancy advances. At its lowest level, which is between the second and third trimester of gestation the ratio indicates that the urea nitrogen is about twice the amino acid nitrogen in the blood. During the following three months of pregnancy the change in the ratio is only slight. This suggests that in the latter part of pregnancy a state of equilibrium is established between the free amino acids in the maternal blood and the process of urea synthesis. According to Michel (quoted by Eden and Holland, 44, 1948) the protein content of the foetus increases from 10 per cent. in the seventh month to 14 per cent. at term. If foetal requirements were the only cause of the raised amino acid level in the maternal blood, such a state of equilibrium would have been unattainable during the last trimester of gestation. The steadily increasing foetal demand would call for a progressively increasing level of amino acids in the maternal blood, and this would cause a gradual fall of the ratio. However the state of equilirbium which exists between urea and amino acids during the last three months of pregnancy provide useful data for comparison with these in toxaemia.

2. PRE-ECLAMPSIA.

The average values * for all cases of pre-eclampsia studied/

* At the time of admission

studied by us were as follows -

Urea 22.55 mgms. per 100 ml.; S.D. 2.72.
Amino Acid Nitrogen 7.46 mgms. per 100 ml.; S.D. 0.91.

Compared with normal pregnancy urea is lowered, and amino acids raised to a small extent in pregnancy toxaemia. The difference of the values is however barely significant. In course of investigation it was observed that both urea and amino acids showed some relationship with the severity of the disease. The results will therefore be analysed accordingly (Figure 14).

1. Mild Toxaemia

The average urea in 50 cases of mild pre-eclampsia was 26.0 mgms. per 100 ml. (= 12.15 mgms. Urea nitrogen); S.D. 1.67. This shows no significant difference when compared with the values obtained during the last trimester of normal pregnancy. The scatter of values between 23 and 30.6 mgms. per 100 ml., also is almost identical with that observed in normal pregnancy.

The plasma amino acid level in this series was 6.29 mgms. per 100 ml.; S.D. 0.38. Here also the difference can not be regarded as significant. The range of variation, viz. 5.5 to 7.5 mgms. per 100 ml. however show a slight shift to the right compared with the values observed in normal pregnancy. But this loses significance owing to the slightly lower value of the average found in this series.

The ratio of the urea N.: Amino acid N. (1.94; S.D. 0.28) thus/

thus shows no significant deviation from normal pregnancy, and it seems reasonable to conclude that mild pre-eclampsia is not attended with any noteworthy change in urea and amino acid nitrogen content of the blood.

11. Severe Pre-eclampsia.

The average plasma urea in 50 cases of severe pre-eclampsia (on admission) was 19.1 (= 8.93 mgms. urea nitrogen) mgms. per 100 ml.; S.D. 2.03. This is significantly lower than that in normal pregnancy and mild pre-eclampsia. The values occupied a range of 15.2 to 23.7 mgms. per 100 ml. Thus the decrease in urea in severe pre-eclampsia affected the whole range of values in this series. The average fall amounted to 28 per cent. of the value in normal pregnancy.

This decrease in blood urea is associated with an increase in the amino acid nitrogen content of the plasma, the average value of which was 8.63 mgms. per 100 ml.; S.D. 0.94, with a range of 7.0 to 11.4 mgms. per 100 ml. It is evident that this represents a true increase in the amino acid nitrogen of the plasma. The extent of this increase is variable. The minimum value obtained in severe toxaemia was 45 per cent. higher than the minimum in normal pregnancy, and the maximum, 62 per cent. more thanthat in the control series. However, 66 per cent. of cases of severe pre-eclampsia showed a 30 to 33 per cent. increase above the average normal.

This increase in amino acids is not confined only to the/

the plasma. The red blood cells also have a proportionately higher content of amino acid nitrogen. Hamilton and Van Slyke (45, 1943) found that in normal human subjects the red corpuscles contain 1.7 to 2.2 times as much amino acids as the plasma. In a series of 14 cases of normal pregnancy we observed that the amino acid content of the R.B.C's. was 61.3 per cent. (S.D.6.2), more than that of the plasma. In an equal number of cases of severe toxaemia the R.B.C's. were found to have a 64.7 per cent. (S.D.9.1) higher value than that of plasma amino acid nitrogen.

Thus, the high level of amino acids in the plasma, described above does not appear to be due to an unequal partition of this substance between plasma and red blood cells. The result of the decrease in urea along with an increase of amino acids is a fall in the U.N.: A.A.N.ratio. The average ratio in our series was 1.07; S.D.0.17. The co-efficient of variation, 15.9 is higher than that in mild pre-eclampsia (14.4) and considerably more than that in normal pregnancy (7.1). The widening of the range is due to the comparatively wide scatter of values of both urea and amino acid nitrogen. The maximum ratio in our series was 1.55 and the minimum 0.75. In 34 per cent. of cases the value of the ratio was less than unity, and in none did it reach even the minimum ratio (1.81) of normal pregnancy. The average fall amounted to 46 per cent. of the normal level.

The difficulty of interpreting values obtained at the time/

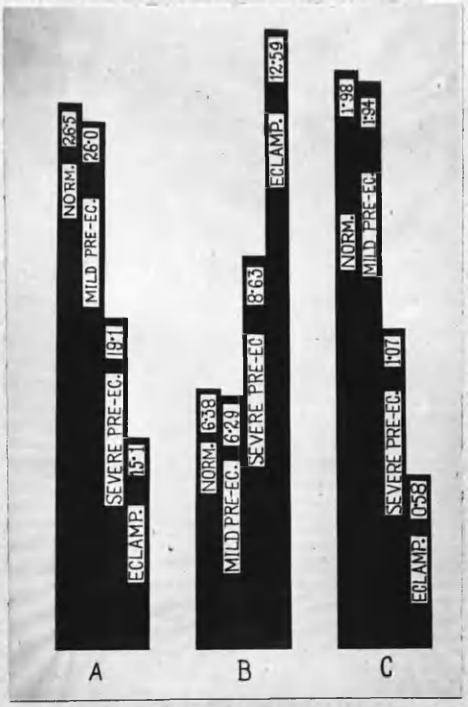

Fig. 14. Average plasma urea amino acid nitrogen and U.N. : A.A.N. ratio in normal pregnancy, pre-eclampsia and eclampsia.

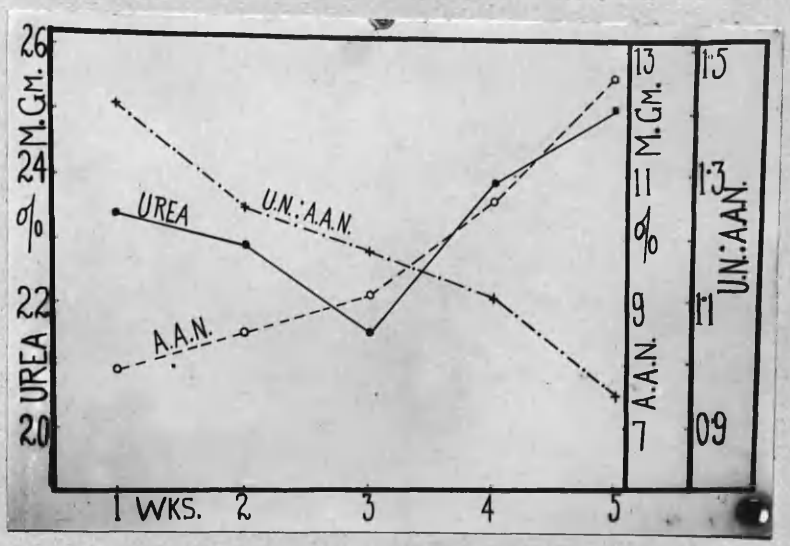

Fig. 15. Plasma urea amino acid nitrogen and U.N. : A.A.N. ratio in relation to the duration of pre-eclamptic toxaemia.

time of admission lies in the fact that the illness is not equally severe in all patients, nor is the duration the same in every case. If toxaemia per se affects the synthesis of urea it should be studied in relation to the duration of the disease, with due consideration to the state of renal clearance of urea. In our subsequent discussion no patient with a subnormal urea clearance has been included.

111. Duration of toxaemia and Urea, A.A.N. and Ratio ✱

✱ In this and subsequent discussions only cases of severe pre-eclampsia have been considered. It has already been pointed out that mild pre-eclampsia shows no appreciable deviation from normality.

In determining the duration of toxaemia reliance was placed on the history of the first onset of oedema for patients who did not attend the ante-natal clinic regularly. In all other cases the first appearance of abnormal blood pressure (above 130/90 mm.Hg.) was regarded as the earliest manifestation of toxaemia. Patients were followed up for varying intervals up to 5 weeks after the onset of toxaemia and the results of this study are presented below. The number of patients who had toxaemia of longer duration were too small for statistical analysis. (Table 31: Figure 15).

The duration of toxaemia was found to have little significant effect on blood urea. There is however a slight but indefinite tendency for the blood urea to rise when toxaemia is of long duration. This change affects only the average/

average values without any effect on the minimum and maximum levels.

Table 31

Duration (weeks)		1	2	3	4	5
Urea mgms/100ml.	Aver.	23.4	22.9	21.5	23.9	25.1
	S.D.	4.6	3.7	3.1	5.3	5.0
	Min.-Max.	16.5-37.7	16.5-30.0	17.5-30.4	17.0-36.0	20.0-31.0
A.A.N. mgms/100ml.	Aver.	7.9	8.5	9.1	10.6	12.4
	S.D.	0.84	0.96	0.99	1.12	1.61
	Min.-Max.	7.0-9.8	7.1-10.2	7.2-16.0	8.1-18.6	8.5-23.0
U.N./A.A.N.	Aver.	1.41	1.25	1.18	1.06	0.95
	S.D.	0.11	0.12	0.14	0.17	0.19
	Min.-Max.	1.0-1.55	0.93-1.40	0.84-1.60	0.80-1.25	0.75-116

The amino acid nitrogen however shows a distinct increase as the toxaemia persists. It is however interesting to note that the lower end of the range is only slightly affected, while the increase in the average is brought about mainly by a shift of the higher values in each series to the right. As a result the scatter in each group increases, but the simultaneous increase in the average keeps the coefficient of variation within a narrow limit and the increase is therefore statistically significant.

Little alteration in blood urea together with a fairly marked increase in the amino acid nitrogen causes the ratio to/

to decline progressively. This drop in the urea N: amino acid N. ratio is significant at all stages. When toxaemia has been of long duration (4 weeks or more) amino acids are found to contribute as much as or even more than urea to the total non-protein nitrogen content of the plasma. This explains partly why the U.N.: N.P.N. ratio has been found by several investigators (13, 46) to be less than normal.

However interesting this observation may be it does not explain the manner in which the change in amino acid nitrogen is brought about in pregnancy toxaemia. In order to find an answer to this we analysed our data in relation to the most important clinical manifestation of the disease, viz. hypertension.

IV. Hypertension and A.A.N. and Ratio U.N./A.A.N.

Many authorities believe that toxaemia of pregnancy is a disease primarily of the vascular system, the principal manifestation of which is vascular spasm. It is difficult to see how vascular spasm, per se, can alter the amino acid content of the plasma. It is however possible that changes in the parenchymatous organs induced by vascular spasm may affect the process of deamination, transamination and utilisation of amino acids. Up till now there is no definite proof that such a thing can occur in the human body, but before such a possibility is explored it is reasonable to analyse the data obtained in the course of this investigation.

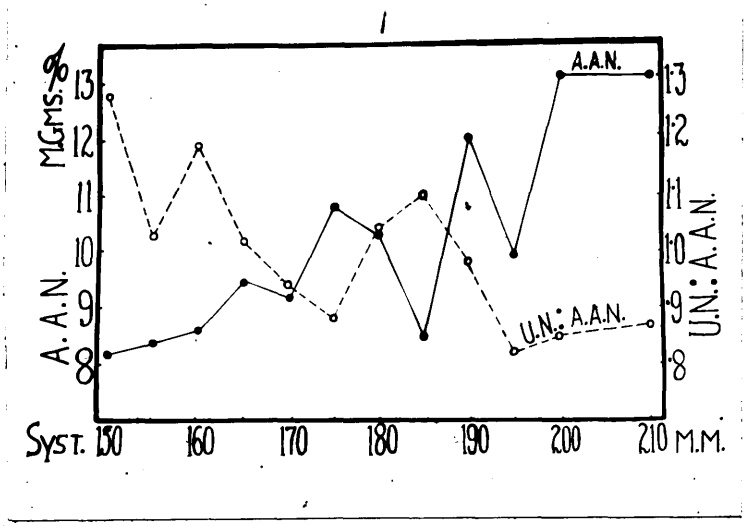

Fig. 16. Plasma amino acid nitrogen and U.N. : A.A.N. ratio in relation to the systolic blood pressure in pre-eclampsia.

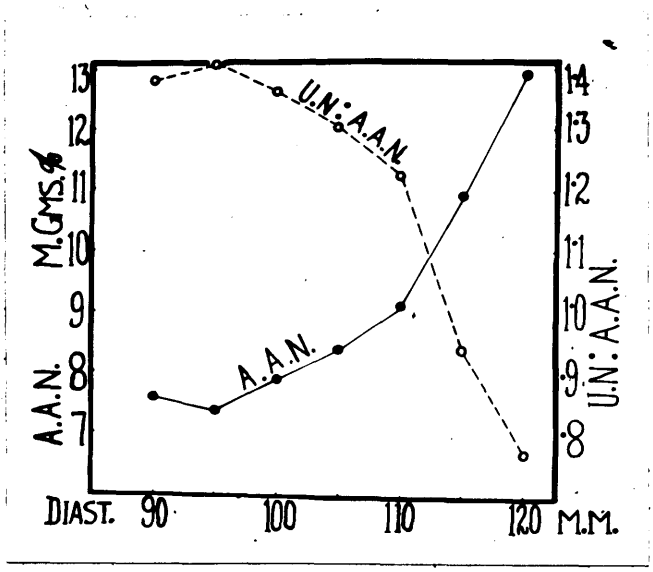

Fig. 17. Plasma amino acid nitrogen and U.N. : A.A.N. ratio in relation to the diastolic blood pressure in pre-eclampsia.

Table 33

B.P. mm. Hg.	A.A.N.	U.N.:A.A.N.	B.P. mm. Hg.	A.A.N.	U.N.:A.A.N.
86-90	7.6±0.30 7.0-8.5	1.38±0.08 1.13-1.60	106-110	9.1±0.46 7.0-13.2	1.22±0.04 0.86-1.33
91-95	7.4±0.20 7.0-7.7	1.41±0.09 1.21-1.50	111-115	10.9±0.50 7.8-11.4	0.95±0.05 0.75-1.10
96-100	7.9±0.48 7.0-9.0	1.36±0.08 1.05-1.55	116-120	12.9±2.3 8.7-23.0	0.77±0.05 0.66-1.0
101-105	8.4±0.52 7.7-10.9	1.30±0.06 1.0-1.40	-	-	-

increase of amino acid nitrogen content of the plasma is slow and gradual until the diastolic pressure reaches 105 mm.Hg., but up to this stage the differences are not statistically significant. Above 105 mm.Hg. the gradient of rise increases steadily up to 120 mm. Hg., which was the highest diastolic pressure in our series. It is interesting to note however, that at its peak the increase loses its statistical significance because of the very wide scatter of values in this group. Thus, the values obtained merely express the general trend for an increase in amino acid with increasing diastolic hypertension.

The ratio of the U.N.:A.A.N. shows the change in a more satisfactory manner. Between 90 and 95 mm. Hg. diastolic pressure the apparent improvement in the ratio is without significance. At each of the subsequent stages of blood pressure the decrease continues steadily, until the minimum

level/

level is reached in those cases where the diastolic pressure is highest. The gradient of fall increases at each stage and the differences are statistically significant. This decline in the average figures is accompanied by a simultaneous decrease of the minimum and maximum values in each successive group. Diastolic hypertension indicates a state of increased vascular spasm. The findings just described suggest that with increasing arterial spasm there is a loss of equilibrium which normally exists between the amino acid level of the blood and the rate of production of urea. It had already been noted that change in blood urea is negligible; if anything, there is a tendency to rise. In presence of a progressive and significant fall in the U.N.:A.A.N. ratio the increase in amino acids described above, inspite of the wide scatter of individual values at high levels of blood pressure, assumes a considerable significance.

V. Diet and Urea, A.A.N. and Ratio.

It has been demonstrated by several investigators that in absence of an abnormal renal function the non-protein nitrogen of the blood varies with the nature and amount of protein present in the diet. The present outlook on diet in the aetiology of toxaemia of pregnancy has already been referred to. It is but proper that the effects of varying contents of protein in the diet on metabolism in pregnancy toxaemia should be known before an attitude is finally adopted

It/

It is but proper that the effects of varying contents of protein in the diet on metabolism in pregnancy toxaemia should be known before an attitude is finally adopted. It is with this object that we tried to analyse the effects of high and low protein diets (already described in the previous chapter) on the urea and amino acid content of blood in pre-eclampsia. The results are summarised below (Figure 18).

Unit A
Medium Protein intake
(Protein 102 gms.)

a. Mild Toxaemia - 24 cases.

Urea	Average 25.9 mgms. per 100 ml.; S.D. 1.58. Maximum 29.5; minimum 24.0.
A.A.N.	Average 6.31 mgms. per 100 ml.; S.D. 0.49. Maximum 7.5; minimum 5.8.
U.N.:A.A.N.	Average 1.91; S.D. 0.10. Maximum 2.30; minimum 1.76.

b. Severe Toxaemia - 18 cases.

Urea	Average 18.3 mgms. per 100 ml.; S.D. 1.86. Maximum 22.5; minimum 16.2.
A.A.N.	Average 8.50 mgms. per 100 ml.; S.D. 0.70. Maximum 9.0; minimum 7.0.
U.N.:A.A.N.	Average 1.07; S.D. 0.18. Maximum 1.30; minimum 0.87.

Unit B
High Protein Intake
(Protein 131 gms.)

a. Mild Toxaemia - 15 cases.

Urea	Average 26.0 mgms. per 100 ml.; S.D. 1.7. Maximum 30.6; minimum 24.6.
A.A.N.	Average 6.30 mgms. per 100 ml.; S.D. 0.26. Maximum 7.0; minimum 5.7.
U.N.:A.A.N.	Average 1.97; S.D. 0.15. Maximum 2.26; minimum 1.72.

b./

b. Severe Toxaemia - 18 cases

Urea	Average 20.4 mgms. per 100 ml.	S.D. 2.07.
	Maximum 23.8; minimum 16.5.	
A.A.N.	Average 9.24 mgms. per 100 ml.	S.D. 1.07.
	Maximum 11.4; minimum 7.5.	
U.N.:A.A.N.	Average 1.05;	S.D. 0.20.
	Maximum 1.55; minimum 0.75.	

Unit C
Low Protein Intake
(Protein 75 gms.)

a. Mild Toxaemia - 11 cases

Urea	Average 25.7 mgms. per 100 ml.	S.D. 1.9.
	Maximum 30.0; minimum 23.0.	
A.A.N.	Average 6.25 mgms. per 100 ml.	S.D. 0.51.
	Maximum 6.9; minimum 5.5.	
U.N.:A.A.N.	Average 1.96;	S.D. 0.12.
	Maximum 2.34; minimum 1.78.	

b. Severe Toxaemia - 14 cases

Urea	Average 18.5 mgms. per 100 ml.	S.D. 1.9.
	Maximum 21.4; minimum 15.2.	
A.A.N.	Average 8.0 mgms. per 100 ml.	S.D. 0.6.
	Maximum 9.0; minimum 7.0.	
U.N.:A.A.N.	Average 1.08;	S.D. 0.17.
	Maximum 1.34; minimum 0.85.	

This analysis shows that as long as toxaemia is of mild degree different levels of protein consumption cause no recognisable difference in the level of urea and amino acids in the plasma. With a low protein intake the average values are slightly lower than those who received a high protein diet, but the difference is not significant.

However, when toxaemia is severe a difference in the plasma concentration of these substances becomes evident. The level of urea in the plasma is slightly higher in the high-protein group, but the difference is barely significant.

Between/

Between low and medium protein groups the difference is negligible. But, the amino acid content of the plasma is found to rise progressively in severe toxaemia as the protein consumption increases. Not only the average but also the minimum and maximum values are higher in the high protein than in the low protein series. It is interesting to note that the range of values observed within low and medium protein diet were identical but the average was higher in the latter group. Moreover, the co-efficient of variation is less in the low protein series, which shows a closer aggregation of values near the mean, and increases the significance of this difference.

Reference to the protein value of the diets will show that (compared with the low-protein series) with an increase of 36.0 and 74.7 per cent. of dietary protein, the amino acid level of the plasma was raised by 6.25 and 13.4 per cent. respectively. Thus, the ratio of the increase in dietary protein to that of plasma amino acid nitrogen is 5.76 and 5.55 respectively. The close resemblance of these two ratios suggest that the increase observed in these cases is not a mere coincidence. One of the conclusions which these data provide is that in severe toxaemia the reserve capacity of the body for utilisation and catabolism of amino acids is comparatively poor and leaves little room for a re-adjustment of the equilirbium at a higher level of protein metabolism.

This/

This effect of overloading the circulation with additional protein derivatives on the amino acids of the plasma was further seen in the small series of cases who received 5 gms. of cystine daily in addition to their usual diet. We shall present our data in two groups.

Group 1 - This consists of 9 cases where the toxaemia deteriorated during their stay in the hospital. The data are presented in Table 34 and figure 20.

Table 34

	Before Cystine	After Cystine - Weeks 1	2	3	4
Urea mgms./ 100ml.	24.0±1.6 16.2-28.0	26.9±2.1 18.9-30.2	26.2±2.6 16.0-30.0	25.7±1.8 17.0-29.4	24.5±2.3 16.6-28.0
A.A.N. mgms./ 100ml.	7.5±0.7 6.0-9.4	8.4±0.8 7.4-10.0	9.1±0.9 7.8-12.2	9.5±1.0 8.5-13.2	12.8±1.2 9.7-18.5
U.N.: A.A.N.	1.48±0.21 0.87-2.06	1.50±0.17 1.06-1.80	1.39±0.10 0.81-1.52	1.27±0.14 0.80-1.50	0.89±0.09 0.77-1.02

Figures represent average ± P.E.; minimum - maximum.

The immediate effect of adding cystine to the dietary is a slight but significant increase in the blood urea during the first week of the study. Simultaneous with this there is a significant rise in the amino acid nitrogen also. Subsequently, the change in blood urea which occurs in each consequitive week is of no statistical significance, although the average shows a slight tendency to fall. The low

value/

value obtained in the fourth week is however significant when compared with that in the first week of treatment.

The amino acid content of the plasma increases steadily as the treatment with cystine continues and the maximum is reached in the fourth week. This increase at each stage satisfies analysis and is not confined to the average, but is also observed in the minimum and maximum values obtained at each week. It is interesting to note that as a result of administration of cystine the value for plasma amino acids in the fourth week was almost identical with that in the fifth week of toxaemia in the whole series (c.f.Table 31). The result of this increase in the amino acids with only little change in the urea content of the blood causes the ratio to decline progressively. The change in the ratio during treatment with cystine is also significant.

Group 2 - This includes 5 cases, in whom the toxaemia improved during the course of cystine therapy. The series is small, but in view of the interesting nature of the findings the data are presented in Table 35 and figure 21.

The figures in the table will indicate the fairly consistent nature of findings in this small group of cases.

As in the previous group, the immediate effect of providing additional amino acids in the diet is an increase of both urea and amino acid nitrogen content of the plasma. During the first week the increase in both amino acids and urea is almost similar in both Groups 1 and 2. But during the/

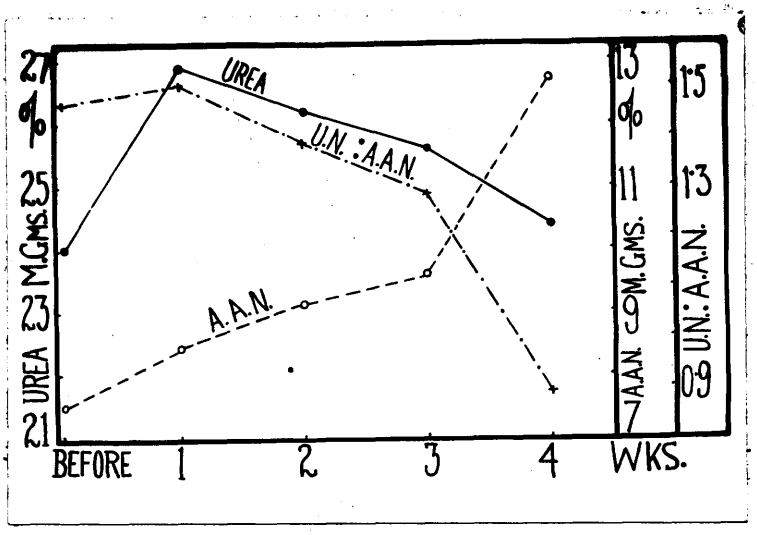

Fig. 20. The effect of adding cystine (5 Gm.) to the diet. The diagram shows the levels of plasma urea and amino acid nitrogen and the U.N. : A.A.N. ratio in those patients where the toxaemia deteriorated during the treatment.

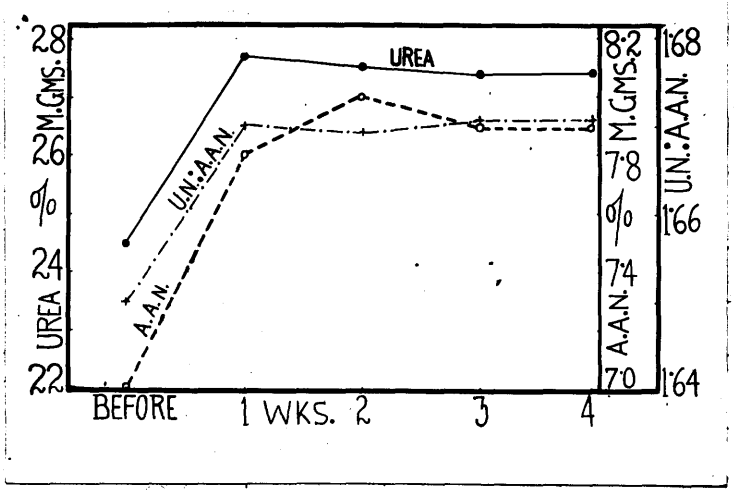

Fig 21. The effect of adding cystine to the diet. Urea, amino acid nitrogen and the ratio of U.N. :A.A.N. in those patients where the toxaemia improved during the treatment.

But during the subsequent three weeks in Group 2 an equilibrium was established, between urea and amino acids so that the concentration of both remained fairly constant. It should be pointed out that the change in the plasma amino acids in this group during the whole period of study did not show any significant variation.

Table 35

	Before Cystine	During treatment with cystine - weeks			
		1	2	3	4
Urea mgms./ 100ml.	24.5±1.2 20.9-27.2	27.8±1.8 24.1-30.2	27.5±1.5 24.0-30.0	27.4±1.7 24.0-30.0	27.4±1.4 24.0-29.4
A.A.N. mgms./ 100ml.	7.0±0.3 6.0-7.7	7.8±0.6 7.0-8.5	8.0±0.6 7.0-9.2	7.9±0.7 7.0-8.9	7.9±0.6 7.0-8.6

Figures represent average ± probable error, maximum - minimum

The behaviour of amino acids after intravenous infusions of plasma is interesting but, at present, difficult to explain (Table 28, and figure 12). During the first two days after the infusion the amino acid content of the plasma remained fairly constant. During the second day there was actually a decrease in blood urea. This finds an explanation in the mechanism of protein storage already described in the previous chapter. From the third day up to the end of the week, the plasma amino acids increased steadily, simultaneous with this there was a slight fall in the blood urea level, preceded by a sudden temporary rise. It is of interest to observe/

observe that this increase in urea occurred inspite of the onset of diuresis.

It may be recalled that the stimulus for protein storage and improvement of the status of plasma proteins is maximum on the second day, when the amino acids are still at a constant level and urea is at its lowest. From the third day after infusion this stimulating effect commences to disappear and the change in amino acid concentration starts. At this stage the blood urea is at its highest. The change in plasma proteins already described together with the behaviour of urea and amino acids suggests an increased metabolism of proteins. The continued persistence of the high amino acid level during the subsequent period indicates the possibility of a defective utilisation of these substances.

3. ECLAMPSIA

The average blood urea in the whole series is 57.0 mgms. (= 26.5 mgms. of urea nitrogen) with a range of value between 13.0 and 2.96 mgms. per 100 ml. This average was obtained from 25 estimations done on 18 patients during the convulsive stage of the disease. This however does not take into account the degree of oliguria and the state of renal clearance present at the time of the test. However, if only those values which were obtained during the state of normal excretory functions of the kidney are considered the average of 12 tests done on 12 patients was found to be 15.1/

15.1 mgms. per 100 ml.; S.D. 0.88 (= 7.05 mgms. of urea nitrogen.) with a maximum and minimum range of 16.2 and 13.9. We have regarded this latter value as representing the state of blood urea in eclampsia in absence of retarded excretion. Compared with severe pre-eclampsia this represents a decrease by 20.8 per cent. Compared with normal pregnancy the fall in blood urea in eclampsia is even more marked. The difference in each case is statistically significant.

When the two averages for blood urea in eclampsia are considered the fallacy of accepting the over-all average for comparative purposes becomes obvious. The corrected average conveys the information regarding the state of urea synthesis in the body, on the other hand the total average superimposes the renal factor on this and obscures the picture. The urea retention which occurs in eclampsia is not due to a disturbed metabolism caused by the disease but to interference with excretion by the kidneys. This also explains why some observers have found very high blood urea, while others very low values. In most of the reports however, where detailed findings are available (5,7,12,13,38) it appears that values occupy both above and below the normal range with an almost equal frequency.

Amino acid nitrogen in eclampsia in our series was 12.57 mgms. per 100 ml.; S.D. 4.6, with a maximum and minimum range of 21.6 and 7.6 mgms. Both Kirk (47, 1933) and

Becher/

Becher and Herrmann (48, 1932) observed that in presence of severe impairment of renal function and when there is abnormal retention of urea the amino acid content of the plasma also increases. Therefore, in evaluating the results of amino acid nitrogen in eclampsia it is necessary to eliminate those cases from the series which are likely to load the values in an abnormal manner. After making this necessary correction the amino acid nitrogen in eclampsia in our series was 10.4 mgms. per 100 ml.; S.D. 1.4 (minimum-7.6 mgms., maximum 18.0 mgms.). Even this corrected value shows that in eclampsia the amino acid content of the plasma is raised above that found in severe pre-eclampsia by about 20.9 per cent. Compared with normal pregnancy this represents a considerably high level of amino acid nitrogen in the plasma in eclampsia.

Thus, if the renal factor is eliminated it appears that eclampsia is associated with a diminished production of urea and an increased level of amino acids in the blood. The result is a considerable fall in the ratio of urea N: amino acid nitrogen.

In order to ascertain how eclampsia brings about this change in amino acids we tried to find if any correlation existed between the plasma amino acid level and the number of convulsions. The number of cases studied by us did not privide sufficient data to subject the material to a statistical analysis. The average values obtained by this study/

study are presented in figure . It shows that with an increasing number of convulsions the amino acid nitrogen content of the plasma showed a distinct tendency to increase. The highest values in this series were seen in 3 patients between 4 to 8 hours before death. Further details in discussion at this stage will be futile because of the smallness of the series, but a more comprehensive idea about the subject can be obtained from the study of three cases where the patients developed eclampsia during their stay in the hospital and we had the opportunity of performing tests days before the onset of convulsions. The results obtained in these cases are presented in Table 36.

Table 36.

No. of Fits	Before	1	2	3	4	5	6	7	8
R.	8.0	8.6	9.1	-	-	-	-	-	-
A.	7.9	9.0	-	-	-	-	-	-	-
H.	8.8	-	9.1	9.6	9.9	-	10.9	14.7	20.5

These three cases clearly demonstrate that the amino acid content of the blood is adversely affected by convulsions. The rise is slow and gradual in the early stages but when convulsions occur in rapid succession this increase becomes marked. This is shown in Mrs. H. where the amino acids increased by nearly a hundred per cent. during the last two convulsions. Yet the effect of the fits appears to be temporary for in all the three cases the amino acid level/

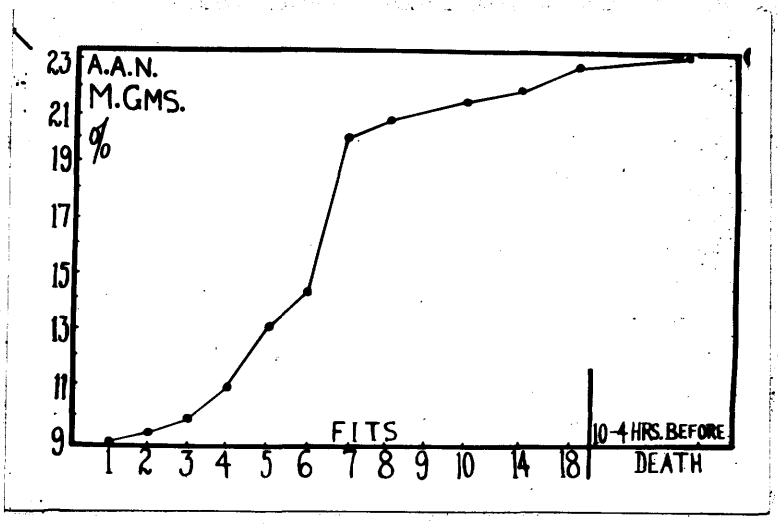

Fig. 22. Plasma amino acid nitrogen in eclampsia. The graph shows the level of amino acids in relation to the number of convulsions. The number of cases in each group is small. The diagram is only meant to show the general trend of changes in the plasma amino acid which occurs in eclampsia.

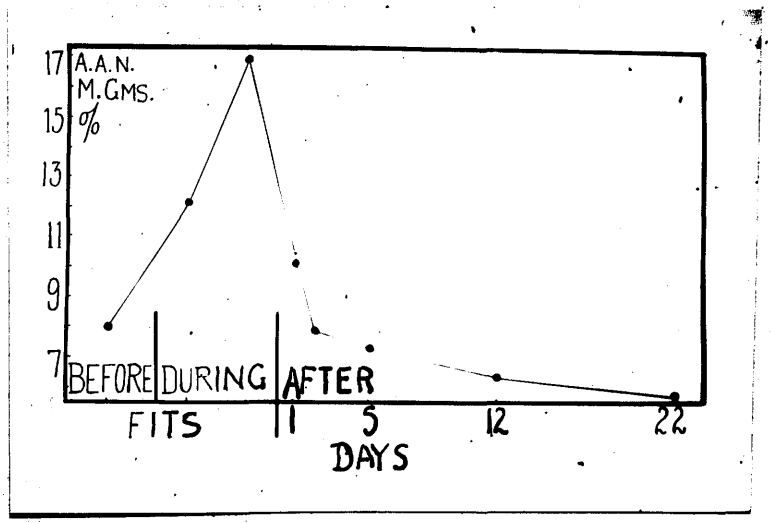

Fig. 23. Plasma amino acid nitrogen in eclampsia. A follow-up study. It shows the changes in the amino acid level in the pre-convulsive, convulsive and convalescent stages of the disease.

level started decreasing from the first day after the convulsions had ceased. (9.0, 8.5 and 18.6 mgms. respectively in the cases presented in Table 36).

This reversible nature of the change in amino acid is very clearly demonstrated in the follow up study to be presently described. Every case of eclampsia who recovered from the illness (15 out of 18 cases) was followed up on the first, second, fifth, twelfth and twenty-second day after the convulsions had ceased. The results in the pre-convulsive (3 cases), convulsive and convalescent stages are presented in Table 37 and figure 23.

Table 37

Pre-convulsive	Convulsive		Convalescent					
	1	2	1	2	5	12	22	Days
8.2	12.4	17.4	10.3	8.1	7.6	6.6	6.0	Average
0.3	4.2	4.1	2.85	0.90	0.70	0.40	0.20	S.D.
7.9	7.6	10.4	7.1	6.8	6.2	6.0	5.5	Minimum
8.8	21.6	23.1	18.6	10.0	8.9	7.4	6.2	Maximum

These data clearly indicate that the effect of convulsions on the amino acid level is of a purely temporatory nature. Yet, it is of considerable magnitude. With the persistence of the convulsive stage for more than one day (9 cases) the amino acid level was raised by 112 per cent. over that of the pre-convulsive stage. The gradient of increase was more marked on the second day of the convulsive phase than/

than on the first. Nevertheless, within 24 hours of the cessation of fits the amino acids dropped by over 40 per cent. of the highest level attained during the convulsions. During the subsequent period of convalescence this decrease continued as a slow but gradual process. By the second week of puerperium normal values were regained. The changes observed in this study are at each stage statistically significant.

COMMENTS

Every investigator has remarked that blood urea shows considerable variation in pregnancy toxaemia. In evaluating these results two factors, however, deserve consideration. (1) During pregnancy the nitrogen metabolism is maintained at a relatively low level, so that the findings in toxaemia can be compared only with those found in such low states of nitrogen metabolism. (2) Toxaemia, per se, does not grossly interfere with the rate of clearance of urea by the kidneys. But even the normal kidneys have a limit to the amount of solids which they can excrete in a given amount of urine, and in the human this maximal limit for urea has been given by Cushney (49, 1917) as 4 to 5 per cent. It has been shown by Austin, Stillman and Van Slyke (50, 1921), that up to this limit, which is seldom reached even by the normal kidney, the rate of excretion of urea per unit of body weight increases in direct proportion to the increase in the concentration of urea in the blood and the rate of urinary output. This second factor naturally imposes a limit to the excretion of urea/

urea, for, just as, an abnormal rise in the volume of urine fails to cause a proportionate increase in urea excretion, so an abnormal fall in the urinary output makes it impossible for the kidneys to excrete all the urea presented to that organ. The inevitable result in the latter case is the retention of urea in the circulation.

Toxaemia of pregnancy is characterised by oliguria. The initial effect of this is an increase in the urea concentration of the urine, but after the limit of maximal concentration for the particular organ is reached, blood urea must inevitably rise.

However, it is interesting to recall at this stage the statement made by de Wisselow and Wyatt (3, 1924), referred to earlier in this chapter, that urea retention in the blood does not occur to an expected degree in pregnancy toxaemias even when the concentration in the urine is not very high and oliguria is marked. The obvious conclusion which follows is that the production of urea is less in toxaemias of pregnancy. The values obtained in severe toxaemia and the corrected average in eclampsia presented above amply corroborates this assumption.

A careful analysis of the data provided by other investigators (details are available in only a few of them) also support this hypothesis. Thus, the figures presented by Stander et al (13, 1925) show that the average blood urea in pre-eclampsia was 30.8 per cent. less than that in normal pregnancy./

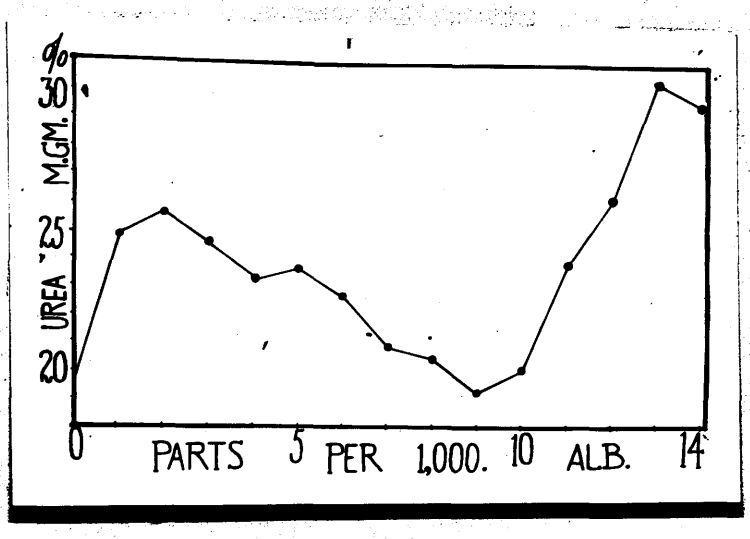

Fig. 24. Plasma urea in pre-eclampsia. The graph shows the relation between the level of urea in the blood to the the degree of albuminuria. The data have been obtained from 304 estimations in 100 cases, and demonstrates that the blood urea commences to rise only when albuminuria is marked.

pregnancy. In eclampsia, where they made no correction for oliguria and consequent chances of urea retention, the average was almost identical with that in normal pregnancy. In 12 out of their 21 cases however the blood urea level was from 30 to 51 per cent. less than that in normal pregnant women. Of Harter's (51, 1900) 6 cases of eclampsia, the blood urea in 4 was 21 to 34 per cent. below the normal pregnancy level. Botella-Llusia (39, 1936) from the analysis of a large series of cases also concludes that "in normal pregnancy urea in the blood is diminished, in toxaemia especially in eclampsia this is more marked." Hellmuth's (12, 1923) figures are widely quoted in the literature. His average in eclampsia is 20 mgms. urea N per 100 ml., but analysis of his data show that in 48 per cent. of his cases it was between 16 to 55 per cent. below the normal level. Elaborate data supplied by Harding et al (52, 1924) also provide a similar conclusion.

On the basis of our observations presented above and the findings just described it seems reasonable to conclude that the change produced by toxaemia itself is a diminished urea concentration in the blood.

In normal pregnancy, as well as in starvation blood urea decreases, due in the former to an increased protein storage and in the latter to reduced catabolism. The fall in blood urea in toxaemia exceeds that of normal pregnancy, which indicates that an additional factor must be responsible for this low urea level.

To understand the mechanism involved in this process a study of amino acid level of the blood appears indispensible. The data from our cases presented above show an increase in the amino acid nitrogen content of the blood in toxaemia and more markedly so in eclampsia.

Studies on the blood amino acids in toxaemia of pregnancy have been reported by only a few investigators and unfortunately these results lack uniformity, no doubt due partly to the different methods of investigation employed by different authors. However, inspite of the difference between the values stated by individual authors the nature of change in each series should provide the necessary information.

As early as 1905 Ewing (53) observed leucine and tyrosine in the urine of eclamptic patients and suggested the presence of a high concentration of unconverted amino acids in the blood in toxaemia of pregnancy. In 1917 Morse (29) concluded from a study of a small series of toxaemias (including nephritis complicating pregnancy) that amino acid values do not show a great deviation from normality, although "in individual cases values much higher than normal were found". Hellmuth (12, 1923) in an elaborate study observed that toxaemia causes an increase in the amino acid level of the blood. Cruickshank, Hewitt and Couper (5, 1927) estimated the amino acids in 18 cases of toxaemia and 42 cases of eclampsia (the largest reported series in the literature) and/

and concluded that these "showed no noteworthy quantitative deviation from normal, except in eclamptic cases, where there was a tendency to a moderate increase, 56 per cent. of the cases having a higher reading than the upper limit of normal". Botella-Llusia (39, 1936) found that the average concentration in non-pregnant women was 5.8 mgms. amino acids per 100 ml. plasma. In pregnancy this was 6.5, in pre-eclampsia values ranged from 6.5 to 22.1 mgms., and in eclampsia from 12.1 to 22.7 mgms. per 100 ml.

It will therefore be evident that inspite of the scantiness of observations in this subject the majority of investigators are of opinion that amino acids in blood increase during pregnancy toxaemia, a statement which our observations amply endorse.

The increase of the amino acids together with a decrease in the blood urea suggest that the synthesis of urea is deficient in toxaemia of pregnancy. This is obviously associated with a defective deamination by the liver. This however does not indicate that deamination of amino acids, as a process, suffers in the body for the liver is not the only site for deamination. Deamination is an essential prerequisite of transamination, which occurs constantly in the tissues for regrouping of amino acids and proteins.

However, the work of Mann and co-workers (54, 1924) demonstrates that deamination for urea synthesis is dependent entirely on the liver, and the results of our investigation suggest/

suggest that this deamination in the liver is adversely affected in toxaemia of pregnancy. This hypothesis is further supported by the results of amino acid feeding (cystine) already described. It is interesting to find that Botella-Llusia (39, 1936) observed a similar reaction after administration of 50 gms. of gelatin to pre-eclamptic subjects. That the deamination in the liver is affected by toxaemia is further shown by the fact that the amino acid content of the blood increases as the duration of toxaemia becomes longer, and in the three cases of pre-eclampsia who developed convulsions during their stay in the hospital.

So far, in ascertaining the cause of increased amino acids in the blood we have only considered it as a passive rise due to deficient deamination and urea-synthesis. But the possibility of an active increase can not be wholly overlooked. Carefully controlled experiments described by Farr and Alpert (55, 1940) indicate that the mechanism controlling the blood amino acid level is highly susceptible to a variety of hormones. These authors observed that in dogs, pitressin, sex hormone, thyroxin and gonadotrophins cause an increase in the amino acid level of the plasma. They also found that the highest level was attained when these animals were treated with gonadotrophins (= an increase of 75 per cent. of the basic level). Increased concentration of gonadotrophins in pregnancy toxaemia has been reported by several investigators. Our observations, which will be described/

described later also provide a similar conclusion. It is possible that the increase in amino acids seen toxaemia is partly due to an increased concentration of gonadotrophins in the circulation. However, this can not be the sole factor responsible for the process, as the increase in amino acids caused by hormones is not found to be associated with any significant change in blood urea.

Thus, it seems reasonable to conclude that while the increase in amino acids found in toxaemia may be partly due to alteration of the hormonic level, it is also closely related to a deficient production of urea. This suggests, but does not prove, that toxaemia of pregnancy is associated with a disturbance of functions of the liver connected with protein metabolism. In this connection the experimental study of Goettsch et al (56, 1942) offers an interesting possibility. These authors demonstrated that in "hypoproteinaemic dogs" retention of amino acids in the plasma was closely related to liver injury. They also showed that if amino acid loading tests (c.f. cystine experiments described above) were done the liver failed to clear the plasma of this excess of amino acids (56a, 1943). The nature of hypoproteinaemia in pre-eclampsia and its influence on liver functions have already been discussed. It seems that a vicious circle of events follow in toxaemia. The initial increase may be attended with an increase of gonadotrophin, the state of hypoproteinaemia of pregnancy (aggravated in toxaemia) probably/

probably interfers with the efficiency of clearance of the surplus amino acids. When toxaemia becomes severe, the hepatic functions suffer, urea synthesis is affected, and an actual accumulation of amino acids in the plasma takes place. As to whether this increased level of amino acids in the blood can have any toxic action is not known yet. Nevertheless it is interesting to recall the findings of Kapeller-Adler (28, 1949) and that of Minot and Cutler (57, 1936). The first named author has repeatedly observed an increased concentration of histamine and the latter a raised level of guanidine in patients suffering from pre-eclampsia and eclampsia.

CONCLUSIONS.

Normal pregnancy causes a lowering of the concentration of blood urea. This appears to be the connected with the mechanism of protein storage and haemodilution which occurs in pregnancy. Plasma amino acids show a tendency to rise as gestation advances, but this does not exceed the limits of normality to any great extent. It is suggested that this change is related to increased gonadotrophic activity which occurs normally in pregnancy.

Toxaemia of pregnancy is associated with a further decrease in blood urea and increase of amino acid content of the plasma. When the blood urea in toxaemia is higher than normal it is caused by oliguria, and a consequent fall in the urea excretion. The increase in amino acids reaches pathological/

pathological limits, but the process is reversible and normal levels are restored when toxaemia is cured. The increase in amino acids is believed to be caused by (1) an increase in the concentration of gonadotrophins and (2) defective deamination in the liver. This appears to be related to the disturbance of hepatic functions brought about by the toxaemic process.

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SECTION 2

CARBOHYDRATE METABOLISM

CHAPTER 1

BLOOD SUGAR IN TOXAEMIA

It is generally agreed that the blood sugar remains within limits in pregnancy and pre-eclampsia. In a recent review of the subject Plummer (1, 1936) observed that "toxaemias in pregnant women show no change of blood sugar levels which would differentiate these from normal gestation". Earlier investigations reported by Morris (2, 1917), Bathin (2, 1922), Stander (3, 1926), Hellmuth (4, 1927) and Novak (5, 1928) amply confirm the above assumption.

Estimation of the fasting blood sugar was done by us in 78 cases of normal pregnancy and 100 cases of pre-eclampsia. The values are presented below.

Normal Pregnancy, 89.9 mgms. per 100 ml.; S.D. 9.7. Maximum 76.6; minimum 101.0.

Mild Pre-eclampsia, 87.03 mgms. per 100 ml.; S.D. 12.3. Maximum 74.7; minimum 103.4.

Severe Pre-eclampsia, 83.7 mgms. per 100 ml.; S.D. 7.4. Maximum 75.0; minimum 101.8.

In both mild and severe pre-eclampsia blood sugar was within normal limits. The small variation in the average does not appear to be significant, and the range is almost identical in the three groups of cases presented above.

Blood sugar values in eclampsia, however, have been a subject/

subject of much controversy. In this connection a review of the literature may appear interesting. Wieden (7,1915), Benthin (3, 1922), Obata (8, 1923), Walthard (9, 1923) and Stander and co-workers (3a, 1925) observed that the blood sugar level is raised in eclampsia. Most of these authors believe that this hyperglycaemia is the effect of convulsions. Stander and Radlet (3, 1926) found that the state of hyperglycaemia persists for an appreciable time after the cessation of convulsions, and Stander and Harrison (3b,1929) believe that this raised level of blood sugar is related to the change in the alkali reserve of the blood, and to a consequent alteration of the hydrogen ion concentration of the liver cells.

Levy (10,1927), Titus (11, 1928), Lefferty (12,1931), Siedentopf (13,1932,1938), Siegel and Wylie (14,1933), Chamina (15,1935) and Posatti (16,1938) found that the convulsions of eclampsia were associated with a state of hypoglycaemia. On the basis of this finding Titus and co-workers advocated the use of hypertonic glucose solutions in the treatment of eclampsia. There is general agreement about the effectiveness of this treatment.

The average blood sugar for 18 cases of eclampsia in our series was 82.1 mgms. per 100 ml.; S.D. 5.0. Individual values occupied a range of 70.5 to 92.3, which, compared with normal pregnancy and pre-eclampsia shows a slight deviation to the left. The fall in the average however, is not/

not statistically significant. Only 5.5 per cent. of the values in this series were below 80 mgms. per 100 ml., but 4 per cent. of pre-eclampsia and normal pregnancy also occupied the same level. It may be of interest to note that in an analysis of 22,808 blood sugar estimations in non-diabetic persons, John (17, 1928) found that 11 per cent. of the values were below this accepted minimum standard of normality. In view of these findings it is difficult to conclude that eclampsia causes either hypo-of hyperglycaemia.

However, a study of this nature represents merely the average state of the blood sugar in eclampsia without indicating the manner in which it is affected by the onset of the eclamptic seizure. Three patients in this series developed eclampsia during their stay in the hospital and we had the opportunity of comparing the blood sugar values in the pre-eclamptic and eclamptic state. The results obtained are given in Table 38..

The three cases demonstrate that eclamptic convulsions per se do not affect the blood sugar level in any consistent manner. In all cases the blood for estimation of sugar was collected immediately after the cessation of convulsions and none of these patients received any form of glucose during this investigation. Thus, the values presented above are comparable with the fasting blood sugar levels given in the first and last columns of the table. It appears that as a result of convulsions the blood sugar level may rise or

fall with an almost equal frequency. In this respect our findings disagree with those of Stander and Harrison (3b, 1929) who observed a consistent increase in blood sugar as a result of convulsions.

Table 38

	Pre-convulsive (fasting)	Convulsive stage								24 hrs. after convulsions
		1	2	3	4	5	6	7	8	
Mrs. H.	87.0 (16 * hrs.)	114.0	87.0	-	-	-	-	-	-	83.8
Mrs. A.	88.0 (21 hrs.)	61.2	107.6	86.5	-	-	-	-	-	91.4
Mrs. H.	90.0 (7 hrs.)	91.7	80.7	134.8	70.0	81.2	80.6	64.7	80.0	98.0

* Figures in parenthesis represent the number of hours before the first convulsion when the test was done.

In order to make a further scrutiny we estimated the blood sugar in 7 patients, 15 to 20 minutes before, 5 minutes after and during an actual convulsion of eclampsia. The results are presented in Table 39 and figure 25.

In 4 of these 7 cases blood sugar increased during the convulsion, but the extent of this increase was outside the scope of experimental error in 3 patients only. In 2 cases there was an appreciable fall and in 1 (probably in 2) instances there was no recognisable alteration in the glucose concentration of the blood. The series presented here is small/

small, but in conjunction with that already discussed (Table 38) it appears that the level of blood sugar is not directly affected in eclampsia. This finding is in concormity with that of Krieger (18, 1934), who made a detailed study of the reducing substances in the blood in eclampsia.

Table 39

	Before	During	After convulsions
1. De.	83.5	86.5	84.7
2. M.	80.6	138.7	108.0
3. H.	64.6	78.4	78.0
4. A.	128.6	158.8	96.2
5. Dn.	156.5	140.0	93.5
6. McL.	76.0	76.0	77.7
7. McI.	93.5	77.6	75.5

Our investigation in this direction was carried further on 2 patients, where the blood sugar was estimated at intervals of a 1/4 hour for 3 hours during the stage of eclamptic convulsions. (Mrs. S. and McC.). The results are graphically represented in figure 26.

These two cases also demonstrate the complete lack of correlation between the blood sugar level and eclamptic convulsions. Both patients had repeated convulsions and both of them received intravenous glucose inorder to prevent hypoglycaemia. It will be seen that convulsions occurred with almost equal frequency when the blood sugar was rising as when it was on a decline.

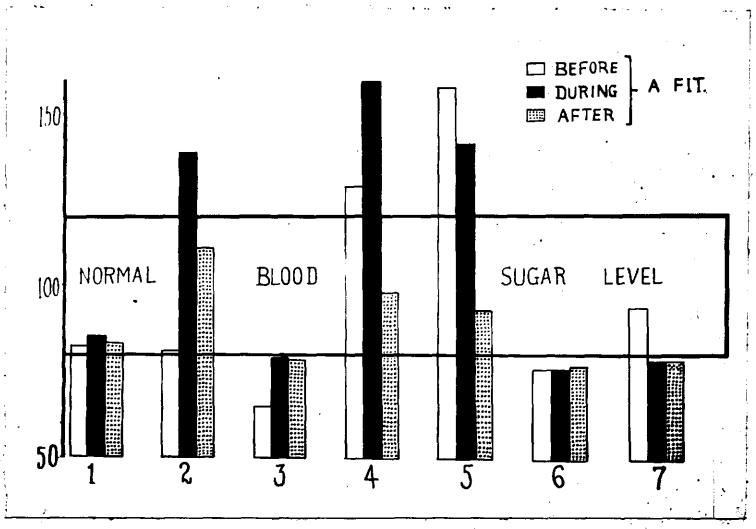

Fig. 25. Blood sugar in eclampsia. The diagram shows the results obtained in seven cases before, during and after a convulsion. Note the complete lack of corelation between the blood sugar level and an eclamptic fit.

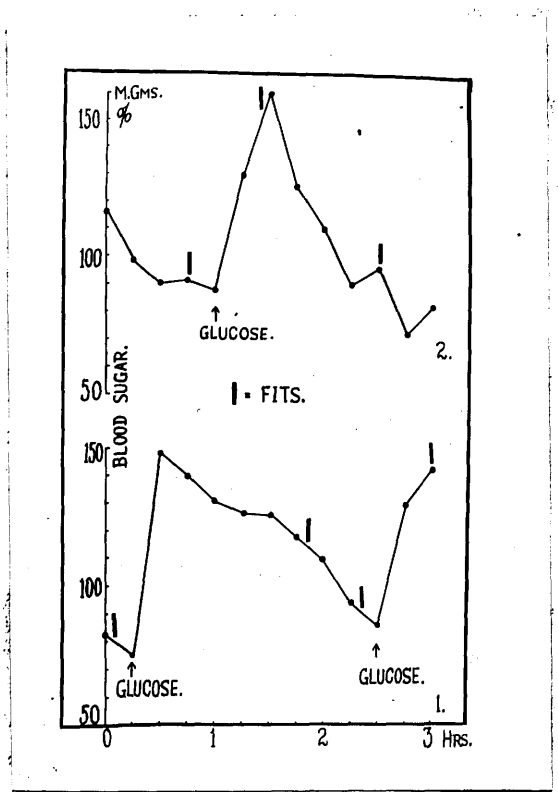

Fig. 26. The levels of blood sugar during the convulsive stage of eclampsia. Two cases. Note that convulsions may occur when the blood sugar is both ascending and descending.

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CHAPTER 2

GLYCOGEN STORAGE

In 1912 Schirokauer (1) first observed that alimentary glycosuria is a common feature of early pregnancy. Since then, considerable work has been done on this subject, and investigators have broadly divided themselves into two groups. (1) Those (2,3,4,5,6) who believe that the glycosuria is due to the lowering of the renal threshold. In this connection it may be mentioned, that Faber (4, 1926; 4a,1927) reported two normal primiparae whose "threshold" fell from 150 and 200 mgms. per cent. to below 130 mgms. per cent. in the course of pregnancy. (11) The second group of observers (7,8,9) believe that the renal threshold may or may not be lowered during pregnancy but the glycosuria is due to defective utilisation of sugar in the body, which is probably of hypothalamico-pituitary origin. Evidence in support of the latter theory is found in the fact that pregnant women often show acetonuria and an increased tendency to Ketosis. Schultze (10,1926) and Bokelmann and Bock (11, 1927) found that pregnancy is associated with an increase of blood lactic acid, Bokelmann ascribed it to a defective coricycle and resynthesis of lactic acid into glycogen. Histological (Hofbauer 12, 1907) and biopsy studies (13,1945) of the liver during pregnancy have revealed centrilobular deposition of fat, which has been ascribed to glycogen deficiency.

Liver glycogen serves as an important reserve source of carbohydrate readily available to all tissues of the body. In normal persons, if the supply is plenty, a large amount can be accumulated in the liver in a few hours; in time of need it can be used with equal rapidity. The rate of this glycogenesis is dependent not only upon the nature of glycogenic material available but also upon the condition of the individual when these materials are ingested. The role of internal secretion of the pancreas in this connection is well established. It is known that an injection of insulin reduces the level of sugar in the blood by increasing the rate of glycogen deposit. (It has never been demonstrated that insulin increases the level of liver glycogen, although muscle glycogen has been known to be raised by this hormone).

In order to observe the rate in which the sugar in the circulation is utilised for storage purposes, we performed a series of experiments on 16 cases of normal pregnancy and 28 cases of toxaemia of which 3 were eclamptics. Immediately after a sample of blood was obtained for the estimation of the basic blood sugar level each patient was given an intravenous injection of 5 gms. of glucose and 3 units of insulin. The small quantity of glucose used for this experiment was in order to avoid any loss through glycosuria. The amount of insulin used was calculated to "cover" the quantity of glucose injected. A sample of blood was examined for its content of sugar at 5 minutes and

20 minutes after the injection. No patient with abnormal fasting blood sugar level or glycosuria (before or during the test) was accepted for this study. The results are submitted in Table 41 and figure 27.

Table 41

	Fall in Blood Sugar (5 min-20 min.after injection)							Total
Mgms./ 100ml.	0-10	10.7-20	20.1-30	30.1-40	40.1-50	50.1-60	60.1-70	
Normal No. of Cases	-	-	2	1	6	3	4	16.
Toxaemia No. of Cases	10	17	1	-	-	-	-	28.

The rise in the blood sugar caused by the injection of glucose varied considerably in individual cases. In 8 out of 16 cases of normal pregnancy, immediately after the injection, a hyperglycaemic level (above 140 mgms.per 100 ml., Peters and Van Slyke, 14, 1946), was reached, but this was of a short duration for in only one patient was the blood sugar above 140 mgms. (= 146 mgms.) per 100 ml., 20 minutes after the glucose-insulin injection. The fall in the blood sugar brought about by the insulin varied from 22 to 67 mgms.per 100 ml., with an average of 48.3; S.D.14.19. In 13 patients (81.5 per cent.) the reduction of blood sugar exceeded 40 mgms.per 100 ml.

In the toxaemia series the injection caused the blood sugar/

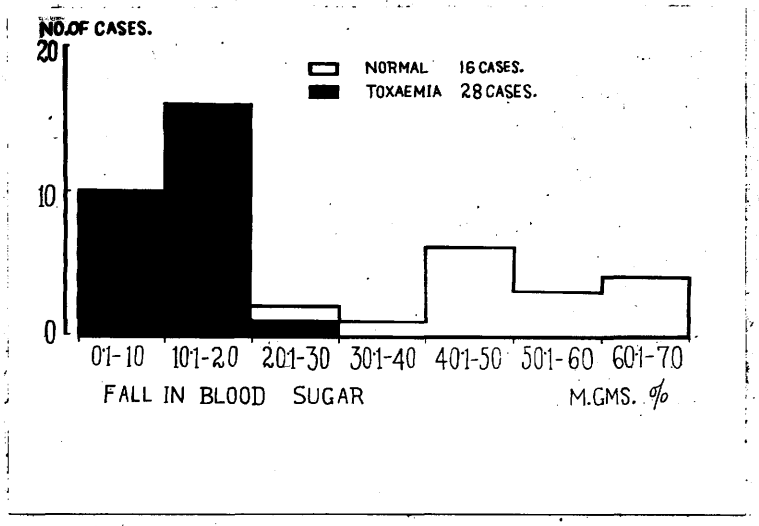

Fig. 27. Glycogen storage in normal and toxaemic pregnancy. The diagram shows the effect of injections of insulin and glucose. The removal of sugar from the circulation by insulim is retarded in toxaemia of pregnancy.

sugar to rise temporarily above 140 mgms. per 100 ml. in 12 cases. The subsequent decrease due to insulin was, however, much less than that in normal pregnancy, the maximum being 20.8 and the minimum 2.8 mgms. per 100 ml. The average fall in blood sugar in toxaemias was 11.7 mgms.; S.D. 5.38. If the single case where the value just exceeded 20 mgms. (20.8 mgms.) is excluded, the storage of sugar stimulated by the insulin in pre-eclampsia and eclampsia was less than 20 mgms. per 100 ml. The difference in the values obtained for glycogen storage in normal pregnancy and toxaemia is considerable and statistically significant.

In order to compare the values obtained during pregnancy with non-pregnant states, the test was carried out on 6 members of the laboratory staff. The fall in blood sugar from its peak-level was between 58 to 79.5 mgms. per 100 ml., with an average of 67.4; S.D. 10.4. These values are higher than those in normal pregnancy and the differences satisfies statistical scrutiny.

The interpretation of these findings is far from easy. One interesting feature which was observed during these experiments was that there was no leakage of sugar in the urine even when the blood sugar reached 190 mgms. for a short period. Lowered renal threshold in pregnancy is probably not as frequent as is believed to exist. It may be mentioned here that Williams and Wills (15, 1926) from a study of 640 glucose tolerence tests also arrived at the same conclusion.

Infusion of concentrated intravenous glucose has been accepted as a recognised treatment of toxaemia. Several authorities inducing Titus (16, 1928) and Dieckmann (17,1941) have claimed considerable improvement in maternal mortality following glucose therapy. Dieckmann states that the amount of glucose prescribed for a case of eclampsia must be sufficient enough to cause a surplus (in order to promote diuresis) over that required to meet the deficiency in the glycogen reserve of the liver. Few investigations have however been done to ascertain the manner in which this glucose is utilised in the body. In the experiments described above it is evident that even if the additional glucose is protected with insulin it is not taken over by the tissues (especially liver and muscles) in toxaemia as quickly as in normal pregnancy, while in both these groups of cases the process is much slower than in the non-pregnant state.

In order to determine how additional glucose is utilised when given alone, we gave 50 gms. of glucose to 20 cases of normal pregnancy and 20 cases of severe pre-eclamptic toxaemia and also to 5 cases of eclampsia after the convulsions had ceased for 18-24 hours. Glucose was given dissolved in 250 ml. of water, the bladder was emptied immediately before the commencement of the test, and the total quantity of urine secreted during the following 4 hours was collected and estimated quantitatively for glucose. It will be seen that the quantity of glucose employed was the/

the same as that for the glucose tolerance test. In a normal person this does not cause glycosuria. In 4 out of 20 cases of normal pregnancy ingestion of 50 gms. of glucose caused sugar to appear in the urine in quantities of 0.8, 1.0, 1.3 and 1.3 gms. respectively (average = 1.10 gms.). In 1? cases of pre-eclampsia glycosuria developed, and the quantity of glucose excreted in the urine was ?.2, ?.4, 2.7, 3.1, 3.6, 3.9, 4.0, 4.?, 4.?, 4.5, 5.3, and 7.4 gms. respectively (average = 3.95 gms.). All 5 cases of eclampsia excreted sugar in the urine in quantities of 5.0, 6.3, 6.9, 7.3, 7.3 and 9.4 gms. respectively (average = 8.64 gms.).

It will be evident from the data presented above that 60 per cent. of the cases of severe pre-eclampsia and all the cases of eclampsia studied in this series failed to completely utilise the glucose given. Of those who showed glycosuria, pre-eclamptics lost 7.3 and eclamptics 17.? per cent. of the ingested sugar in the urine.

As all the pre-eclampsia cases in this series were selected (from the first group of cases already described) for their <u>not</u> showing an abnormal renal threshold, it can be concluded that during the post-absorptive phase the additional/

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*- The urine was collected every ½ hour. Estimation for sugar was done on each fresh specimen and calculated for the total quantity of urine secreted during 4 hours. In no specimen was sugar detected in the ninth sample (4½ hours).

additional glucose reaching the circulation was being allowed to accumulate until it exceeded the threshold level and was excreted in the urine. This suggests that by merely raising the blood sugar in toxaemia it is not possible to stimulate glycogenesis.

However, these experiments do not provide positive evidence for a lack or otherwise of the glycogen store of the body. The only interesting quantitative work on animals in the literature, which throws some light on the subject is that of Schmidt and co-workers (18,1927). These authors estimated the glycogen content of the liver and muscles of "well-fed" dogs during pregnancy. They found that pregnancy was associated with a fall of liver glycogen from 6 per cent. (non-pregnant animals) to 2.15 per cent. They also noticed a similar decrease of the glycogen level of the muscles. This would account for the increased tendency of acidosis during pregnancy. The danger of Ketosis is increased markedly in toxaemias (vide infra). These observations together with the results of the experiments described above suggests that the glycogen store is probably low in pregnancy toxaemia. Indirect evidence in support of this is found in the markedly high incidence of toxaemia in diabetes, a condition in which the carbohydrate metabolism is known to be upset.

The cause of this disturbed carbohydrate metabolism is not quite clearly understood. Factors which normally control carbohydrate utilisation and storage are numerous, and among/

among them endocrines play an important part. Both anterior and posterior lobe of the pituitary body, the adrenal medulla and cortex and to some extent oestrogens (Dolin, et al, 19, 1941; Ingle, 20, 1943) have been known to have a contra-insular effect. Normal pregnancy is attended with some degree of pituitary hyperactivity and a marked excess of oestrogens in the circulation. These could account for the reduced tolerence for glucose seen in this condition. Reference has already been made to the increased concentration of gonadotrophins observed by Smith and Smith and several other investigators in pregnancy toxaemia. Our own investigation described in a subsequent section demonstrates considerable basophil hyperactivity of the pituitary in pre-eclampsia and eclampsia. Cushing's (21, 1912) earlier experiments, the Houssey animal (22, 1931) and clinical investigations on basophilism (Dorfman et al, 23, 1940; Albright, 24, 1943) clearly indicates how pituitary over-activity can inhibit the effects of the pancreatic hormone, reduce the glycogen store of the body, and predispose to a state of decreased carbohydrate tolerence. In view of these indirect evidences it seems probable that the disturbed carbohydrate metabolism seen in pregnancy toxaemia is connected with endocrine dysfunction in which pituitary hyperactivity plays an important role either directly or through the intermediary of the adrenal cortex. The present state of our knowledge does not permit any further elaboration on the subject.

CONCLUSION

The results of the experiments described in this section suggest that the capacity for the system to accelerate the storage and utilisation of sugar in presence of induced hyperglycaemia is notably affected in pre-eclampsia and eclampsia. There appears to exist in these conditions, a mechanism in the body which counteracts the action of insulin. Available evidences suggest that this mechanism is connected with the hyperactivity of the anterior lobe of the pituitary body. Further work is necessary for a complete understanding of the process.

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CHAPTER 3

SUGAR MOBILISATION

Organic changes in the liver revealed by necropsy have sometimes suggested a deficiency of glycogen in this organ. However, adequate proof of a depletion of the hepatic glycogen reserve has never been offered. The experiments described in the preceding chapter and the results of glucose tolerence tests merely suggest a delayed utilisation (and probably storage) of sugar in toxaemia. An attempt was made to further investigate the point with the help of adrenalin. It is known that administration of adrenalin causes the blood sugar to rise rapidly often to the extent of provoking glycosuria. It is also known that this hyperglycaemia results from hepatic glycogenolysis, the muscle glycogen being normally not affected in this process (1,2). Moreover, it has been pointed out (3,4) that in diseases of the liver, as this organ does not contain the normal quantity of glycogen blood sugar rises less than usual after the injection of a standard dose of adrenalin. This forms the basis of the experiments to be presently described.

Every patient (normal or otherwise) in this series was kept in basal condition with a rich carbohydrate meal on the night before the test. The experiment was done in the morning 2 hours after a breakfast consisting of sweet tea and toast. Before the test the blood pressure was taken every minute until both systolic and diastolic readings were constant./

constant. At this stage venous blood was collected for estimation of the basic blood sugar level. Immediately thereafter an intramuscular injection of 0.5 ml. of adrenalin was given./ Twenty minutes later a second sample of blood was obtained for sugar. The interval of 20 minutes was decided upon from a preliminary study on 16 cases of normal pregnancy where blood sugar was estimated every 5 minutes after the injection in order to determine the point of maximum rise due to adrenalin. The difference between the basal and post-adrenalin blood sugar value was accounted for by the mobilisation of the hepatic glycogen caused by adrenalin, and described as the sugar mobilisation index.

1. NORMAL PREGNANCY

As our object was to ascertain the nature of changes which occur in toxaemias of pregnancy, we confined our experiments on normal cases to only the last trimester of gestation. The data presented here are based on 83 tests done on 53 patients, who were between 29 and 40 weeks pregnant.

The average sugar mobilisation was 19.1 mgms.per 100 ml.; S.D. 2.52, with a maximum and minimum of 26.0 and 13.1 mgms. respectively. The scatter was almost identical both above and below the mean, but in just over two-thirds of the experiments the mobilised sugar exceeded 18 mgms.per 100 ml. of blood.

On 6 members of the laboratory staff under similar conditions/

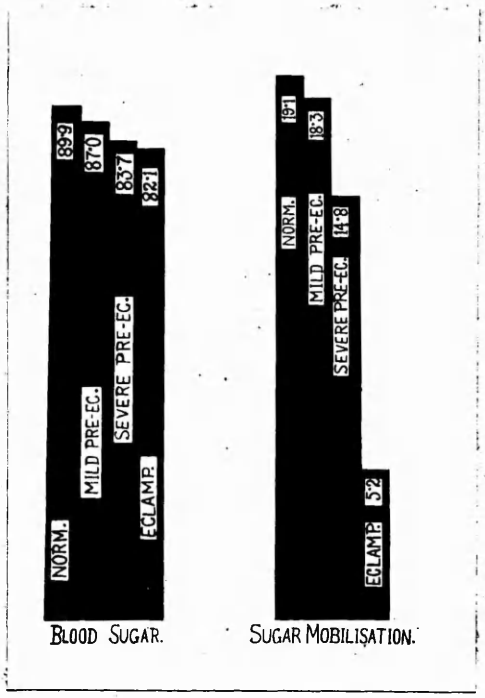
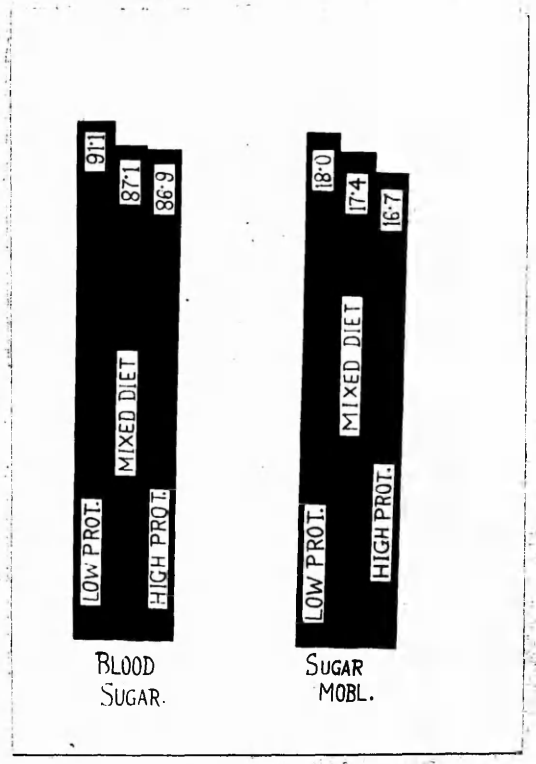


Fig. 28. Blood sugar and sugar mobilisation in normal and toxaemic pregnancy.

Fig.29. Blood sugar and sugar mobilisation in pre-eclampsia in relation to the dietary protein intake. The low-protein group also received a high carbohydrate diet. The slight difference in the values shown in the diagram is not of statistical significance.



mean for this group, 38 per cent. in mild and 10 per cent. in severe pre-eclampsia occupied the same position. It is therefore, apparent that sugar mobilisation diminishes to an appreciable extent in severe pre-eclampsia. In mild pre-eclampsia the decrease in sugar mobilisation is not a notable feature.

Table 40

Frequency mgms. per 100 ml.	Normal Pregnancy	Mild pre-eclampsia	Severe pre-eclampsia	Total pre-eclampsia
6.1 - 8.0	-	-	1	1
8.1 - 10.0	-	-	2	2
10.1-12.0	-	-	7	7
12.1 - 14.0	-	-	6	5
14.1 - 16.0	14	2	16	18
16.1 - 18.0	16	10	9	19
18.1 - 20.0	24	28	8	37
20.1 - 22.0	17	9	1	10
22.1 - 24.0	9	1	-	1
24.1 - 26.0	3	-	-	-
Average	19.1	18.3	14.8	16.7
P.E.	1.62	1.0	1.08	1.99
Maximum	26.0	22.6	21.0	22.6
Minimum	15.1	14.8	7.6	7.6

SUGAR MOBILISATION AND THE CLINICAL COURSE OF TOXAEMIA

Experiments to determine the sugar mobilisation were repeated/

repeated at weekly intervals with a view to ascertain if any relationship existed between the clinical course of toxaemia and the capacity of the liver to mobilise glycogen. The results obtained are presented in Table 41 and figure 30.

Table 41

Weeks after Admission	Improved			Deteriorated		
	Average	P.E.	Min. - Max.	Average	P.E.	Min. - Max.
1	16.2	1.66	11.4 - 22.6	14.4	1.43	7.6 - 19.1
2	17.7	1.39	12.0 - 23.0	12.6	1.41	7.0 - 19.0
3	18.9	1.23	15.5 - 22.0	10.8	1.41	6.4 - 13.6
4	20.1	0.74	17.0 - 21.4	8.6	1.20	6.0 - 10.5

It will be evident from the data that the amount of sugar mobilised by adrenalin bears a relationship to the clinical course of toxaemia. Sugar mobilisation increases with the improvement of the clinical condition and decreases with its deterioration. In patients who were cured, normal pregnancy level was reached between the third and fourth weeks. In the cases where the toxaemia grew worse the initial values were lower than those of the other group. This is probably due to the initial severity of the toxaemia. During the subsequent period of investigation sugar mobilisation deteriorated steadily. In the first week of study the reduction amounted to 24.6 per cent. of the normal level at term. During the following three weeks this changed into 34.0, 43.5 and 55.0 per cent. respectively. It is interesting to/

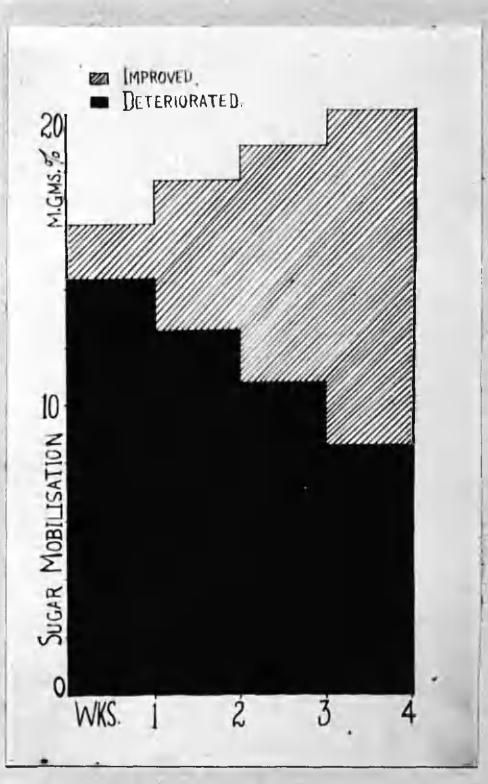


Fig. 30. Sugar mobilisation in relation to the clinical course of toxaemia (pre-eclampsia.).

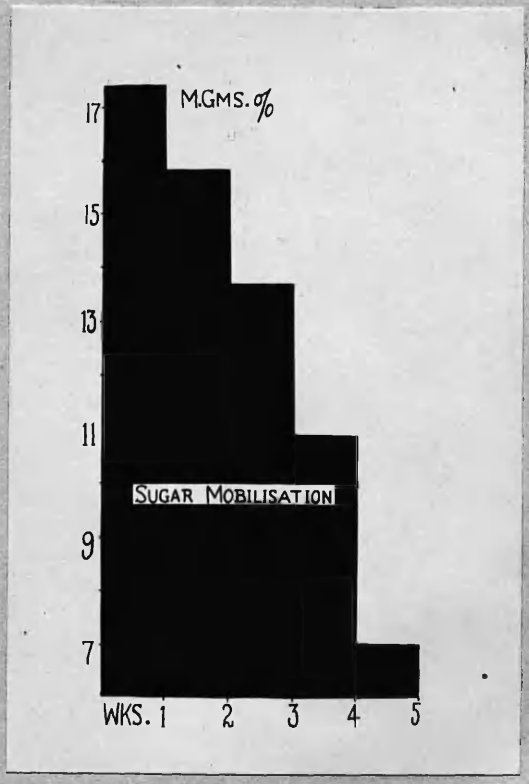


Fig. 31. Sugar mobilisation in pre-eclampsia. The diagram shows the relation to the duration of toxaemia in those patients where the toxaemia persisted or increased in severity.

to observe that although the averages satisfy statistical scrutiny in both groups, the scatter shows that the improvement of values is brought about by an increase of the minimum while deterioration is caused mainly by a fall in the values at the upper end of the range. The maximum value in improved cases and the minimum in deteriorated ones show only little variation. This was believed to be due to considerable overlapping of values in each group. So, all the deteriorated cases were subjected to further analysis in relation to the duration of toxaemia irrespective of their time of admission. The manner in which this was done has already been described. The results obtained from this study are submitted in Table 42 and figure 38.

Table 42

Duration Weeks	1	2	3	4	5
Average	17.4	15.8	13.7	10.9	7.0
P.E.	2.21	2.25	2.02	1.68	0.79
Minimum	12.7	8.5	7.5	7.1	6.0
Maximum	22.6	20.0	19.7	17.0	8.2

The change in sugar mobilisation brought about by the persistence of toxaemia is evident from the figures presented here.. It is obvious that as the duration of toxaemia is prolonged, the capacity of the liver to mobilise glocygen becomes progressively less. Compared with the sugar mobilisation in normal pregnancy the decrease in each successive week/

week of toxaemia amounts to 6.1, 17.3, 28.2, 41.8 and 63.5 per cent. respectively. It will be seen that the gradient of fall increases appreciably after the toxaemia has persisted for more than three weeks. The change in the values satisfies statistical significance at each stage. The decrease affects not only the average but also the range of values. The lower values seem to be affected earlier than the higher ones in each series.

SUGAR MOBILISATION AND BLOOD PRESSURE

It has been pointed out already that the changes observed in relation to protein metabolism bear some relation to the level of diastolic blood pressure in a case of toxaemia It was therefore considered that an analysis of sugar mobilisation in relation to the blood pressure, at any given stage of the disease, might prove interesting.

A study of the results obtained from these experiments in relation to systolic blood pressure did not prove to be of much interest. There was a general tendency to decline with an increase of systolic pressure but this was neither uniform nor significant at all stages. The lowest value was obtained at 200 mm.Hg., yet when the pressure was 210 mm.Hg. the value was actually higher than that at 175 mm. The results are represented in figure 32. With an increase of diastolic pressure however there was a gradual deterioration of sugar mobilisation. The results are given in Table 43 and figure 32.

Table/

Table 43

B.P. mm. Hg.	Aver.	P.E.	per cent. <norm.	Min.-Max.	B.P. mm. Hg.	Aver.	P.E.	per cent. <norm.	Min-Max
86- 90	18.9	1.41	1.04	15.7-21.0	106-110	15.1	0.87	20.9	10.6-13
91- 95	20.0	1.41	4.7	15.8-22.6	111-115	12.6	0.64	34.0	7.0-11.3
96-100	17.5	2.14	8.4	14.5-22.0	116-120	8.9	0.41	53.5	6.0-10.6
101-105	16.6	1.27	13.1	13.0-19.2	-	-	-	-	-

It will be evident that with slight rise of diastolic pressure there is no significant decrease in glucose mobilisation. On the contrary there is a slight increase in the average value between 91 and 95 mm.Hg. diastolic pressure. Compared with normal this is barely significant. When the blood pressure reaches above 100 mm. Hg. the fall in glucose mobilisation becomes significant for the first time. Subsequent to this, the decrease is maintained steadily with statistical significance at each stage. The gradient of fall is at first slow, but becomes marked when the blood pressure rises higher than 110 mm. Hg. Between 110 and 115 mm.Hg. the amount of glucose mobilised under experimental conditions was about one-third of the normal, while at 120 mm. Hg. glucose mobilisation was less than half of that in normal pregnancy.

3. ECLAMPSIA

The average value for our series of eclampsia was 5.2 mgms. per 100 ml.; S.D. 2.6 (maximum = 11.0 mgms.; minimum = 3.2 mgms.). This was obtained at the time of admission irrespective/

irresepctive of the condition of the patient, and represents a fall of 72.8 per cent. below the normal pregnancy level. However in order to study the effects of eclampsia on glucose mobilisation, we shall present here the analysis of three cases, whom we had the opportunity of following up from the pre-eclamptic state. The glucose mobilisation in these three patients, 7 to 21 hours before the onset of convulsions, was 16.0 (H.), 11.6 (A.) and 12.5 (R.) mgms. During the stage of eclampsia the values obtained in these cases were 3.5 (H.), 9.0 (A.), and 7.0 (R.) mgms. respectively. Thus, in these three patients glycogen mobilisation decreased by 39.8 to 78.2 per cent. of their respective pre-convulsive values. The greatest fall was seen in H., who had the most number (six fits) of convulsions.

The effect of the number of convulsions on glycogen mobilisation is shown in figure . Detailed discussion on this subject is avoided as the number of cases studied in each group is small. It is however evident that glycogen mobilisation becomes less as the number of convulsions increase. An interesting thing was observed in three cases. A short description is given below.

1. McKenzie (11) primigravida; 39 weeks; admitted with 5 eclamptic convulsions. On admittion B.P. 178/112; Albumin 0.9 per cent.; Oedema ++, coma++. Initial blood sugar was 70.5 mgms. per 100 ml. Glucose mobilisation 3.4 mgms. After 2 more convulsions, blood sugar was 60.3; sugar mobilisation was/

was - 7.4. The test was repeated 4 hours before death. There was a further fall of blood sugar to 47.1 mgms., and injection of adrenalin caused a further lowering of the sugar to 36.9 mgms.; the sugar mobilisation thereby being - 10.2 mgms.per 100 ml.

2. Henderson (12) primigravida; full term; admitted after 14 convulsions. On admission B.P. was 115/60; coma ; Albumin 1.7 per cent.; oedema++. Blood sugar concentration was 76.0 mgms.per 100 ml. Sugar mobilisation nil. She had 4 more convulsions, at the end of which the test was repeated. Blood sugar concentration decreased to 60.0 and sugar mobilisation was - 17.1 mgms.per 100 ml.

3. McLeod (16) primigravida; 38 weeks; admitted after 1 eclamptic fit. On admission B.P. 180/110. Albumin 1.3 per cent.; oedema+++; coma+. Blood sugar at this stage was 80.2 mgms. and sugar mobilisation was 9.2 mgms.per 100 ml. The coma deepened, although the patient did not have any more convulsions. On the following day blood sugar was 80.0 mgms.per 100 ml.; sugar mobilisation was nil. Experiment repeated 16 hours before death (3rd day after admission) showed that the blood sugar was 50.4 mgms., and sugar mobilisation was - 10.0 mgms.per 100 ml.

The significance of these findings will be discussed later.

Follow up study similar to that already described (Section 1, chapter 3) shows that sugar mobilisation is considerably/

considerably affected if the convulsive stage persists for any length of time, but in patients who recover, the process appears to be reversible, for by the end of the second week normal values are nearly restored. The results are presented in Table 44 and figure 34.

Table 44

	pre-convulsions	Convulsions. Days		Post-convulsive stage Days				
	7-21 hrs.	1	2*	1	2	5	12	22
Aver.	13.2	5.9	2.7	4.6	9.4	14.2	18.3	20.2
S. D.	1.91	2.69	0.62	1.19	1.79	2.73	1.55	1.64
Min.	11.6	3.2	2.1	3.0	6.9	13.8	14.3	19.0
Max.	16.0	11.0	3.6	7.3	12.7	16.6	19.7	21.0

* Cases with negative mobilisation are excluded.

Compared with the sugar mobilisation at the pre-convulsive stage, the first day of convulsions caused 55.2 per cent. fall in the amount of mobilised liver glycogen. When the convulsions persisted for more than a day sugar mobilisation dropped to 79.5 per cent. of that in the pre-eclamptic state. Moreover, it will be noticed that the basal and post-adrenalin blood-sugar level varied to such a small extent that the difference can hardly be regarded as being outside the margin of experimental error. To all intents and purposes, sugar mobilisation at this stage may be regarded as 0. However, during the post convulsive stage the/

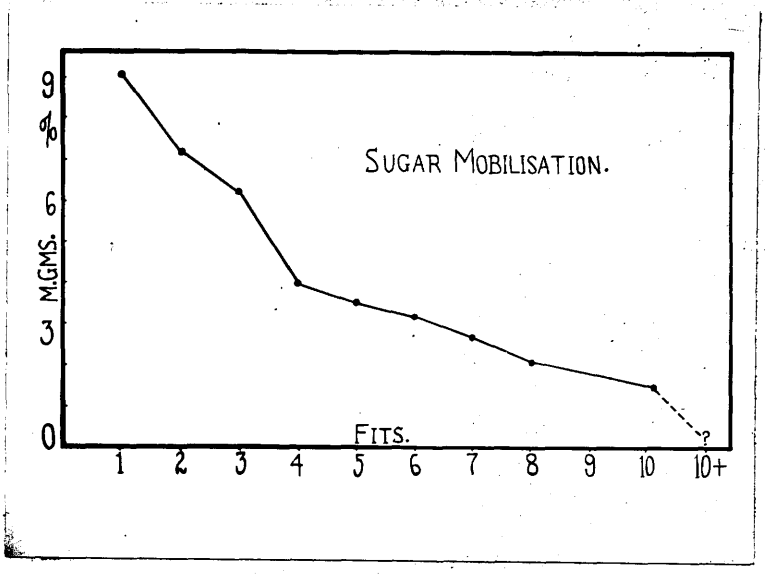


Fig. 33. Sugar mobilisation in eclampsia, in relation to the number of convulsions. Owing to the small number of cases in each group the details have been omitted from the text. The graph shows that the sugar mobilisation suffers with increasimg number of convulsions.

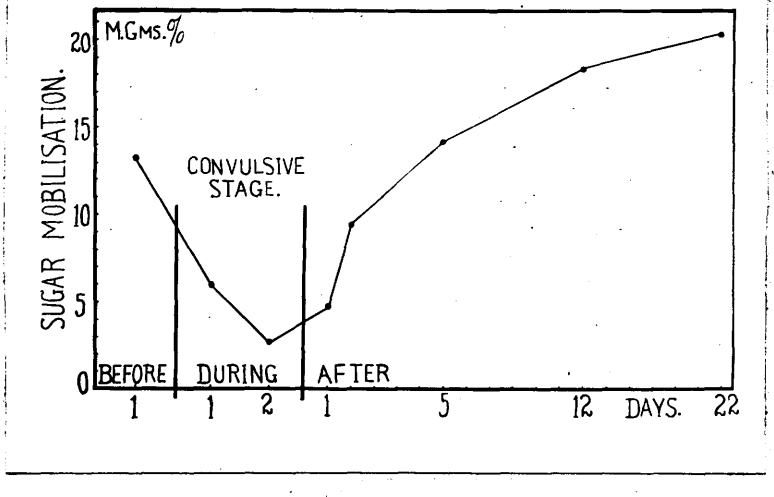


Fig. 34. Sugar mobilisation in eclampsia, showing the changes in the pre-convulsive, convulsive and convalescent stages of the disease.

the improvement was rapid during the first week of convalescence and steady and gradual during the subsequent period of recovery.

COMMENTS

The results of the experiments described here suggest that the capacity to mobilise hepatic glycogen under the influence of adrenalin is less than normal in pregnancy, and less than normal pregnancy in toxaemia. The degree to which this function suffers appears to depend on the severity of toxaemia. This is revealed not only by the lower averages obtained in severe pre-eclampsia but also by the follow-up studies described above. The small number of normal non-pregnant individuals studied as "controls" offer an interesting contrast. Pregnancy (during the last trimester) was associated with a 38.0 per cent. decrease in sugar mobilisation. Mild toxaemia lowered this a little more (40.6 per cent.) but not to a significant degree. In severe pre-eclampsia sugar mobilisation was reduced by 52 per cent., whereas in eclampsia a further decrease was noted (83.2 per cent. of non-pregnant level).

Pre-eclampsia and eclampsia are diseases of pregnancy, so the results obtained in these cases are not strictly comparable to those obtained in non-pregnant persons. The change from normal pregnancy to mild pre-eclampsia is not marked. Severe pre-eclampsia caused a 22.5 per cent., and eclampsia 72.8 per cent. reduction in sugar mobilisation.

It/

It is interesting to note that difference of values between eclampsia and severe toxaemia of long duration (5 weeks) is slight and of little statistical significance. A study of individual cases of eclampsia however, demonstrates that convulsions, per se, have a dilaterious effect on the capacity of the liver to mobilise sugar.

The cause of this defective sugar mobilisation in toxaemia may be either (1) insufficient glycogenic reserve in the liver, or (2) an abnormal failure of the glycogenolytic response. The second condition has been known to exist in von Gierke's disease, in which there is an excessive deposit of glycogen in the liver and other affected organs, but this glycogen is not available for glycogenolysis. In some respects this condition simulates hepatic inefficiency as seen in toxaemia (e.g. hypoglycaemia, ketosis, occasional convulsion, prolonged hyperglycaemia after ingestion of glucose or fructose (6) and reduced sugar mobilisation (7) after adrenalin), but from a clinical point of view there is no resemblance at all between toxaemia of pregnancy and von Gierke's disease. Moreover, infants suffering from von Gierke's hepatomegaly are extremely sensitive to insulin. The results obtained in toxaemia of pregnancy with injections of intravenous glucose and insulin described in the previous chapter are in striking contrast with this condition. To summarise, evidences available do not suggest that toxaemia of pregnancy is associated with an abnormal glycogenolytic/

glycogenolytic function of the liver. This is further manifested by the negative sugar mobilisation observed in some cases of eclampsia. Such a condition is possible only when the hepatic glycogen store is exhausted and the ability to produce glycogen from lactic acid (originating in the muscles as a result of adrenalin injection) is grossly interfered with. It should however be mentioned that such a negative reaction was observed in only three fatal cases of eclampsia in our series.

Nevertheless, the circumstantial evidence provided by these cases, together with the results obtained in the whole series of toxaemias provide sufficient support to the belief that the glycogen store of the liver in toxaemias is depleted to an extent depending upon the severity of toxaemia and the occurrence of convulsions. Deficiency of the glycogen reserve in toxaemia of pregnancy has been a subject of considerable speculation in the aetiology and management of this condition. In a fairly recent review, Bokelmann (8, 1936) summarised the attitute by stating "The liver in the pregnant woman and more so in toxaemia is poor in glycogen, and so there is a need of carbohydrates in the body". It will be evident from the investigations described in the previous chapter, that mere supplying additional carbohydrate (Glucose) does not help the liver in building up the glycogen reserve. The cause of the deficient glycogen storage appears to be connected not

with reduced carbohydrate consumption, but with faulty metabolism of sugars, which is manifested by an abnormal utilisation, storage and mobilisation of glucose.

The present state of our knowledge is too inadequate to explain the nature of the processes involved. The relation between blood pressure and sugar mobilisation indicate that a rising diastolic hypertension lessens the mobilisation of hepatic glycogen. This is presumably due to depletion of the glycogen reserve of this organ. Normal mobilisation of hepatic glycogen under the influence of adrenalin or sympathetic stimulation depends upon an alteration of the hepatic circulation, which causes some degree of asphyxia, and a consequent change in the pH of the liver cells. High diastolic blood pressure indicates increased vascular spasm which would have the same effect on the liver cells with regard to glycogen mobilisation as adrenalin. The continuous drain on the hepatic glycogen can reduce the sugar mobilisation only if the Cori cycle in toxaemia. The only evidence available in this direction is from the work of Zweifel (9, 1923), Kienlin (10,1926), Loesser (11, 1926), Schultze (12, 1926) and Stander (13,1926) who report an increased concentration of lactic acid in the blood in eclampsia and severe toxaemia. This has been confirmed by us in a small series of cases of pre-eclampsia and eclampsia, but the value of this evidence at present is only indirect.

The/

The disturbed metabolism of carbohydrates in toxaemia is associated with a state of acidosis, lipaemia and disordered protein metabolism. The role of the pituitary body in this respect requires more thorough investigation. Pitressin causes a loss of glycogen from the liver (13) and an increase of lactic acid in the blood (14), anterior pituitary extracts are known to interfere with the utilisation of carbohydrate in the peripheral tissues (15), hyperglycaemia and Ketonaemia (16). It may be recalled that some observers (17,19) have recorded evidences of hyperfunction of the pituitary body in toxaemias of pregnancy, which our investigations amply confirm (vide infra). The relation between the disordered carbohydrate metabolism in pre-eclampsia and eclampsia and the functional status of the pituitary body may prove to be of considerable significance.

CONCLUSIONS

The results of the investigations described here show that the ability of the liver to mobilise sugar under conditions of stress (created artificially by injection of adrenalin) is impaired in toxaemia of pregnancy. This seems to be associated with a diminished reserve of hepatic glycogen, and is most marked in eclampsia. This investigation also explains why both hypo and hyperglycaemia has been observed in eclampsia, and the susceptibility of toxaemic patients to obstetric shock. It is suggested that the/

the depleted glycogen reserve of the liver is dependent upon a state of long continued spasm of the vessels supplying the liver. This is probably accompanied with a deficiency of the mechanism involved in the glycogen cycle. A state of hyperfunction of the anterior lobe of the pituitary body may have an important share in this disturbance of carbohydrate metabolism, which is present in toxaemia of pregnancy.

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SECTION 3

FAT METABOLISM.

CHAPTER 1

PLASMA CHOLESTEROL

It is generally agreed (1-7) that pregnancy, in both human and animals, causes an increase in plasma cholesterol, which is associated with a somewhat smaller increase of fatty acids (1,6,7) and phospholipides (4,6,7). Slemons and Stander (8, 1923) found that the total lipoids of the plasma at term were raised by 50 per cent. above the non-pregnant level. Tyler and Underhill (9, 1925) also observed that at term cholesterol, cholesterol esters and lecithin were about one-third higher than at the third month of gestation.

These investigators have shown that the increase of plasma lipoids and especially that of cholesterol is progressive throughout pregnancy and reaches maximum at the ninth month of gestation, when there is a slight preparturient decrease. Total and ester cholesterols have been estimated by Bloor and Knudson (10, 1916), Gardner and Gainsborough (5, 1929) and Boyd (7, 1934). The first author observed that the increase was particularly confined to the ester fraction. The second author expressed an entirely opposite view and found that esters actually diminish/

diminish at term, while the last named author stated that the ratio of the cholesterol fractions at term remained unaltered.

Our study of plasma cholesterol in normal pregnancy, based on 194 estimations in 93 patients are presented in Tables 45 (total cholesterol) and 46 (total cholesterol: ester cholesterol ratio).

Table 45

Total cholesterol frequency mgms./100 ml.	Lunar months of gestation.							
	3	4	5	6	7	8	9	10
161-170	3	-	-	-	-	-	-	-
171-180	-	1	-	-	-	-	-	-
181-190	6	1	2	1	-	-	3	2
191-200	7	5	3	-	2	-	4	5
201-210	2	9	8	4	1	-	4	3
211-220	-	3	6	9	4	3	7	6
221-230	-	-	4	4	6	5	6	7
231-240	-	-	-	4	4	10	4	3
241-250	-	-	-	1	3	4	2	1
251-260	-	-	-	-	2	4	-	-
261-270	-	-	-	-	-	2	-	-
Average	191.5	204.9	211.6	220.0	234.1	237.5	221.0	216.0
S.D.	11.8	10.6	12.1	13.6	17.0	13.8	17.0	15.8
Minimum	170.0	179.6	185.5	184.0	198.6	212.0	190.0	188.0
Maximum	209.7	220.0	228.5	241.5	256.0	269.0	248.5	240.0

These/

These results confirm the findings of the previous investigators with regard to the increase of cholesterol during pregnancy. Our data show that this increase is progressive up to the eighth month (28 to 32 weeks) of gestation after which there is a gradual fall until term is reached. At its highest level, the cholesterol content of the plasma in our series was 24 per cent. more than that in early pregnancy. Inspite of the decrease of the plasma cholesterol at term, it is still higher than that

Table 46

Total:Ester cholesterol Frequency	Lunar months of gestation							
	3	4	5	6	7	8	9	10
1.11-1.20	4	2	-	-	-	-	-	-
1.21-1.30	9	7	6	2	-	-	-	2
1.31-1.40	5	9	8	5	4	2	6	7
1.41-1.50	-	5	5	7	5	7	11	10
1.50-1.60	-	-	2	6	9	10	8	5
1.61-1.70	-	-	-	3	4	9	5	3
Average	1.28	1.34	1.40	1.47	1.51	1.53	1.49	1.45
S.D.	0.06	0.08	0.087	0.10	0.09	0.085	0.088	0.098
Minimum	1.12	1.13	1.24	1.27	1.37	1.39	1.35	1.29
Maximum	1.40	1.47	1.56	1.63	1.65	1.69	1.68	1.64

in early pregnancy (= 13 per cent.).

The rise affects the free more than the ester cholesterol. Both Sperry (10, 1936) and Peters and Man (11,1943)/

(11,1943) agree that in normal adults the ratio of free: ester cholesterol is between 0.24 and 0.32 (= 1.24 to 1.32 for total cholesterol: cholesterol esters). It will appear that in early pregnancy the ratio remains practically unaltered. But as gestation proceeds the ratio increases reaching a maximum when the total cholesterol content of the plasma is highest. At this stage the increase in free cholesterol amounts to 90 per cent. of the early pregnancy value. Compared with this, the increase of cholesterol esters is insignificant (= 4.35 per cent.). Between thirty-second week and full-term the cholesterol content falls and the ratio decreases. But this is brought about by a reduction in the free cholesterol. The level of ester cholesterol throughout the pregnancy remains practically unchanged. It is, thus, evident that increase of cholesterol during gestation is entirely due to free cholesterol. In this respect our findings agree closely with those of Gardner and Gainsborough (5, 1929) although the very high ratio of free:total cholesterol (= 0.90) observed in some of their cases was absent in our series. The average values for the last trimester in our cases were:- Total cholesterol - 224.8 mgms.; S.D. 17.1; Ester cholesterol - 151.2 mgms. per 100 ml., S.D.11.4; T.C.:E.C. - 1.48, S.D. 0.096.

COMMENTS

The lipaemia of pregnancy is believed to be in preparation/

preparation for lactation. This is supported by the fact (Boyd, 7, 1934) that plasma lipoids decrease steadily after lactation. This has been repeatedly confirmed by us in course of our investigation. However, very little is known about the cause of the hypercholesterolaemia of pregnancy, which appears to be an active process (Kaufmann and Muhlbock, 12, 1933), for the increase of plasma cholesterol is associated with a negative sterol balance. It has been suggested (Boyd 7, 1934) that the high concentration of oestrogenic hormones is responsible for the condition. Bogdanovitch and Mann (13, 1938) demonstrated that neither oestradiol nor chorionic gonadotrophin raises the level of plasma cholesterol, although both these substances considerably augment the fatty acid content of the liver and blood.

There are four possible factors which may be connected with the state of hypercholesterolaemia in pregnancy. (1) Hyperactivity of the pituitary body. Crude extracts have been known (14,15) to cause lipaemia with increase of blood cholesterol. Man is stated (16) to have observed hypercholesterolaemia in acromegaly. (2) Disturbed carbohydrate metabolism manifested by diminished storage and inadequate utilisation of sugars. (3) Alterations of plasma proteins. Proteins undergo a considerable change during pregnancy and normally a large quantity of lipoids are bound with proteins, especially the large molecules of globulin/

globulin and fibrinogen. Eufinger (30, 1938) observed that pregnancy is associated with an increase of the lipoid-protein combinations. (4) Physiological anaemia of pregnancy Several investigators (Fishberg, 17, 1929; Johanson, 18, 1930; Chamberlain, 19, 1932) have observed that anaemia induced in animals by repeated bleeding causes an increase in the plasma cholesterol and lipoid phosphorus. The similarity between the 'physiological anaemia' of pregnancy and these experimental anaemias has been demonstrated by Melnick and Cowgill (36, 1937).

2. PRE-ECLAMPSIA

The average values obtained from all cases of pre-eclampsia in our series were -

1. Total cholesterol, 253.6 mgms. per 100 ml.; S.D. 12.9.
2. Ester cholesterol, 163.3 mgms. per 100 ml.; S.D. 11.0.
3. Total:Ester cholesterol ratio 1.55; S.D. 0.10.

These are significantly higher than the values obtained in normal pregnancy. However, for the purpose of analysis mild and severe cases will be considered separately.

1. Mild Pre-eclampsia.

The average total plasma cholesterol in 50 cases of mild pre-eclampsia was 238.5 mgms. per 100 ml., S.D. 18.9. Compared with normal pregnancy this shows a small but significant increase, amounting to 6.1 per cent. of the normal pregnancy level. This affects cholesterol esters as well, which are raised by 9.3 mgms. per 100 ml. (=160.5 mgms./

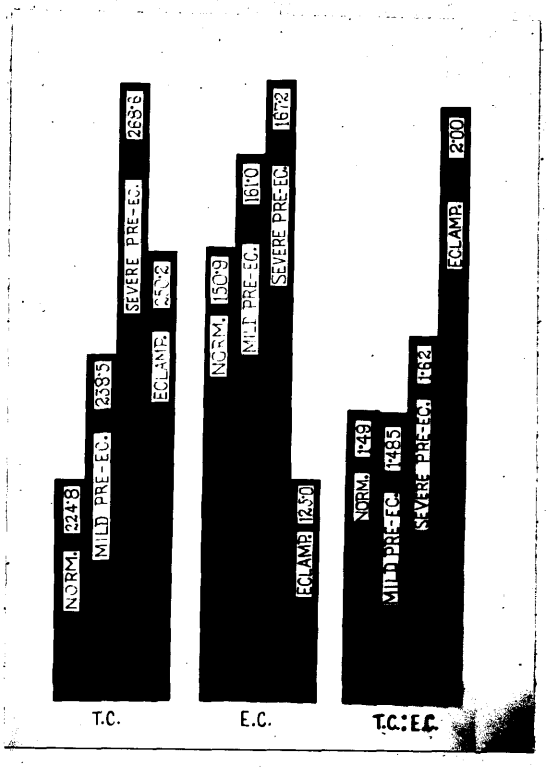

Fig. 35. Plasma cholesterols in normal pregnancy, pre-eclampsia and eclampsia. The diagram shows the values for total cholesterol, cholesterol esters and the ratio of total : ester cholesterol (T.C. : E.C.).

mgms. per 100 ml.) or 6.15 per cent. Thus, the increase in plasma cholesterol is shared by the free and ester fractions in a proportionate manner, so that the ratio of total:ester cholesterol remains unchanged. To summarise, mild pre-eclampsia is associated with a slight increase of plasma cholesterol without any alteration of the relative proportions of free and esterified cholesterol (Figure 31).

11. Severe Pre-eclampsia.

The total plasma cholesterol in this group was 268.6 mgms. per 100 ml.; S.D. 15.1. This is significantly higher than that of either of the two previous groups of cases, and represents an increase of 19.5 per cent. over that in normal pregnancy. Ester cholesterol was however only raised (169.7 mgms. per 100 ml.; S.D. 8.25; difference = 18.5 mgms. per 100 ml.) by 11.8 per cent., thus causing the ratio of total:ester cholesterol to increase to 1.62; S.D. 0.10. (Figure 31). Table 47 shows the frequency distribution of cholesterol and total:ester cholesterol ratio.

Comparison of the frequency distribution in toxaemia and in normal pregnancy clearly shows the shift of the scatter to the right when toxaemia becomes severe. In 58 per cent. of cases of severe toxaemia the plasma total cholesterol values exceeded the maximum in normal pregnancy, but the ratio exceeded the normal maximum in only 20 per cent. of severely pre-eclamptic patients. Comparison with normal averages, however, shows a more striking contrast, for/

Table 47

Total Cholesterol			Total:Ester cholesterol		
Frequency mgms./ 100 ml.	Mild Toxaemia	Severe Toxaemia	Frequency	Mild Toxaemia	Severe Toxaemia
171-180	1	-	1.36-1.40	2	-
181-190	1	-	1.41-1.45	7	-
191-200	2	-	1.46-1.50	34	9
201-210	1	-	1.51-1.55	5	6
211-220	4	-	1.56-1.60	2	10
221-230	6	-	1.61-1.65	-	12
231-240	11	3	1.66-1.70	-	3
241-250	11	8	1.71-1.75	-	-
251-260	7	4	1.76-1.80	-	1
261-270	5	6	1.81-1.85	-	2
271-280	1	11	1.86-1.90	-	5
281-290	-	13	1.91-1.95	-	2
291-300	-	5	1.96-2.00	-	-
Average	238.5	268.6	Average	1.485	1.62
P.E.	12.7	10.1	P.E.	0.02	0.067
Minimum	178.0	237.0	Minimum	1.38	1.49
Maximum	274.0	300.0	Maximum	1.57	1.94

for both the total cholesterol and the cholesterol ratio in severe toxaemia exceeded the corresponding averages of normal pregnancy in all cases. The change from normal pregnancy to mild toxaemia is less striking, for in 98.0 per cent. of mild pre-eclampsias the total cholesterol level/

level remained within the normal range, and in none, did the ratio exceed the normal limit.

Thus, it appears that marked changes in plasma cholesterol are expected only when the toxaemia is of a severe nature, and the disturbance of the total and ester cholesterol ratio only occurs in a certain percentage of these cases.

In order to study the manner in which toxaemia affects the cholesterol level we have analysed our data in relation to the clinical progress. The results are presented below.

1. Clinically Improved. In this group 36 cases were followed until the toxaemia was cured or labour ensued. The period of investigation extended over a period of two to four weeks after admission. No patient was examined during albour as it is known to raise the level of plasma cholesterol (5, 7). The values for total and ester cholesterol and the ratio are given in Table 48 and figure 38, and 37.

Clinical improvement was characterised by little change in the total cholesterol content of the plasma. There was a tendency for the cholesterol esters to increase slightly. Statistical significance is, however, not marked. The result of this change is a slight reduction of the ratio of the total:ester cholesterol, but it is difficult to attach any importance to such small variations in the results.

Table/

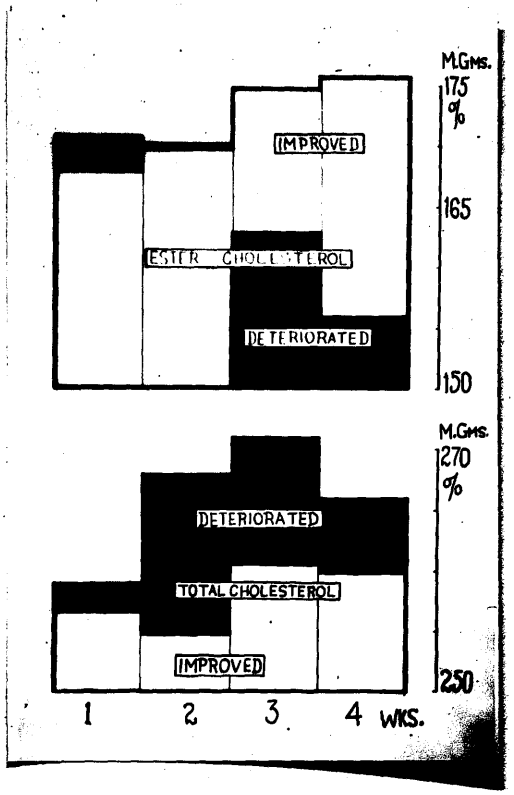

Fig. 36. Total and ester cholesterols of plasma in pre-eclampsia, showing their relation to the clinical course of the disease.

Fig. 37. The ratio of total : ester cholesterol in pre-eclampsia. The diagram shows its relation to the clinical course of toxaemia.

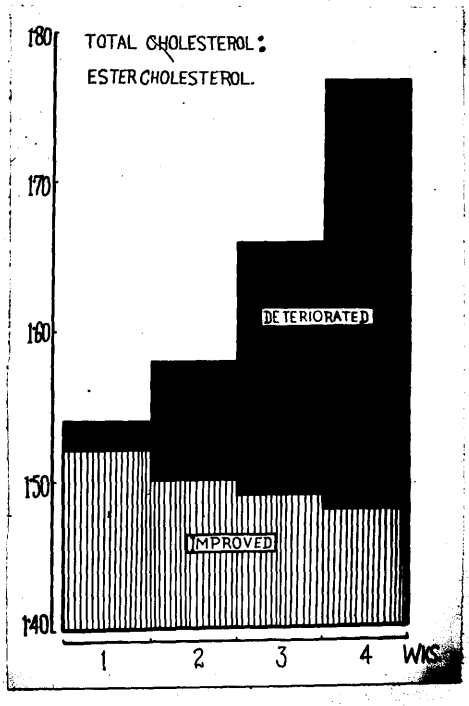

Table 48

	Weeks	1	2	3	4
Total Cholesterol	Average	256.5	254.6	260.4	259.7
	P.E.	10.6	11.6	14.2	12.4
	Min.-Max.	240-273	236-274	231-282	237-281
Ester Cholesterol	Average	167.9	169.7	174.9	175.6
	P.E.	10.8	10.9	11.6	10.7
	Min.-Max.	150-175	151-180	153-186	156-189
Total:Ester Cholesterol	Average	1.52	1.50	1.49	1.48
	P.E.	0.033	0.027	0.020	0.020
	Min-Max.	1.47-1.60	1.46-1.55	1.46-1.53	1.46-1.49

2. Condition Deteriorated. This group consisted of 46 cases where follow-up study was undertaken. The results are submitted in Table 49 (figure 36).

Table 49

	Weeks	1	2	3	4
Total Cholesterol	Average	259.4	268.1	271.0	269.5
	P.E.	12.4	11.8	9.3	10.4
	Min.-Max.	246-282	248-292	251-300	246-296
Ester Cholesterol	Average	171.7	169.8	163.1	154.0
	P.E.	11.0	11.9	10.4	10.0
	Min.-Max.	144-189	148-189	140-181	136-174
Total:Ester Cholesterol	Average	1.53	1.58	1.66	1.77
	P.E.	0.040	0.040	0.054	0.060
	Min-Max.	1.47-1.62	1.51-1.70	1.58-1.93	1.64-1.98

In these cases also the persistence or deterioration of toxaemia caused no significant change in the total cholesterol content of the plasma, an appreciable reduction of the cholesterol esters. The change between the first and the fourth week of investigation shows a drop of 10.3 per/

per cent. of the former level. This difference is statistically significant. The change is noticeable even in the earlier part of the study, although up to the third week it is slow and small in amount. The decrease of cholesterol esters is manifested in a progressively increasing ratio of total:ester cholesterol, which reaches its maximum when the cholesterol ester is lowest. At this stage the ratio has increased by 15.7 per cent. of its initial value. The tendency for the ratio to increase is shown in the average as well as the range of values in each group. It thus appears that the plasma cholesterol level is adversely affected when the state of toxaemia persists for any length of time or becomes aggravated. In this respect the behaviour of the total cholesterol is of little or no importance. Toxaemia seems to cause a lowering of the ester cholesterols, as a result of which the ratio is raised.

111. Cholesterol Ratio and Blood Pressure.

The importance of the ratio of total:ester cholesterol has already been observed. It has also been noticed that in these cases the alteration of the ratio is caused by a change in the concentration of cholesterol esters. Total cholesterols take very little part in it. In view of these facts the following discussion refers only to the ratio.

A. Systolic Blood Pressure. (Figure 30). With an increase of systolic blood pressure, the ratio has a tendency to rise. However/

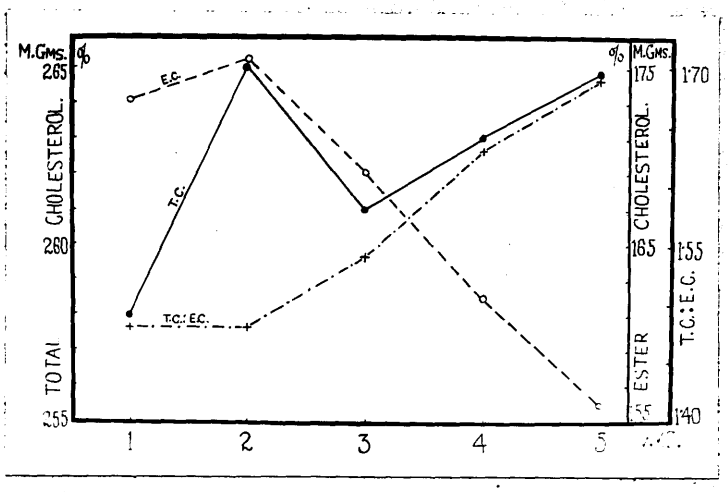

Fig. 38. Total cholesterol, ester cholesterol and total : ester cholesterol ratio in relation to the duration of pre-eclampsia in those patients where the toxaemia persisted or deteriorated.

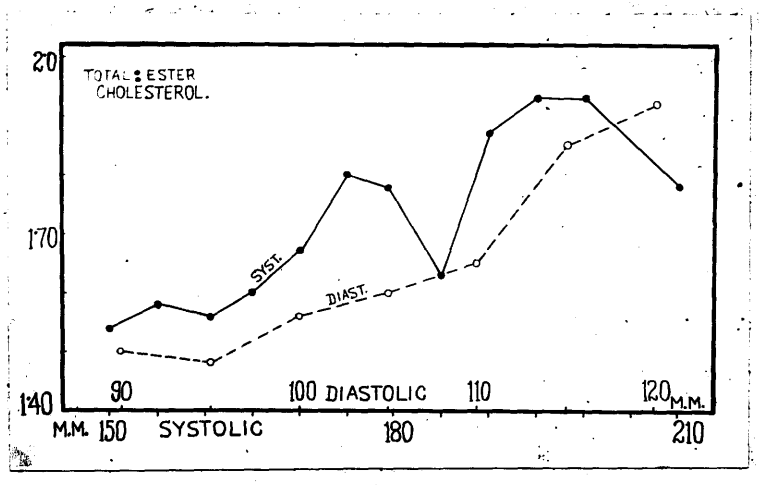

Fig. 39. The ratio of total : ester cholesterol in pre-eclampsia in relation to the systolic and diastolic blood pressure.

However, this is neither uniform nor significant at all stages. Between extremes of blood pressure levels the change is of a striking nature, but in intermediate stages it is slightly inconsistent. This inconsistency even more manifested in the range of values in each group. The results are presented in Table 50.

Table 50

B.P. mm. Hg.	Aver.	S.D.	Min.-Max.	B.P. mm. Hg.	Aver.	S.D.	Min.-Max.
146-150	1.54	0.08	1.48-1.71	176-180	1.78	0.15	1.49-1.97
151-155	1.58	0.05	1.50-1.64	181-185	1.63	-	-
156-160	1.56	0.07	1.47-1.83	186-190	1.87	0.09	1.70-1.97
161-165	1.60	0.08	1.49-1.71	191-195	1.93	-	-
166-170	1.67	0.09	1.48-1.96	196-200	1.93	0.03	1.89-1.97
171-175	1.80	0.10	1.61-1.98	200+	1.78	0.13	1.52-1.94

B. Diastolic Blood Pressure. (Figure 34). Diastolic hypertension seems to be more closely related to the cholesterol ratio than the systolic blood pressure. There is a progressive rise in the ratio with increase of diastolic pressure. Up to 110 mm. Hg. however the change is slow and does not appear to be statistically significant. The range of values also show only a slight variation. But when the diastolic pressure exceeds 110 mm. Hg. the ratio is found to increase abruptly. The increase at this and subsequent stages satisfies statistical analysis and affects not only the average but also the individual values obtained in each group./

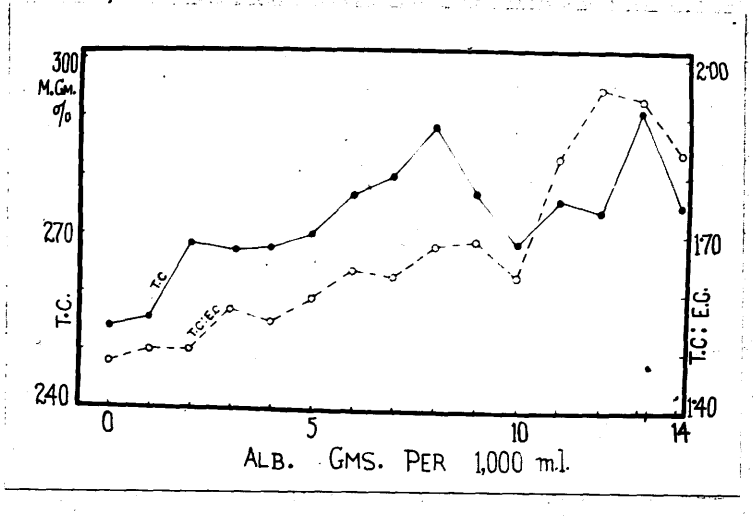

Fig. 40. Plasma total cholesterol, ester cholesterol and the ratio of total : ester cholesterol in pre-eclampsia. the graph shows their relation to albuminuria.

severity of the condition throughout the whole period of investigation was used for this analysis. The results are submitted in Table 52 and figure 46.

Table 52

Albuminuria Gms./1000 ml.	Total cholesterol			T.C.:E.C.		
	Aver.	S.D.	Min-Max.	Aver.	S.D.	Min.-Max.
0	254.0	8.65	246-268	1.48	0.01	1.47-1.50
Tr.- 1.0	255.5	12.70	240-290	1.50	0.03	1.47-1.55
1.1- 2.0	268.4	11.57	255-292	1.50	0.02	1.47-1.54
2.1-3.0	267.4	17.31	246-298	1.57	0.10	1.49-1.94
3.1- 4.0	267.8	13.75	242-284	1.55	0.06	1.49-1.66
4.1- 5.0	270.0	16.83	244-294	1.59	0.13	1.49-1.88
5.1- 6.0	276.9	16.82	250-290	1.64	0.12	1.49-1.89
6.1-7.0	280.6	8.61	270-299	1.63	0.14	1.49-1.90
7.1- 8.0	288.8	4.71	239-294	1.68	0.13	1.52-1.89
8.1- 9.0	277.3	8.10	249-293	1.69	0.12	1.49-1.90
9.1-10.0	268.6	17.60	240-294	1.63	0.02	1.57-1.67
10.1-11.0	276.0	16.0	240-296	1.83	0.09	1.63-1.98
11.1-12.0	274.2	10.10	268-290	1.95	0.02	1.88-1.97
12.1-13.0	291	-	-	1.93	-	-
13.1-14.0	275	8.19	270-289	1.84	0.10	1.73-1.97

It is evident that there is no consistent relationship between the degree of albuminuria and the cholesterol content (both ester and free cholesterol) of the plasma. There is a general tendency for both the total cholesterol and/

and the cholesterol ratio to increase when albuminuria is marked, but the results do not satisfy statistical analysis at any stage. The range of values remain almost unaltered irrespective of the severity of albuminuria. The general nature of the change is apparently due to the fact that the albuminuria tends to increase as toxaemia becomes marked. This analysis however reveals an interesting feature which is in striking contrast to that seen in nephrosis. Lichtenstein and Epstein (23, 1931) observed that the increase of cholesterol in nephrosis is associated with a disproportionate increase of cholesterol esters, consequently the ratio of total:ester cholesterol is markedly reduced. The change in the ratio observed in toxaemia, if at all, suggests a reversal of this process, in which the esters are diminished instead of being increased. Inspite of the presence of lipaemia in both nephrosis and toxaemia of pregnancy, the nature of fat metabolism in these two conditions appears to be different.

3. ECLAMPSIA

The values obtained in our series of eclampsia were as follows:-

1. Total cholesterol 250.2 mgms.per 100 ml.; S.D.30.2
   Minimum 128 mgms.; Maximum 288 mgms.
2. Ester cholesterol 125.0 mgms.per 100 ml.; S.D.25.8
   Minimum 32.8 mgms.; Maximum 149 mgms.
3. Total:Ester cholesterol 2.00; S.D.0.46.
   Minimum 1.59; Maximum 3.9.

The total cholesterol content of the plasma is slightly less than that in severe pre-eclampsia, but is higher than that/

that in normal pregnancy. However, the scatter of the values in eclampsia is so wide that these differences do not appear to be statistically significant. The ester cholesterol however shows a significant reduction compared with both pre-eclampsia and normal pregnancy. This is not confined to the average only, but is also shown in the width of the range. The fall in the cholesterol ester content of the plasma amounts to 26.2 per cent. of the normal pregnancy level. The marked reduction in ester cholesterol is manifested in the change in the cholesterol ratio which is raised by 35 per cent. over its normal level.

The values stated here are based on estimations done at the time of admission irrespective of the clinical severity of the condition. In order to study the change caused by the onset of eclamspa we shall present (Table 52) the values obtained in three cases who were first examined during the stage of pre-eclampsia.

Table 52

	Pre-eclampsia		Eclamptic stage (No. of fits)							
			1	2	3	4	5	6	7	8
R. 7 days* 16 hrs.	272/ 162	312/ 182	280/ 156	237/ 122	-	-	-	-	-	-
A. 21 hrs.	297/159.5		275/ 1456	-	230/ 120	-	-	-	-	-
H. 8 days 7 hrs.	271/ 171	301/ 167	290/ 158	-	279/ 143	-	268/ 128.5	-	-	354/ 114

* Time of estimation: before the first eclamptic fit. Figures indicate T.C./E.C. in mgms. per 100 ml.

The/

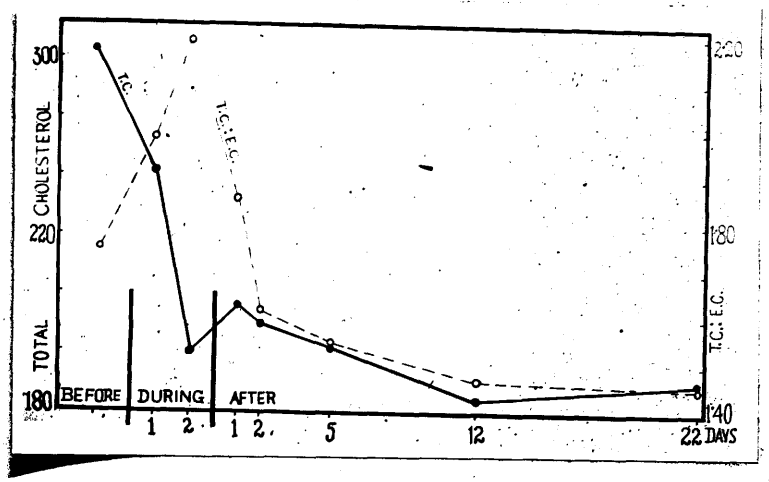

Fig. 41. Plasma total cholesterol and the T.C. E.C. ratio in the pre-convulsive, convulsive and convalescent stages of eclampsia.

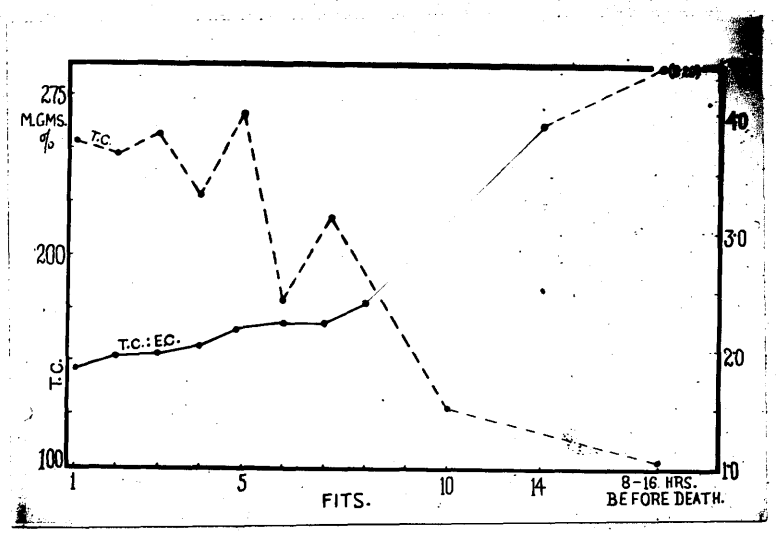

Fig. 42. Plasma total cholesterol and the T.C. : E.C. ratio in relation to the number of convulsions in eclampsia. The number of cases in each group is too small to represent the exact state. The graph only shows the general trend of the change.

The interesting feature in these cases is the drop in the cholesterol level of the plasma caused by eclamptic convulsions. This affects both the free and ester cholesterols although the latter is affected more than the former. Thus the ratio of the total:ester cholesterol rises. Repeated convulsions accentuates this change so that after several fits the ester cholesterol drops out of proportion to the total cholesterol. However, the change does not bear a strict relationship to the number of convulsions although when this is great the decrease in total plasma cholesterol may be appreciable, and that of the esters even more marked, so that the ratio is markedly raised. In three of our cases 8 to 16 hours before death cholesterol esters almost disappeared from the circulation and the ratio increased to 8.20 ± 1.66. The relation of cholesterol and cholesterol ratio to the number of convulsions is shown in figure 36.

The results of our follow-up study in eclampsia are given in Table 53 and figure 42.

These figures show clearly the effects of long continued convulsions. On the first day of the convulsive stage the total cholesterol decreased by 20.1 per cent. of the pre-convulsive level. But the fall in cholesterol ester was 29.2 per cent. On the second day further decrease of total and ester cholesterols occurred, to the extent of 34.4 and 52.5 per cent. respectively. Convulsions of eclampsia cause a disproportionately greater fall in the ester/

Table 53

		Pre-conv. stage	Conv. stage		Post convulsive stage				
	Days		1	2	1	2	5	12	22
T.C.	Average	303.0	242.0	200.0	216.0	210.0	202.4	184.1	189.0
	S.D.	6.3	22.4	22.3	29.9	29.5	28.8	24.6	25.4
	Min-Max	297-312	220-288	160-219	163-264	154-252	160-243	157-240	161-240
T.C.: E.C.	Average	1.77	1.99	2.19	1.86	1.63	1.51	1.48	1.45
	S.D.	0.09	0.11	0.14	0.16	0.07	0.03	0.02	0.02
	Min-Max	1.64-1.86	1.90-2.24	2.03-2.31	1.69-2.19	1.54-1.74	1.49-1.58	1.45-1.51	1.44-1.48

ester cholesterol content of the plasma. During the convalescent stage the total cholesterol remain comparatively lower than that in normal pregnancy at term, while the ester cholesterol increases steadily causing a progressive lowering of the ratio. Thus, the cholesterol ester seems to follow the clinical course and severity of toxaemia in both pre-eclampsia and eclampsia.

CHOLESTEROL FEEDING

Turner and Steiner (24,1939) failed to detect any rise in serum cholesterol when 20 gms. of cholesterol was added to a breakfast meal rich in fat. Gardner and Gainsborough (5a,1928) also made a similar observation. Experimental animals (rats - Cook, 25, 1936; rabbits - Turner and Bidwell, 24a, 1935) however respond to cholesterol feeding in a striking manner. Carefully controlled human experiments described by Brun (26, 1940) also indicate clearly that after feeding cholesterol or cholesterol containing diet

the/

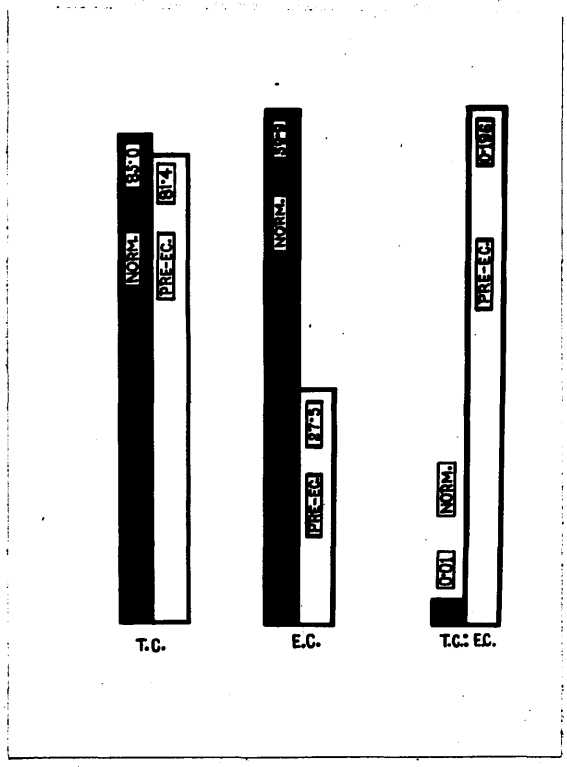

Fig. 43. The effects of cholesterol feeding in normal pregnancy and pre-eclampsia. The diagram represents the increase in the total and ester cholesterols in the plasma and the change in the T.C. : E.C. ratio.

increased to 208.7 (182-222); S.D. 10.9. Thus the total cholesterol was raised by 39 per cent. and ester cholesterd by 40 per cent. of the initial values. The effect on the ratio is therefore negligible. This proportionate increase of both free and ester cholesterol is in contrast to the observations made by Brun (26,1940) in normal healthy males, and indicates a relatively greater increase of free cholesterol in pregnant women. However, this does not seem to be unusual when the normal behaviour of total and ester cholesterols during pregnancy is taken into consideration.

2. Toxaemia of pregnancy. The total cholesterol concentration of plasma reacted in the same manner as in normal pregnancy. The average initial value was 271.6 mgms.per 100 ml. (248-294 mgms.); S.D.12.9. As a result of the experiment it increased to 353.0 mgms.per 100 ml. (318-390 mgms.); S.D.19.5. This represents a 30 per cent. increase above original level.

The rise of cholesterol ester was considerably less. Feeding of cholesterol caused it to increase from 162.5 mgms. (149-184 mgms.) per 100 ml.; S.D.10.6 to 190.0 (166-230 mgms.) S.D.15.7, i.e. only 16.9 per cent. of the basic level.

The relative increase of total and ester cholesterol in normal and toxaemic pregnancy is shows in Table 54.

The abnormally small increase in cholesterol ester is in striking contrast to that observed in normal pregnancy. The results obtained from these experiments appear to be in keeping with the general trend of behaviour of the cholesterol/

Table 54

mgms./ 100 ml.	Increase in Total Cholesterol			Increase in Ester Cholesterol		
	Aver.	S.D.	Min.-Max.	Aver.	S.D.	Min.-Max.
Normal 10 cases	85.0	7.75	71.0-99.0	59.9	7.98	49.0-76.0
Toxaemia 15 cases	81.4	8.86	62.0-99	27.5	8.99	15.0-46.0

cholesterol esters in pregnancy toxaemia, and suggests some disturbance of the normal mechanism of esterification of fatty acids. A recent case of eclampsia demonstrated this in a most remarkable manner. After two convulsions this patient developed oliguria and was put on a continuous drip-feeding of pea-nut oil and glucose. The total plasma cholesterol concentration increased from 284 mgms. (basic) to 340 mgms., and 402 mgms. per 100 ml. after 16 and 24 hours respectively. During the same period the cholesterol esters increased from 154 mgms. (basic), to 172 mgms., and then declined to 140 mgms. per 100 ml.

COMMENTS

The study of plasma cholesterols in toxaemia of pregnancy provide some interesting features which are however difficult to explain. Toxaemia is characterised by a state of hypercholesterolaemia. This has been observed by other investigators also. Colvin and Bartholomew (27,1939) consider that an abnormal cholesterol metabolism is an important feature of pregnancy toxaemia. They observed that when/

when the blood cholesterol was 209 mgms.per 100 ml. or more (with a B.M.R. of -10 or less) the incidence of toxaemia was 50 per cent., but when it was 179 mgms.per 100 ml. or less (with B.M.R. of +10 or more) no patient developed toxaemia. Boyd (7a, 1935) found that pre-eclampsia was associated with an increase of cholesterol which is 14.6 per cent. of the normal pregnancy level. Dieckmann and Wegner (28, 1934) also made a somewhat similar observation. Our investigations show an increase of 19.5 per cent. of cholesterol in severe pre-eclampsia. The values are not comparable except in a general fashion because of different methods of estimation employed by each investigator. The decrease of plasma cholesterol with the onset of eclampsia has also received the attention of some of the authors. From the figures provided by Boyd, eclampsia is found to cause a decrease of the total cholesterol by 8 per cent. of the average for pre-eclampsia. In our cases a similar fall was noticed, which amounted to 6.7 per cent. Colvin and Bartholomew also observed a decrease of cholesterol with an increase in B.M.R. as eclampsia developed.

Thus, the changes in the total cholesterol content of the plasma in toxaemia of pregnancy appear to be consistent and our findings are in close agreement with those of others reported in the literature. But the interesting feature which we observed in the progressive fall of cholesterol esters when toxaemia increased in severity. The values

obtained/

obtained in pre-eclampsia and eclampsia as well as the follow-up studies presented above clearly demonstrates this change. Few other investigators have studied the cholesterol fractions in toxaemia, and we have not been able to trace any follow-up study in this respect in the literature. From the 7 cases presented by Boyd (7a, 1935) where estimation of cholesterol fractions was done, it appears that the total: ester cholesterol ratio was raised in severe pre-eclampsia from 1.46 to 1.62 and in eclampsia to 1.64. The tendency to a decrease of cholesterol esters in severe toxaemia is evident even in this small series of cases. In our series the ratio increased from 1.48 in normal pregnancy (last trimester, 85 estimations) to 1.62 in severe pre-eclampsia (50 cases) and 2.0 in eclampsia (18 cases). These results suggest that esterification of cholesterol is adversely affected when toxaemia is of moderate or marked severity.

It has already been pointed out that little is known about the cause of hypercholesterolaemia in normal pregnancy. The cause of the raised cholesterol concentration of the blood in toxaemia is even less properly understood. Patterson, Hunt and Nicodemus (29,1938) believe that the altered state of the blood cholesterol is due to a "sub-clinical hypothyroidism" aggravated in toxaemia by a "foetal hypometabolism". However, there is no evidence to support such an hypothesis. Colvin and Bartholomew (27,1939) postulated their theory of toxaemia on the basis of hypercholesterolaemia/

hypercholesterolaemia causing placental infarction without explaining the cause of the raised concentration of cholesterol in the blood. It is not known at present how far the alteration of the plasma proteins in toxaemia (especially that of globulin and fibrinogen) can be responsible for the change in plasma cholesterol in pre-eclampsia and eclampsia. Investigations of Eufinger (30,1928), Turner and Gibson (31,1932) and other observers indicate the importance of protein lipoid combinations in the maintenance of the lipoid level of the plasma. The part played by the endocrine disturbances which accompany toxaemia in maintaining a high cholesterol content of the blood is as yet unknown.

The cause of the decrease of cholesterol esters appears to be connected with hepatic dysfunction in toxaemia. Experiments aimed to produce hypercholesterolaemia (25,26,32) in normal animals and human beings cause an increase of ester cholesterol in both the liver and blood. Toxaemia gives rise to a diminished concentration of cholesterol esters even when the total cholesterol is raised. This suggests the conclusion that esterification of cholesterol is adversely affected in severe pre-eclampsia and eclampsia. Apart from the intestines during the absorption of fat, esterification is a function of the liver, and the results of our own investigations, as well as those of others show that pregnancy toxaemia gives rise to hepatic dysfunction. The suggestion made above finds support from the fact that cholesterol/

cholesterol esters almost disappeared from the plasma in those cases who had a fatal outcome. Decrease of ester cholesterol with a consequent alteration in the "cholesterol esterstwiz" has been observed in hepatic parenchymatous disease by several investigators (33,33a,34). Infact Epstein and Greenspun (33a,1936) have recorded instances of fatal cases where cholesterol esters completely disappeared from the circulation. There appear to be some resemblance between the behaviour of plasma cholesterol in pregnancy toxaemia and that in experimental hepatic poisoning with chemical agents. (Hawkins and Wright, 35,1934). It is interesting to note the relationship existing between the level of diastolic pressure and the ratio of total to ester cholesterol.

CONCLUSION

Normal pregnancy is associated with an increase of plasma cholesterol. The free cholesterol is initially affected more than ester cholesterol in this process. But at term the ratio of total and ester cholesterol is only slightly higher than normal.

Toxaemia, when severe, causes an increase of total cholesterol which is accompanied with some reduction of the esters. Thus, the ratio at this stage is raised to a small extent. When toxaemia becomes very severe and in eclampsia there is usually a reduction of both total and ester cholesterol, the latter being affected more than the former.

In/

In some of the fatal cases of eclampsia the ester cholesterol content of the plasma was too low for a proper estimation. The cause of hypercholesterolaemia is not known. The decrease of ester cholesterol is probably due to hepatic dysfunction.

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CHAPTER 2

PLASMA LIPOID PHOSPHORUS

Most investigations on lipoids of the blood and plasma in normal and toxaemic pregnancy are confined to the estimation of cholesterol. Lipoid phosphorus has received very little attention. The theoretical background of the possible behaviour of phospholipoids in toxaemia is extremely confusing. Infact when one considers the antagonistic properties of cholesterol and phospholipoids (1, 1931), the constant relation which is maintained between these two substances in the blood and tissues (2, 1934), and the state of hormonic in equilibrium which exists in toxaemia, it becomes impossible to predict the nature of change which the lipoid phosphorus level of the blood may undergo. The few published reports on blood phospholipoids are not uniformly consistent, and the number of cases investigated in each series is not large enough to offer a definite conclusion. Thus, Lindemann (3, 1913) found that all blood lipoids were increased in pregnancy toxaemias. In the 6 cases reported by Slemons and Stander (4, 1923) no significant change was observed. Hellmuth (5, 1926) reported 4 cases with similar findings. Boyd (6, 1935) in a study of 5 casts of eclampsia and 2 of "eclamptic state" concluded that the concentration of plasma lipoids varied greatly in eclampsia and no significant variation occurred in the value of any single lipoid fraction. This author however laid/

Table 55

Distribution mgms. per cent.	1-3 months	4-7 months	8-10 months	Total
9-10	2	2	3	8
10-11	5	6	5	16
11-12	3	6	5	13
12-13	1	5	8	14
13-14	-	2	7	9
14-15	-	1	5	6
15-16	-	-	4	4
Total	11	22	37	70
Average	11.1	11.8	12.6	12.1
P.E.	± 0.58	± 0.87	± 1.16	±1.11
Maximum	12.7	14.1	15.4	15.4
Minimum	9.1	9.3	9.3	9.1

As toxaemia of pregnancy is a disease of the last three months of gestation, the values obtained for this period of normal pregnancy were subjected to further scrutiny (Table56). It was found that the lipoid phosphorus continued to increase up to the thirty-second week of pregnancy, when the maximum level was attained. During the following eight weeks, there was a decline, but this was slight and insignificant. For practical purposes therefore the average for the last trimester could be considered as fairly representative of the plasma lipoid phosphorus at any period between twenty-eight week of gestation and full term.

laid considerable stress on the plasma phospholipoid: cholesterol ratio and even suggested the level of 1.40 as the dividing line between eclamptic and non-eclamptic states. It was therefore felt that a study of plasma phospholipoids might prove to be of interest.

1. NORMAL PREGNANCY

Of 70 cases of normal pregnancy studied by us, 11 were in the first trimester, 22 in the second, and 37 in the third trimester of gestation. The average lipoid phosphorus of all cases was 12.1 mgm. per cent.; S.D. 1.25. In the three trimester periods, the values were 11.1; S.D. 0.76; 11.8, S.D. 1.30; and 12.6, S.D. 1.73 mgms. per cent. respectively. These figures indicate that the plasma phospholipoids commence to increase early in pregnancy. The earliest pregnancy examined in our series was 10 weeks (2 cases). The lipoid phosphorus level in these two patients was 9.8 and 10.1 mgms. per cent., these figures seem to be slightly higher than the average for normal persons (Peters and Man, 11, 1943) though not statistically significant. The increase of plasma lipoid phosphorus continues, as gestation proceeds, but the difference between the individual trimesteric groups is not significant. The minimum values obtained were about the same in all three groups and with about equal frequency, but the maximum levels in the different groups showed a tendency to climb as pregnancy advanced. The distribution frequency is given in Table 55.

Table/

Table 56.

Period of Gestation Weeks	No. of Cases	Maximum	Minimum	Average	S.D..	P.E.
28-30	6	15.4	9.4	12.5	2.70	1.81
30-32	7	15.4	9.3	12.9	2.30	1.54
32-34	6	15.3	9.6	12.7	2.57	1.72
34-36	5	15.2	9.7	12.5	2.66	1.76
36-38	7	15.4	9.5	12.4	2.76	1.85
38-40	6	15.2	9.4	12.3	2.59	1.74

2. PRE-ECLAMPSIA

The average lipoid phosphorus content of the plasma of all cases of toxaemia was 14.55 mgms.per 100 ml.; S.D. 1.61, compared with the value for normal pregnancy, this difference is significant and amounts to 1.9 mgms.per cent. or a gain 15.1 per cent.

In the series of 50 cases of mild pre-eclamspia the average lipoid phosphorus was 13.5 mgms.per 100 ml.; S.D. 1,45, which again was 0.9 mgms.per cent. more than that in normal pregnancy, an increase of 7.51 per cent. of the normal pregnancy level.

The lipoid phosphorus of the 50 cases of severe toxaemia was 15.6 mgms.per 100 ml.; S.D.1.64, which denoted a rise of 3.0 mgms.or 23.8 per cent. of the value observed in normal pregnancy.

The distribution frequency is given in Table 57.

Table 57

Distribution mgms. per cent.	Mild	Severe	Total
10-11	2	1	3
11-12	7	2	9
12-13	10	2	12
13-14	17	7	24
14-15	6	7	13
15-16	5	12	17
16-17	3	15	18
17-18	-	4	4
Total	50	50	100
Average	13.5	15.6	14.55
P.E.	1.01	1.41	1.08
Maximum	16.2	17.9	17.6
Minimum	10.1	10.8	10.6

It will appear that the increase in the lipoid phosphorus level affects not only the average value but also the minimum and maximum limits of the range. It is of interest however, that the frequency distribution of both normal and mild toxaemias shows an almost similar peak level between 12 and 14 mgms. per 100 ml., but that for severe toxaemias shows a distinct shift to the right, viz; 15 to 17 mgms. The increase of plasma lipoid phosphorus in this series of cases thus appears to be progressive from normal pregnancy to/

to mild and severe toxaemias - the difference in each case being statistically significant.

To ascertain whether this difference is apparent or real, 46 cases where the toxaemia persisted were followed up in relation to the duration of toxaemia, dating from the commencement of the illness. The results are compiled in Table 58. The average values show a steady rise for the first three weeks and then seem to attain a plateau during the fourth week, while the fifth week shows a slight decline from the maximum level.

Table 58

Weeks	1	2	3	4	5
Average	13.9	14.8	16.1	15.9	15.1
P.E.	1.09	1.06	1.02	1.96	2.03
Maximum	15.7	16.6	17.8	18.0	18.9
Minimum	10.4	11.2	14.2	11.1	10.0

The difficulty in interpreting these figures correctly lies in the fact that the rate of deterioration of the state of toxaemia was not the same in all cases, and as a result all the figures under each of the individual week-groups may not be strictly comparable. In order to avoid this difficulty the figures were resolved into three groups. Group 1 represents the average of the values obtained at the time of admission, Group 111 that of the values found on the day when labour was induced because of the severity of toxaemia/

toxaemia (39 out of 36 cases in this series were induced) and Group 11 the results obtained about the middle of the period between admission and termination of pregnancy. The results show clearly that the lipoid phosphorus content of the plasma increases steadily up to a stage, after which it shows a distinct fall (Table 59). The change in this series at each stage is statistically significant and is shown not only in the average but also in the minimum and maximum range of values. The co-efficient of variation also is almost uniform.

Table 59

	Group 1	Group 11	Group 111
Maximum	16.7	19.4	15.1
Minimum	12.9	13.6	11.0
Average	14.8	16.9	13.0
P.E.	1.12	1.38	1.04

The possible role of phospholipoids in causing oedema in toxaemias of pregnancy has been discussed by Boyd (6, 1935). A study of the lipoid phosphorus content of the plasma in relation to oedema was thus considered necessary. The figures obtained, however, do not show any definite correlation between the severity of oedema and the level of plasma phospholipoids. This does not of course, disprove the theory mentioned above, for the tissue phospholipoid content may increase without showing a remarkable change in the blood. This has been discussed in connection with

the/

the investigation of oedema. The results are summarised in Table 60. There seems to be significant difference in the lipoid phosphorus content of [redacted] plasma and between normal and oedematous patients, but as the values obtained in different degrees of oedema are analysed it is found that the level of the lipoid phosphorus of the plasma bears little relation, if any, to the degree of water retention in the tissues.

Table 60

	Normal	Oedema.			
		±	1+	2+	3+
		BLOOD			
No. of cases	37	12	23	44	21
Average	12.6	13.7	14.8	14.8	14.0
S.D.	1.73	1.92	2.46	2.79	3.30
P.E.	1.16	1.29	1.65	1.87	2.21
Maximum	15.4	15.9	17.5	17.8	17.6
Minimum	9.3	10.0	10.2	10.1	10.0

3. ECLAMPSIA

The average of lipoid phosphorus at the time of admission was 15.9 mgms. per cent.; S.D. 2.48. Compared with the figures obtained for severe pre-eclampsia the difference is not significant. Thus, it might appear that the onset of convulsions does not cause any alteration in the level of the plasma phospholipoids. However, an analysis of the distribution frequency of these cases (Table 61) shows that the minimum in eclamptic group was distinctly higher than that/

that in pre-eclampsia and the maximum was above the maximum value of severe pre-eclampsia in 22.2 per cent. of cases. It is of interest that maximum distribution of frequency, viz. 14-15 mgms. per cent. was lower than that in the severe pre-eclampsia.

Table 61

Distribution mgms. per cent.	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20	20-21
No. of cases	1	2	2	4	1	1	3	2	1	1

Average = 15.9. S.D. = 2.48. P.E. = 1.66.

Maximum = 20.7. Minimum = 12.0.

The results obtained in the three cases of pre-eclampsia who developed fits during their stay in the hospital indicate that convulsions in an eclamptic subject cause the plasma lipoid phosphorus to increase. This was evident after the first fit in all cases, while the second fit showed a further rise in both the cases who had more than one convulsion. The third fit which followed in both instances within one hour of the preceding one, appeared to be responsible for a slight, though significant decrease of lipoid phosphorus. Mrs. H., whose blood was examined after 4 and 8 fits showed a further drop. The findings appear to be consistant, the difference of the averages is significant and the variability low (Table 62).

Of the eighteen cases three died, and these showed a definite and progressive fall of the plasma lipoid phosphorus/

Table 62

Name	Pre-convulsive Stage	Convulsive Stage				
		No. of fits				
		1	2	3	4	8
1. Mrs. A.	18.2	18.8	19.4	19.0	-	-
2. Mrs. H.	17.5	18.4	19.1	18.3	10.7	7.0
3. Mrs. R.	16.6	19.3	-	-	-	-
Average	17.5	18.8	19.25	18.65	-	-
S.D.	0.68	0.37	0.15	0.35	-	-
P.E.	0.46	0.25	0.10	0.23	-	-
Significance	+	+	+	+		

phosphorus as their condition deteriorated (Table 63). The blood in the early convulsive stage was obtained after the first convulsion, the specimen for the late convulsive stage, after the third or fourth fit, that in the stage of coma when unconsciousness lasted for 4 to 8 hours, and the last sample in the pre-terminal stage was taken 3 to 6 hours before death. In the case of Mrs. McK. the interval between the last two specimens of blood was less than 2 hours.

Table 63

Name	Early Convulsive	Late Convulsive	Coma	Pre-terminal
1. Mrs. McK.	17.5	14.2	11.0	9.4
2. Mrs. McL.	20.7	-	13.4	12.5
3. Mrs. HN.	-	17.8	10.7	6.5

The/

The figures indicate that as the condition of the patient grew worse, the lipoid phosphorus level of the plasma diminished. When the cases presented in Tables 62 and 63 are simultaneously considered, it shows clearly that the onset of eclampsia is characterised at first by an increase of the phospholipoid content of the plasma. But when the convulsions are rpeated at frequent intervals and coma sets in, it commences to fall until the minimum level, which is reached in the pre-terminal stage of the fatal cases. At this stage, the lipoid phosphorus level is slightly lower than that found in normal non-pregnant individuals. It must be pointed out however, that the extent of this fall is not in any way related to the height reached by the lipoid phosphorus earlier on, in the course of the disease. There appears to be a closer relation between the fall in the lipoid phosphorus and the severity of the condition and number of convulsion. This is however not of a striking nature. Thus, Mrs. HN., who had 18 convulsions had a terminal drop which amounted to 63.5 per cent. of the highest level attained by her. The corresponding decrease in Mrs. McK. (15 fits) was 46 per cent. and in Mrs. McL. (1 fit)39.6 per cent. Coma seems to have more effect than the number of convulsions alone, for the state of deep coma was associated with a decrease of lipoid phosphorus by 37.1 (McK.), 35.6 (McL.) and 39.8 (HN.) per cent. respectively of their corresponding highest values. These figures are fairly comparable.

LIPOID PHOSPHORUS: CHOLESTEROL RATIO

In view of the important antagonistic physico-chemical properties of cholesterol and phospholipoids and the finding by Boyd (6, 1935) of increased phospholipoid: cholesterol ratio in eclamptic states, this point was considered worthy of investigation. The results are briefly summarised in Table 64. Our estimations were confined to the lipoid phosphorus and not total phospholipoids. Phospholipoids expressed as cephalin could of course be calculated from the lipoid phosphorus value by multiplying the results by 25, but it was considered that no useful purpose would be served by this calculation as cephalin does not constitute more than 52 per cent. of the total plasma phospholipoids (Artom, 18, 1945). So the ratio presented here is that of lipoid phosphorus: total cholesterol of the plasma.

Table 64

	Average	S.D.	P.E.	Min. - Max.
Normal pregnancy	0.057	0.001	-	0.005-0.059
Mild Toxaemia	0.058	0.002	0.001	0.054-0.061
Severe Toxaemia	0.058	0.004	0.003	0.055-0.062
Eclampsia	0.063	0.007	0.004	0.056-0.071

It will appear from the above figures that though the ratio shows a tendency to increase from normal pregnancy to eclampsia, the difference in none of the stages is significant. It is interesting to note that there is no change in/

in the ratio as the toxaemia passes from the mild to the severe variety. This implies that the rise in phospholipoids at this stage of the disease is proportional to that of cholesterol. The difference in the average lipoid phosphorus content between severe pre-eclampsia and eclampsia has been found negligible. The increase in the ratio at this stage is just significant, and is brought about by a fall in the total cholesterol content of the plasma. Analysis of the ratio in relation to the number of convulsions did not reveal anything of importance, apart from a tendency for the ratio to increase when the clinical condition showed marked deterioration.

A study of the ratio was also made in relation to oedema in view of the antagonistic physico-chemical properties of cholesterol and phospholipoids. But as in the case of lipoid phosphorus, so in that of the ratio no definite relationship was found to exist between the latter and the degree of the oedema. Between normal pregnancy and slight oedema the ratio showed no alteration. With 1+ oedema there was a slight but insignificant rise in the ratio, but with further increase of oedema the ratio was intermediate between those of the previous two groups. The variability in these two groups, however showed a noticeable increase. The results are summarised in Table 65.

Table/

Table 65

Oedema	Average	S.D.	Max. - Min.
±	0.057	0.001	0.055-0.059
1+	0.060	0.003	0.056-0.063
2+	0.059	0.004	0.054-0.064
3+	0.059	0.004	0.055-0.066

COMMENTS

The average normal lipoid phosphorus content of the human plasma is given by Peters and Man (7, 1943) as 9.2± 1.41 mgms. per cent. It is generally agreed that the lipoid content of the plasma is increased during pregnancy, and that this change manifests itself as early as the second month of gestation. A rise in phospholipoids has also been noted by Boyd (6a, 1934) Fahrig and Wacker (8, 1932) and Oser and Karr (9, 1925). This however is not as marked as the rise in cholesterol. The cause of this is not quite understood. Lipaemia during pregnancy is generally believed to be related to the increase in female sex hormones, and Loeb (10, 1942) demonstrated the oestradiol benzoate, in large doses increased strikingly the total lipoids of the serum. Boyd (6a, 1934) observed a 25 per cent. increase of plasma phospholipoids in pregnancy. Schwartz et al (11, 1940) also noted a gestational rise of the plasma phospholipoid content. Compared with the normal figures supplied by Peters and Man (7, 1943) our average value for lipoid phosphorus/

phosphorus in normal pregnancy shows a gain of 31.5 per cent. On the other hand if only the last trimester is considered the increase appears to be to the extent of 36.9 per cent.

The onset of toxaemia in the series under investigation was denoted by a further rise in the lipoid phosphorus content of the plasma. This rise was intensified as toxaemia became severe, but between severe toxaemia and eclampsia there was no significant difference in the values obtained. Boyd (6, 1935) also noted a similar happening and described such severe pre-eclampsia as "eclamptic state". It appears, therefore, that whatever may be the nature of the change in the phospholipoid metabolism of the body at this stage, the convulsions of eclampsia, per se, neither affects nor are affected by it. It was not possible to estimate the lipoid phosphorus of the plasma immediately preceding a convulsion. Serial estimations, however, were made in three cases throughout the period of convulsions. No significant change could be found in these cases when results were compared with those obtained in cases of severe non-convulsive toxaemia. It is therefore likely that the altered plasma lipoid phosphorus value in severe pre-eclampsia is an expression of the disordered metabolism and has no aetiological significance. A similar state of affairs was also noted in connection with oedema.

It will be observed that in nearly 78 per cent. of cases of toxaemia the lipoid phosphorus value remained below the

maximum/

maximum level seen in normal pregnancy. The variability in this group was not insignificant, and was more than doubled in eclampsia. The individual values encountered were thus widely scattered. If alteration of the lipoid phosphorus metabolism was the primary factor in toxaemia one would have expected the values to be reasonably constant at the varying stages of severity of the disease. Widely varying levels of plasma lipoids have been noted by other workers also (Boyd, 6, 1935); Stander and Slemons (4, 1923).

The cause of this increase of the plasma phospholipoid is difficult to explain in the present state of our knowledge. It is of interest to note, however, that retention of inorganic phosphorus in the plasma has also been found in toxaemias of pregnancy. Our observations indicate that there is some parallelism between the inorganic phosphorus and phospholipoid content of the plasma. Toxaemia of pregnancy is associated with a state of diminished alkali reserve, and Bloor (12, 1939) pointed out that phospholipoids normally take part in base-sparing activity. It appears from the figures supplied by Boyd (6a, 1935) that the total fatty acids in the plasma show an appreciable rise in the type of pre-eclampsia described by him as the "eclamptic state". It is possible that the increase in the phospholipoid concentration is merely an expression of a compensatory mechanism by which phosphorus is diverted in order to conserve the alkaline base.

Continued/

Continued observation of our cases showed that after the disease had attained a certain degree of severity the plasma lipoid phosphorus concentration started to decrease. This was particularly notable in eclampsia as the condition progressed and the decline in phospholipoid values continued up to the preterminal stage. Phosphorylation is one of the functions of the liver. Hahn and Hevesy (13, 1938) with the help of radioactive phosphorus demonstrated the synthesis of phospholipoids from inorganic phosphate in the surviving perfused liver. There are evidences to show that when toxaemia persists for a long time or when repeated convulsions ensue, and in the preterminal stage of eclampsia the liver functions, especially those normally concerned with metabolism suffer considerably. It seems possible that the fall in the plasma lipoid phosphorus at this stage might be due to deficient phosphorylation by the liver. This suggestion is supported by the fact that when the lipoid phosphorus level is at its lowest the inorganic phosphate level is at its peak. It seems likely that one is related to the other and both to deficient phosphorylation by the liver.

It has been demonstrated by Man, Kartin, Durlacher and Peters (14, 1945) that the plasma lipoid phosphorus rises considerably in biliary obstruction and rapidly drops to normal when obstruction is relieved. It has also been shown by Wachstein (15, 1936) that in presence of obstructive/

obstructive jaundice large quantities of unsaturated fatty acids are present in the plasma. The increase in the lipoid phosphorus in this condition is therefore due to increased phosphorylation of a large concentration of unsaturated fatty acids present. Man et al (14, 1945) observed that known chemical poisons such as chloroform, carbontetrachlorid and phosphorus cause a fall in the plasma lipoid phosphorus, but Gray (16, 1933) demonstrated that this was preceded by an initial rise in the phospholipoid level. The former observers noted a similar change in lipoid phosphorus in those cases of toxic hepatitis where terminal hypocholesterolaemia results.

Without assuming the existence of a hypothetical toxin, one could expect a similar stage of affairs in toxaemias of pregnancy. In the early stages the disordered fat metabolism together with retention of inorganic phosphorus demands increased phosphorylation by the liver and a consequent rise in the lipoid phosphorus content of the plasma, in order to conserve the alkali which is already deficient. In the later stages of toxaemia however, when the metabolic functions of the liver are undermined, conjugation of phosphorus to the fatty acids suffers, with a consequent fall in the plasma phospholipoid level.

Peters and Van Slyke (17, 1946) observe that so long as the cholesterol content of the blood is higher than 100 mgms. per cent. its relation to lipoid phosphorus in normal/

normal and most diseased states remain within certain limits which could be expressed by the formulae stated by them. Analysis of the figures in normal pregnancy in the series studied by us shows that the mutual quantitative relationship between cholesterol and phospholipoids does not alter during normal gestation.

Our study of phospholipoid cholesterol ratio is not comparable with that of Boyd for our estimations were done on lipoid phosphorus and not on total phospholipoids. However, the rise from the normal pregnancy ratio of 0.057 to 0.063 in eclampsia is appreciable, though our figures do not satisfy statistical analysis. Study of individual cases, however, shows an unmistakable rise in the ratio in all, in whom the disease progressed and the condition deteriorated.

Increase in the lipoid phosphorus value has been observed in mild and early severe toxaemias, but the little alteration in the ratio at these stages indicate a proportionate rise in the blood of cholesterol and lipoid. In late and severe toxaemias however, the ratio rises in spite of a fall in the plasma lipoid phosphorus content. This occurs because of a greater fall in the cholesterol level of the blood. The cause of the alteration of the ratio appears to be centred round the role played by the liver in fat metabolism. Man et al (14, 1945) found similar hypocholesteralaemia and low lipoid phosphorus with high phospholipoid:/

phospholipoid: cholesterol ratio in severe toxic hepatitis.

CONCLUSION

Normal pregnancy is associated with an increase of the plasma lipoid phosphorus above that of the non-pregnant state.

Toxaemia causes a further rise in the lipoid phosphorus content of the plasma. This is at first progressive, but in very severe cases it commences to decline after the maximum level has been reached. The changes are more marked in eclampsia than in pre-eclampsia. It is suggested that the initial increase of phospholipoids depends on a raised concentration of fatty acids in the plasma and effort on the part of the body to conserve the alkaline base. The fall in lipoid phosphorus concentration in late stages is probably connected with a disturbance of hepatic functions.

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CHAPTER 3

ACIDOSIS AND ALKALI RESERVE

As early as 1915 Hasselbach (1) demonstrated that pregnancy is associated with a decrease of the alveolar carbon dioxide tension, which becomes manifest in the second month of gestation. During subsequent years several observers (2-7) have noticed that the carbon dioxide combining power of the blood decreases as pregnancy approaches term. Some authors (3,5,6,8) believe that this acidosis of pregnancy is due to the accumulation of Ketone bodies and lactic acid in the blood, caused by a defective carbohydrate and altered fat metabolism (6). Estimation of the hydrogen-ion concentration of the blood by Myers et al (9, 1932), Kyd and co-workers (10, 1932), Nice (11, 1936), Oberst and Plass (12, 1940) and several other investigators do not show any evidence of a decrease of the pH. Studies of Kyd, Oard and Peters (10, 1932) and Stander (7a, 1934) suggest that the acidosis of pregnancy is due to a deficiency of the base concentration of the serum, but, this is maintained in a well-compensated state in a normal patient.

In 2 out of 4 cases of eclampsia Hasselbach and Gammeltoft (1, 1915) found a marked increase of the fixed acids in the blood, whic gave rise to uncompensated acidosis. Subsequent investigations by Bokelmann and Rother (8a,1928), Vozza (13, 1927), MacNider (14, 1928), Stander (7, 1930), Osman (15, 1930) and several other observers show that the reserve/

reserve alkali ia markedly diminished in pregnancy toxaemia, and especially in eclampsia. Yet, Gradwohl (16, 1928) states that in "toxaemias of pregnancy many authorities believe that instead of acidosis in extreme cases we have alkalosis".

In studying the alleged acidosis of pregnancy and toxaemia we used the ratio of $H.HCO_3$:$B.HCO_3$, upon which principally the pH of the blood depends. Direct potentiometric estimation of the pH was done on a few cases only.

1. NORMAL PREGNANCY

Fourteen cases of normal pregnancy between 30 weeks and term, admitted for the treatment of contracted pelvis were investigated as "controls". In this series -

The total carbon dioxide combining power of the plasma was 51.85 ml.; S.D. 2.00. The maximum was 55.3 ml. and minimum 49.3.

The $H.HCO_3$ content of the plasma varied from 2.80 ml. to 2.35 ml. per 100 ml. of plasma. The average value was 2.48 ml.; S.D. 0.10.

The $B.HCO_3$ (combined carbon-dioxide) of the plasma measured, 49.37 ml. of carbon dioxide per 100 ml. of plasma; S.D. 1.36. The maximum was 52.7 ml; and minimum 47.2 ml.

The distribution of values in relation to the mean for total combined and free carbonic acid and is given below:-

	—	Mean ± P.E.	+
No. of cases	4	8	2
Percentage	28.6	57.7	14.3.

Hydrogen/

Hydrogen ion concentration of the plasma was estimated in 6 cases of normal pregnancy by the potentiometric method. The values obtained in these cases were 7.39, 7.40, 7.42, 7.42, 7.43 and 7.45; average 7.42, S.D.0.02. The estimated pH in normal pregnancy is in conformity with the value of the ratio of $H.HCO_3$: $B.HCO_3$, which in the series presented above was 1:20, (S.D.0.21).

COMMENTS

The total carbon dioxide (free + combined) content of the plasma in normal resting adults is stated by Van Slyke (17, 1918) to vary between 53 and 80 ml. per 100 ml. plasma, with an average of 65 ml. Compared with this normal standard, there is a carbon dioxide deficit during pregnancy. In this respect the values obtained in our cases are in close agreement with those of other investigators (1-10). The fall in the total carbon dioxide combining capacity amounts to a little over 20 per cent. of the normal value. In a normal individual the carbonic buffer is maintained in such a manner that the ratio of $H.HCO_3$:$B.HCO_3$ remains 1:20. In pregnancy this ratio is not altered. There is indeed a decrease of the combined carbon dioxide to the extent of about 20.5 per cent. of the normal level but this is accompanied with a corresponding decrease of free carbon-dioxide. There is a deficit of the reserve alkali but this is well compensated, so that the pH of the blood does not differ from that in the non-pregnant state. The so called acidosis/

acidosis of pregnancy is thus, a compensated alkali deficit. In the maintenance of this compensation, both the kidneys and the lungs play an important part, the former conserves base by increasing the excretion of ammonia and probably also by augmenting phosphorylation of fatty acids (Bloor) (phospholipoids are raised in pregnancy, chapter 2), and the latter conserves the base by eliminating excess of carbondioxide by hyperventilation. The investigations of Nice and co-workers (11, 1936) and particularly those of Oberst and Plass (12, 1940) prove that pregnancy is actually associated with hyperventilation of the lungs.

Nevertheless, the compensation which exists in the acid-base balance does not protect a pregnant woman from a susceptibility of Ketosis. It will be seen in the latter part of this chapter that starvation causes acetonuria more frequently during pregnancy than in the non-pregnant condition. Such starvation Ketosis as produced by our experiments was accompanied by a slight decrease of the carbondioxide combining capacity of the blood but was not associated with a failure of compensation. In this respect the acidosis of pregnancy (18, 1923) is different from the acidaèmia (18, 1923) of diabetes and uraemia.

2. PRE-ECLAMPSIA.

The carbon dioxide and bicarbonate content of the plasma was estimated in 30 cases of pre-eclampsia, consisting of an equal number of mild and severely toxic patients./

patients. As there was a slight difference in the results in these two groups they will be presented spearately.

1. Mild Pre-eclampsia. The average total carbon dioxide content of the plasma was 49.96 ml. per 100 ml. plasma; S.D. 3.28, with a range of variation from 44.3 to 53.8 ml. The distribution is given below -

	-	Mean ± P.E.	+
No. of cases	2	12	1
Percentage	13.3	80.0	6.7

The average concentration of free carbon dioxide in these cases was 2.38 ml. per 100 ml. plasma; S.D. 0.13. The maximum was 2.70 and the minimum 2.10. The distribution of values was as follows -

	-	Mean ± P.E.	+
No. of cases	2	10	3
Percentage	13.3	66.7	20.0

The combined carbon dioxide (bicarbonate) content of the plasma was, average 47.58 ml. per 100 ml. plasma; S.D. 2.22; minimum 42.2 ml.; maximum 51.1 ml. The distribution of values were -

	-	Mean ± P.E.	+
No. of cases	1	13	1
Percentage	6.7	86.6	6.7

It will be evident from the values stated above that the ratio $H.HCO_3 : B.HCO_3$ is 1:20 (S.D. 0.33). The range of variation was, Minimum - 1:19.6 and maximum - 1:20.6.

11. Severe Pre-eclampsia. The values obtained in this group of cases were to some extent lower than those in the former/

former group of toxaemia. The average total carbon dioxide was 47.18 ml.; S.D.2.04. The maximum and minimum values were 50.9 ml. and 44.2 ml. respectively per 100 ml. plasma.

The values for free carbon dioxide in this series were, average - 2.24 ml., S.D.0.097; maximum - 2.4 ml; and minimum - 2.1 ml. per 100 of plasma.

The bicarbonate level of the plasma in severe toxaemia was, average - 44.94 ml., S.D.2.14; maximum - 48.5 ml.; and minimum - 42.1 ml. per 100 ml. plasma. The distribution of values in relation to the mean is given below -

	−		Mean ± P.E.		+	
	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.
Total CO_2	2	13.3	9	60.1	4	26.6
$B.HCO_3$	2	13.3	9	60.1	4	26.6
$H.HCO_3$	2	13.3	10	66.7	3	20.0

The ratio of $H.HCO_3$: $B.HCO_3$ remains practically the same as in the mild toxaemia, the average being 1:19.93; S.D.0.24; maximum - 20.3 and minimum - 19.6.

The fact that the ratio of $H.HCO_3$:$B.HCO_3$ does not alter in either of the two types of cases described above suggests that the change in the bicarbonate content of the plasma is accompanied by a proportionate readjustment of the level of free (or dissolved) carbon dioxide. Under such a condition the total carbon dioxide combining capacity of the plasma reflects fairly the state of the alkali reserve of the body. In order to demonstrate the nature of the change in the alkali reserve in normal

pregnancy/

pregnancy, mild and severe pre-eclampsia, the frequency distribution of the total carbon dioxide combining power in these cases is presented in Table 66. Comparison of

Table 66

Frequency ml. CO_2/100 ml.	Normal Pregnancy 14 cases	Mild Pre-eclampsia 15 cases	Severe Pre-eclampsia 15 cases
44.1-45.0	-	1	2
45.1-46.0	-	-	1
46.1-47.0	-	1	7
47.1-48.0	-	-	1
48.1-49.0	-	2	1
49.1-50.0	1	3	1
50.1-51.0	3	3	2
51.1-52.0	3	4	-
52.1-53.0	5	-	-
53.1-54.0	1	1	-
54.1-55.0	-	-	-
55.1-56.0	1	-	-
Average ± P.E.	51.85 ± 1.02	49.96 ± 1.39	47.18 ± 1.13

these figures demonstrates the progressive fall of the alkali reserve of the plasma in mild and severe toxaemias of pregnancy. The difference of averages at each stage is statistically significant. The scatter of values also shows this change. Thus, in 26.6 per cent. of cases of mild/

mild, and in 80 per cent. of cases of severe toxaemia the alkali reserve of the plasma was below the minimum in normal pregnancy. The steady decline of the maximum value is also equally striking.

3. ECLAMPSIA

Ten cases of eclampsia were studied for this purpose. The change in the alkali reserve in these cases is much more noticeable than in pre-eclampsia. The total carbon dioxide combining capacity varied considerably in individual cases. The range of values was from 20.8 to 40.1 ml. per 100 ml. of plasma, with an average of 35.70ml.; S.D. 6.41. The bicarbonate content was 33.34 ml. per 100 ml. of plasma; S.D. 6.41, the maximum and minimum values being 37.7 and 17.4 ml. respectively. Free carbon dioxide of the plasma was, average 2.36 ml. per 100 ml.; S.D. 0.28 (1.8 to 2.6 ml.). The ratio of $H.HCO_3$:$B.HCO_3$ was thus raised to 1:14.2 (S.D. 3.65) average, 1:6.7 maximum and 1:18.6 minimum.

In these calculations no moribund patient was included. One patient (Henderson) in this series had a fatal outcome. The first estimation, done after 16 convulsions showed -

Total CO_2	20.8 ml. per 100 ml.
Combined "	17.4 ml. " "
Free "	2.6 ml. " "
$H.HCO_3$: $B.HCO_3$	= 1 : 6.7.

The patient was at this stage moderately comatose. Second estimation was done after 11 hours. The values for total, combined and free carbon dioxide were 14.2, 11.1 and 3.1 ml. respectively per 100 ml. of plasma. The

H./

B.HCO_3: B.HCO_3 was 3.6. Between the time of the first and the second estimation the patient had two more convulsions and passed into a state of very deep coma. Death occurred from anuria 16 hours after the second test was done. We had occasions to repeat the estimations on 3 other cases. The results are presented in Table 67.

Table 67

Name	I				II				Interval
	Total CO2	B. HCO3	H. HCO3	H.HCO3 / B.	Total CO2	B. HCO3	H. HCO3	H.HCO3 / B.	
1. Crawford 4 fits	37.8	35.6	2.2	1 / 16.2	30.0	27.9	2.1	1 / 13.9	17 hrs.
2. Pardee 1 fit	43.0	40.8	2.2	1 / 18.6	34.2	32.1	2.1	1 / 15.3	5 hrs.
3. Ferguson 2 fits	40.1	37.7	2.4	1 / 15.7	36.6	34.4	2.4	1 / 14.3	3 hrs.

The indication for repeating the experiment was an aggravation of the state of coma. In the second patient only, two fits occurred between the first and the second test. The nature of the change of the alkali reserve is almost identical in all three cases. Acidosis and coma in eclampsia appear to be related phenomena. This was found not only in the cases presented in Table 67, but also in the whole series, as the following analysis will show -

Coma/

Coma	No. of cases	Total CO_2	$\frac{B}{H}$ HCO_3
±	2	40.8; 43.0.	18.8; 18.6.
+	3	40.1; 38.0; 38.6.	15.7; 17.7; 15.8.
++	5	34.2; 36.6; 37.0; 37.8; 30.2.	15.3; 14.9; 14.7; 16.2; 12.7.
+++	3	30.7; 30.0; 20.8.	16.1; 13.3; 6.7.
++++	1	14.2.	3.6.

Owing to the small number of investigations no attempt has been made to obtain average values in this analysis, but ~~an~~ examination of the individual figures amply demonstrates the change. Our series is not large enough to show the progressive deterioration which occurs with increasing frequency of convulsions. It was however evident that patients who had several and frequent convulsions showed a greater depletion of the alkali reserve than those who had only a few fits.

Hydrogen Ion Concentration of the plasma was estimated in 8 cases of severe pre-eclampsia and 6 cases of eclampsia in this series. The pH in the cases of pre-eclampsia were 7.41 (1), 7.39 (2), 7.40 (3), 7.41 (4), 7.40 (5), 7.41 (10), 7.42 (13), 7.41 (14), average 7.41; S.D. 0.01. (The serial number of cases are given in brackets). The difference from normal cases can hardly be regarded as worthy of notice.

Of the cases of eclampsia 3 patients (Nos. 2, 7 and 9) had the plasma pH of 7.37, 7.34, and 7.37 respectively. Two of/

of these patients (2 and 9) had only one fit and the other (7) had 2 fits just before the specimen of blood was obtained. The degree of come in all of them was slight.

The other 3 cases of eclampsia were deeply comatose (Nos.1, 8 and 10). The pH of the plasma in these patients at this stage was 6.88, 7.22 and 7.27 respectively. The first of these patients had a fatal outcome and 16 hours before death (11 hours after the first test) the pH dropped to 6.56. It is evident that all compensatory efforts of the buffer mechanism of the blood had failed in this patient. Nevertheless, in the other two cases inspite of a subnormal pH of the blood recovery occurred, and when they regained consciousness the pH had risen to 7.36 and 7.39 respectively.

KETONURIA

It has been pointed out by several investigators that a pregnant woman and more so a case of toxaemia, is easily susceptible to Ketosis. In this connection Ketosis and acidosis have been used somewhat synonymously by most authors. It has already been seen that the acidosis of pregnancy and pre-eclampsia is of the nature of a "compensated" alkali deficit without any alteration of the hydrogen ion concentration of the plasma. It was considered that the problem of Ketosis in toxaemia in relation to alkali reserve was worthy of investigation.

1. Spontaneous Ketonuria. In order to study if normal

pregnancy/

pregnancy under ordinary living conditions gives rise to Ketosis, 472 specimens of fresh urine obtained from the antenatal clinic belonging to patients in the last trimester of gestation were examined for Ketone bodies (qualitative test of Rothra). In 5 specimens Ketone bodies were present (1.03 per cent.). But in none was the quantity detected any more than a mere trace. All patients were examined 1 to 3 hours after the mid-day meal and consequently the question of starvation acidosis was ruled out.

Similar examination was carried out on 269 cases of toxaemia of whom 93 had severe pre-eclampsia and 176 were mildly toxic. The incidence of Ketonuria in these cases was 1.14 per cent. (2 cases) in mild and 4.30 per cent (4 cases) in severe toxaemia. In mild toxaemias the blood pressure was between 140/80 to 150/100. They had varying amount of albuminuria from 0.5 to 3 parts of Esbach. The degree of oedema also showed considerable variation. Of the two cases who had Ketonuria one had B.P. 140/90; Alb.2.5 parts; and ++ oedema, the other had B.P. 150/100; Alb.7 parts and +++oedema. In severe toxaemias the blood pressure varied from 155/105 to 220/135, and albuminuria ranged from 2 parts to 16 parts Esbach. The four cases of Ketonuria had B.P. 160/110, Alb.6 parts; B.P. 170/120, Alb.3 parts; B.P. 170/110, Alb.9 parts; and B.P. 195/115, Alb.5 parts respectively. All of them had +++oedema. The quantity of acetone in pre-eclampsia varied from a trace to +.

Twenty/

Twenty-nine cases of eclampsia were also investigated before they received any form of corrective treatment. The interval between the last convulsion and the time for the collection of the specimen of urine varied from a few minutes to 4 hours. In all cases Ketonuria was detected. No correlation could be observed between the number of convulsions and the degree of Ketonuria. Infact, one patient who had 6 convulsions had 1+ "acetone" in the urine, yet in another patient with only 2 fits the urine was loaded with Ketone bodies. However, the degree of coma appeared to have some relation to the severity of Ketonuria, as the analysis presented below will show. In order to present an undistorted picture no attempt is made to calculate averages.

	Degree of Coma.	No. of Cases	Ketonuria.
1.	0	4	Trace - 3 cases + - 1 "
2.	±	6	Trace - 3 cases + - 2 "
3.	+	8	+ - 5 cases ++ - 3 "
4.	++	6	++ - 2 cases +++ - 4 "
5.	+++	5	+++ - 5 cases.

In three fatal cases of eclampsia in the pre-terminal stage (7 to 21 hours before death) the urine was loaded with Ketones and gave a positive reaction to diacetic acid.

11. Induced Ketonuria. In a smaller series of normal and toxaemic/

toxaemic patients an attempt was made to induce ketosis by a short period of starvation, during which only drinks of water were allowed. The period of starvation extended from 6.30 p.m. to 10 a.m. on the following morning. Such a short fasting seldom, if at all, induced Ketonuria in normal individuals. Twenty cases of normal pregnancy, and 38 cases of severe toxaemia were subjected to this regime. At the end of the period of starvation, 1 case of normal pregnancy (5 per cent.) and 6 cases of toxaemia (15.2 per cent.) showed the presence of Ketone bodies in the urine. The patient with normal pregnancy and 5 cases of toxaemia had only a trace of "acetone" in the urine. In the remaining case of pre-eclampsia it was 1+. It is interesting to note that in this patient the toxaemia markedly deteriorated during the following 48 hours and labour had to be induced on the third day after the test was done. At this stage her urine contained 1+ acetone even during the post absorptive period after a meal containing a liberal amount of carbohydrate.

Plasma pH and alkali reserve were estimated in these 7 cases (1 normal + 6 toxaemia) who had Ketonuria. Their findings are given in Table 68.

It is clearly evident from these cases that slight Ketonuria in either normal pregnancy or toxaemia does not disturb the acid-base balance of the plasma to any appreciable degree. The total carbon dioxide combining capacity/

Table 68

Cases	B.P.	Alb.	Oed.	Ketonuria	CO2 combining capacity			B.HCO3 / H.HCO3	pH
					Total	Fixed	Free		
N.1	118/70	-	-	±	49.2	46.95	2.25	20.9	7.43
T.1	165/115	7.5	+++	+	44.1	42.05	2.05	20.5	7.41
T.2	170/100	3	++	±	48.6	46.26	2.34	19.8	7.40
T.3	160/100	4	+	±	47.7	45.53	2.17	21.0	7.44
T.4	180/110	5	++	±	48.0	45.71	2.29	20.0	7.41
T.5	170/105	2.5	+	±	49.0	46.62	2.38	19.6	7.41
T.6	160/105	3	+	±	47.1	44.90	2.20	20.4	7.415

capacity of the plasma in these cases was to some extent less than that in the series already described, but this was associated with a proportionate diminution of both the bicarbonate and free carbon dioxide of the plasma. Consequently neither the ratio of H.HCO3: B.HCO3, nor the pH showed any recognisable deviation from those of the previous groups. The Ketosis in these conditions therefore is accompanied by a state of compensated acidosis.

Ketonuria in eclampsia however presented a different picture. It has already been pointed out that spontaneous Ketonuria was observed in all cases of eclampsia. The state of the alkali reserve and hydrogen ion concentration in eclampsia has also been described. It is evident that a state of true (uncompensated) acidosis exists in eclampsia simultaneous with Ketonuria. However, our present investi-

gations/

investigations are not elaborate enough to point out how much of this eclamptic acidosis is dependent upon the accumulation in the blood of products of incomplete oxydation of fat, and to what extent it is due to an increase of fixed acids in the blood.

Further observations on acidosis of the blood and tissue fluid will be found in the section on oedema.

COMMENTS

According to the nomenclature suggested in the British Medical Research Council Report (18, 1923) the state of alkali reserve in toxaemia comes within the scope of acidosis. This however is not associated with an increase of the hydrogen ion concentration of the blood, nor an alteration of H:B.HCO3 ratio. These are maintained within normal limits. The accepted average pH of the blood is 7.4 (Stirling, 19, 1947). But even normal subjects show considerable variation in this respect. Thus, Cullen and Robinson (20, 1925) found that in normal persons the pH may vary between 7.28 to 7.41, and that variations of this value may occur at different hours of the day depending upon the state of digestion and activity. When these factors are taken into account, it appears that the state of the acid-base balance in toxaemia is almost similar to that found in normal pregnancy. In both conditions a compensated deficit of alkali is present. The net available alkali is slightly less in pre-eclampsia than in normal pregnancy/,

pregnancy. This would account for the high ammonia coefficient of the urine observed in toxaemia by Williams (21, 1924), Stander (7, 1930) and other investigators.

The state of the alkali reserve in eclampsia, however, indicates the presence of an uncompensated alkali deficit, named "acidaemia" in the Medical Research Council Report (18, 1923). In this respect our findings are in close agreement with those of the previous investigators (1,7, 7a, 8a, 14, 22). However the degree of this acidaemia varies and consequently the range of pH in these cases shows a wide dispersion. Nevertheless, the pH seldom falls below the minimum normal limit given by Cullen and Robinson (20, 1925) and the H.HCO3: B.HCO3 seldom becomes less than 1:16. From a prognostic point of view we have found these absolute values to be of little importance, for if convulsions do not recur at frequent intervals, the pH and the ratio soon return to normal. In 7 out of 9 cases of eclampsia in our series the H:B.HCO3 was less than 1:16, at the time of examination but none of these cases ended fatally. The decrease of the pH and the ratio, however, appear to be closely related to the degree of coma; and in this respect eclamptic and uraemic coma bear some resemblance to each other.

The cause of this uncompensated alkali deficit is not wholly understood. Several authors (7,8) have reported the presence of increased concentrations of fixed acids in the blood of eclamptic patients. Our investigations in the/

the few cases where estimation of lactic acid was done by us confirms this finding. But besides this accumulation of acids, (which also occurs in a normal individual after violent exercise, without any accompanying acidaemia), there are other interfering factors which give rise to a state of decompensation. These are - (1) The level of alkali reserve is initially low. (2) During an eclamptic attack there is serious interference with the respiratory functions. (3) The severe cases of toxaemia who drift into eclampsia suffer from marked oliguria, which often develops into anuria. (4) Disturbances of the metabolic functions of the liver, which are present in pre-eclampsia are markedly aggravated in eclampsia (vide part II): This would interfere with the resynthesis of the accumulated lactic acid into glycogen. It is evident that all these factors impose a load on the normal mechanism of compensation. With frequently repeated convulsions larger quantities of fixed acids accumulate in the blood before the body has the opportunity of removing them. With increasing coma, circulatory disturbance is always present, and this also interferes with the restoration of the compensation. A fall in the alkali reserve in eclampsia can give rise to dangerous consequences only if deep coma and frequent convulsions are present.

Ketosis in pre-eclampsia appears to be related to a disordered carbohydrate and fat metabolism and does not represent/

represent a loss of compensation in the acid-base balance of the body. Only in eclampsia they assume a considerable importance, for these Keto acids cause a demand for bases when they are already grossly depleted and the compensation is on the verge of breaking down. From this point of view preventing Ketosis in eclampsia provides the patient with a chance of restoring her reserve alkali and establishing compensation. Ketosis in eclampsia, unlike diabetes, is therefore a secondary factor responsible for an uncompensated acidaemia.

CONCLUSION

Normal pregnancy is attended with a decrease of the bicarbonate reserve of the plasma. This is associated with a proportionate fall in the free carbon dioxide, so that the ratio of H.HCO3: B.HCO3 remains unaltered. Consequently the pH of the plasma does not change from normal values.

In pre-eclampsia there is a further deterioration of the alkali reserve, but this is compensated by a decline in the concentration of the free carbonic acid - the ratio of H.HCO3: B.HCO3 and pH still persist within the normal range.

The "acidosis" of pregnancy and pre-eclamptic toxaemia is therefore a state of "compensated alkali deficit".

In eclampsia a greater decrease of the bicarbonate content of the plasma takes place. This may or may not be associated with a compensatory drop in the free carbonic acid./

acid. The conditions which decide the fate of this compensatory mechanism are coma and frequency of convulsions. Respiratory embarassment and oliguria also play an important part. In severe cases compensation as a rule breaks down, and then the "acidosis" of eclampsia becomes a true "acidaemia" or a state of "uncompensated alkali deficit".

The susceptibility to Ketosis is increased during pregnancy, more so in pre-eclampsia and is most marked in eclampsia. In the two former conditions it does not grossly upset the compensatory buffer mechanism of the plasma. It is possible that in eclampsia it helps in the final breakdown of the compensatory process.

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CHAPTER 4

FINAL SUMMARY ON GENERAL METABOLISM

Metabolism in pre-eclampsia and eclampsia can not be compared with that of non-pregnant individuals, for toxaemia is a disease peculiar to pregnancy and normal pregnancy is attended with some remarkable changes in the metabolic activity of the body.

The most striking changes in toxaemia is seen in connection with protein metabolism. The positive nitrogen balance of normal pregnancy is replaced by a negative balance in toxaemia. Two conditions at least, contribute to this change in nitrogen metabolism. (1) The loss of protein in the urine. This factor is of considerable importance, for in absence of albuminuria the balance of nitrogen in the body does not become actually negative. (2) A slightly increased rate of protein catabolism. This by itself does not give rise to a negative balance but brings about a reduction of the normal protein storage which occurs during pregnancy. The increased catabolism appear to be caused not by an increased tissue destruction, but by an inability on the part of the body to use all the available assimilated protein for anabolism and protein synthesis. This is shown also by the behaviour of plasma proteins especially that of serum albumin. These decrease progressively as toxaemia increases in severity. Compensation/

compensation for the hypoalbuminaemia with a relative increase of fibrinogen and globulin fails to meet the requirements. In very severe toxaemia even this feeble compensation breaks down. Protein synthesis and increase of plasma proteins can not be encouraged satisfactorily by merely raising the protein level of the diet. The most effective means of stimulating protein regeneration appears to be infusions of concentrated human plasma. In absence of this, increasing the dietary protein intake above the level of the loss due to catabolism and albuminuria is the only means of ensuring a positive balance. The average minimum daily protein requirement for this purpose is about 100 gms.; the optimum level is about 12 to 20 gms. higher.

The disturbed protein metabolism is associated with an altered state of amino acids in the blood. In severe toxaemia the amino acid nitrogen level is raised. This is not due to impaired excretion. It appears to be connected with a deficient protein synthesis and defective deamination. This is responsible for a reduction of the concentration of urea in the blood in toxaem ia. Marked oliguria is present when, toxaemia is very severe, as well as in many cases of eclampsia. When the limit of concentration of urea by the kidney is reached retention of urea commences. Increase of blood urea in pregnancy toxaemia occurs inspite of retarded urea synthesis and a maximum concentration of urea in the urine. At this stage

the/

the manifestations of altered deamination become masked.

The nature of carbohydrate metabolism in toxaemia does not show a qualitative difference from that in normal pregnancy. The capacity for both storage and mobilisation of glycogen is further deminished in toxaemia. Tolerence for sugar becomes less. Blood sugar level however does not show any consistent alteration. Even in eclampsia the response of the blood sugar is atypical. The occurrence of a hypo-, or hyper-glycaemia is decided by the amount of sugar which can be mobilised and to what extent the cori cycle is affected.

The fat metabolism in toxaemia is characterised by an increase in the lipaemic state of the plasma, in which both cholesterol and phospholipoids take a part. The hypercholesterolaemia is associated with a slight reduction of cholesterol esters, which increases as toxaemia becomes severe. In very severe toxaemia and in eclampsia, the cholesterol concentration of the blood falls, and in this, the esters are more affected than the free cholesterol. In fatal cases ester cholesterol may almost disappear from the circulation. The increase of phospholipoids caused by pregnancy is further augmented in toxaemia, but when the disease attains considerable severity the phospholipoid level starts to decrease.

The disordered carbohydrate metabolism together with the hyperlipaemia state increases the predisposition of a case/

case of toxaemia to Ketosis. In moderate toxaemia however, this does not give rise to a state of "acidaemia". The alkali deficit of normal pregnancy is increased in pre-eclampsia, but compensation does not break down even in presence of slight Ketonuria. In severe cases of eclampsia associated with deep coma and frequent convulsions the compensated "acidosis" passes on to a stage of uncompensated "acidaemia". It is at this stage that the pH of the plasma commences to fall.

The causes of disturbed metabolism in toxaemia are not wholly understood. Nevertheless, the deterioration of the metabolic state appears to be related to the severity of diastolic hypertension, and thereby to the degree of vascular spasm present. The available evidence suggests that the disturbed metabolism in pre-eclampsia and eclampsia is brought about by the vascular spasm affecting the functional efficiency of the liver.

Thus, the investigation of the hepatic functions in toxaemia of pregnancy assumes a remarkable importance. In the next part of our study we shall present and discuss the results of some of the hepatic function tests employed for this purpose.

PART II

HEPATIC EFFICIENCY TESTS IN TOXAEMIAS OF PREGNANCY

CHAPTER 1

INTRODUCTION.

As early as 1856, Parnier drew attention to a state of "insuffisance hepatique" during pregnancy. This view was generally upheld at that time by other authorities of the French school. In 1886 Jurgens (1) declared that eclampsia was associated with liver changes, and few years later Schmorl (2, 1893) demonstrated the pathological changes in the liver in puerperal eclampsia. In the beginning of the present century the role of the liver in pregnancy toxaemia became a subject of considerable discussion. Hofbauer (3, 1907) described the "Schwangerschaft's leber", and Pinard (4, 1909) developed the theory that the liver changes were aetiologically connected with toxaemia, eclampsia being a "hepatotoxemie gravidique". Some of the subsequent investigators (5,6) failed to confirm these observations, others (7,8) agreed with them.

Studies in the functional efficiency of the liver in pregnancy and toxaemias, however were not undertaken until several years later. Hofbauer (4, 1907) one of the earliest investigators observed that increased urobilinuria exists during pregnancy. Hein and Messtorff (9, 1923) found that Widal's haemoclastic test is positive in one-third of a series of normal/

normal pregnant women during the last month of gestation. During the last thirty years numerous tests for determining the functional status of the liver in normal pregnancy have/been employed by different investigators, but the results obtained provide extremely conflicting views.

Investigations in toxaemia also have not been free from contradictions. Different authors employing different tests have secured divergent results. Some of the important contributions are however worthy of notice. Barkeley and co-workers (10, 1924; Fouchet's and Schlesinger's test), Kerbes and Dieckmann (11, 1924; Phenoltetrachlorphthalein), Soffer (12, 1933) and Sullivan and others (13, 1934; Bilirubin excretion), Cantarow et al (14, 1935, Brom-sulphthalin and other tests) and Lyon (15, 1933, Bilirubin test) observed that in toxaemia hepatic functions deteriorate and that some of the tests could be of value for prognostic and diagnostic purposes. On the other hand, De Wisselow (16, 1922, 16a, 1924), Cruickshank, Hewitt and Couper (17, 1927), and Freiheit (18, 1932) failed to detect any consistent alteration of hepatic functions in pregnancy toxaemia.

One of the reasons for the conflicting nature of the results lies in the fact that the liver normally has an enormous reserve capacity and is endowed with a considerable power of regeneration of cells. It is believed (19,1927) that the normal hepatic functions can be maintained if only about/

about 20 per cent. of the liver substance is preserved in a healthy state. It is because of this that the liver function tests have never been found entirely satisfactory. The liver has more functions to perform than any other organ in the body. It has been said that in many cases of derangement one of these functions may be more marked than that of the others, and consequently the results of several tests must be compared together in order to assess the degree of damage. However, some investigators (Soffer, 12, 1933) have stated that one abnormal test is as significant an index of hepatic pathology as the finding that all tests are abnormal. Others (20, 1941) point out that there are indications that certain types of liver function may be selectively disturbed during pregnancy. In a recent discussion on the subject Thordarson (21, 1941) observed that there is a selective disturbance of the excretory and enzymatic functions of the liver during pregnancy.

Numerous tests have been devised for estimating the functional efficiency of the liver. For the purpose of the present investigation we have employed:-

1. Excretory function -
   Bilirubin Excretion Test.

2. Special functions -
   (i) Alkaline Phosphatase,
   (ii) Prothrombin concentration,
   (iii) Response of Prothrombin to Vit.K.
   (iv) Thymol Turbidity.

3. Metabolic functions -
   (i) Galactose tolerance.
   (ii) Reference to other metabolic disturbances has already been made in Part 1.

CHAPTER 2

BILIRUBIN EXCRETION TEST IN NORMAL PREGNANCY

Excretion of bilirubin is one of the important functions of the liver, and consequently has been a subject of considerable investigation in conditions in which hepatic efficiency is believed to suffer. The results from the estimations of plasma and urinary bilirubin and urobilin have, however, not been uniform in pregnancy. Thus, Hofbauer (3, 1907) observed increased urobilinuria during pregnancy. Seitz (22, 1927) also found this in 64 per cent. of his cases of normal gestation. Schimdt (24, 1928), Mikeldase (25, 1928) and Breda (26, 1929) also made similar observations, but the values for plasma bilirubin stated by these authors seldom exceeded 0.7 mgms. per cent. Recently, Cantarow, et al (27, 1935) reported that serum bilirubin remains within normal limits during pregnancy.

Von Bergman (28, 1927) and Eilbott (29, 1927) studied the behaviour of the rate of pigmentary excretion after intravenous injection of bilirubin. The method was employed by Kauffman (30, 1932) who found increased bilirubin retention in 23 out of 26 cases of normal pregnancy. Soffer (31, 1933) modified the technique and observed that in a series of 10 cases the retention of bilirubin increased from 1.6 per cent. during the first half of pregnancy to 7.1 per cent. in the second half. Hofbauer (32, 1933) also observed a high incidence (35 per cent.) of abnormal results/

results in the later stages of pregnancy. Sullivan, Tew and Watson (32, 1934) made further similar observations. Individual values presented by each of these authors however showed considerable variation. A proper study of the bilirubin excretion capacity of the liver in normal pregnancy was, therefore, considered necessary before the results obtained in toxaemia could be evaluated. The test was carried out as recommended by Soffer and Paulson (33, 1936). One m.gm. of bilirubin per kilogram of the body weight, not exceeding 70 m.gms., dissolved in 15 ml. of 0.1 M solution of Sodium Carbonate was employed for intravenous injection.

The analysis is based on a study of 87 cases of whom 49 were primigravidae and 38 multigravidae. These cases have been divided into 2 groups. (1) 72 cases belonging to different periods of gestation selected from the antenatal clinic. (2) 15 cases, who were followed up from early pregnancy at monthly intervals to term. All patients were subjected to a very careful clinical examination in order to eliminate organic diseases, hepatomegaly, and condition which may interfere with hepatic efficiency. The second group of cases were also used for study during labour and puerperium.

A careful watch was kept for the onset of toxic manifestations in each instance. Watson (34, 1933) reported that delayed excretion of intravenously injected bilirubin is associated with subsequent toxic manifestations. In our series however severe toxic manifestations were not seen in any/

any of the cases studied in spite of frequent repetition of the experiment. Untoward reaction was noticed in the form of rigor of short duration in 3 cases; subcutaneous extravasatio which occurred in one instance was painful and caused some amount of inflammation. Two patients developed mild urticarial rash during the test, which was attributed to the injection, but both of them responded easily to ordinary treatment.

1. PREGNANCY

Group 1

The amount of bilirubin retained in the circulation at the end of 4 hours was found to vary consdierably not only in individual cases but also in the different periods of gestation. The range extended between no retention (5 cases) and 14.6 per cent. (one case). The average degree of retention in the whole series of 72 cases irrespective of the stage of pregnancy when the test was performed was 4.47 per cent., S.D. 3.23. But this hardly represents the true state of affairs, for the results of the test were found to vary considerably at different periods of pregnancy. Thus, among the 36 cases between the third and seventh months of gestation complete excretion of bilirubin occurred in 4 cases, whereas in an equal number of cases belonging to the last trimester this was never seen. The behaviour of bilirubin excretion in different months of gestation is given in Table 69.

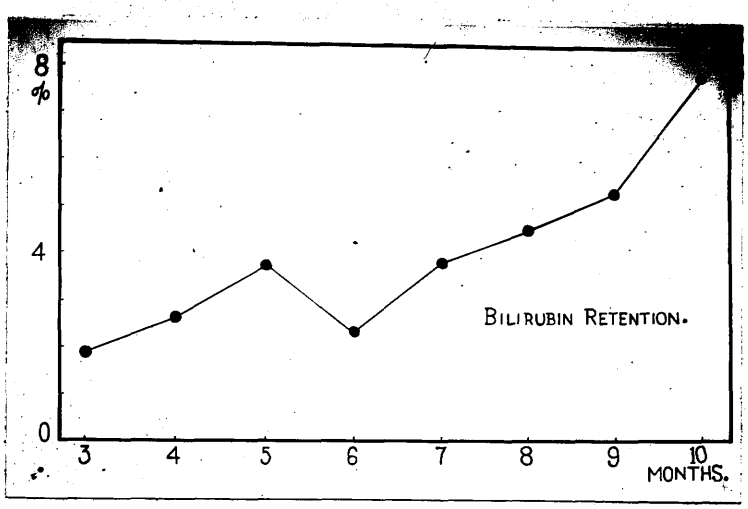

Fig. 44. Bilirubin excretion test in normal pregnancy. The results are expressed in per cent of bilirubin retention at various months of pregnancy four hours after an intravenous injection of bilirubin(1 mg. per Kgm. body weight).

Table 69

Period of Pregnancy (Lunar months)	No. of Cases	Values of Bilirubin Retention (%)	Average per cent.	S.D.
3	6	2.1; 0; 3.4; 3.1; 2.1; 1.0.	1.95	1.07
4	8	2.6; 4.0; 0; 1.3; 3.5; 1.4; 3.7; 3.0.	2.43	1.31
5	7	4.3; 1.6; 1.0; 4.5; 5.9; 7.0; 3.4.	3.81	2.01
6	7	5.4; 0; 1.1; 3.2; 2.5; 1.8; 2.2.	2.31	1.31
7	8	1.4; 3.2; 4.7; 6.3; 5.1; 0; 1.6; 3.5.	3.85	2.58
8	12	2.4; 2.7; 7.9; 9.2; 1.6; 5.5; 4.6; 7.9.	4.58	2.61
9	12	3.4; 11.2; 1.6; 3.3; 1.4; 9.9; 6.3; 6.0; 5.0; 2.5; 7.8; 2.0.	5.33	2.86
10	12	2.8; 14.6; 2.8; 7.9; 6.5; 5.4; 12.5; 10.6; 9.2; 8.7; 10.2; 8.8.	8.22	3.57

The table shows a general tendency of increased bilirubin retention as gestation proceeds. This however is neither uniform nor significant up to the end of the second trimester. In the last 3 months of pregnancy, however, the retention is more marked and progressive, the difference at each stage being statistically significant. It is further evident that, the increase in retention during the last months of pregnancy is about four times the corresponding increase during the preceding month. Maximum retention of bilirubin was noticed in the last month of pregnancy. If 5 per cent. is accepted

as/

as the maximum limit of retention in normal cases (Soffer, 31, 1933), the incidence of abnormal retention in the present series was 0, 0, 14.28, 14.28, 37.5, 33.3, 41.67, 33.3 per cent. from the third to the tenth month of gestation respectively.

The range of variability of the values obtained in the individual groups of cases was considerable. But during the last four months of pregnancy the variability diminished. During this period, however, the minimum values in each group did not show a significant change, but the maximum retention showed a distinct tendency to rise.

Group 2

The results of the follow-up study in 15 cases are presented in Table 70.

When these cases are studied as a separate series it is noticed that the average values for bilirubin retention at different months of pregnancy correspond closely with those in the former series. Of the 11 cases examined in the third month of pregnancy none showed an abnormal retention. Eight among these who were re-examined in the fourth month maintained a normal bilirubin excretion rate. Except for one instance however, (Case No.1) all of them showed an increase in the retention of the injected dye. In the fifth month of pregnancy in one of them (Case No.7) the retention had exceeded the range of normality. In the sixth month another patient showed a similar response. By the seventh month of gestation/

Table 70

Lunar months of gestation.
(Bilirubin retention%)

	3	4	5	6	7	8	9	10
1.	3.6	2.4	-	3.7	4.7	5.8	7.8	10.9
2.	-	0	1.0	1.6	2.0	-	3.4	6.5
3.	0	1.8	4.3	2.6	6.2	6.9	7.0	9.2
4.	-	2.1	3.5	5.5	-	7.9	-	12.8
5.	2.0	-	-	5.0	5.4	5.6	-	8.8
6.	3.0	3.5	4.5	-	5.1	-	9.9	14.5
7.	1.0	4.0	5.9	-	-	9.2	11.2	12.1
8.	0	0	-	3.0	3.0	3.0	3.5	5.4
9.	2.1	-	1.6	2.4	2.5	2.8	2.9	-
10.	1.4	-	1.5	1.2	-	1.3	3.3	6.2
11.	-	-	0	1.0	2.2	3.3	4.0	6.7
12.	1.5	3.0	2.5	3.6	4.6	5.1	5.3	-
13.	-	-	0	-	2.0	-	2.6	3.8
14.	1.6	2.0	3.5	-	5.6	-	9.0	-
15.	1.0	-	-	4.8	5.9	-	10.7	-
Aver.	1.5	2.1	2.6	3.1	4.1	5.1	6.2	8.8
S.D.	0.99	1.13	1.81	1.62	2.07	2.08	3.22	3.52
Min.	0	0	0	1.0	2.0	1.3	2.9	3.8
Max.	3.6	3.5	5.9	5.5	6.2	9.2	11.2	14.5

gestation 5 cases, and presumably 7, had an abnormal retention. In the eighth and nine months 9 patients had more than normal retention/

retention, where as at term, only one (and possibly ?) out of the series of 15 cases showed evidence of normal bilirubin excretory capacity. As the results obtained in the individual cases are examined, a progressive tendency towards increased retention of bilirubin becomes clearly evident. The rate at which this retention increases is however neither constant nor uniform. Infact some of the cases (Nos.1, 3, 9 and 12) showed an erratic response once or twice up to the sixth month of pregnancy. In the latter part of gestation, however a steady increase in bilirubin retention was noticed in all cases, including those where the values did not reach an abnormal figure.

If both series of cases are included the average bilirubin retention in the last 3 months of pregnancy is found to be 6.36 per cent.; S.D.3.69.

Serum Bilirubin and Bilirubin Retention

The serum bilirubin content in none of the cases in this series exceeded 0.5 mgms.per cent. This value was obtained from the examination of the blood collected immediately before the injection of bilirubin, and may therefore be expected to represent the basic value, before overloading of the circulation by the pigment occurred. The object of this study was to ascertain if the basic bilirubin level in the blood bore any relationship to the reserve excretory capacity of the liver. The values of bilirubin retention corresponding to the basic serum bilirubin level is given in Table 71.

Table/

Table 71

Serum Bilirubin Conc.%	Bilirubin Retention%
1. 0 - 0.1 m.gms. (6 cases)	1.4; 4.5; 4.7; 1.3; 5.0; 10.2. Average - 4.5; S.D. 3.22. Max. - 10.2; Min. - 1.3.
2. 0.1 - 0.2 m.gms. (18 cases)	2.1; 4.0; 1.3; 3.5; 0; 5.9; 2.9; 10.6; 1.6; 3.3; 9.2; 5.1; 2.5; 6.5; 4.1; 3.4; 2.8; 3.1. Average - 3.9; S.D. 2.94. Max. - 10.6; Min. - 0.
3. 0.2 - 0.3 m.gms. (22 cases)	1.0; 0; 2.6; 3.4; 2.4; 2.1; 3.7; 2.7; 7.0; 3.4; 7.9; 4.6; 7.9; 5.0; 1.1; 6.0; 1.8; 14.6; 8.2; 6.3; 2.8; 5.4. Average - 4.5; S.D. 3.18. Max. - 14.6; Min. - 0.
4. 0.3 - 0.4 m.gms. (24 cases)	3.0; 4.3; 1.6; 0; 5.4; 0; 3.2; 2.2; 1.4; 1.6; 3.5; 1.6; 5.5; 1.4; 9.9; 6.8; 2.5; 7.8; 2.8; 7.9; 12.5; 92; 8.7; 8.8. Average - 4.6; S.D. 3.66. Max. - 12.5; Min. - 0.
5. 0.4 - 0.5 m.gms. (2 cases)	11.2; 1.0. Average - ? 6.1.

The above figures indicate that the basic level of serum bilirubin bears no relationship with the rate and level of clearance when an overloading test is done. The average values for bilirubin retention at different initial levels of serum bilirubin showed but little change, and whatever difference was present was insignificant. The maximum bilirubin retention in this series was observed when the serum bilirubin level was 0.23 m.gms. per cent., yet in 2 cases, where the bilirubin content of the serum was 0.34 and 0.39 m.gms. respectively there was no retention of bilirubin at

the/

the end of 4 hours. One case with bilirubin level of 0.5 m.gms. showed only 1.0 per cent. retention.

2. LABOUR

In 11 of the 15 cases in this series the level of bilirubin retention at term was known. The remaining four who could not be traced during the last month of pregnancy were examined at the very start of labour and the values thus obtained were regarded as being equivalent to those at term. In 9 cases in this series the test was repeated both early and late in labour. In 4, among these the labour was prolonged for more than 48 hours and we had the opportunity of repeating the test when the first stage was well advanced and labour lasted a considerable time (30 to 40 hours). In the remaining 6 cases the test was done only during the second stage of labour. The results of this study are presented in Table 72.

The analysis reveals a striking uniformity in the increase in bilirubin retention towards the end of second stage of labour. This is however purely qualitative, for the quantitative increase showed considerable individual variation in the series, the range extending between 1.9 (2 cases) and 16.3 (1 case of prolonged labour). It is interesting to point out at this stage that serum bilirubin level also rises slightly but significantly as labour progresses to the second stage, although in none of the cases of the present series was an abnormal value for serum bilirubin encountered. The

average/

Table 72

	Before Labour		First Stage		Late First Stage		Second Stage	
	Serum bil. mgms%	Bil. Ret. %	Serum bil. mgms%	Bil. Ret. %	Serum bil. mgms%	Bil. Ret. %	Serum Bil. mgms%	Bil. Ret. %
1	0.25	10.9	0.20	11.2	-	-	0.23	14.8
2	0.30	6.5	0.18	7.2	-	-	0.20	9.4
3	0.10	9.2	0.10	10.5	-	-	0.10	12.8
4*	0.15	12.8	0.15	13.2	0.22	20.1	0.30	24.9
5	0.13	8.8	0.28	8.8	-	-	0.34	10.7
6	0.28	14.5	0.30	16.0	-	-	0.40	22.0
7	0.40	12.1	0.33	13.4	-	-	0.35	17.5
8	0.26	5.4	0.28	6.0	-	-	0.25	8.6
9e	0.47	3.6	-	-	-	-	0.40	8.1
10*	0.12	6.2	0.14	8.0	0.20	12.4	0.20	19.5
11*	0.18	6.7	0.15	8.1	0.51	11.0	0.22	17.3
12e	0.28	8.3	-	-	-	-	0.30	10.2
13*	0.34	3.8	0.30	4.9	0.30	11.3	0.34	20.1
14e	0.46	9.9	-	-	-	-	0.48	15.4
15e	0.40	11.2	-	-	-	-	0.51	17.0
Aver.	0.27	8.26	0.22	9.76	0.22	13.70	0.31	15.22
S.D.	0.12	2.53	0.094	3.12	0.05	4.33	0.11	5.25

e Results of estimation done at the very commencement of labour.

* Labour prolonged for more than 48 hours.

average increase of bilirubin retention as labour proceeded to the second stage was 6.96 per cent.; S.D. 5.05. This amounts/

amounts to an increase of 84.4 per cent. of the initial level at term.

Between the early first stage of labour and the terminal stage of pregnancy the difference in bilirubin retention was only slight (0.50 per cent.). This is hardly significant and does not deserve undue attention.

A more careful study of the cases presented above, easily separates those who had prolonged labour, from those where it was not unduly delayed. In the 11 cases of normal labour the average bilirubin retention in the second stage was 13.32 per cent.; S.D. 4.36. The increase in these cases, which amounts to 4.52 per cent.; S.D. 0.91 is significant, and equals to 51.4 per cent. of the initial level at term. In the 4 cases of delayed labour, the average bilirubin retention in the second stage was 20.45 per cent., S.D. 2.62. The increase here is to the extent of 13.08 per cent.; S.D. 3.44. Compared with the level of bilirubin retention at term the increase is of the order of 177.4 per cent. of the basic value. This very marked deterioration of the bilirubin excretion capacity of the liver in cases of prolonged labour as revealed by the test is not a sudden process, nor does it seem to depend entirely on the bearing down efforts of the second stage of labour. The change shown by these cases in the early first stage of labour is in no way different from those in whom labour followed a normal course. But in the late first stage of labour, after it had lasted for 30 to

40 hours the bilirubin retention level had already exceeded that in the second stage of normal labour. Further deterioration occurred with the onset of the second stage. After 30 to 40 hours of labour the bilirubin retention had increased by 85.9 per cent. of its initial level. Further prolongation of the second stage was responsible for a further rise of 49.2 per cent. of the late first stage value, and 91.5 per cent. of that at term. It would thus appear that the prolongation of labour by itself exerts a harmful effect on the bilirubin excretion capacity of the liver and this is more intense than the effect of mere expulsive pains of a normal second stage.

Obstetric anaesthesia and analgesia may be supposed to have a harmful effect on the liver. None of the cases in this series however received any form of anaesthesia until the tests were over. No patient received more than a single dose of 1/4 gr. morphia. But, that the marked increase in bilirubin retention in the 4 cases of delayed labour were not due to morphine is shown by the fact that, of the remaining 11 cases 3 also received the same drug (Nos. 1, 5 and 15), and in these cases the amount of increase in the retention of bilirubin was only 3.9, 1.9 and 5.8 per cent. respectively. Barbiturates were not used in any instance. All 4 cases of prolonged labour and 5 cases of normal labour (Nos. 1, 2, 6, 9 and 14) in this series received pethidine. But here also as in the case of morphine the difference is so considerable that/

that the analgesia can hardly be held responsible for the enhanced values obtained.

3. PUERPERIUM

The test on all these patients was repeated on the third day in order to determine if the emptying of the uterus on one hand, and involutional processes on the other showed any effect on the bilirubin excretion capacity of the liver. The results obtained are summarised in Table 73.

Table 73

Bil.Ret. (Puerper -ium)	No. of Cases	Bil.Ret. (2nd stage)	Bil.Ret. (at term)
0 - 2	4	12.8; 10.7; 86; 10.2.	6.5; 8.8; 5.4; 8.3.
2 - 5	7	14.8; 9.4; 17.5; 8.1; 19.5; 17.0; 20.1.	10.9; 6.5; 12.1; 3.6; 6.2; 11.2; 3.8.
5 - 8	3	22.0; 15.4; 17.3.	14.5; 9.9; 6.7.
8 - 10	1	24.9.	12.8

The average bilirubin retention in this series was 3.92 per cent.; S.D.2.81, the minimum and maximum values obtained were 0, and 9.2 per cent. respectively. The level of bilirubin excretion at term did not bear any significant relationship with that in the puerperium in this series of cases. Maximum bilirubin retention during labour was associated with maximum retention in puerperium in one case (No.4). But this patient had a prolonged labour lasting for nearly 58 hours. It is difficult to state if in absence of this/

this complication such an abnormal value (9.2 per cent. retention) would have been found here. If 5 per cent. retention is regarded as the maximum of the normal limit, 5 out of 15 cases in this series showed abnormal retention on the third day of puerperium. Two out of these 5 cases suffered prolonged labour, the remaining 3 cases had only 5.1, 5.3 and 5.4 per cent. retention respectively, values which only slightly exceed the limit of normality. In this series of 11 cases of normal labour, 72.7 per cent. of cases returned to normal level of bilirubin excretion by the third day of puerperium, where as, only 2 out of 4 cases of prolonged labour showed similar results. Two cases in the puerperium where complete excretion of bilirubin was observed on the third day showed 12.8 and 8.6 per cent. retention respectively in the second stage of labour. It is interesting to note that both of these cases (Nos.3 and 8) showed also a complete absence of retention in the third month of pregnancy.

Bilirubin Retention in Pregnancy and Prognosis

Three patients in this series had an interesting outcome which are recorded here. They showed abnormal retention at the time of investigation but none of them presented any evidence of toxaemia at the time when the test was performed. A short history of these three cases is given below.

Case No.1 - Mrs. McN.; age 34; primigravida; 37 weeks; no subjective complaints; blood pressure 125/80. Urine contained no albumin; no oedema; general and obstetric examination/

examination revealed no abnormality. Bilirubin excretion test done on 10.6.48 showed 14.6 per cent. retention. On 19.6.48 the patient noticed slight oedema of the ankles. On 25.6.48 blood pressure was 160/105; urine contained 2 parts of albumin (Esbach), legs and ankles were slightly oedematous. Bilirubin excretion test done on 26.6.48 showed 28.0 per cent. retention. During the following two days the blood pressure rose to 180/120, and albumin in the urine increased to 7 parts (Esbach). Labour was induced. On the eight day of puerperium, the blood pressure had come down to normal level, and bilirubin retention was 1.6 per cent.

Case No.2 - Mrs. T.; age 31; second gravida; previous obstetric history normal; 36 weeks; no subjective symptoms, clinical examination revealed no abnormality; blood pressure 120/70; urine contained no albumin. Bilirubin excretion test done on 2.4.48 showed a retention of 11.2 per cent. On 16.4.48, the patient complained of severe headache and vomited twice. On the following morning her blood pressure was 160/100; urine contained 2 parts (Esbach) albumin, and bilirubin excretion test showed 20.3 per cent. retention.

Case No.3 - Mrs. M.; primigravida; age 26, 37 weeks; completely free from symptoms and clinical examination failed to detect any abnormality. Bilirubin excretion test was done on 7.8.48 and showed 12.5 per cent. retention. At this time the blood pressure was 124/80, and urine was free from albumin. On 12.8.48 the patient noticed slight swelling of the hands and feet and complained of headache. Blood pressure

was/

was 140/90, and urine contained 3 parts albumin (Esbach). On the following day bilirubin excretion test showed 19.6 per cent. retention. Three days later (16.8.48) the patient developed accidental haemorrhage.

The interesting feature common to all the three cases was the abnormal bilirubin retention, which was observed a week to ten days before toxaemia became clinically manifest. It is however difficult to conclude that abnormal bilirubin retention can be of prognostic significance in pregnancy, for 5 other cases presented in this paper showed equally high bilirubin retention values, but did not develop toxaemia. More intensive study of a larger series of cases is necessary before the test can achieve a prognostic value.

COMMENTS

Bilirubin excretion test was claimed by von Bergman (28, 1927) and Gilbott (29, 1927) as a satisfactory measure of hepatic efficiency. Harrop and Barron (35, 1931) observed that "the bilirubin excretory power of the liver is the most delicate method so far proposed for testing the functional capacity of the organ". Soffer and Paulson (33, 1936) also arrived at a similar conclusion. The recent experimental study of Drill and Ivy (36, 1944) however does not wholly substantiate this claim.

The standard of normal retention has been a subject of controversy. Both von Bergmann (28) and Gilbott (29) regarded more than 10 per cent. retention as abnormal.

Kaufmann/

Kaufmann (30, 1931) stated that 15 per cent. retention was the maximum limit of normality. Harrop and Barron (35) considered that there should be no retention at the end of 4 hours. Stroebe (37, 1931) agreed with Kaufmann and accepted 15 per cent. as the limit of normal retention. Hofbauer's (3a, 1933) maximum standard for normal cases was 4 per cent. retention. Soffer (31, 1933) and soffer and Paulson (33, 1933) observed that more than 5 per cent. retention should be viewed as abnormal. Sullivan et al (13, 1934) employing Soffer's technique, found 5 per cent. retention as the average for 21 normal non-pregnant women in child bearing period.

Accepting this criterion of normality (retention of not more than 5 per cent. at the end of 4 hours) in our first series of 72 cases of "normal" pregnancy, 26 or 36.1 per cent. showed abnormal bilirubin retention. If only the cases in the last trimester of gestation are considered, the incidence of abnormal response increased to 52.8 per cent. (19 out of 36 cases) in the first series and 86.7 per cent. in the second series of 15 cases. Sullivan and co-workers noted an abnormal retention of bilirubin (according to the accepted standards) in 15 out of 47 cases, an incidence of 31.9 per cent. In Soffer's (12, 1933) series of 10 normal cases in the latter half of gestation the incidence of abnormal response to bilirubin excretion test was present in 90 per cent. (9 out of 10 cases) of cases. Hofbauer's

(3a/

(3a, 1933) incidence of abnormal values in the latter part of pregnancy was 35 per cent. (17 out of 30 cases), whereas Kaufmann (30, 1931) inspite of a high normal standard found abnormal retention in 23 out of 26 cases, an incidence of 88.4 per cent. Such high incidences of "abnormal" values in "normal" pregnancy makes it evident that the standard of normal bilirubin excretion in pregnancy requires to be defined if its implications are to be studied and compared in pathological complications of gestation.

There appears to be a general acceptance of the hypothesis that such abnormal bilirubin retention values in pregnancy, as found in the literature, are manifestations of hepatic dysfunction in normal pregnancy. The results of other hepatic function tests, e.g. excretion of bromsulphthalein (Cantarow et al, 14, 1935) does not offer support to such a contention. Investigations of Cruickshank, Hewitt and Couper (38, 1927), de Wisselow and Wyatt (39, 1924) and Huwer (40, 1933) did not reveal any evidence of gross hepatic dysfunction in pregnancy. Recent biopsy studies of the liver in normal pregnancy by Ingerslev and Teilum (41, 1946) failed to demonstrate any evidence of abnormality in the liver cells, except slight fat infiltration in the central zone of the lobules. On reviewing the literature the evidence for assumption of a gross disturbance of the function or functions of the liver in normal pregnancy appears extremely unconvincing.

Pregnancy/

Pregnancy is attended with a marked change of the normal physiological functions of the body. The importance of raised intra-abdominal pressure caused by the enlarging uterus was demonstrated by Paramore (42, 1932) and Theobald (43, 1932). The former author demonstrated evidences in support of a state of altered circulation in the liver caused by the pressure of the enlarging uterus. Dilatation of the biliary canaliculi in normal pregnancy has been noted by several observers. The liver is displaced upwards and to the right, bile production is increased (Greenhill, 44,1947) and the gall bladder is often distended. Man and Higgins (45, 1927) noted that in pregnant dogs and guinea-pigs the gall bladder usually did not empty following a meal of fat. Levyn, Beck and Aaron (46, 1928) were unable to visualise the gall bladder in the majority of normal pregnant women at term, in spite of a completely negative gall-bladder history. Westphal (47, 1923) found that during pregnancy the tone of the sphincter of Oddi increased appreciably.

In view of these normal physiological changes in pregnancy a minor degree of delay in bilirubin excretion or a slight retention need not be an unexpected event when an overloading test is performed. This is borne out by the fact that the incidence of so-called abnormal retention increases progressively as gestation proceeds to term. It is difficult to conceive that any degree of hepatic insufficiency exists in as many as 80 to 90 per cent. of pregnant/

pregnant women who are to all intents and purposes healthy and normal throughout pregnancy. Further, these patients show a rapid return to normal non-pregnant levels of bilirubin excretion during the first week of the puerperium. In view of such a quick return to the biochemical "norm" one would expect some associated clinical manifestation of "improvement", but there is no subjective or objective change to be observed. Each subsequent pregnancy is apparently associated with this "abnormal" bilirubin retention, normality being restored after parturition. Thus, it becomes obvious that the standard for the non-pregnant state is hardly applicable in pregnancy especially in the latter half of gestation.

All available literature and our own observations indicate that according to the hitherto accepted standard there is seldom an abnormal retention of bilirubin in the first half of pregnancy. The position is however different in the second half of gestation. In view of the fact that most complications arising out of pregnancy develop during the last trimester of gestation the state of bilirubin excretion in clinically normal pregnant women at this period of pregnancy should be known.

For this purpose we have made a collective review of the cases reported by Soffer (12, 1933), Sullivan et al (13, 1934) and added our own observations.

From this collected series of 86 cases of normal pregnancy/

pregnancy during the last trimester of gestation the average bilirubin retention appears to be 7.02 per cent.; S.D. 5.67; P.E. 3.80. It is therefore suggested that the average bilirubin retention for the last trimester of normal gestation be regarded as 7 per cent., and the maximum limit of normality in gestation as 11 per cent. (7.02+ 3.80 = 10.82). According to this standard 6.9 per cent. in our series of 87 cases 14.9 per cent. among the 47 cases reported by Sullivan, Tew and Watson, and 30 per cent. in Soffer's 10 cases showed abnormal retention. It is conceivable that some degree of hepatic dysfunction existed in these cases.

The increase in bilirubin retention during labour is of considerable significance. According to the new standard suggested above, 4 out of 15 cases in the present series (26.7 per cent.) showed abnormal retention when the first stage of labour was established, but in the second stage of labour all but 3 cases (66.6 per cent.) gave evidence of an abnormal response. Labour appears to throw an extra load on the reserve functional capacity of the liver. This is further shown by the fact that in all 4 cases where labour was prolonged bilirubin excretion was abnormally delayed. This need not be an unexpected finding when we consider the amount of extra work the liver is called upon to perform in presence of continuous and strenuous muscular contractions, especially when intra-abdominal pressure is considerably raised by repeated bearing down efforts. This has a far-reaching/

reaching significance in the management of cases of dystocia.

Interference with the bilirubin excretion capacity of the liver during pregnancy and labour, however, does not appear to be a permanent disability. Whatever hepatic dysfunction it indicates, the condition spontaneously returns to normal during the early puerperium. Our results add corroborative evidence in this direction to similar observations made by Sullivan, Tew and Watson (13, 1934).

CONCLUSIONS

Results of bilirubin excretion test, as modified by Soffer and Paulson, in a series of 37 cases of normal pregnancy, of whom 15, were followed throughout pregnancy, and during labour and puerperium indicate that according to the hitherto accepted standard 52.3 per cent. of cases shows abnormal retention in the second half of pregnancy. Bilirubin excretion is considerably impeded during labour. In all cases of prolonged labour abnormally high bilirubin retention values are obtained. The duration of the labour appeared to have a dilaterious effect on bilirubin excretion. A suggestion is made that bilirubin retention of 11 per cent. should be regarded as the upper limit of normality, and that a retention of 7 per cent. should be regarded as the average during the last trimester of normal pregnancy. The reasons for making this suggestion are discussed.

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CHAPTER 3.

BILIRUBIN EXCRETION TEST IN TOXAEMIAS OF PREGNANCY & ALLIED CONDITIONS

From time to time the liver in pregnancy toxaemia has received considerable attention because of the presence of degenerative and haemorrhagic lesions, which are present in this organ in eclampsia and hypertensive toxaemia. The results of the hepatic function tests however have been extremely variable and can scarcely be said to substantiate the importance many people attribute to these lesions. It is generally believed that all the functions of the liver can be maintained if only 15 to 20 per cent. of the liver tissue is normal. Obviously therefore, in cases of partial damage to the liver parenchyma, ordinary hepatic function tests may yield normal results. The degeneration of the liver tissue is however attended with a diminution of the functional reserve capacity of the organ, and herein lies the value of a saturation or overloading test, such as the study of the rate and level of bilirubin excretion after an intravenous injection of this substance.

Estimation of the bilirubin content of the plasma and icteric index, which is the measure of the normal bilirubin excretion capacity of the liver has shown indifferent results in pregnancy toxaemias. Thus, Herrmann (1, 1929) found that the serum bilirubin level was raised in pre-eclampsia, eclampsia and hyperemesis gravidarum. Eufinger and Bader

(2/

(2, 1926), and Cantarow, Stuckeurt and Gartman (3, 1935) also made similar observations. Yet, Cruickshank, Hewitt and Couper (4, 1927), Cross (5, 1929) and few other observers, failed to notice any significant alteration of the serum bilirubin concentration or icterus index in toxaemias of pregnancy.

It was therefore considered that a solution of the apparent discrepency in these results may be obtained by employing a saturation or overloading test. Several investigators have observed that the bilirubin excretion test is a satisfactory measure for determining hepatic efficiency. Soffer (6, 1933) suggested that "one abnormal test is as significant an index of hepatic pathology as the finding that all tests are abnormal" and considered the bilirubin excretion test as the most delicate single test for hepatic dysfunction.

The method employed for this investigation was that of Soffer and Paulson (7, 1936). Besides the series of pre-eclampsia and eclampsia already described the test was also done on 5 cases of nephritis complicating pregnancy, 10 cases of pregnancy with essential hypertension, and 5 cases of accidental haemorrhage. Follow-up studies were undertaken in pre-eclampsia and eclampsia in the manner described in connection with investigations on metabolism. The results of these investigations have been viewed in the light of the newly proposed standards, viz. average normal retention 7 per cent., and average maximum retention 11.0 per cent.

1. PRE-ECLAMPSIA

The bilirubin retention in 100 cases of pre-eclampsia was 9.65 per cent., S.D. 6.20. The individual results varied very considerably. The minimum retention was 1 per cent. (1 case) and the maximum 23.9 (1 case).

Mild pre-eclampsia - (50 cases). The average bilirubin retention was 5.53 per cent., S.D. 3.24. The lowest value was 1 per cent. and the highest 12.9 per cent. According to the normal standard proposed above 39 per cent. of normal pregnant women and 32 per cent. of mild pre-eclamptics had an abnormal retention of bilirubin. The difference between these two values however is not statistically significant.

Severe Pre-eclampsia - (50 cases). The average bilirubin retention was 13.70 per cent., S.D. 4.92. The range of values was between 3.9 and 23.9. Ninety-two per cent. of the values were above the standard proposed for normal pregnancy. In 32 per cent. of cases in this series the degree of bilirubin retention exceeded the maximum observed in both normal pregnancy and mild pre-eclampsia. Seventy per cent. of the values in this group were above the proposed maximum for normal pregnancy. Compared with the proposed average, severe pre-eclampsia showed an increased retention of bilirubin to the extent of 95.7 per cent. of the basic normal pregnancy level. The difference between the values in severe pre-eclampsia and in normal pregnancy/

pregnancy or mild pre-eclampsia is statistically significant. The frequency distribution of bilirubin retention in pre-eclampsia is shown in Table 74.

Table 74

Bilirubin Retention Per cent.	No. of cases.		
	Mild Toxaemia	Severe Toxaemia	Total
0 - 5	27	2	29
5.1 - 10	19	8	27
10.1 - 15	4	26	30
15.1 - 20	-	6	6
20.1 - 25	-	7	7
25.1 - 30	-	1	1
Total	50	50	100
Aver. Retention (per cent.)	5.53	13.70	9.65
S.D.	3.24	4.92	6.20
S.E.	2.17	3.30	4.15
Significance	- *	+	
Minimum	1.0	3.9	1.0
Maximum	12.9	28.9	28.9

* Compared with the average of the last trimester of normal pregnancy.

BILIRUBIN RETENTION & DIET IN TOXAEMIAS OF PREGNANCY

In recent years diet poor in protein has been held responsible for toxaemias of pregnancy. Hough and Freeman

(3/

(8, 1942) demonstrated that dogs deprived of protein diet showed an increase of plasma phosphatase and a decrease in the hepatic clearance of Rose Bengal. It was thus considered that a study of the results of the bilirubin excretion test in relation to the protein content of the diet in toxaemia may be useful. The patients were selected from 3 units of the hospital and the results are briefly stated below. The total caloric value of the diet in all the units was approximately the same (2,280 calories).

Unit A. Consisted of patients receiving 102 gms. of protein daily of which 71 gms. were first class protein. A total of 42 cases were studied in this group. The average bilirubin retention was 9.11 per cent., S.D. 6.45. Twenty-four cases of mild pre-eclampsia in this series had an average retention of 5.33 per cent., S.D. 3.57. The minimum and maximum values were 1.0 and 12.9 per cent. respectively. There were 18 cases of severe toxaemia in this series, where the average bilirubin retention was 14.16 per cent., S.D. 5.05. The minimum was 8.9 and the maximum 28.6 per cent.

Unit B. This consisted of 33 cases, 15 of whom were mild, and 18 severe pre-eclampsia. Each patient received 131 gms. of protein daily of which 115 gms. consisted of first class protein. The average bilirubin retention in the whole series was 9.88 per cent., S.D. 5.84., and that for mild toxaemias was 6.11 per cent., S.D. 3.42, (1.2 to

10.3/

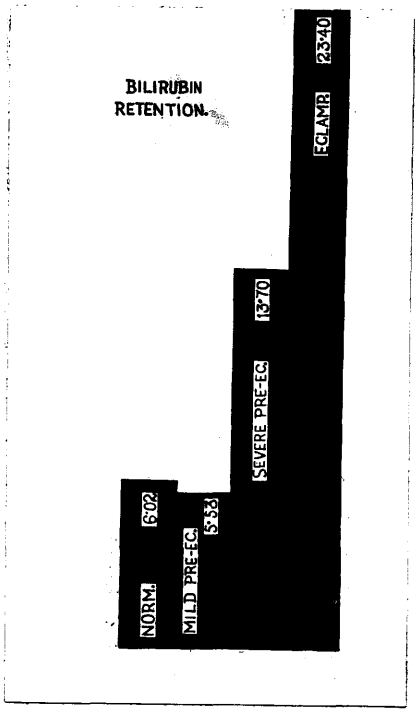

Fig. 45. Bilirubin retention in in normal pregnancy, pre-eclampsia, and eclampsia.

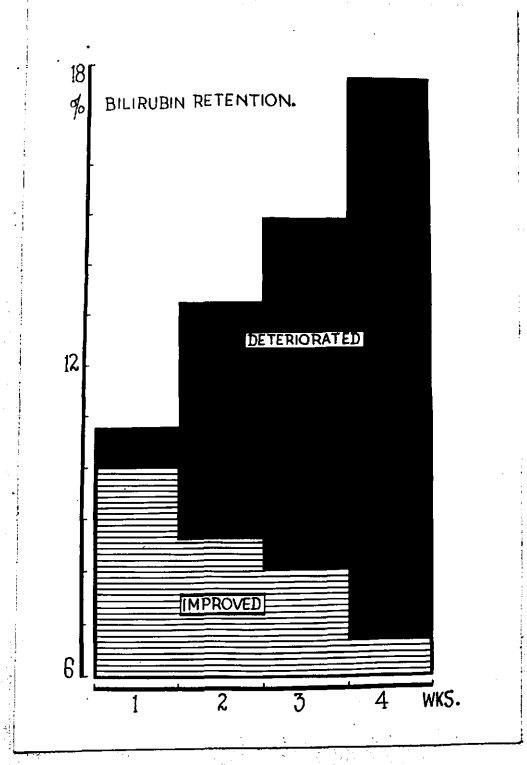

Fig. 46. Bilirubin retention in pre-eclampsia in relation to the clinical course of the disease.

10.3 per cent.). The severe toxaemias in this unit showed an average retention of 13.03 per cent., S.D.6.09, with a range of variation from 3.9 to 24.2 per cent.

Unit C. This consisted of 25 cases. There were 14 cases of severe toxaemia in this series, the remaining 11 had manifestations of mild pre-eclampsia. Each patient in this unit received 75 gms. of protein daily of which 43 gms. were first class protein. The average retention in this series was 10.0 per cent., S.D.6.05. The retention in mild cases was 4.97 per cent., S.D.3.00, average 1.8 per cent. minimum and 10.9 per cent. maximum. The severe pre-eclamptics had an average retention of 13.96 per cent., S.D.5.82. The maximum and minimum values in this group were 4.9 and 25.0 per cent. respectively.

The slight difference in bilirubin retention in the three units does not bear any statistical significance. This holds good not only for the overall average of all toxaemias but also for the mild and severe cases separately.

BILIRUBIN RETENTION & CLINICAL COURSE OF TOXAEMIA

A follow-up study was undertaken in all cases of pre-eclampsia. The results obtained in relation to the clinical course and progress of the disease are shown in Table 75.

These figures indicate that when the clinical condition improves the percentage of bilirubin retention becomes less and by the fourth week reaches the average of the last trimester of normal pregnancy. It is however interesting/

interesting to note that while there is a significant improvement of bilirubin excretion during the first week, the change noticed during the subsequent weeks is small, and very gradual. Simultaneous with a fall in the average values there is a decrease of the maximum values in the series, but the decline in the minimum is only slight. It appears that the improvement in the average figures is brought about by a swift return to normal of those cases showing high values in the series, while those who showed low bilirubin retention at the beginning of the investigation showed little alteration when the toxaemia improved clinically.

Table 75

	Improved			Deteriorated		
Weeks	Average	Range of Values	S.D.	Average	Range of Values	S.D.
1	10.0	1.0-22.0	61.0	10.8	2-23.7	6.24
2	8.6	0.5-20.5	5.55	13.3	2.9-26.3	6.72
3	8.0	0.5-12.9	4.24	14.9	4.3-28.9	6.64
4	6.7	0.4-12.6	4.38	17.5	7.9-26.1	5.2

In those cases where the toxaemia persisted or deteriorated bilirubin retention increased steadily and progressively every week. This increase was noted not only among the average values, but also in the minimum and maximum in each week-group. The difference of values at each stage of/

of the disease is statistically significant. It is interesting to note that the difference in the bilirubin retention at the time of admission between the series of improved and deteriorated cases is only slight. The higher values in each group did not show much change. The change in the average was brought about by a shift of the lower values to the right. After the third week no patient in this series had a normal rate of bilirubin excretion. The variation in the maximum values of each week-group was probably related to the unequal rates of deterioration of the condition in different patients. To avoid this fallacy these patients were regrouped according to the duration of toxaemia. For this purpose, where proper antenatal history was not available the earliest onset of oedema was regarded as the time of commencement of toxaemia. The results of this study are shown in Table 76.

Table 76.

Weeks	1	2	3	4	5
Average	9.36	10.86	12.44	15.47	19.43
S.D.	4.12	5.68	6.44	5.88	5.82
P.E.	2.76	3.80	4.31	3.94	3.90
Minimum	2.0	2.4	2.0	7.7	11.9
Maximum	14.9	21.4	25.0	26.3	28.9
Significance	+ *	-	±	+	+ +

* Compared with the average for normal pregnancy.

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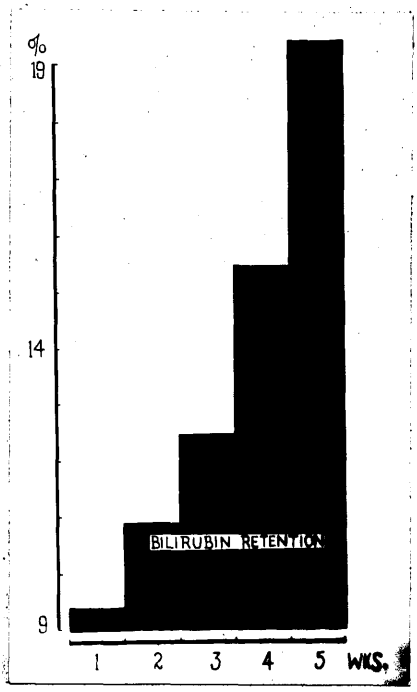

Fig. 47. Bilirubin retention in pre-eclampsia, in relation to the duration of the toxaemia.

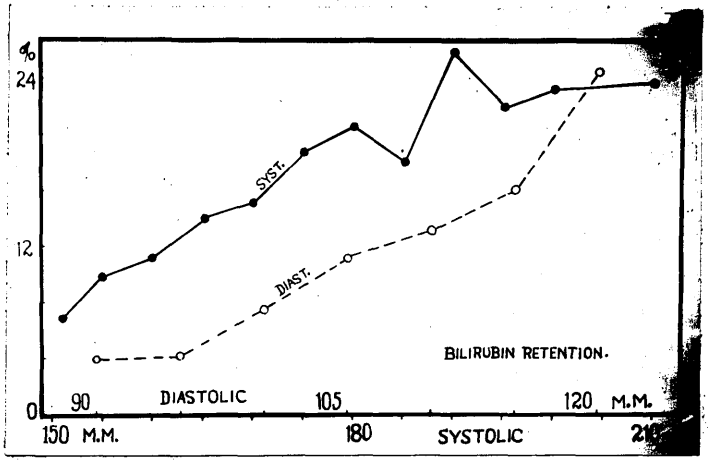

Fig. 48. Bilirubin retention in pre-eclampsia in relation to the different levels of blood pressure. Rise of both systolic and diastolic blood pressure is associated with an increase in the retention of bilirubin. The correlation is better and more marked with diastolic than with systolic hypertension. This graph provides an interesting comparison with the results of similar metabolic studies already described.

It is evident from the above table that there is a uniform and progressive rise in bilirubin retention as the duration of toxaemia becomes longer. At the very onset of the toxaemia bilirubin excretion was more delayed than that in the last trimester of normal pregnancy. The maximum in this series exceeded the proposed maximum for normal gestation in 4 cases. The increase in retention above the normal average is statistically significant. During the following week a further deterioration in bilirubin excretion was noted. The degree of retention was now further advanced by 16 per cent. The maximum value showed a considerable increase but the minimum level altered only slightly. Compared with the preceding week the change during the second week is not statistically significant. The two following weeks seemed to bring about a striking change. During this period the increase was noticeable not only in the average but also in the maximum and minimum levels of bilirubin retention. No case during the fourth and fifth weeks of toxaemia had a normal excretory rate. The increase in the average values during these two weeks amounted to 24.4 per cent. and 25.8 per cent. respectively of those in the corresponding preceding weeks. The variability of the figures declined, and statistical significance of the difference increased appreciably. By the end of the third week toxaemia seemed to affect the hepatic efficiency to a considerable extent, as measured by the bilirubin excretion test.

LABOUR IN PRE-ECLAMPSIA & BILIRUBIN EXCRETION

Ten cases of pre-eclampsia who went into labour or had labour induced on account of severity of toxaemia were submitted to this test in the second stage of Labour. The values of bilirubin retention in these cases are presented in Table 77.

Table 77

No.	Bilirubin Retention (%)			
	Before Labour	During Labour	Net Increase	Puerperium
1. H.	26.1	27.9	11.8	9.6*
2. O.	25.0	36.0	11.0	8.0
3. McM.e	14.8	23.2	8.4	5.0
4. D.	28.9	49.3	20.4	13.0*
5. C.	23.2	37.6	14.4	5.2
6. McI.	25.7	41.6	15.9	11.4*
7. S.	23.5	33.9	10.4	4.8
8. H.K.e	18.9	39.0	10.1	7.2
9. F.	26.1	36.7	10.6	10.4*
10 McD.	23.7	34.1	11.4	6.8
Average	23.59	36.03	12.44	8.14
S.D.	4.29	4.93	3.49	3.12
P.E.	2.84	3.30	2.33	2.06

e Spontaneous labour, remainder surgically induced.
* Re-examined post-partum.

The highest value for bilirubin retention during labour was/

was 49.3 per cent., in a patient (D.) who had also the maximum bilirubin retention before labour. The lowest value, 23.2 per cent., was similarly observed in a case (McM.) who had the most satisfactory bilirubin excretion rate in the present series before the commencement of labour. The parallelism, however, ends here, for in the remaining 8 cases the initial status of bilirubin excretion was found to bear no resemblance to the degree of retention found during labour. Thus, in one instance (McI.) with an initial retention level of 25.7 per cent., the increase in retention during labour amounted to 15.9 per cent., yet in another patient (H.) an increase of only 11.8 per cent. occurred when the initial level of retention was 26.1. Throughout the series, considerable variation in the individual values was present (variability of the net increase in retention - 28.1). The average gain, was however more marked than that found in normal labour, and almost equalled to that observed in prolonged labour in non-toxaemic patients, although in none of the cases in the present series labour lasted for more than 32 hours. The difference between the net increase in retention caused by labour in normal and pre-eclamptic subjects is significant. On superficial examination this finding may be interpreted as an expression of the adverse effect which labour has on a pre-eclamptic subject. But when the initial levels of bilirubin retention are taken into account, it is found that while in [illegible]

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net increase in retention caused by labour (provided it is not prolonged) is 51.4 per cent. of its initial value, in pre-eclampsia this rise is 52.7 per cent. This difference can hardly be regarded as beyond the limits of experimental error. It thus appears that uncomplicated labour by itself does not cause in a pre-eclamptic patient any more over-loading of the liver than in a normal subject. The difference in the values obtained is caused by the initially, high level of bilirubin retention in toxaemic patients.

BILIRUBIN EXCRETION IN PUERPERIUM IN PRE-ECLAMPSIA

The test was repeated on the third day of puerperium on these patients. The results will be found in Table 77. Two out of the series of 10 patients returned to the normal levels of bilirubin excretion, compared with non-pregnant conditions. Four patients (O., C., H.K., and McD.) had slightly increased bilirubin retention. The remaining 4 were definitely abnormal (H., D., McI., and F.). The test was repeated on these four patients two weeks after parturition. Bilirubin retention values obtained in this examination were 3.1, 2.6, 3.0 and 1.9 per cent. respectively. Pre-eclampsia therefore causes a delay in the return to normal bilirubin excretion rates in the puerperium. There is no reason to believe, however that such a return to normality is completely prevented by an attack of toxaemia during pregnancy. The time taken for normal rate of bilirubin excretion to be restored evidently

varies in different cases and appears, to some extent, to be related to the degree of hepatic insufficiency present during labour. This however need not be the only factor concerned. The case of O. is interesting on this point. On the third day of puerperium this patient showed 8 per cent. retention of bilirubin. On the following day she developed a mild pyrexia which continued for 8 days, and was associated with slight local uterine infection. Her bilirubin retention increased to 10.7 per cent. on the tenth day of puerperium.

2. ECLAMPSIA

Eighteen cases of eclampsia examined at the time of admission (without any consideration for the severity of the disease in individual cases) showed an average bilirubin retention of 18.32 per cent., S.D.4.08. In individual values at this stage were between 10.6 and 25.7. The average is 4.62 per cent. higher than that in severe pre-eclampsia, and this difference is statistically significant. Nine patients in this series had further convulsions after admission. These patients showed that with persistence of the convulsive state, bilirubin excretion rate markedly deteriorated. The average retention in these 9 cases was 31.98 per cent., S.D.7.98, with individual values ranging between 21.4 and 48.9. This increase above the value obtained at the time of admission shows statistical significance.

The/

The striking feature of the results of the bilirubin excretion test not only in normal pregnancy but also in toxaemias is the extreme variability of individual figures. Thus it becomes difficult to depend on the average values to any great extent. This can however, be obviated by following individual cases. It was possible for us to study 3 cases who were admitted in a state of pre-eclampsia and subsequently developed eclamptic convulsions. The results of these three cases are submitted in Table 78.

Table 78

No.	Bilirubin retention (per cent.)	
	Pre-eclampsia	Eclampsia
1. R.	19.3	25.2 (2)*
2. A.	17.3	20.1 (1)*
3. H.	15.9	26.6 (3)*

* These figures indicate the number of fits preceding the test.

In each of these 3 cases the onset of eclampsia seemed to affect adversely the bilirubin excretion capacity of the liver. There appears to be a tendency for this function to deteriorate when fits recur. Unless a series large enough is studied and followed up, it is difficult to say whether bilirubin retention increases directly with the number of fits. Taking the whole series of 18 cases of eclampsia we found that one patient with 10 fits had 44.1 per cent. retention of bilirubin, while another, who had 18 convulsions showed/

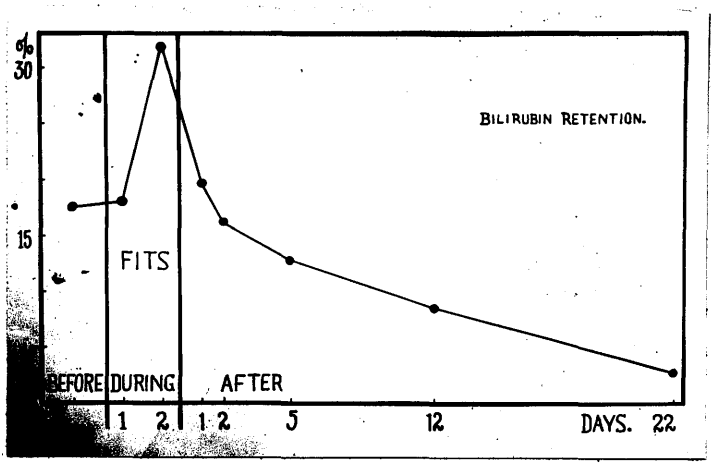

Fig. 49. Bilirubin retention in eclampsia, showing the change in the bilirubin excretory capacity of the liver in the pre-convulsive, convulsive and the convalescent stages.

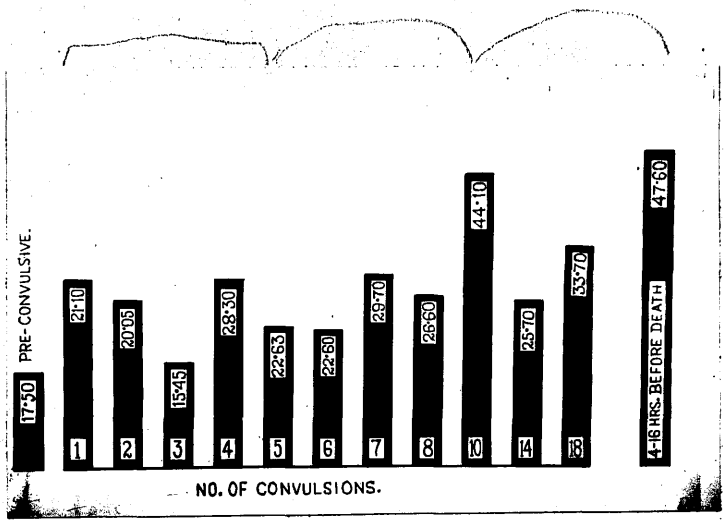

Fig. 50. Bilirubin retention in eclampsia in relation to the number of convulsions. The absence of correlation may be due to the small number of cases in each group. In the pre-terminal stage (3 cases) nearly half the total amount of bilirubin injected was retained in the circulation at the end of four hours.

showed only 33.7 per cent. retention. It must be admitted that the rate of bilirubin excretion in the pre-convulsive and early convulsive stages was not known and so the degree of deterioration in bilirubin excretion caused by convulsions could not be determined.

The problem was, however, investigated from another point of view. In 9 patients in this series the stage of convulsion, with or without an increase in coma, persisted for more than a day. These cases showed retention of bilirubin to an extent which was almost twice as much on the second day of the convulsive stage as on the first. The values obtained in the whole series, in the pre-convulsive, convulsive and convalescent stages are given in Table 79.

Table 79

Stage of the Disease	Bilirubin Retention per cent.	Range of Values	S.D.
Pre-convulsive(3 cases)	17.50	15.9-19.3	1.83
Convulsive			
Days			
1 (18 cases)	18.0	10.6-25.7	3.87
2 (9 cases)	31.98	21.4-48.9	7.98
Convalescence (18 cases)			
Days			
1	19.64	14.9-28.3	4.64
2	16.21	10.3-20.8	2.80
5	12.69	8.0-18.3	3.38
12	8.61	4.9-12.9	2.16
22	2.90	0-6.7	2.89

The slight difference seen in the above table between the pre-convulsive and early convulsive stage is to some extent/

extent misleading. However, the results shown in Table 78 clearly demonstrates that if all the patients in this series were seen in the pre-convulsive stage the difference would have been more marked and significant. The interference in the bilirubin excretion capacity of the liver caused by a prolonged persistence of the stage of convulsion and coma becomes clearly evident on comparing the values obtained on the first and second day of the eclamptic state. The difference is not only significant in the average, but is also manifested in the maximum and minimum values. As convalescence sets in, the improvement in bilirubin excretion becomes clearly noticeable. The decrease in percentage retention is significant, steady and progressive, affecting both ends of the range of values. Normal non-pregnant values were restored between the second and third week of convalescence. Some of the cases however reached the normal level during the second week. In only one patient in this series (R. Table 78) bilirubin excretion was deficient (6.7 per cent. retention) even on the twenty-second day of the puerperium. We had occasion to examine this patient 3 months after her pregnancy was over, when the bilirubin retention was 5.5 per cent. This may be interpreted as a slight permanent liver damage caused by eclampsia, but what appears more probable is that this value represents the basic state of her bilirubin capacity.

In order to avoid interference with the results caused by convulsions, 5 cases in this series were chosen who went into labour without further occurrence of fits. The results in these cases are shown in Table 30.

Table 30

No. *	Bilirubin Retention (per cent.)		
	Convulsive Stage	Labour (second stage)	Increase in Retention
1. Dm. (5)	19.9	40.4	20.5
2. Dv. (4)	28.8	47.3	18.5
3. R. (2)	25.2	56.4	31.2
4. Ds. (7)	29.1	50.1	21.0
5. McC. (4)	27.8	50.0	22.2
Average	26.16	48.84	22.68
S.D.	3.95	6.12	4.80

* Figures in parenthesis indicate the number of convulsions.

It will appear from the small series of cases presented above that labour in eclampsia also causes an increase in bilirubin retention. The average of the net increase in bilirubin retention in eclampsia is however, considerably more than that found in either pre-eclampsia or normal labour. Compared with the values found in these latter conditions the increase in retention in eclampsia statistically significant. Of special interest in the present analysis is one case (R.) who was followed from the pre-eclamptic state/

state (Table 78). The bilirubin retention showed an increase with the onset of convulsions (30.6 per cent. of the initial level). As she went into labour further increase in retention occurred, which amounted to 123.7 per cent. of that in the convulsive stage. This patient, however had the maximum bilirubin retention during labour. The number of convulsions preceding labour apparently does not bear any direct relationship to the amount of retention which can be expected during labour. Thus R., who had the maximum increase (31.2 per cent.) in retention had only 2 fits, while Dv. had 4 fits and yet her bilirubin retention increased by only 18.5 per cent. during labour. The degree of deterioration in the bilirubin excretion capacity of the liver caused by labour per se, in an eclamptic subject can be best studied by comparing the increase in retention during labour with the value obtained before its commencement. In the present series this amounted to 86.9 per cent. of the pre-parturition level. This indicates a greater interference with the excretion of bilirubin during labour in eclampsia than in pre-eclampsia. The findings suggest that labour commencing soon after the convulsive stage of eclampsia deprives the liver markedly of its reserve functional capacity.

3. ACCIDENTAL HAEMORRHAGE

Five cases of accidental haemorrhage were studied with regard to the results of the bilirubin excretion test. The data/

data are presented in Table 81.

Table 81

No.	Bilirubin Retention		
	Before Haemorrhage	After Haemorrhage	Presence of Shock
1. P.	-	23.4	±
2. B.	-	25.1	0
3. McI.	-	41.5	+
4. O'R.	21.4	31.2	±
5. M.	-	54.6	++
	Average	36.16	
	S.D.	14.0	

This small series of cases show that bilirubin retention is considerably increased in accidental haemorrhage, being actually higher than that in severe eclampsia, when the convulsive stage has persisted for more than a day. The initial level of bilirubin excretion was not known except in one instance (O'R.), who was admitted in the pre-eclamptic state and developed accidental haemorrhage during her stay in the hospital. In this case, the onset of uterine haemorrhage has associated with a further increase in retention by 9.8 per cent., or 45.7 per cent. of the initial value. The effect of accidental haemorrhage on bilirubin retention appears to be more marked than the onset of eclamptic convulsions, which in the series of cases presented above shows an increase of bilirubin retention to only 36.9 per/

per cent. of the value obtained pre-convulsive stage.

The lowest bilirubin retention in this series was in a patient (B.) who did not develop any clinical evidence of shock. On the other hand the patient (M.) where shock was most marked the degree of bilirubin retention was highest. The three other cases in this series seem to occupy intermediate positions depending upon the degree of shock present at the time when the test was performed.

4. NEPHRITIS AND PREGNANCY

Five cases of nephritis complicating pregnancy were examined with regard to their bilirubin excretion capacity. Cases in the last trimester of gestation only were chosen for this study in order to obtain results comparable to those of pre-eclampsia. The values are presented in Table 82.

Table 82

No.	Blood Pressure	Parity	Alb. (Esbach)	Bilirubin Retention (per cent.)	Urea Clearance (per cent.)
1. C.	160/94	2	9	6.4	60
2. M.	145/85	1	3	1.0	54.5
3. K.	175/100	3	8	4.3	46.2
4. W.	138/85	2	4	7.0	50.5
5. McQ.	160/100	4	2	8.3	52.3
			Average	5.5	
			S.D.	2.88	

It will appear from the above figures that in none of the 5 cases the degree of retention of bilirubin exceeded

the/

the proposed maximum, and in only one, it exceeded the proposed average. The general average of this series, 5.5 per cent., compares well the state of bilirubin excretion in normal pregnancy. Neither the level of the blood pressure nor the degree of renal damage, as revealed by albuminuria and urea clearance, seemed to bear any relationship to the rate of clearance of bilirubin.

5. ESSENTIAL HYPERTENSION AND PREGNANCY

Ten cases were studied in this series. As in the previous group, cases were selected only during the last trimester of gestation so that the findings could be compared. The results are submitted in Table 83.

Table 83

No.	Blood Pressure	Alb.	Parity	Bilirubin Retention (%)
1. S.	200/130	3	1	7.2
2. P.	180/120	2	2	4.5
3. B.	210/135	6	2	14.6
4. McD.	195/120	1	1	4.0
5. McK.	190/115	±	1	6.9
6. K.	135/110	-	1	2.0
7. H.	190/120	-	2	4.1
8. Pr.	200/120	1.5	1	5.3
9. J.	200/110	1	1	7.0
10. C.	188/115	4	3	6.4
			Average	6.25
			S.D.	2.88

All cases in the present series excepting 2 (S. and B.) show that rate of bilirubin excretion in pregnancy complicated with essential hypertension is not in any way different from that in uncomplicated gestation. The slight increase in retention seen in S. is not significant, and although it exceeds slightly the proposed average it is well below the proposed maximum for normal pregnancy. The other case (B.), who showed a 14.6 per cent. retention of bilirubin is interesting. Six days after the test was performed she complained of severe epigastric pain, vomited several times and developed a concealed accidental haemorrhage. It is possible that the abnormal retention seen in this case indicated the existance of a state of hepatic dysfunction brought about by organic vascular changes and spasm, a manifestation of which in the form of retroplacental haemorrhage was evident later on in the course of the disease. However, the average bilirubin retention for the whole series compares favourably with that in pre-eclampsia and is below the average proposed for normal pregnancy.

COMMENTS

Pre-eclampsia and eclampsia develop as complications of pregnancy. If the results of the bilirubin excretion test are to be of any value as a diagnostic or prognostic aid in pregnancy, they need to be compared with values which are usually found in pregnancy and not with those obtained in non-pregnant conditions. The reasons for suggesting 7

per/

per cent. as the average and 11 per cent. as the maximum standard of bilirubin retention in the last trimester of gestation have been already discussed. All subsequent discussions, which will follow will be based on these new proposed standards for pregnancy.

In the series of 100 cases of pre-eclampsia 37 per cent. showed normal excretion of bilirubin. However, when pre-eclampsia was severe 94 per cent. of cases showed abnormal retention. It is interesting to note that neither nephritis complicating pregnancy nor essential hypertension, per se, showed any appreciable degree of abnormal bilirubin retention. Although it may be premature to suggest, it appears that in bilirubin retention one may have a diagnostic aid which to help isolating the cases of true pre-eclampsia from a mixed group of toxaemias. Analysis of the data given by Sullivan, Tew and Watson (9, 1934) also offers the same conclusion. These authors divided their cases in to two groups "nephritic" and "hepatic". The term hepatic toxaemia of pregnancy is no longer in use and has rightly been given up in view of the recent knowledge of the subject of pregnancy toxaemias. But if the argument over nomenclature is set aside, the cases presented by these authors clearly indicate that nephritis complicating pregnancy does not interfere with bilirubin excretion. The cases studied by us amply confirm this observation.

Abnormal bilirubin retention in severe true pregnancy toxaemia/

toxaemia has been reported also by other investigators. Gantarow, Stuckart and Gartman (3) observed 30 per cent. retention of bilirubin in 2 out of 4 cases of "moderate" toxaemia and more than 10 per cent. retention in 3 out of 20 cases of mild pre-eclampsia. Lyon (10, 1933) also found delayed bilirubin excretion in a small group of cases. It is interesting to observe that this author also suggested that bilirubin excretion test may be of aid in differentiating true pre-eclampsia from nephritis occurring in pregnancy. In a mixed group of cases he found that the average bilirubin retention in toxaemia was 11.8 per cent., which, it may be noted, is higher than the maximum for normal pregnancy proposed by us. Out of 14 cases of pre-eclampsia of varying severity, reported by Sullivan et al (9, 1934) 7, or 50 per cent. showed more than 11 per cent. retention of bilirubin. The average value in their cases of pre-eclampsia was 14 per cent. which is very similar to that observed by us in severe pre-eclampsia. It will thus appear that abnormal bilirubin retention has been a fairly constant finding in the cases of pre-eclampsia so far reported in the literature. This obviously indicates that a degree of hepatic dysfunction constantly accompanies pregnancy toxaemias. It is further corroborated by our follow up study which clearly indicates that as the toxaemia improves, bilirubin excretion also shows improvement, and conversely, when the clinical condition deteriorates the amount of retained bilirubin/

bilirubin increases. This suggestion of hepatic insufficiency in toxaemias of pregnancy is not necessarily contrary to the observations made by Cruickshank et al (4), Cross (5) and other investigators who failed to detect an increased serum bilirubin and icteric index in pre-eclampsia. Bilirubin excretion is a saturation or over-loading test. It indicates the amount of functional reserve capacity of the liver, so far as the excretion of this pigment is concerned. A decline in the functional reserve does not indicate a complete functional failure. It is only natural that, in absence of obstruction in the biliary passage, abnormal increase in the serum bilirubin can occur only when the functional reserve has been completely exhausted or very nearly so. Hellmuth is stated to have noted (11) that in eclampsia the mortality was higher where serum bilirubin level was abnormally increased. This would be an expected event in view of the part played by the liver in bilirubin excretion. The advantage of bilirubin excretion test in toxaemias of pregnancy over estimation of icteric index or serum bilirubin level lies in the fact that the test indicates depletion of the reserve capacity of the liver and indicates insufficiency long before clinically recognisable hepatic damage and consequent increase in the serum bilirubin occurs.

In the present state of our knowledge it is difficult to judge how far one is justified in assuming the presence of a general hepatic dysfunction in toxaemias of pregnancy

on/

on the basis of the results of bilirubin excretion test alone. In a recent comparative experimental study Bodansky and Jaffe (12, 1934) came to the conclusion that increase of plasma phosphatase and serum bilirubin represent different functions of the liver. Soffer (6) however observes that a positive bilirubin excretion test indicates hepatic inefficiency as much as when all the tests are positive. Our observations on plasma phosphatase in toxaemias of pregnancy (Chapter 4) offers sufficient proof to assume the existence of a state of hepatic dysfunction in pregnancy toxaemias, and bilirubin excretion test, in this respect, appears to be as efficient as the estimation of plasma alkaline phosphatase.

The onset of eclampsia and persistence of the convulsive stage in our series showed even a greater increase in bilirubin retention than that in pre-eclampsia. The existence of a state of hepatic dysfunction in eclampsia and pregnancy toxaemias has been suggested by Hofbauer (13,1933), Botella-Llusia (14, 1936), Herold (15, 1939), Rowe, McManus and Plummer (16, 1936) and several other observers. Our results of the bilirubin excretion test confirms the hypothesis. This is however not an unexpected phenomenon in view of the vascular spasm and increased intra-abdominal venous pressure which accompany eclamptic convulsions. The morphological changes which can be induced in the liver cells by increasing the intra-abdominal pressure have been demonstrated/

demonstrated by Theobald (17, 1932) in experimental animals. It is interesting however that in spite of high abnormal values of bilirubin retention clinical jaundice is not a frequent complication of eclampsia. The explanation for this obviously lies in the fact that the liver is an organ endowed with considerable reserve functional capacity, and in absence of biliary obstruction, jaundice can only develop when this reserve capacity is completely exhausted.

The augmented retention of bilirubin during labour in an eclamptic subject is not of the same nature as that seen in normal labour or even in pre-eclampsia. The reasons for such an assumption have already been discussed. Labour in eclampsia appears to impose a strain upon the liver which is of a considerably greater magnitude than that seen in pre-eclampsia. This, we believe, has an important clinical significance in obstetric management of an eclamptic patient. If labour has not already started during the course of the disease, and induction is under contemplation it may be wise to defer this operation until the results of hepatic function tests show signs of improvement. This may be of help in lessening the present rate of mortality from eclampsia.

The increase of bilirubin retention in accidental haemorrhage is as striking as that in eclampsia. The mere onset of haemorrhage unaccompanied with shock does not affect the hepatic functions so adversely. In spite of the

smallness of the series presented in this paper the role of shock associated with accidental haemorrhage appears to be of remarkable importance. There is considerable evidence to believe that a state of vascular spasm exists in toxaemias of pregnancy. Haemorrhage also induces vascular spasm as a compensatory mechanism. It is probable that the state of exaggerated vascular spasm, coupled with the fall of blood pressure and the loss of oxygen carrying elements of the blood, devitalises the liver cells, and curtails their reserve capacity to such an extent as to interfere considerably with their metabolic functions. Experimental work of Engel, Harrison and Long (18, 1944) prove that irreversible functional changes occur in the liver cells if anoxaemia is allowed to persist for any length of time. The viviperfusion studies made by Frank, and co-workers (19, 1946) also provides ample evidence for the above hypothesis.

It is clear however that inspite of an evident hepatic dysfunction (as revealed by the bilirubin excretion test) which develops in the course of pregnancy toxaemias the process is neither irreversible nor leaves behind a legacy or tendency to permanent hepatic damage. The results obtained in eclampsia where cases were followed up for three weeks amply prove this assumption. The results obtained of pre-eclampsia on the third day of puerperium in our series however were not so conclusive. This is obviously due to the fact that all cases were not followed until basic values were/

were returned. But the four cases where this was done two weeks post-partum, the results are sufficiently confirmatory. As may be expected the return to normal values of bilirubin retention is sooner in pre-eclampsia than in eclampsia. This restoration of the normal functions of the liver after the disappearance of the exciting factor is not surprising when the enormous potentialities for regeneration present in the liver cells is taken into account.

CONCLUSIONS

The results of bilirubin excretion test point out the presence of a hepatic dysfunction in toxaemia of pregnancy. Nephritis and uncomplicated essential hypertension in pregnancy do not give rise to abnormal bilirubin retention. Both pre-eclampsia and eclampsia on the other hand cause delayed excretion of bilirubin. It has been suggested that this may prove to be a useful diagnostic aid. Accidental haemorrhage has been found to give a response similar to that seen in other toxaemias of pregnancy. The presence of shock however should be taken into account in evaluating the results in this condition. It has been observed that the disturbance of the functional activity of the liver as measured by the bilirubin excretion test in toxaemias of pregnancy is a reversible process.

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CHAPTER 4

PLASMA ALKALINE PHOSPHATASE IN PREGNANCY

Since the first discovery of alkaline phosphatase by Robison (1, 1923) the role of this enzyme in the metabolism of bone has been studied by numerous workers. In pregnancy, the primary ossification centres of the foetal bones commence to develop as early as the eighth week, but it is during the latter part of gestation that foetal bone formation becomes a rapid and active process. The investigations of Givens and Macy (2, 1933), Mitchel (cited by Eden and Holland, 3, 1948) and other observers point out the existence of a great foetal demand for minerals, especially calcium and phosphorus, during the last trimester of gestation. It is only natural to assume that active foetal bone formation should be associated with an increased demand for the enzyme essential for this process. Indeed, this is amply confirmed by the work of Meranze et al (4, 1937), Bodansky (5, 1939), Young, King, Wood and Wootton (6, 1946) and Hoch and Marrack (7, 1948). All these investigators observed a high level of maternal plasma phosphatase during the last three months of gestation.

The significance of the plasma alkaline phosphatase level as a measure of hepatic efficiency has also received considerable attention in recent years. Increase in the concentration of this constituent of the plasma has been observed in non-haemolytic and obstructive jaundice by Roberts (8, 8a, 1930, 1933); Bodansky and Jaffe (9, 1933); Rothman,

Meranze/

Meranze and Meranze (10, 1936) and other investigators on the subject. Similar increase is stated (4) to have been noted in malignant involvement of the liver also. Freeman, Chen and Ivy (11, 1938) remarked that plasma phosphatase was increased in all forms of liver injury and its estimation was a more sensitive indicator of liver damage than a rise in serum bilirubin.

Several investigators including Hofbauer (12, 1933); Rowe et al (13, 1936); Herold (14, 1939); Barkeley and co-workers (15, 1924) and Dieckmann (16, 1947) believe that a state of hepatic dysfunction probably exists in toxaemias of pregnancy. Other observers (de Wisselow and Wyatt, 17, 1924);(Cruickshank, et al, 18, 1927) have not been able to convince themselves of this. It was therefore considered that a study of the plasma alkaline phosphatase may be a useful investigation in this condition.

It has been pointed out in the previous section that normal pregnancy in associated with an increase of the level of the plasma alkaline phosphatase. In order to evaluate the results obtained in toxaemias of pregnancy the normal value during gestation must be known. The difficulty in depending on the figures reported so far in the literature lies in the fact that not only the standard of unit of phosphatase used for estimation varies considerably with different authors but also where the same standard has been employed the results do not wholly agree (Young et al, 6, 1946),/

1946), (Hoch and Marrack 7, 1943).

Ninety-three cases of normal pregnancy were therefore studied for determining the normal standard. Seventy-eight among them, were unselected cases from the antenatal clinic at varying periods of gestation. The remaining 15 cases were selected from early months of pregnancy and were followed to term, examination being undertaken once every month. These last 15 cases were also studied at different stages of labour and in puerperium.

The group of toxaemias consisted of 146 cases. This was composed of 100 cases of pre-eclampsia, 18 cases of eclampsia, 10 cases of accidental haemorrhage, 10 of essential hypertension and 8 of nephritis in association with pregnancy.

In order to keep our results in conformity with these reported from the British Isles by Young et al (6, 1946) and Hoch and Marrack (7, 1943) the method employed was that of King and Armstrong (19, 1934) as modified by King, Haslewood, Delory and Beall (20, 1942). Disodium phenyl phosphate was used as the substrate and the liberated phenol was estimated by colorimetry. The unit of phosphatase being considered as the amount of enzyme necessary to liberate 1 mg. of phenol from the substrate.

RESULTS

1. NORMAL PREGNANCY

First Series

Of the 78 cases of normal pregnancy 39 belonged to the last/

last trimester of gestation. The earliest pregnancy in our series was one of 9 weeks. The frequency distribution in different lunar months of pregnancy is given in Table 84.

Table 84

Phosphatase units/ 100 ml.	Duration of Pregnancy - Lunar months							
	3	4	5	6	7	8	9	10
5.1-6	2	2	-	-	-	-	-	-
6.1-7	4	3	2	1	-	-	-	-
7.1-8	2	3	5	4	5	-	-	-
8.1-9	-	-	-	2	3	-	-	-
9.1-10	-	-	-	-	-	3	-	-
10.1-11	-	-	-	-	-	6	1	-
11.1-12	-	-	-	-	-	2	6	1
12.1-13	-	-	-	-	-	1	3	3
13.1-14	-	-	-	-	-	-	2	5
14.1-15	-	-	-	-	-	-	-	6
No. of cases	8	8	8	7	8	12	12	15
Av. Phosphatase content of plasma.	6.50	6.63	7.40	7.30	7.90	10.70	12.10 12.24	13.65
S.D.	0.71	0.72	0.64	0.66	0.55	0.94	0.94 1.53	1.00

The figures indicate that up to the end of the second trimester of gestation the alkaline phosphatase level of the plasma remains within the normal limits. Statistical analysis however shows a significant but slight rise in the value as gestation/

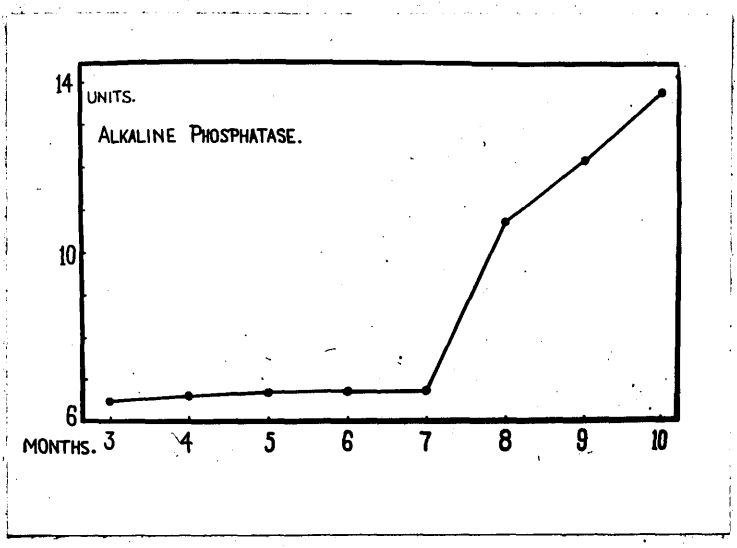


Fig. 51. Plasma alkaline phosphatase cocentration in normal pregnancy showing its increase during the last trimester.

gestation proceeds. The range of normal values is however exceeded in the eighth month of pregnancy and during the following two months the plasma phosphatase rises appreciably to what may ordinarily be regarded as an abnormal level. This change is statistically significant. The average alkaline phosphatase content of the plasma in our series was 12.24; S.D.1.53 during the last 3 months of pregnancy, and 13.65; S.D.1.00 at term.

Second Series

The second series consists of 15 cases of normal pregnancy who were followed through the period of gestation commencing at the time of their first antenatal visit. The test was performed every 4 weeks. The results in these cases are submitted in Table 35.

In general the results obtained agree closely with those of the previous series. The increase of alkaline phosphatase of the plasma during the last 3 months of pregnancy thus appears to be a consistent finding. If the non-pregnant standard of 10 units (King, 19a, 1947) is accepted as the limit, then it appears that normal values were obtained in only 6 out of 45 tests; an incidence of 86.7 per cent. abnormality. All these normal values were found before the 32nd week of gestation. The change which takes place subsequently is sudden.

If both the first and the second series of cases are jointly considered the average alkaline phosphatase content

Table 35

	LUNAR MONTHS OF GESTATION Phosphatase: Units per 100 ml. plasma.							
	3	4	5	6	7	8	9	10
1	6.1	6.1	6.8	7.0	7.0	10.3	11.6	13.3
2	-	5.9	6.4	7.2	8.8	11.0	13.3	15.1
3	4.3	4.6	5.6	6.0	6.5	9.3	10.9	12.7
4	-	3.1	3.6	3.9	9.7	10.0	12.0	13.0
5	5.8	7.0	7.3	8.6	9.3	10.3	10.9	13.6
6	7.2	8.1	8.6	9.5	10.0	11.1	12.7	14.6
7	6.6	6.4	7.4	8.5	8.9	11.0	12.0	13.5
8	6.3	6.9	7.3	8.0	8.5	10.5	11.5	13.1
9	6.3	5.7	5.8	7.8	8.4	9.5	11.8	13.3
10	6.4	6.0	6.3	6.3	6.5	9.4	10.8	12.6
11	-	5.3	5.4	5.5	6.5	10.0	11.2	12.7
12	7.0	6.0	5.5	7.0	7.6	10.3	11.2	13.0
13	-	6.0	6.3	6.0	8.2	10.2	11.4	13.4
14	6.7	7.0	7.5	7.6	9.0	11.0	12.3	13.7
15	7.0	7.8	7.1	7.7	9.0	10.0	12.6	13.4
Aver.	5.8	6.5	7.2	7.5	8.2	10.3	11.8	13.5
S.D.	1.05	0.95	1.08	1.20	1.15	0.57	0.85	0.72
P.E.	0.70	0.63	0.72	0.80	0.77	0.38	0.57	0.43

of the plasma during the last 3 months of gestation obtained from 84 tests done on 54 cases is found to be 12.05 units per 100 ml. of plasma; S.D.1.37. In our subsequent discussion of alkaline phosphatase in toxaemias of pregnancy we shall regard this as the normal standard for comparison.

ALKALINE PHOSPHATASE DURING LABOUR

Cases belonging to the second series were studied also during the first and second stages of labour. Samples of blood were obtained when the first stage was well established and the second stage advanced. In 4 cases, labour was prolonged for more than 43 hours, and a third sample of blood was obtained after the first stage had lasted for nearly 40 hours. The results obtained are detailed in Table 86. For the sake of comparison values obtained at term are also included in this table.

The interesting feature which is shown by all the cases in this series is the appreciable increase of the phosphatase content of the plasma during the second stage of labour. Not only the average but also the individual figures indicate that the phosphatase level hardly alters during the initial stages of labour. When however labour is prolonged it shows an increase during the late first stage. Compared with the values obtained at term, or early first stage, this increase is statistically significant. The significance of prolonged labour is further shown on careful analysis of the values obtained in the second stage. The average phosphatase level of the whole series in the second stage was 18.2 units per cent.; S.D.2.53. When labour was of normal duration this was 17.05 units per cent.; S.D.1.06. It will be evident that this level was exceeded as early as the late first stage in prolonged labour. With labour advanced into the second stage/ the/

the cases of prolonged labour showed a further increase of the alkaline phosphatase to 21.4 units per cent.; S.D. 0.71.

Table 36

No.	Alkaline Phosphatase: Units per 100 ml. plasma.				
	At Term	First Stage	Late First Stage	Second Stage	Puerperium
1	13.8	14.1	-	16.3	9.2
2	15.1	15.0	-	19.0	11.4
3	12.7	12.5	-	15.1	8.6
4*	13.0	13.5	16.3	20.6	12.0
5	13.6	13.5	-	16.5	10.3
6	14.6	14.9	-	16.9	9.5
7	13.5	14.2	-	17.0	9.0
8	13.1	13.0	-	16.3	11.6
9	13.8	13.8	-	17.8	10.4
10*	12.6	13.3	17.0	21.2	15.3
11*	12.7	13.0	13.6	21.9	13.9
12	13.0	13.6	-	17.0	10.0
13*	13.4	13.0	13.0	22.0	16.4
14	13.7	14.1	-	18.2	12.7
15	13.4	13.9	-	17.0	10.3
Aver.	13.5	13.7	17.5	18.2	11.4
S.D.	0.72	0.74	1.11	2.53	2.45

* Prolonged labour: more than 48 hours.

This is statistically significant when the late first stage value/

value of the corresponding cases and that of the second stage of normal labour are considered. Compared with the basic values of alkaline phosphatase at term, second stage caused an increase in 26.3 per cent. in normal labour and 58.5 per cent. in prolonged labour.

ALKALINE PHOSPHATASE IN PUERPERIUM (Table 36)

In the 15 cases studied in this series the plasma phosphatase level on the fourth day of puerperium was average 11.4 units per cent., S.D.2.45; minimum 8.6, and maximum 16.4 units. Much of variability of the values is due to the comparatively high results obtained in cases of prolonged labour. If these cases are excluded from the series the average alkaline phosphatase level in immediate puerperium after normal labour appears to be 10.3 units per 100 ml.; S.D.1.30. The phosphatase content of the plasma in puerperium is thus less than that at term and this difference is significant. However, in none of the cases early pregnancy level was reached.

In the 4 cases of prolonged labour the alkaline phosphatase level of the plasma was 14.5 units per 100 ml. average; S.D.2.34, which is not only higher than the accepted maximum normal limit but also higher than values obtained at term. It is of interest to observe that while in normal labour/the decline in the level of the alkaline phosphatase in the early puerperium amounted to 39.4 per cent. of the highest level attained during labour, the corresponding fall in/

in cases of prolonged labour was 32.2 per cent. On analysis this difference appears to be statistically significant.

2. PRE-ECLAMPSIA

The average alkaline phosphatase content of the plasma in the whole series of pre-eclampsia was 16.6 units per 100 ml., S.D.3.44. The co-efficient of variation, 21.5 is high and is due to a wide scatter of the individual values.

The average for mild pre-eclampsia was 14.20 units per cent.; S.D.1.01, and that for severe pre-eclampsia, 18.98 units per cent.; S.D.3.96. The range of values in the mild cases extended between 12.5 and 16.5 units per 100 ml. of plasma. The corresponding dispersion in severe cases was from 13.4 to 29.5 units per 100 ml. Compared with the standard obtained in our normal cases both mild and severe pre-eclamptics have an increased phosphatase content of the plasma. The differences between the values obtained in normal pregnancy and those in both mild and severe pre-eclampsia are statistically significant. Similar significance is also present between the two groups of pre-eclamptics. The extent of the increase is phosphatase in mild pre-eclampsia amounts to 17.9 per cent. of the normal pregnancy value, while in severe pre-eclampsia the corresponding increase is 57.5 per cent. The frequency distribution of the values of alkaline phosphatase in toxaemias are given in Table 87.

Comparison of the frequency distribution of the normal and toxaemic cases reveals that 28.6 per cent. of the values

in/

in normal pregnancy, 56.0 per cent. of those in mild pre-eclampsia, 94.0 per cent. in severe pre-eclampsia were above 14 units per 100 ml. The maximum frequency in normal cases was between 10 to 12 units, in mild pre-eclamptics 14 to 16 units and in severe pre-eclamptics 18 to 20 units. This shift to the right of values, with the onset of toxaemia and increase in severity of the conditions, is significant.

Table 37

Units per 100 ml. Plasma	Mild Pre-eclampsia	Severe pre-eclampsia	Total
12.1-14	22	3	25
14.1-16	25	10	35
16.1-18	3	9	12
18.1-20	-	12	12
20.1-22	-	7	7
22.1-24	-	5	5
24.1-26	-	1	1
26.1-28	-	1	1
28.1-30	-	2	2
Total	50	50	100
Maximum	16.5	29.5	29.5
Minimum	12.5	13.4	12.5
Average	14.26	18.98	16.62
S.D.	1.13	3.59	3.44
P.E.	0.75	2.40	2.30

As has been pointed out in the previous section, the increase/

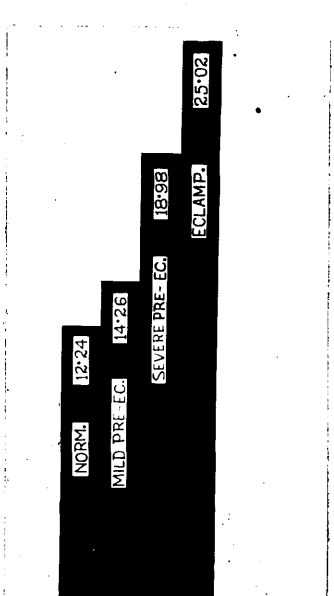


Fig. 52. The average plasma alkaline phosphatase in normal pregnancy, pre-eclampsia and eclampsia.

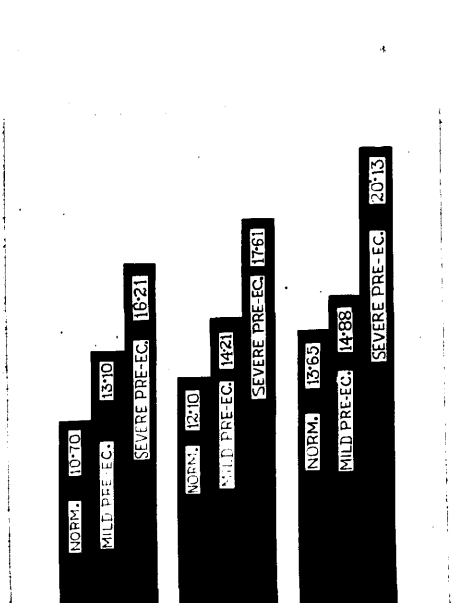


Fig. 53. Plasma alkaline phosphatase in normal and toxaemic pregnancies at different periods of gestation.

increase in the plasma alkaline phosphatase level is progressive in normal pregnancy during the last three months of gestation. In order to determine if the duration of pregnancy in toxaemia affected the values, all results were co-related to the duration of gestation. These are presented in Table 33.

Table 33

Duration of Gestation Weeks	Alkaline Phosphatase: Units per 100 ml.					
	Mild Toxaemia		Severe Toxaemia		Normal *	
	Average	S.D.	Average	S.D.	Average	S.D.
28-32 Mild - 9 Severe-12	13.1 (12.5-14.4)	0.91	16.2 (13.0-14.4)	1.01	10.7 (9.6-12.6)	0.94
32-36 Mild -15 Severe-8	14.21 (13.6-15.7)	1.2	17.61 (14.0-20.8)	1.30	12.1 (10.8-13.4)	0.94
36-40 Mild -26 Severe-30	14.88 (12.9-16.5)	1.31	20.13 (18.0-29.5)	3.22	13.65 (11.8-14.8)	1.00

* First series.

It will appear that the difference which exists between normal, mild and severe toxaemias is significant even when the duration of pregnancy is taken into account.

ALKALINE PHOSPHATASE AND DIET IN TOXAEMIAS OF PREGNANCY

From an experimental study Bodansky and Jaffe (18, 1931) suggested that the physical and chemical processes associated with the state of nutrition are closely linked with the level of the alkaline phosphatase of the plasma. Hough and Freeman (21, 1942) demonstrated in dogs that removal of protein from the diet causes an increase in the content of the/

this group. In mild pre-eclampsia the values were between 12.9 and 15.7 units per cent., with an average of 14.27; S.D. 0.645. In severe pre-eclampsia this was 19.79 units per cent.; S.D. 3.35, with a scatter between 14.0 and 23.0 units per 100 ml. plasma.

Unit C. - Twenty-five cases were studied from this unit of which 11 had mild and 14 severe pre-eclampsia. Each patient in this series received 75 gms. of protein daily, the amount of first class protein in the diet being 43 gms. The overall average in this series was 17.03 units of phosphatase per 100 ml. of plasma, S.D. 3.91. In mild cases where the values extended between 13.6 and 16.2, the average being 14.62 units per cent.; S.D. 0.90. The average for severe cases in this group was 18.92; S.D. 4.85, minimum 13.8 and maximum 29.5 units per 100 ml. plasma.

It is evident that increasing the protein content of the dietary, even that of essential protein has no apparent effect on the alkaline phosphatase content of the plasma in toxaemias of pregnancy. The difference in the values which exists in these three groups of cases does not satisfy statistical scrutiny.

STATE OF TOXAEMIA AND ALKALINE PHOSPHATASE

In order to ascertain whether the increase of plasma phosphatase is directly related to the toxaemic process in pre-eclampsia, phosphatase determination was carried out at weekly intervals in all cases of toxaemia, and an attempt

made/

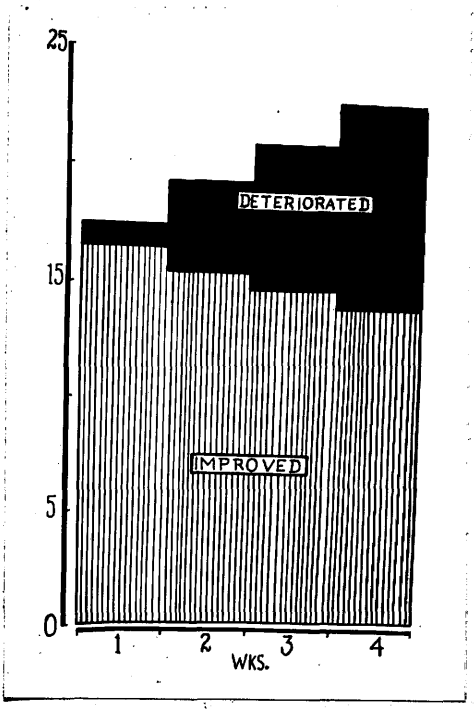
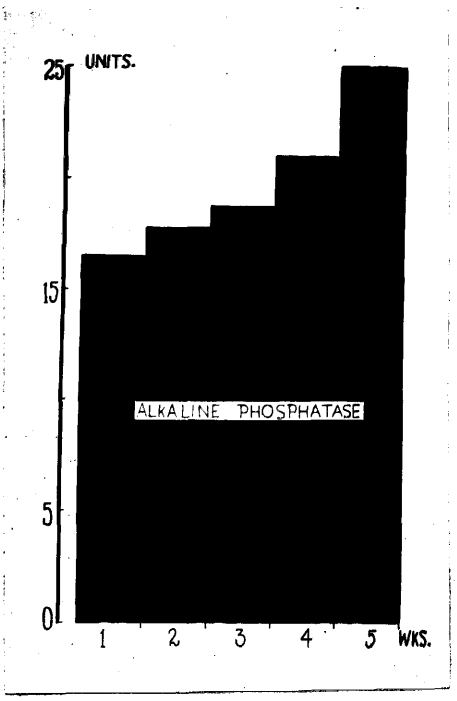


Fig. 54. Plasma alkaline phosphatase in pre-eclampsia in relation to the clinical course of the toxaemia.

Fig. 55. Plasma alkaline phosphatase in pre-eclampsia in relation to the duration of the toxaemia.



made to correlate the level of the plasma alkaline phosphatase with the clinical state of the patient. The results are shown in Table 89.

Table 89

	Improved			Deteriorated ⊖		
Weeks *	Aver.	S.D.	Min.-Max.	Aver.	S.D.	Min.-Max.
1	16.43	4.64	13.1-23.7	17.57	4.84	12.9-28.3
2	15.43	4.93	13.0-26.5	19.35	5.40	13.5-28.8
3	14.74	1.04	13.0-16.6	21.04	5.28	14.3-30.4
4	14.23	1.09	12.5-15.8	22.73	4.40	16.8-32.5

⊖ Includes also cases where toxaemia was stationary.
* Refer to the period after admission into hospital.

The level of the alkaline phosphatase in the plasma is related to the manner of progress of the disease. With improvement in the clinical condition the level drops and nearly approaches the normal value at term. This drop is however slow and is not statistically significant. The minimum values obtained at each stage change to a small extent, but the maximum values decline considerably. As a result of this the co-efficient of variation of the values becomes less at each successive stage. This indicates a significant shift of the values towards normality as the condition improves.

The "deteriorated" cases on the other hand show a progressive increase of the phosphatase level of the plasma as the toxaemia becomes worse. This is seen not only in the average values but also among the minimum and maximum. The change/

change in the average value as toxaemia progresses is statistically significant.

In a further study of the relation between the alkaline phosphatase level and the clinical manifestations of toxaemia it was observed that neither albuminuria nor oedema showed any significant relationship with the level of the plasma phosphatase. With increasing levels of blood pressure in these cases, on the other hand the alkaline phosphatase content of the plasma appeared to increase. This was observed with both systolic and diastolic blood pressure, though the tendency was more marked and significant in relation to the latter, especially at higher levels of diastolic pressure. The results are summarised in Table 90.

ALKALINE PHOSPHATASE AND LABOUR IN PRE-ECLAMPSIA

Toxaemia of pregnancy is known to increase the susceptibility to obstetric shock. The present study was undertaken to find out if labour causes more metabolic upset and derangement of hepatic function in toxaemia than in normal cases. Fifty one cases of pre-eclampsia where the toxaemia persisted or deteriorated were studied for this purpose. These cases are divided into two groups. The first group consists of 39 cases where labour followed a normal course. Phosphatase was estimated in early first stage and when second stage was well advanced. In the second group of cases numbering 12 labour was prolonged for more than 48 hours and three estimations were done on each patient: in the early first/

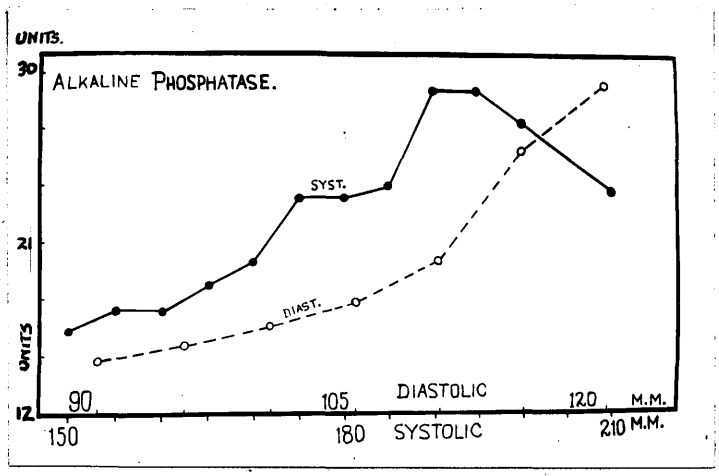


Fig. 56. Plasma alkaline phosphatase in pre-eclampsia in relation to the levels of systolic and diastolic blood pressure.

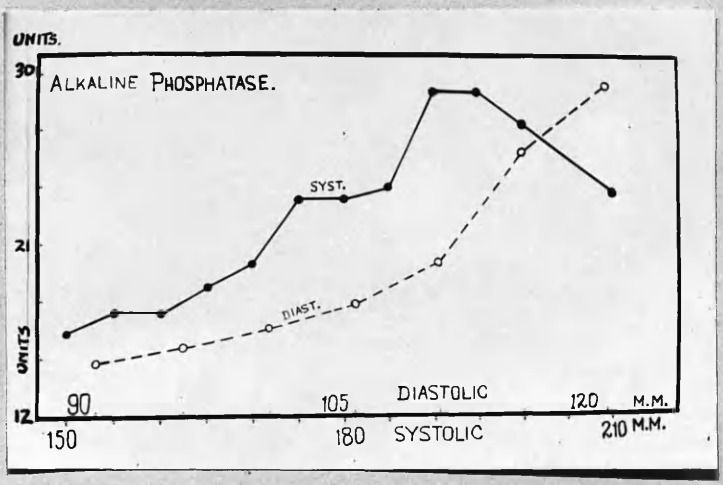


Fig. 56. Plasma alkaline phosphatase in pre-eclampsia in relation to the levels of systolic and diastolic blood pressure.

first stage, late first stage after labour had lasted for over 40 hours, and in the second stage. The results in these two groups of cases are show in Tables 90 and 92 respectively.

Table 90

Systolic Blood Pressure

mm.Hg.	150	155	160	165	170	175	180
Average	16.53	17.68	17.62	18.82	20.22	23.71	23.81
S.D.	2.32	3.16	2.84	2.42	2.32	4.36	6.90
Minimum	13.2	13.7	13.8	14.5	16.5	16.7	13.5
Maximum	21.5	22.8	29.8	20.8	27.8	29.8	32.5

Mm.Hg.	185	190	195	200	205	210	
Average	24.0	29.06	29.0	27.32	-	23.73	
S.D.	4.3	2.9	-	2.25	-	7.23	
Minimum	19.7	23.7	-	23.2	-	13.4	
Maximum	28.3	32.5	-	29.5	-	29.8	

Diastolic Blood Pressure

mm.Hg.	90	95	100	105	110	115	120
Average	14.93	15.70	16.41	17.73	20.03	25.96	28.96
S.D.	1.23	1.06	1.45	1.41	1.84	2.51	1.34
Minimum	12.8	14.4	13.4	16.7	18.6	21.2	25.6
Maximum	17.6	17.5	19.0	20.0	28.7	29.8	32.5

Table 91

	Before Labour	First Stage	Second Stage	Puerperium
Average	20.71	21.03	26.29	16.74
S.D.	5.05	4.63	4.33	3.00
P.E.	3.38	3.10	2.90	2.01
Maximum	32.5	32.0	37.1	12.5
Minimum	15.5	15.3	21.4	20.6

The/

The 39 cases of severe toxaemia who went into normal labour (Table 91) had initially a higher alkaline phosphatase content of the plasma than that in normal pregnancy. This was, of course, caused by the toxaemia. The onset of first stage of labour gave rise to only a slight change in the phosphatase value. This reaction is similar to that seen in normal labour. In the second stage the values rose sufficiently to be statistically significant compared with both the initial and early first stage level. This increase affected not only the average but also the minimum and maximum. It is however interesting to note that the increase of alkaline phosphatase caused by the second stage of labour amounts to 26 per cent. of the initial value in toxaemia, and 26.3 per cent. in normal cases.

When labour is prolonged in a case of toxaemia the rise in the phosphatase level markedly surpasses the limits of normal labour in both toxaemic and normal pregnancy (Table 92). As in normal labour the difference between the initial value and that in the early first stage was almost negligible. Between the first and second stage however there was a considerable difference in the phosphatase content of the plasma. The second stage value in this series was 37.11 units per cent.; S.D. 4.41. This compared with the basic value shows an increase of 74 per cent. as against 53.5 per cent. in normal cases. This difference is significant. When the first stage was prolonged for 40 hours in toxaemia the alkaline phosphatase

was/

was 28.2 units per cent .; S.D. 5.09. This is significantly higher than the second stage values in toxaemia when labour pursued a normal course. A comparison of Tables 90 and 91 reveals also that up to the early first stage of labour the two series of cases show no appreciable difference, which only appears/when labour is prolonged beyond a certain time.

Table 92

No.	Before Labour	Early First Stage	Late First Stage	Second Stage	Puerperium
1. D.	23.2	23.0	31.3	39.8	28.5
2. McA.	17.0	18.1	25.0	33.8	20.4
3. McD.	20.0	20.0	25.9	36.2	26.6
4. G.	22.7	22.0	28.3	36.8	24.5
5. P.	28.6	29.2	34.5	40.8	31.3
6. O.	29.1	30.0	37.1	46.2	29.0
7. C.	14.9	15.4	23.1	31.8	20.0
8. L.	17.9	19.0	25.0	34.9	22.2
9. F.	22.6	22.0	28.8	39.1	27.5
10. McN.	22.0	21.0	26.8	34.0	25.7
11. S.	15.2	16.0	22.5	32.0	23.8
12.	22.8	23.2	30.4	39.9	28.7
Average	21.33	21.57	28.22	37.11	26.10
S.D.	4.78	3.24	5.09	4.49	3.40
P.E.	3.20	2.17	3.40	3.01	2.28

An analysis of these data suggests that if labour is normal, the liver suffers no additional strain on toxaemic cases,/

cases, but if labour is prolonged metabolism seems to be affected more adversely in a toxaemic than in a non-toxaemic pregnancy with similar prolongation of labour. This has an important significance in the management of dystocia complicating pregnancy toxaemias.

ALKALINE PHOSPHATASE IN PUERPERIUM IN PRE-ECLAMPTIC SUBJECTS

Tables 91 and 92 show the values of alkaline phosphatase obtained in this series of 51 cases on the fourth day of puerperium.

Group 1 - In normal labour the average alkaline phosphatase in 39 cases of pre-eclampsia was found to be 16.74 units per cent., S.D. 3.00. Compared with the corresponding series of normal cases this value is high and on statistical analysis appears to be significant. In the normal series 45.4 per cent. of the values in the puerperium were above the mean average. In the toxaemic series 55.4 per cent. of the values occupied a similar position. The fall in the alkaline phosphatase level in the immediate puerperium amounted to 23.3 per cent. of the pre-parturition value in normal cases, and 19.4 per cent. in toxaemia. This difference is significant.

Group 2 - When labour was prolonged beyond 48 hours, the average value on the fourth puerperal day was found to be 26.10 units per cent.; S.D. 3.40. This value is higher than that in Group 1 and the difference is statistically significant. Unlike normal patients the values obtained in the immediate puerperium of pre-eclamptic patients are significantly/

significantly higher than those before the commencement of labour. On superficial examination this may be interpreted as a manifestation of a persistent hepatic dysfunction. If however this gradient of fall is measured from the highest level attained during labour, it isseen that the rate of decline in toxaemia is only slightly less than that in normal cases. The values obtained from such a calculation are:-

1. In normal Labour -

39.6 per cent. in normal pregnancy
and 36.3 per cent in toxaemias.

2. In prolonged Labour -

33.2 per cent. in normal pregnancy
and 29.7 per cent. in toxaemic pregnancy.

It is evident that the rate of recovery from the effects of toxaemia, so far as the hepatic functions are concerned, is satisfactory once the underlying cause is removed.

3. ECLAMPSIA

At the time of admission the phosphatase content of the plasma in 18 cases of eclampsia varied from 20.0 to 30.3 units per cent., the average being 25.02; S.D.3.33. This is 8.42 units per cent. higher than that in pre-eclampsia and the difference is significant. Three patients in this series (Table 93) were examined 1 to 3 days before the eclampsia developed. The average alkaline phosphatase in these cases was 19.76 units per cent.; S.D. 1.21 before the onset of fits. The convulsions caused the phosphatase to increase/

increase to 24.36 units; S.D.2.38. This is statistically significant.

Table 93

No.	Pre-convulsive	No. of convulsions. 1	2	3	4	5	6	7	8
1. R.	30.6	22.5	26.8	-	-	-	-	-	-
2. A.	18.5	21.8	-	-	-	-	-	-	-
3. H.	20.2	20.8	21.0	-	24.5	-	26.0	-	30.0
4. D.	-	-	23.7	30.8	32.4	35.7	-	-	-
5. McK.	-	-	-	18.6	19.5	20.0	23.4	29.8	34.0

In 9 cases in this series the convulsive stage persisted for more than one day after admission. On the first day the average phosphatase content was 24.91 units per 100 ml.; S.D. 1.25. On the second day of the convulsive stage this rose to 32.64 units per cent.; S.D. 2.98. The minimum value in these cases increased from 20.0 to 23.8 with the persistence of the convulsive stage and the maximum changed from 30.8 to 39.7.

There were 3 deaths in this series. Estimation of phosphatase was done in these cases 6 to 16 hours before death. The alkaline phosphatase contents of the plasma in these three cases were 39.4, 39.5 and 39.7 units per 100 ml. respectively, but 24 hours before death the corresponding values were 29.8, 35.9 and 21.8 units per cent. respectively.

With the cessation of convulsions phosphatase level diminished progressively. By the second day of convalescence it came down to 19.66 units per 100 ml.; S.D. 3.26 with a

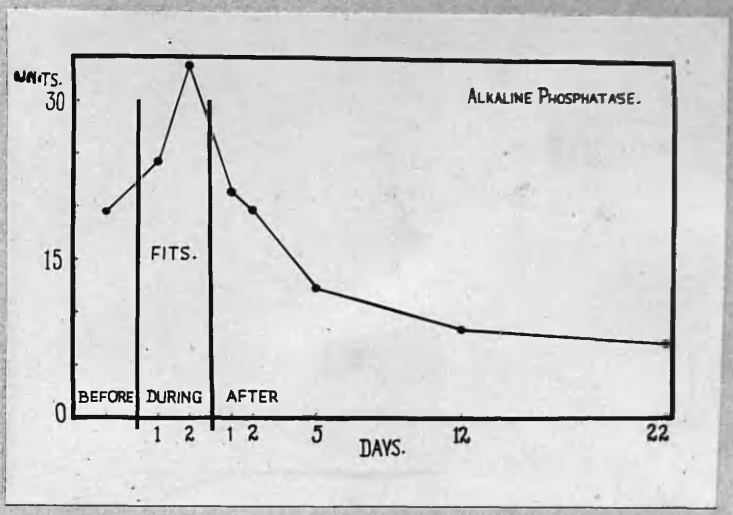


Fig. 57. Plasma alkaline phosphatase in eclampsia, showing the changes in the phosphatase level in the pre-convulsive, convulsive and the convalescent stages of the disease.

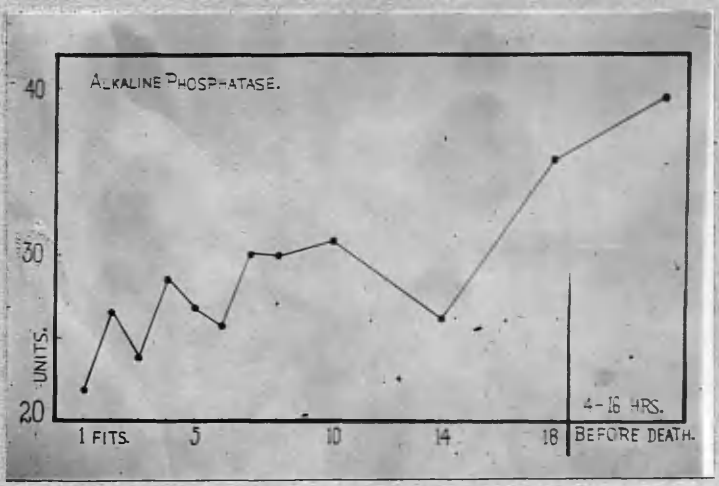


Fig. 58. Plasma alkaline phosphatase in eclampsia in relation to the number of convulsions. The small number of cases in each group does not show any definite corelation, which is better demonstrated in the follow-up study of three cases described in the text.

range of variation from 12.4 to 24.5 units per cent. Normal values were restored in all cases in the third week of convalescence.

A study of the relationship between the number of convulsions in eclampsia and the alkaline phosphatase level was found to be difficult because of the individual variation in the values in the pre-convulsive stage. We had the opportunity of examining the blood in 3 patients who came under observation during pre-eclampsia and in 2 others at frequent intervals (immediately after convulsions) and these results are presented in Table 93.

It will be seen that with frequent convulsions, the phosphatase content of the plasma rises. The extent of this however, does not seem to be directly related to the number of convulsions. Thus, in R. after 3 fits, phosphatase level rose by 6.2 units above the initial pre-convulsive value. In H. after the same number of fits the amount of increase was less than 1 unit per cent. Again, between the second and the fourth convulsion the increase in phosphatase was by 8.7 units per cent. in one patient (D.), and only 3.5 units in another (H.).

ALKALINE PHOSPHATASE & LABOUR IN ECLAMPSIA

In order to avoid the interfering influence of intra-partum convulsions 5 cases of antepartum eclampsia were studied to ascertain the manner in which the plasma alkaline phosphatase level was affected by an immediately preceding eclamptic/

eclamptic state. In no patient did the last convulsion occur 6 to 8 hours before the onset of labour. The duration of labour did not exceed 28 hours. The results are presented in Table 94.

Table 94

No. *	Alkaline Phosphatase Units per 100 ml.		
	Convulsive Stage	First Stage	Second Stage
1. Dm. (5)	24.3	29.3	38.7
2. Dv. (4)	30.8	32.5	41.6
3. R. (2)	26.8	29.4	43.0
4. Ds. (7)	35.7	36.7	45.0
5. Mcl. (4)	28.3	29.6	44.5
Average	29.38	31.50	42.56
S.D.	2.69	2.53	2.53

* Figures in parenthesis indicate the number of convulsions.

Unlike the two preceding types of cases already discussed labour, even of normal duration following soon after an eclamptic state, is associated with a marked increase in phosphatase level of the plasma. This increase becomes evident even in the early first stage of labour, which in this series amounted to 2.12 units. The onset of second stage was associated with a considerable rise in the phosphatase level. The net increase, compared with the value obtained before labour, varied between 9.3 (Ds.) and 16.2 (R.) units per cent., the average being 13.18 units per 100 ml., S.D. 3.26.

This/

This increase amounts to 44.5 per cent. of the initial ante-partum value. It thus appears that the increased metabolic strain caused by labour, even of normal duration immediately following eclampsia, is considerably more than that caused by labour in pre-eclampsia. This observation is in conformity with what we already observed in connection with bilirubin excretion test. The importance of this lies in the obstetric management of a case of eclampsia.

4. NEPHRITIS COMPLICATING PREGNANCY

There were 8 cases in this series. All of them had a history of a renal disease and showed albumin and casts in the urine. Urea clearance was in all cases below 60 per cent. All cases were between 32 and 36 weeks of gestation. The results are submitted in Table 95.

Table 95

No.	Parity	Blood Pressure	Albumin Esbach	Urea clearance per cent.	Alkaline Phosphatase Unit/100 ml.
1. C.	2	160/94	9	60	11.0
2. M.	1	145/85	3	54.5	10.7
3. K.	3	175/100	8	46.2	13.3
4. W.	2	138/85	4	50.5	9.8
5. McQ.	4	160/100	2	52.3	11.5
6. S.	1	148/92	3	55.8	13.0
7. H.	2	150/90	2	49.7	11.8
8. B.	2	160/95	4	58.4	12.1
				Average	11.51
				S.D.	1.34

The average alkaline phosphatase of the plasma in this series was 11.51; S.D. 1.34 with minimum, and maximum values of 9.3 and 13.3 units per 100 ml. Compared with normal pregnancy at the corresponding periods of gestation the difference in the average is slight and not significant. Neither the level of blood pressure nor the degree of renal damage as measured by albuminuria and urea clearance seemed to affect the phosphatase level in these cases.

5. ESSENTIAL HYPERTENSION AND PREGNANCY

Ten cases were examined in this series. All of them were known to have hypertension before the occurrence of pregnancy. No case with abnormal urea clearance was included in this study. All cases belonged to 32-36 weeks of pregnancy. The results are presented in Table 96.

The average value of alkaline phosphatase in essential hypertension complicating pregnancy was 12.07 units per 100 ml. plasma; S.D.2.30. It is interesting to note that 3 patients had more albuminuria (S.,B.,& C.) than the remaining cases and in these cases high values were obtained. Yet, this albuminuria was not related to the degree of organic renal involvement as the results of urea clearance indicate. It appears that some cases of essential hypertension are associated with functional disturbances during pregnancy which are similar to those found in pre-eclampsia.

6. ACCIDENTAL HAEMORRHAGE

Ten cases of accidental haemorrhage were studied in this series./

Table 96

No.	Parity	Blood Pressure	Albumin (Esbach)	Urea Clearance per cent.	Alkaline Phosphatase Units/100 ml.
1. S.	1	200/130	3	94.5	14.2
2. P.	2	180/120	2	113.0	11.6
3. B.	2	210/135	6	91.6	16.5
4. McD.	1	195/120	1	99.5	11.0
5. McK.	1	190/115	±	104.5	10.7
6. K.	1	185/110	-	100.5	12.0
7. H.	2	190/120	-	97.6	9.3
8. Pr.	1	200/120	1.5	93.5	10.6
9. J.	1	200/110	1	102.3	10.4
10. C.	3	183/115	4	109.4	14.5
				Average	12.07
				S.D.	2.30

series. The data are presented in Table 97. In 4 cases in this series phosphatase was estimated sometime before the complication developed, and these have been included in the table in order to provide a comparison.

The average alkaline phosphatase in this series was 20.57 units per cent., S.D. 6.05. Individual values however, provide an interesting study when the degree of shock taken into consideration. Four patients in this series developed little or no shock as a result of accidental haemorrhage. Their average alkaline phosphatase was 16.17 units per cent.; S.D./

S.D. 0.67, which is almost similar to the value obtained in pre-eclampsia. Three cases who developed some amount of

Table 97

No.	Before Haemorrhage*	During Haemorrhage	Shock
1. W.	-	19.6	+
2. M.	-	33.2	++
3. D.	13.9	29.5	++
4. P.	-	16.8	±
5. B.	-	15.9	0
6. McI.	-	17.3	+
7. McV.	-	17.0	+
8. O'R.	15.1	15.5	±
9. McK.	14.7	27.4	++
10. McG.	16.3	16.5	0
Average	15.0	20.87	
S.D.	1.08	6.05	

* Only values obtained within 72 hours before the onset of haemorrhage are included.

shock as a result of the haemorrhage, had a phosphatase content varying from 17.0 to 19.6 units per cent. The average of 17.96; S.D. 1.51, compared with the pre-haemorrhagic level indicates a significant increase. The remaining 3 cases in the series developed moderate or severe degree of shock and had a phosphatase content of 30.0 units per cent. S.D. 3.10. This is considerably higher than the value obtained before/

before haemorrhage, and almost approaches that of the most severe form of eclampsia.

COMMENTS

All studies on plasma alkaline phosphatase in normal pregnancy indicate that during the first six months of pregnancy values do not deviate from normal. The first appearance of abnormal values is evident in the seventh month of pregnancy. During the subsequent weeks the rise in phosphatase level is not only maintained but is infact enhanced. This has been clearly shown in the present series and also in those reported by Cayla and Fabre (24, 1935), Meranze et al (4, 1937), Vermehren (25, 1939), Bodansky (5, 1939) and Hoch and Marrach (7, 1943). Comparison of the actual values obtained by us with those of most of these authors is however not possible because of different units of measurement employed. In a series of 220 cases belonging the last 3 weeks of pregnancy presented by Young, King, Wood and Wootton (6, 1946) the average alkaline phosphatase level of the plasma was 10.4 units per cent. From the figures supplied by Hoch and Marrach who also employed the same unit of measurement the phosphatase level of the plasma between 27 weeks and term appears to be 11.3 units per 100 ml. Our findings using a similar method agree with these findings.

The cause of this sudden increase in alkaline phosphatase however, has inspired several interesting hypotheses. Thus, Ramsay, Thierens and Magee (26,1933) observed/

observed that the high phosphatase level is probably associated with disordered calcium and phosphorus metabolism in pregnancy. Possibility of a "pathogenic or a potentially pathologic state of bone metabolism in mother or foetus" is not excluded by Meranze et al (4, 1937). Bodansky (5, 1939) suggests an increased parathyroid function to be responsible for high phosphatase value. Young and co-workers (6, 1946) suggested that the high maternal phosphatase could be associated with infantile rickets and deficient calcium metabolism. These theories are based on inadequate data.

Ebbs and Scott (27, 1940) found high phosphatase values in twin pregnancy. Meranze et al (4, 1937) also made a similar observation, and records a case of triplets where the phosphatase level was even higher. Our findings are not in accordance with these but agree rather with that of Young, King, Wood and Wootton (6, 1946). There were 4 cases of twin pregnancy in our series. The average phosphatase was 12.34 units per cent., which is not any higher than that in single pregnancies.

The work of Givens and Macy (2, 1933) and of other investigators on maternal metabolism during pregnancy clearly indicate a high foetal demand for minerals, especially calcium and phosphorus during the last trimester of gestation. This is related among other things to the deposit and formation of osseons tissue in the foetal skeleton. The foetus possesses a low level of plasma phosphatase. We estimated the/

the phosphatase content of the cord blood in 21 normal newborn babies. The phosphatase content of the umbilical blood varied from 3.0 to 6.1 units per cent. with an average of 4.67 units per 100 ml.; S.D. 1.21. This is extremely low considering the high level of osteoblastic activity in the foetus. Under such conditions a compensatory mechanism usually develops in the mother, whereby the foetal requirements can be met as and when necessary. A low phosphatase content of the foetal blood has been observed also by Stearns and Warweg (28, 1933) and Meranze and co-workers (4, 1937). Examination of the placental tissue for histochemical reactions for phosphatase shows that there is an appreciable difference in the phosphatase content of the chorion between early and late months of pregnancy. In view of these findings we believe that the high level of maternal phosphatase is an expression of the physiological demands made by the foetus on the mother.

The increase of phosphatase in toxaemia of pregnancy however does not appear to be in any way related to this physiological process. Reference has already been made to the work of various investigators who consider that pregnancy toxaemias are associated with some degree of hepatic dysfunction. Our own study of bilirubin excretion support this hypothesis. The increase in the phosphatase value from 12.24 units in normal pregnancy to 18.98 units in severe toxaemia [illegible]

That/

That the increase in plasma phosphatase in eclampsia and pre-eclampsia is related to the toxaemia is further shown by the change brought about by alteration in the clinical condition of the patient. In this connection it is interesting to observe that neither nephritis nor compensated essential hypertension complicating pregnancy causes any pathological increase of plasma phosphatase. Decompensated hypertension however shows a response somewhat similar to that found in pre-eclampsia. Determination of alkaline phosphatase as an aid to diagnosis in a composite group of toxaemias of pregnancy is thus not without limitations. In judging the clinical course of the disease however estimation of phosphatase seems to be of considerable value.

Increase of plasma phosphatase in accidental haemorrhage seems to be associated with a state of deranged hepatic function. Haemorrhage in absence of shock does not appear to alter the phosphatase content to any appreciable extent. It is only when accidental haemorrhage is attended with shock that a marked increase of the phosphatase occurs. Shock is attended with a fall of blood pressure, diminished oxygenating capacity of the blood, and vascular spasm. These factors, superimposed on a pre-existing vascular spasm caused by toxaemia, undermines the functional efficiency of the liver cells. The histological changes in the liver in shock described by Davidson and co-workers (29, 1946) and the experimental observation made by Engel, Harrison and Long/

Long (30, 1944) on the effects of anoxaemia on liver cells offer ample support to this suggestion.

Sufficient attention has not been paid to the effect of labour on alkaline phosphatase. Meranze et al (4, 1937) mention that they observed an increase of phosphatase level during "active labour". Our investigation indicates that this increase is related to the duration of labour. When labour is prolonged the phosphatase level is abnormally high. Labour is attended with prolonged muscular contraction and increase of intra-abdominal pressure. The strain of these factors on the metabolic functions of the liver are apparently responsible for the high values for phosphatase obtained during labour, especially when it is prolonged. The effect of this is greater in presence of toxaemia, where the hepatic efficiency is already below normal even before the commencement of labour. The significance of this can be appreciated in the light of the vivi-perfusion experiments of Frank, Seligman and Fine (31, 1946). These authors demonstrated the important part played by the liver in preventing irreversible changes in shock. The findings described above indicate at least one of the reasons why a patient suffering from pregnancy toxaemia is more susceptible to obstetric shock. The importance of these observations in the management of labour in a case of pre-eclampsia or eclampsia is obvious.

CONCLUSIONS

Normal/

Normal pregnancy is attended with a rise in plasma alkaline phosphatase. This is most manifested in the last trimester of gestation. It is suggested that this increase in phosphatase occurs in response to the physiological demands of the foetus.

Pre-eclampsia and eclampsia cause an even greater increase in plasma phosphatase. It is suggested that this is due to a disturbance of the hepatic functions caused by toxaemia. Neither nephritis, nor uncomplicated essential hypertension in pregnancy is associated with a similar change in plasma alkaline phosphatase. Accidental haemorrhage, accompanied by shock causes a marked impairment of liver functions as determined by the estimation of phosphatase.

Labour appears to impose an additional strain on the liver, especially when it is prolonged. The significance of this in toxaemia of pregnancy is discussed. The changes in hepatic functions brought about by pregnancy toxaemias are reversible, although the rate of restoration of plasma phosphatase to normal levels seem to be slightly retarded in presence of toxaemia.

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CHAPTER 5

PROTHROMBIN CONCENTRATION AND RESPONSE

The few investigations, which have been done on the behaviour of plasma prothrombin during pregnancy, are all related to haemorrhagic diseases of the new-born, and puerperal thrombosis. The effect of pregnancy toxaemia on the prothrombin concentration of the blood and the ability of the liver to produce prothrombin under the influence of additional Vitamin K is not known. The only follow-up study is that of Javert and Macri (1, 1941) who observed that in the early pregnancy plasma prothrombin is slightly decreased. They attribute it to nutritional disturbances, e.g. vomiting, which are present at this period of gestation. According to these authors, from the third month the level of prothrombin starts to rise but this is intercepted by a second fall at the end of the second trimester. The maximum is reached during the third trimester of gestation when the average prothrombin content is 95 per cent. In some of their cases as much as 100 per cent. concentration was attained. Other investigators (2,3,4) also agree that at term the concentration of prothrombin in the plasma is high. One of the observers (2, 1940) stated that the prothrombin level at term may be as high as 130 per cent. of normal.

1. NORMAL PREGNANCY

In 72 normal cases, belonging to various periods of pregnancy the prothrombin concentration of the plasma, and the/

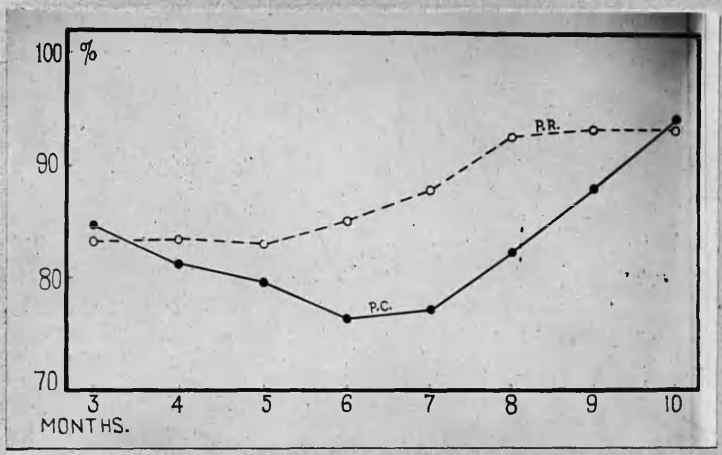

Fig. 60 . Plasma prothrombin concentration and prothrombin response to vitamin K in normal pregnancy.

the response of prothrombin to intravenous injections of 20 mgms. of Vitamin K (Sodium 2 methyl - 1, 4 naphthohydroquinone diphosphoric acid - synkayvit) was studied. The results are presented in Table 98. The earliest case examined by us was one of 9 weeks pregnancy.

During the third and sixth months of gestation the prothrombin concentration showed a slight tendency to decrease. This however was not of statistical significance. The lowest level attained was between the second and third trimester, after which there was a steady increase to term. At the point of maximum decrease, the prothrombin concentration was 9.2 per cent. less than that in early pregnancy, and 18.3 per cent. below the value obtained at term. These cases showed that pregnancy causes an increase of prothrombin concentration by 11.7 per cent. of the value in the early months of pregnancy. The maximum prothrombin concentration observed by us was 102 per cent. of normal. The increase which occurs during the last trimester is statistically significant. The average at this period was 88.4 per cent.; S.D. 6.25, with a minimum and maximum range of 74.3 and 102 per cent.

The prothrombin response to Vitamin K was about equal to the concentration of prothrombin in the plasma. Up to the fifth month of gestation this was almost constant (88.0 - 88.4 per cent.), but after this period there was a steady rise in the response, until the ninth month, when the maximum

response/

Table 93

Months	3		4		5		6		7		8		9		10	
Frequency - %	P.D.	D.D.	P.D.	D.D.	P.D.	D.D.	P.D.	D.D.	P.D.	D.D.	P.D.	D.D.	P.D.	D.D.	P.D.	D.D.
71-75	-	-	1	-	2	-	3	-	3	-	1				-	
76-80	1	-	3	2	1	2	2	-	3	-	2		1		-	
81-85	3	4	3	4	3	4	1	3	2	1	7		3		-	
86-90	-	2	1	2	1	1	1	4	-	6	1	3	3	3	2	2
91-95	2	-	-	-	-	-	-	-	-	1	1	8	4	6	5	7
96-100	-	-	-	-	-	-	-	-	-	-	-	1	1	3	4	3
101-105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
Average	84.5	83.3	81.1	83.4	79.6	83.0	76.7	85.7	77.3	88.2	89.4	92.7	88.2	93.4	94.4	93.4
S.D.	7.2	2.7	8.0	2.7	6.1	3.1	5.6	2.9	3.9	2.9	5.0	2.7	5.6	3.0	4.9	3.0
Min.	76.2	80.6	73.2	79.3	70.5	79.6	70.5	81.5	71.0	81.5	74.3	86.5	73.5	88.2	88.5	88.0
Max.	93.0	86.7	90.0	87.2	90.0	90.0	87.6	89.7	84.5	92.0	93.1	95.0	96.2	93.0	102.0	96.8

response to Vitamin K was observed. During the last month of pregnancy this level did not show any variation. The average prothrombin response during the last trimester of gestation was 94.0 per cent.; S.D. 2.78 with a range of values from 86.5 to 98.0 per cent.

Labour was found to cause a marked increase in prothrombin concentration. This was estimated at the beginning of the second stage in 15 cases of normal labour. Control values were obtained by determining the concentration of prothrombin immediately after the commencement of labour. The average initial prothrombin concentration in this series was 103.4 per cent.; S.D. 8.8 (maximum 111.4; minimum 93.2 per cent.). The increase caused by labour amounted to 38.6 per cent.; (maximum 42.0; minimum 34.0). The prothrombin concentration during labour in this series was, average 142.0 per cent., S.D. 6.7; (minimum 131; maximum 150.9 per cent.). These values are briefly presented here, as they provide useful data for comparison with the effect of labour in toxaemia of pregnancy.

2. PRE-ECLAMPSIA

Prothrombin concentration and response were determined in all cases of toxaemia in our series. The average for the prothrombin concentration was 65.3 per cent.; S.D. 9.20 and that for the prothrombin response was 60.85; S.D.9.75. The mild and severe cases deserve separate description.

1. Mild Pre-eclampsia (50 cases).

Prothrombin/

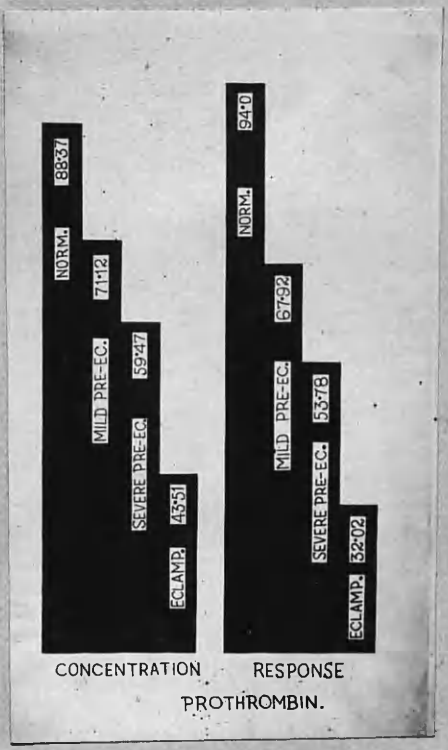

Fig. 61. Plasma prothrombin concentration and prothrombin response to vitamin K in normal pregnancy, pre-eclampsia and eclampsia.

Prothrombin concentration in this series on admission varied from 60.9 to 80.3 per cent. with an average of 71.1; S.D. 6.05. The average, minimum and maximum values were significantly lower than those in normal pregnancy.

The prothrombin response in this group was 67.92; S.D. 6.35 with a range of variation of 51.0 to 80.0 per cent. These values also show significant reduction from normal.

The frequency distribution of prothrombin concentration and response in mild toxaemias is given in Table 99.

Table 99

Frequency percent. Normal	Mild Toxaemia (50 cases)		Severe Toxaemia (50 cases)		All cases	
	P. Conc.	P. Resp.	P. Conc.	P. Resp.	P. Conc.	P. Resp
30.1-35	-	-	-	1	-	1
35.1-40	-	-	-	5	-	5
40.1-45	-	-	3	5	3	5
45.1-50	-	-	6	8	6	8
50.1-55	-	3	6	8	6	11
55.1-60	1	2	11	12	12	14
60.1-65	5	9	15	6	20	15
65.1-70	11	20	8	3	19	23
70.1-75	22	10	1	1	23	11
75.1-80	7	6	-	1	7	7
80.1-85	4	-	-	-	4	-
Average	71.12	67.92	59.47	53.78	65.3	60.8
S.D.	5.44	5.13	7.33	8.97	9.20	10.7
P.E.	3.64	3.78	4.91	6.01	6.17	7.18

11. Severe Pre-eclampsia. (50 cases). Prothrombin concentration in severe pre-eclampsia varied from 42.0 to 75.0 per cent. with an average of 59.47 per cent.; S.D. 7.33

The response to Vitamin K was 53.78 per cent. (average); S.D. 8.97 with a range of values from 34.0 to 80.0.

Comparison of Tables 98 and 99 reveal that toxaemia causes a decrease of both prothrombin concentration and response, and affects the range of values in such a manner that even the maximum value in severe toxaemia is less than the minimum in normal pregnancy. In spite of some overlapping of the individual values, the distribution shows a distinct shift to the left, which becomes marked in severe toxaemias. This change in the values shows statistical significance at each stage. The prothrombin response in severe pre-eclampsia shows a wider variability than that in either mild toxaemia or normal pregnancy. But quantitatively the prothrombin response seems to suffer more than the basic concentration of prothrombin in the blood. The reduction of the concentration and response of prothrombin in severe toxaemia amounts to 32.7 and 42.8 per cent. of the values in normal pregnancy. The corresponding decrease in mild pre-eclampsia is 19.6 and 30 per cent. respectively.

111. Clinical Course of Toxaemia.

Prothrombin concentration and response reached, in general, to the clinical course of toxaemia in the same manner as the other tests for hepatic function already described./

described. Improvement of toxaemia was associated with an increase in both the concentration and response of prothrombin to Vitamin K. The former was raised from 66.78 to 81.91 per cent. in the course of four weeks, and the latter changed from 59.73 to 83.40 per cent. The range of values, however, shows a wide distribution until the final stage of improvement. The change of values just satisfies statistical analysis at individual stages, although between the first and the fourth week of study the values obtained show marked statistical significance. The values obtained at this stage are very nearly normal. (Table 100, figure 62). Deterioration of the toxaemia caused a fall in both prothrombin concentration and prothrombin response. The prothrombin concentration dropped by 9.1 per cent., and prothrombin response by about 20 per cent. from its initial value during the course of 4 weeks. It is interesting to note that with gradual deterioration of toxaemia the distribution of values in each group tends to get wider (especially for prothrombin response). This is the result of increasing number of low values and the progressive decrease of the minimum in each series. The maximum values at each period are not affected until the toxaemia has been of very long duration (Table 100, figure 63).

IV. Duration of Toxaemia.

A study of the behaviour of prothrombin in relation to the duration of toxaemia (dated from the time of its initial/

Table 100

	Improved				Deteriorated			
Wks.	1	2	3	4	1	2	3	4
P. Conc. *	66.78± 6.80	63.65± 7.26	72.62± 6.46	31.91± 4.49	62.91± 5.46	60.07± 6.45	57.82± 6.43	53.33± 7.34
	42.6- 32.4	43.5- 37.8	59.7- 39.0	72.4- 93.0	42.0- 30.4	40.6- 30.2	33.9- 73.5	36.0- 76.0
P. Resp. *	59.73± 7.69	63.30± 6.36	70.62± 3.18	33.40± 2.03	59.70± 7.23	53.41± 8.39	46.66± 7.33	40.03± 7.16
	39.6- 80.2	44.0- 81.2	50.2- 81.5	74.6- 90.0	34.0- 80.0	39.5- 80.0	24.4- 80.0	24.0- 62.0

* Figures represent, Average ± Probable error
Minimum - Maximum.

initial onset) in those cases where the disease persisted or became worse shows a more striking change. The figures are presented in Table 101 and figure 64. There is a gradual deterioration in both the concentration and response of prothrombin to Vitamin K as the duration of toxaemia becomes longer. The fall in prothrombin concentration indicates statistical significance.

The decrease of the prothrombin response to Vitamin K, is more marked. This affects the minimum values more than the maximum during the first three weeks of toxaemia but after the third week the range becomes smaller due to a decline in the higher values. The gradient of fall of the average increases as the duration becomes longer. The change in the values show statistical significance at each stage,/

stage, but this increases markedly when the toxaemia has persisted for more than three weeks.

Table 101

	Proth. Conc.			Proth. Resp.		
Wks.	Average	S.D.	Min.-Max.	Average	S.D.	Min.-Max.
1	66.77	9.72	50.0-80.4	60.0	13.71	37.6-79.6
2	62.35	9.22	45.0-80.2	57.21	11.12	30.3-74.7
3	57.85	9.50	38.7-78.5	51.33	11.59	23.0-79.0
4	51.01	8.74	36.5-76.0	44.47	10.11	24.4-59.0
5	46.39	5.75	36.0-56.5	33.34	7.33	24.1-45.3

V. Blood Pressure and Prothrombin Concentration and Response.

As in previous tests, the results of prothrombin concentration and response also were analysed in relation to systolic and diastolic blood pressure (Figure 65). Systolic blood pressure showed little correlation, if any, with the level of prothrombin in the plasma and the response of prothrombin to Vitamin K. The results are given in Table 102.

Diastolic blood pressure seems to have a more notable relationship with the concentration and response of prothrombin. Both decrease steadily as the diastolic blood pressure rises (Table 103), but the prothrombin response suffers more than the prothrombin concentration. The change in the prothrombin response reveals statistical significance at all stages, but the fall in the concentration of plasma prothrombin/

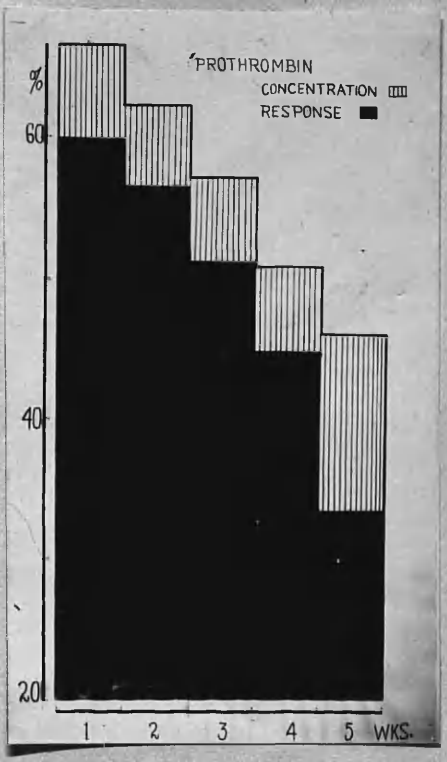

Fig. 64. Prothrombin concentration and prothrombin response in pre-eclampsia, showing their relation to the duration of toxaemia.

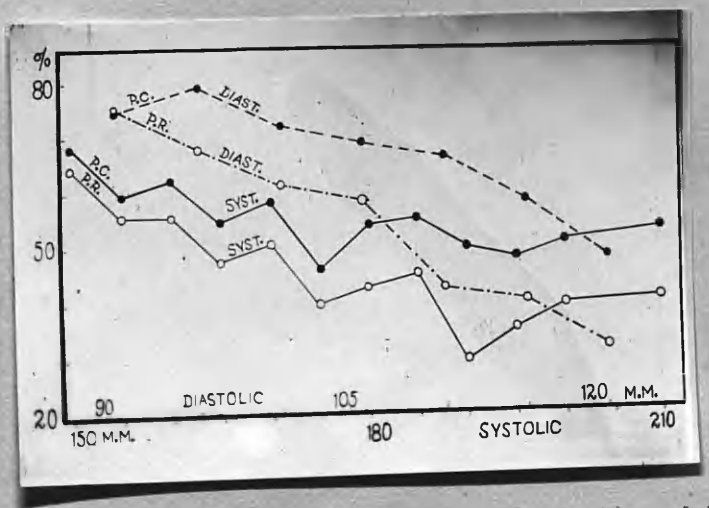

Fig. 65. Prothrombin concentration and prothrombin response in pre-eclampsia in relation to the systolic and diastolic blood pressure.

Table 102.

B.P. mm. Hg.	P. Conc.	P. Resp.	B.P. mm. Hg.	P. Conc.	P. Resp.
146-150	63.27±7.69 50.0 -91.5	64.26±10.57 34.0 -88.8	176-180	53.78±6.42 38.9 -79.3	42.67±6.70 24.7- 53.0
151-155	59.15±4.66 44.8 -67.5	55.53±9.75 40.0- 74.6	181-185	54.8±5.74 42.0-64.0	42.13±6.32 37.6-54.2
156-160	62.16±5.79 42.6-89.0	55.64±7.35 31.0 -80.2	186-190	49.95±6.34 40.2 -58.5	29.16±3.85 24.4 -36.8
161-165	54.44±7.91 40.0-65.0	47.17±7.26 33.7 -64.0	191-195	47.8	35.0
166-170	53.07±4.91 45.5 -70.0	50.54±7.66 24.0 -69.0	196-200	50.84±2.64 47.5-58.5	33.90±4.16 33.6 -48.4
171-175	45.90±3.35 39.0 -60.0	39.72±6.14 24.0- 60.0	200+	52.66±0.67 51.6 -54.0	40.40±6.35 29.7 -50.0

Table 103

B.P. mm. Hg.	P. Conc.	P. Resp.	B.P. mm. Hg.	P. Conc.	P. Resp.
Less than 90	74.63±7.46 52.7 -91.5	75.01±7.32 50.5 -90.0	106-110	66.02±5.12 46.0-76.0	42.22±5.35 33.7 -69.0
91-95	78.93±5.00 67.5 -91.5	67.95±4.78 58.0 -78.0	111-115	58.14±3.43 42.6-65.0	40.20±5.51 29.7 -56.0
96-100	71.69±7.73 44.8 -87.6	61.19±6.70 42.0 -80.2	115-120	47.69±3.91 38.9 -53.8	31.54±4.21 24.0 -41.5
101-105	68.76±6.80 50.0 -80.0	58.46±6.00 40.6 -71.5	-	-	-

prothrombin is not always significant. The gradient of fall is small at lower ranges of blood pressure, but when the diastolic pressure is high the decrease in both prothrombin concentration and response becomes marked. [illegible] lowest

lower/

level, the prothrombin concentration is about half that of normal, and the response to Vitamin K is about one-third of that observed in normal pregnancy.

3. ECLAMPSIA

The average prothrombin concentration in our series of eclampsia on admission, was 43.51 per cent.; S.D. 3.30, with a range of values from 32.7 to 61.0 per cent. At this stage the response to Vitamin K was 32.02 per cent.; S.D. 4.56. The maximum and minimum values were 40.3 and 25.0 per cent. The change in the values caused by eclampsia is statistically significant. If however, all the values obtained during the "eclamptic state" are considered, the averages for the concentration and response to prothrombin is found to be 39.45; S.D.10.60 (20.0-61.0), and 28.55; S.D. 6.72 (17.0-40.8) per cent. respectively. The coefficient of variation increases because of the further shifting of the lower values to the left.

The effect of the eclamptic convulsions on the prothrombin concentration and response was studied particularly in the three cases already referred to. The results are presented in Table 104. These cases show that the convulsions have a dilaterious effect on both prothrombin concentration and response, although the latter seems to be more susceptible than the former. In these patients, the early convulsive stage did not cause a marked change in the prothrombin concentration of the plasma. The concentration of prothrombin appeared to suffer only after

the convulsive stage had persisted for a certain length of time. The response of prothrombin however was affected early and the deterioration continued steadily through the stage of convulsions. This was particularly evident in three fatal cases in this series, where the prothrombin response was negligible in one and negative in the other two. Yet the concentration of prothrombin in the plasma was still maintained at 20 to 30 per cent.

Table 104

Name	Pre-eclamp.	Convulsive Stage 1	2	3	4	5	6	7	8
R.	50.0 / 48.8	53.0 / 40.0	50.0 / 34.3	-	-	-	-	-	-
A.	69.7 / 57.2	65.7 / 50.0	56.0 / 40.5	43.2 / 31.3	-	-	-	-	-
H.	73.0 / 60.5	75.8 / 55.5	74.6 / 50.0	-	60.0 / 44.7	-	50.0 / 39.6	41.6 / 30.0	30.0 / 17.0

The numerator denotes the Proth. conc; the denominator Proth. Resp.

The follow-up study in this series reveals that the prothrombin concentration and response improve rapidly after the convulsions have ceased. Normal values are regained between the second and third week of convalescence. At this stage values were often obtained which were even higher than those in normal non-pregnant women.

The prothrombin response to Vitamin K appears to be more labile than the basic prothrombin concentration. The decrease during the convulsive stage is as marked as the

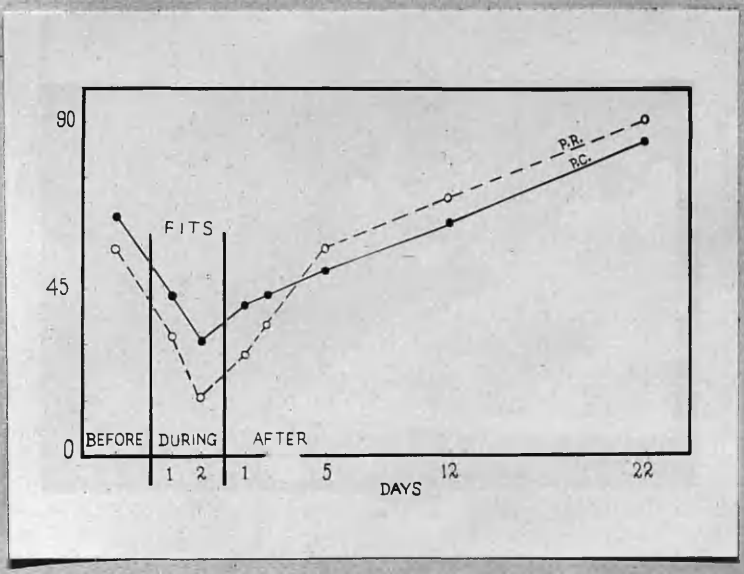

Fig. 66. Prothrombin concentration and prothrombin response in eclampsia showing the changes which take place in the pre-convulsive, convulsive and the convalescent stages of the disease.

recovery from it in the convalescent period. The changes observed in this follow-up study statisfies statistical analysis, and are shown in Table 105.

Table 105

	Pre-conv. Stage	Convulsive Stage		Post Convulsive Stage				
		1	2	1	2	5	12	22
P. Conc.	64.23± 6.81	43.51± 5.89	31.27± 3.98	41.59± 3.98	43.54± 2.23	50.09± 3.09	63.15± 5.71	85.35± 5.03
	50.0- 73.0	32.7- 61.0	20.1- 40.0	20.1- 51.0	34.0- 51.9	40.5- 59.7	51.8- 77.9	74.0- 98.4
P. Resp.	55.50± 2.90	32.02± 3.06	16.13± 5.56	27.70± 3.64	35.10± 5.63	55.36± 4.69	69.72± 3.73	90.63± 3.42
	48.8- 60.5	25.0- 40.8	3.1- 24.6	20.0- 34.0	22.5- 40.9	40.6- 64.5	59.7- 79.3	84.7- 97.7

The results represent, Average ± probable error, minimum - maximum.

EFFECT OF LABOUR IN TOXAEMIA

In order to study this only cases of normal labour were selected so as to compare values with those in normal pregnancy. All cases of prolonged labour have been excluded as they were found to produce a somewhat erratic response, and require investigation in a sufficiently large series for a proper evaluation. The nature of the changes in normal labour were sufficiently consistent to deserve consideration.

In thirty-one cases of severe pre-eclampsia the prothrombin concentration were determined at the commencement of labour and again when the second stage had started.

The/ [illegible]

The results are presented below -

Prothrombin Concentration:-

	Early	Late	Gain
Average	54.48:S.D.8.46	67.71:S.D.9.10	13.23:S.D.6.31
Min.-Max.	41.9 - 67.0	49.8 - 83.7	6.8 - 24.9

The average increase in prothrombin concentration caused by labour in severe pre-eclampsia was only 34.9 per cent. of the normal value. The maximum rise in this series was less than the minimum in normal labour. The difference in the values between normal labour and pre-eclampsia is significant.

Five cases of eclampsia studied during labour showed a reaction which varied from a decrease (negative reaction) in prothrombin concentration to an increase of 17 per cent. (one case). The results obtained in these cases are shown in Table 106.

Table 106

	Early Labour	Late Labour	Gain
1. Dm.	40.0	40.0	0
2. Dv.	29.0	21.5	- 7.5
3. R.	43.7	60.9	+17.2
4. S.	45.0	49.0	+ 2.0
5. McC.	40.0	29.4	-10.6

The general trend of the reaction is a poor response provided by the stimulus of labour. Both patients who showed a decrease of prothrombin concentration during labour had

had 4 fits, but in a patient (Dm.) who had 6 fits the prothrombin level of the plasma was maintained unaltered during labour. The two patients who showed a positive reaction had 2 and 3 fits (R. and S.) respectively. The number of convulsions, per se, do not seem to have a significant influence on the behaviour of prothrombin during labour.

COMMENTS

Toxaemia of pregnancy affects both prothrombin concentration and response in an adverse manner. The decrease in prothrombin is progressive as the disease increases in severity and bears the same relation to the clinical conditions and blood pressure as the bilirubin excretion and alkaline phosphatase. Prothrombin response to Vitamin K appears to be a more sensitive indicator than the plasma prothrombin concentration as regards the course and prognosis of the disease. We have not come across any reference in the literature where prothrombin response has been studied in toxaemia of pregnancy. Unger and Shapiro (5, 1943) have studied prothrombin response in liver disease and observed that in presence of hepatic inefficiency the temporary hyperprothrombinaemia, which is produced by Vitamin K may be slight or absent. Infact in severe liver disease they found even a negative response to prothrombin. We came across such an "exhaustion phenomenon" in 3 out of 3 fatal cases of eclampsia several hours/

hours before death. A similar reaction was also noticed in 3 out of 5 cases of eclampsia during labour. These findings leave little doubt as to the fact that a state of functional disturbance of the liver exists in severe cases of eclampsia. The results obtained in pre-eclampsia do not indicate such a gross disturbance of function. Exhaustion phenomenon, described above, was never observed in pre-eclampsia.

Rhoads (6, 1939), Pohle and Stewart (7, 1940) and other observers have reported a 40 to 47 per cent. decrease of the prothrombin level of the plasma in hepatic parenchymatous disease. If the normal "pregnancy level" is taken as the standard it is evident that nearly 30 per cent. of mild, 70 per cent. of severe pre-eclamptic patients had less than the minimum normal level of plasma prothrombin. The results of prothrombin response were more striking, for all values obtained in toxaemia were below the normal range (last trimester). The significance of these findings is increased by the fact that Russel's viper venom was used for thromboplastin in these experiments. For, it has been pointed out by some observers (Wilson, 9, 1947; McFarline, 10, 1948; Toohey, 11, 1950) that this thromboplastic substance tends to give low prothrombin time when the prothrombin concentration of the plasma is low. The effect of this is to give comparatively higher values for prothrombin concentration than what really exists.

The/

The liver is regarded as the principal site of formation of prothrombin, although Drinker and Drinker (3, 1910) observed that the bone-marrow is also another site of its origin. The results of clinical investigation in hepatic diseases point out that in presence of a positive result with other hepatic function tests, the fall in the prothrombin concentration and in its response to Vitamin K suggests a disfunction of the liver. In this respect the results presented above indicate that toxaemia of pregnancy is associated with some degree of hepatic functional derangement. The relation of prothrombin to blood pressure suggest that this is probably due to vascular spasm which is associated with toxaemia of pregnancy.

The low prothrombin level of the plasma and the comparatively poor increase labour may provide an explanation for some of the cases of toxic purpura seen during pre-eclampsia and eclampsia, and also for the tendency to haemorrhagic diseases, from which, the infants born of toxaemic mothers sometimes suffer.

CONCLUSIONS

A normal pregnant woman has a high level of prothrombin in the plasma and can mobilise a considerable amount of prothrombin with an additional supply of Vitamin K.

The level of prothrombin in toxaemia is less than that in normal pregnancy. The response of such a patient to Vitamin K is also less than normal. In eclampsia this change is of a very marked nature.

Labour normally causes an increase in prothrombin concentration. This increase is less evident in toxaemia. In some cases of eclampsia even a negative response may occur.

It is suggested that the change in the behaviour of prothrombin is due to a state of hepatic dysfunction. Prothrombin response seems to be a better guide than prothrombin concentration in determining this.

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CHAPTER 6

THYMOL TURBIDITY TEST

The thymol turbidity test, first described by MacLagan (1, 1a, 1944, 1944a) is recognised as a test for damage to the hepatic parenchyma. According to the author himself it "does not test any known function of the liver and should be regarded as an indicator of disturbed liver metabolism rather than a function test". Recent study by Franklin, Popper, Steigmann and Kozoll (2, 1943) indicates the presence of a relationship between histological liver damage and the results of the thymol turbidity test. The test itself is allied to the colloidal gold reaction (1a, 1944a) and the cephalin-cholesterol floculation test (3, 1943).

For the purposes of the present investigation MacLagan's original method (1a, 1944a) was employed, in which the serum turbidity produced by a thymol buffer is compared with standard turbidity comparators. The results were expressed in units. Ley, Lewis and Davidson (6,1946) demonstrated that more precise values can be obtained by using barium sulphate suspension and comparing the turbidity in a photoabsorptiometer, which gives results in terms of ml. of barium sulphate standard. As our investigations were concerned more with a comparative study than with absolute values we regarded this as an unnecessary refinement.

We/

We are not aware of any investigations done on thymol turbidity in either normal pregnancy or toxaemia. The results are presented below.

1. NORMAL PREGNANCY

Seventy two cases of normal pregnancy at different periods of gestation attending the ante-natal clinic were selected for this study.

Table 107

Duration of pre-nancy (months)	No. of Cases	Thymol Turbidity (Units)	Aver.	S.D.
3	6	1.0; 0.8; 0.6; 0.75; 1.1; 0.8.	0.82	0.17
4	8	1.1; 1.0; 0.9; 0.8; 0.75; 0.7; 0.65; 0.80.	0.82	0.15
5	7	1.3; 1.1; 0.6; 1.0; 1.0; 0.7; 0.6;	0.86	0.25
6	7	1.0; 1.0; 1.1; 0.8; 0.9; 0.7; 0.7.	0.88	0.13
7	8	0.9; 1.3; 1.4; 1.0; 0.8; 1.0; 1.2; 1.2.	1.12	0.21
8	12	1.0; 1.3; 1.2; 1.0; 0.9; 1.0; 1.3; 1.2; 1.0; 1.0; 1.3; 1.4.	1.14	0.15
9	12	1.2; 1.6; 1.4; 1.7; 1.3; 1.5; 1.6; 1.7; 1.9; 1.8; 1.8; 1.9;	1.66	0.19
10	12	1.4; 1.8; 2.0; 1.8; 1.9; 1.8; 2.1; 2.0; 1.7; 1.6; 1.9; 1.8.	1.81	0.17
Average	72	0.6 - 2.1	1.22	0.52
Aver. last 3 months	36	0.9 - 2.1	1.54	0.38

The thymol turbidity test was uniformly negative (less than

4 units) in all cases. The density of the turbidity however appears to increase as pregnancy advances to term. Values were uniformly low in early pregnancy. Up to the middle of gestation the maximum turbidity was 1.3 units (one case). At term however values as high as 2.1 units were observed. The average turbidity for the whole series was 1.22 units; S.D. 0.58 and that at term was 1.54 units; S.D. 0.42. The difference between these two values is not of much statistical significance (Table 107).

2. PRE-ECLAMPSIA

The thymol turbidity test was, on an average, negative in pre-eclamptic patients. The turbidity was only 2.07 units S.D. 0.95, i.e. just over 50 per cent. of the maximum allowed for normal individuals. Nevertheless, compared with normal pregnancy the increase in turbidity in toxaemias is 76.4 per cent. Individual values were scattered between wide limits (0.3 to 4.5). The thymol turbidity in 50 cases of mild pre-eclampsia varied from 0.3 to 2.5 units, with an average of 1.19; S.D. 0.55. This actually is a little less than the average for the last trimester of normal pregnancy. Cases of severe pre-eclampsia had a slightly higher thymol turbidity. The average was 2.95; S.D. 0.80 units; and the range was from 1.0 to 4.5 units. A positive result was obtained in only 2 cases (4 per cent.). The frequency distribution is shown in Table 108.

Although the figures do not exceed the maximum limit of normal in 98 per cent. of all cases of toxaemia the

distribution/

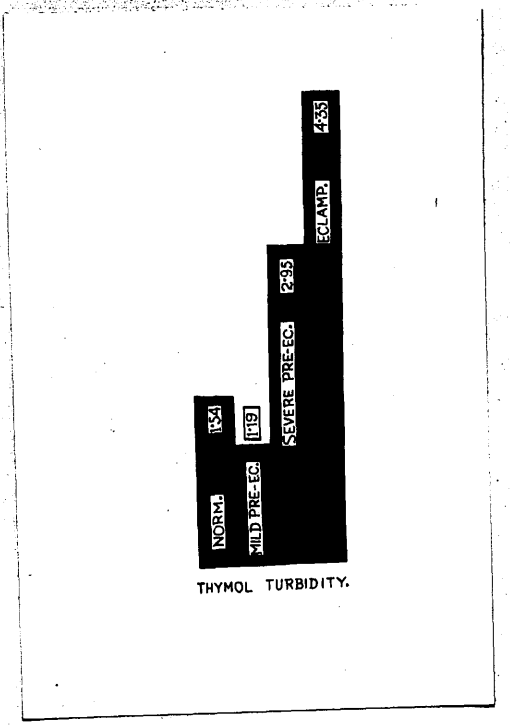

Fig. 67. Thymol turbidity in normal pregnancy, pre-eclampsia and eclampsia.

distribution frequency clearly demonstrates that there is an increasing number of higher values when toxaemia becomes severe. However, in the two patients, where the test was positive, the turbidity was only slightly more than the normal maximum (4.2 and 4.5 units respectively). One of them (W., No.34) was jaundiced at the time the test was done.

Table 108

Frequency Units	Normal	Mild Pre-Eclampsia	Severe Pre-eclampsia	Total (Tox.)
0-1.0	6	26	2	28
1.1-2.0	29	21	11	33
2.1-3.0	1	3	19	22
3.1-4.0	-	-	13	13
4.1-5.0	-	-	2	2
Average	1.54	1.19	2.95	2.07
P.E.	0.38	0.55	0.80	0.95

It is interesting to note, however, that during the three weeks following her admission into hospital the toxaemia deteriorated, although the jaundice showed some apparent improvement. Because of the bad state of her toxaemia labour was induced, and at this time the serum thymol turbidity increased to 5.1 units. In the other patient (McN., No.30) the toxaemia improved during the treatment and the turbidity decreased to 3.5 units. It is interesting to note that on the fifth day after confinement the thymol turbidity in both cases was found to be 0.2 units.

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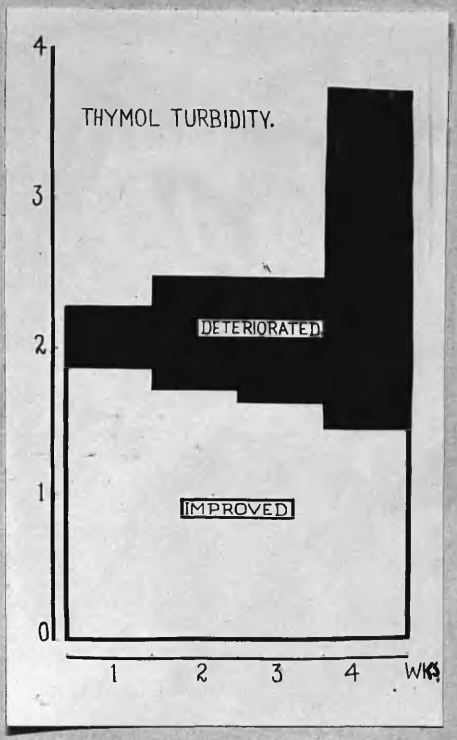

Fig.68. Thymol turbidity in pre-eclampsia showing its relation to the clinical course of the disease.

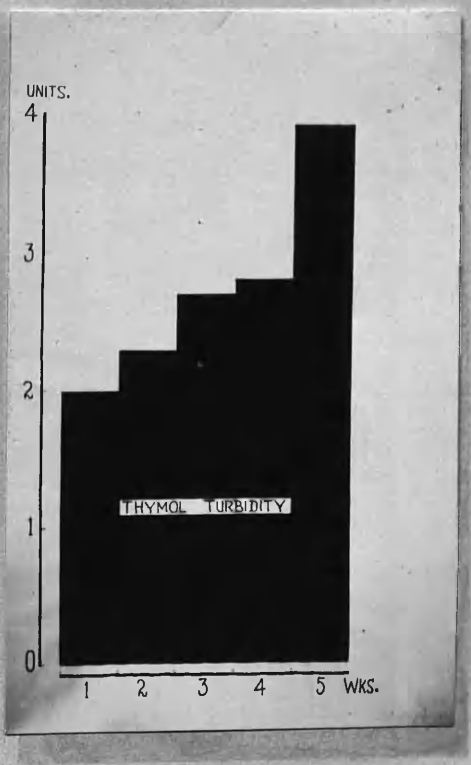

Fig. 69. Thymol turbidity in pre-eclampsia, showing the change in turbidity in relation to the duration of the toxaemia.

11. Clinical Course of Toxaemia.

The clinical course of toxaemia appeared to affect the values in a manner already observed with other hepatic function tests. Abnormal values were observed in a small number of cases only when the disease had attained marked severity. The results are presented in Table 109 and in figures 68 and 69 .

Table 109

	Improved			Deteriorated		
Wks.	Average	S.D.	Min.-Max.	Average	S.D.	Min.-Max.
1	1.89	1.05	0.3-4.2	2.33	1.06	0.7-4.5
2	1.73	1.00	0.3-4.3	2.49	1.18	0.3-4.9
3	1.64	0.99	0.3-4.0	2.49	1.37	0.3-5.1
4	1.45	0.87	0.3-3.0	3.75	0.33	3.0-4.7

One patient in each group had a value of more than 4 units at the time of admission. The position remained unaltered during the second week. But when improvement occurred during the third and fourth weeks abnormal values were no longer observed. The case where the thymol turbidity was 4.3 units (McG.,No.63) during the second week was a case of toxaemia, with jaundice. The jaundice persisted during this investigation. When her condition showed almost complete return to normal the thymol turbidity was 3.6 units.

As the toxaemia deteriorated the incidence of abnormal values increased in each successive week. During the four weeks of study the percentage of cases with abnormal thymol turbidity/

turbidity was, 1.96, 10.6, 31.2 and 60.5 per cent. respectively. A better understanding of the behaviour of thymol turbidity is possible when this is studied in relation to the duration of toxaemia from the time of its onset. The results obtained from such an analysis are submitted in Table 110. These figures demonstrate that up to the second week of toxaemia values higher than maximum normal

Table 110

Duration of Toxaemia Weeks	1	2	3	4	5
Min.-Max.	0.7-3.6	0.8-4.0	1.0-4.9	1.0-4.8	2.1-5.1
Average	1.99	2.29	2.65	2.80	3.94
S.D.	0.90	0.92	0.99	1.19	0.81

did not occur. Subsequently the number of abnormal values increased progressively as the toxaemia persisted or became worse. The incidence of abnormal values in the third, fourth and fifth weeks of toxaemia was 10,5, 43.6 and 79.0 per cent. respectively. This is the cause of the progressive increase of the average values in each group. A study of the range of distribution and of the standard deviation shows the gradual shift of the values to the right throughout this period, the lower values being gradually elevated, while the maximum moves only slightly. Grossly abnormal values from a quantitative point of view were not observed in pre-eclampsia. The change appears to be more of a qualitative/

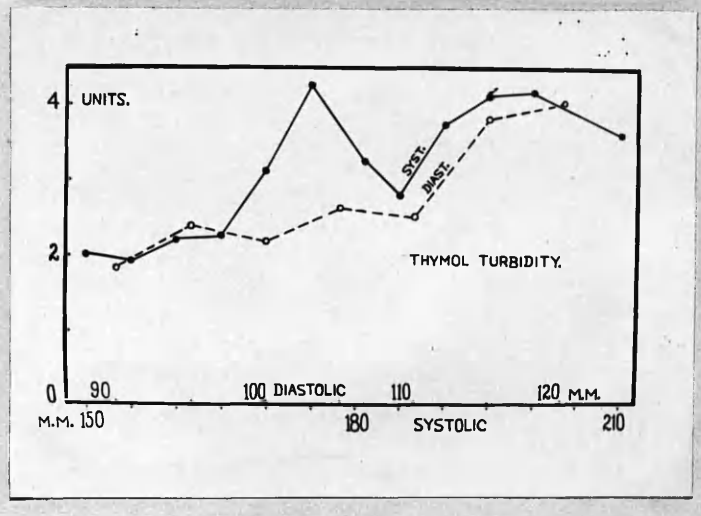

Fig. 70. Thymol turbidity in relation to the systolic and diastolic blood pressure in pre-eclampsia.

qualitative nature and is revealed only when the cases are followed during successive weeks of toxaemia.

111. Blood Pressure and Thymol Turbidity.

When the systolic blood pressure reaches the hypertensive level the thymol turbidity also shows some increase. The average values, however seldom exceed the limit of normality. Individual abnormal values appear to be scattered in each blood-pressure group above 170 mm.Hg. Below this level however the maximum values were below the maximum normal standard, although considerably higher than the maximum observed in normal pregnancy. No definite correlation could be found between the levels of systolic blood pressure in pre-eclampsia and thymol turbidity. For this reason the details of the values are not presented. The results are presented in figure 70.

A study of the diastolic pressure seems to show a slightly closer relationship with thymol turbidity. (Table 111). As in the case of systolic blood pressure, the average shows some fluctuation at the lower ranges of diastolic hypertension, but these variations are small and reveal a general tendency to an increase. At higher levels of diastolic pressure (110 mm.Hg. or more) these variations almost disappear. The first abnormal values in this series (4.2 units) was noticed in a patient with a diastolic pressure of 100 mm.Hg. A consistent increase of thymol turbidity was observed when the diastolic blood pressure

exceeded/

exceeded 110 mm. and at each stage above this level the incidence of abnormal values increased (14.6, 43.6 and 36.1 per cent. respectively) steadily. However, the statistical significance of these values is variable.

Table 111

B.P. mm. Hg.	Aver.	S.D.	Min-Max.	B.P. mm. Hg.	Aver.	S.D.	Min-Max.
<90	1.79	0.35	0.5-2.3	106-110	2.54	1.06	1.5-4.7
91-95	2.37	0.64	1.5-3.4	111-115	3.35	0.27	3.5-4.3
96-100	2.15	0.31	1.0-4.2	116-120	3.99	0.90	1.51-5.1
101-105	2.70	0.51	2.6-3.5	-	-	-	-

3. ECLAMPSIA

The average thymol turbidity in eclampsia was 4.35 units; S.D.1.33. Individual values were found between 1.8 and 7.5 units. Thirty-nine per cent.(7 out of 18 cases) of patients in this series had less than the maximum normal value inspite of convulsions. One of these patients (McL. No.16) presents a particularly interesting feature. She was admitted with a history of one convulsion and in semi-comatose state with a blood pressure of 130/110 mm.Hg. and 13 parts (Esbach) albumin in the urine. At this stage the serum thymol turbidity was 3.7 units. She remained in a semi-comatose state for 3 days when the test was repeated, and thymol turbidity was found to be raised to 9.7 units. This case had a fatal outcome. The lowest thymol turbidity in our series of eclampsias was 1.3 units in a

patient/

patient (B.No.17) whose blood was examined after 3 convulsions. This patient was comatose for less than an hour and made a spontaneous recovery. It may be of interest to mention that she was a subject of essential hypertension before pregnancy occurred. Two other patients, one with 3 and another with 4 convulsions showed only 2.3 and 2.7 units of serum thymol turbidity. In general the number of convulsions, per se, do not seem to have a consistent effect on the level of thymol turbidity. Of the three patients who were under investigation before the onset of eclampsia, one (A. No.13) showed no change (2.3 units) in thymol turbidity after the occurrence of eclamptic convulsions. Another pa tient showed an actual decrease (from 3.6 to 3.3 units; R.No.3). In only one case (H.No.14) there was an increase of thymol turbidity from 2.4 to 4.4 and then to 5.7 units. Nevertheless when the series is taken as a whole, it is found that repeated convulsions tend to raise the thymol turbidity to abnormal levels. In 3 patients who had a fatal outcome, the thymol turbidity values were 10.1, 10.5 and 9.7 units 7 to 21 hours before death.

However, the changes in the liver function, which are responsible for high thymol turbidity values in eclampsia, appear to be of short duration, for the values were found to return to normal in most of thecases within 43 hours after the cessation of convulsions. The results of the follow-up study, presented in Table 112 demonstrate the changes caused by eclampsia.

Table./

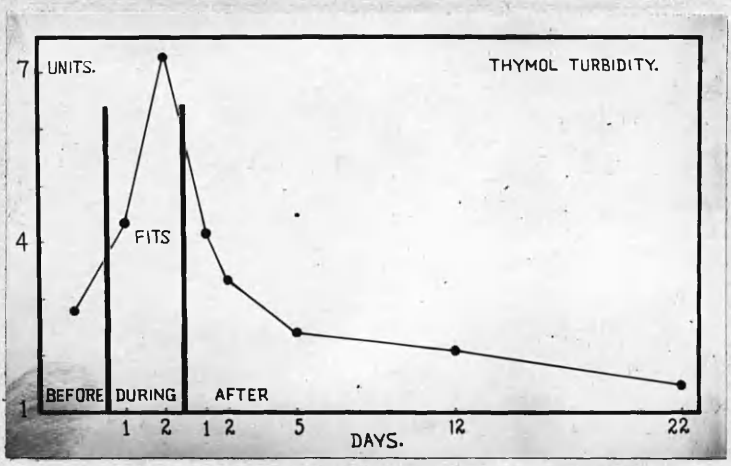

Fig. 71. Thymol turbidity in the pre-convulsive, convulsive and convalescent stages of eclampsia.

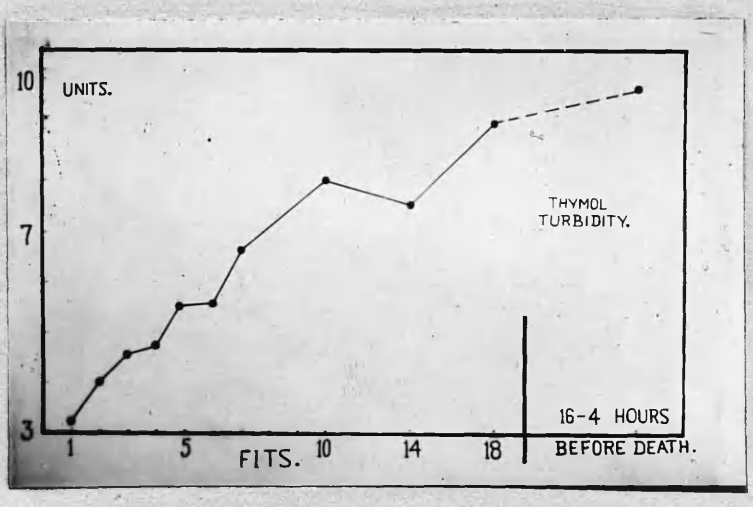

Fig. 72. Thymol turbidity in relation to the number of convulsions in eclampsia.

Table 112

	Pre-convulsive Stage	Convulsive Stage		Post-convulsive Stage				
		1	2	1	2	5	12	22
Min-Max.	2.4-4.4	1.3-7.5	5.7-9.7	3.0-5.0	2.6-4.8	1.3-3.6	1.1-3.0	1.0-2.0
Average	3.3	4.35	7.26	4.17	3.33	2.40	2.10	1.47
S.D.	0.61	1.01	1.41	1.07	0.83	0.94	0.38	0.39

The persistence of the convulsive stage seems to affect the thymol turbidity more than the mere onset of eclamptic convulsions. In 9 patients in our series the convulsive stage was prolonged for more than 24 hours, and in each patient the value obtained was higher than normal. In spite of this, 24 hours after the cessation of convulsions in one-third of the patients in this series normal values were obtained, after a further 24 hours only 16.6 per cent. of the values were above 4 units. By the latter part of the first week the values returned to normal in all cases.

COMMENTS

The results of thymol turbidity in normal pregnancy are uniformly negative. Machagan (1a, 1944a) studied the results of this test in 12 cases of normal pregnancy and arrived at the same conclusion. The mechanism of a positive thymol turbidity reaction is not yet clearly understood, but from comparative studies (1a,3,4) with colloidal gold and cephalin-cholesterol floculation tests, it appears that the turbidity depends mainly upon gamma globulin. Gray and Barron (5, 1943) and several other

investigators/

investigators have pointed out that infective hepatitis and cirrhosis, conditions which cause organic and functional damage of the liver, are associated with an increase in plasma globulin, and it is usually these cases, which give the most strongly positive results. From this point of view normal pregnancy does not appear to be associated with a gross metabolic change. There is one obvious difficulty in interpreting the results of this test as an evidence of hepatic dysfunction. There is no absolute proof that the protein responsible is actually produced by the liver; a possible origin in the reticulo-endothelial system must be considered, and it appears that diseases of the reticulo-endothelial system, e.g. glandular fever, and lympho-granuloma also give a positive result to this test. The significance of this lies in the fact that there are some evidences of abnormal formation of globulin in pregnancy toxaemias (Pt.1. Ch.3). Nevertheless, the incidence of positive results in pre-eclampsia is low. In 304 estimations only 17 positive results were obtained (= 5.6 per cent.). However, from these frankly abnormal values obtained at the time of admission, the follow-up study in pre-eclampsia reveals that, with the progress of the disease the density of the thymol turbidity tends to increase. These facts suggest that the process of toxaemia imposes a continuous strain on the liver, and probably reduces it reserve capacity. Abnormally high values are obtained only when this reserve is exhausted. It is possible that this is

dependent/

dependent upon the degree of vascular spasm (indicated by the level of diastolic blood-pressure) which accompanies toxaemia.

The incidence of positive results in eclampsia (on admission) was much higher than that in pre-eclampsia (39.0 per cent.). If however all the values obtained during the stages of convulsions and coma are considered the incidence of positive results increases to 71.5 per cent. The nature of the change in thymol turbidity revealed by the follow-up study in both the fatal and surviving cases suggest that eclampsia is usually attended by marked disturbance of liver function. The results seem in conformity with those described in the previous chapters.

CONCLUSIONS

The results of the thymol turbidity test in normal pregnancy are uniformly negative. In toxaemia of pregnancy turbidity is found to increase, when compared with that in normal gestation. But abnormal values are obtained in cases of toxaemia only when the disease is of long duration and of marked severity. The incidence of positive results is higher in eclampsia than in pre-eclampsia. The results obtained from this test indicate that there is no gross hepatic damage except in a few cases of severe pre-eclampsia and eclampsia, but they also indicate that there is progressive decrease in the functional reserve of that organ when the disease persists or increases in severity.

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REFERENCES

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CHAPTER 7

GALACTOSE TOLERANCE TEST

Galactose tolerance tests for estimating the functional efficiency of the liver has been performed in several different ways. They can be briefly summarised as follows:-

1. Oral galactose, followed by blood sugar deterioration (Beaumont and Dodds, 1, 1931).

2. Oral galactose followed by estimation of urinary sugar (Shay and co-workers, 2, 1931).

3. Forced galactosuria after graded test meals of galactose (Rowe et al, 3, 1935.).

4. Oral galactose followed by determination of blood galactose (Althausen and Mever, 4, 1937; MacLagan, 5, 1940).

5. Intravenous galactose followed by estimation of blood galactose (King, 6, 1940).

Each method has it advantages provided due consideration is given to conditions which modify or interfere with the results. For the purposes of our investigation we have used the method described by MacLagan (5, 1940) and expressed the results as a galactose index. MacLagan suggested the use of this term (G.I.) as the sum of the four blood-galactose values at 1/2, 1, 1½ and 2 hours in m.gms.per 100 ml. after ingestion of 40 gms. of galactose dissolved in 250 ml. of water. The test was performed in each instance on an empty stomach and after a period of over-night fast. In another series of cases forced galactosuria (Rowe et al, 3, 1935) test was also employed.

A. GALACTOSE INDEX

1/

1. NORMAL PREGNANCY.

Galactose index was estimated in 10 cases of normal pregnancy, between 36 weeks of gestation and term. The average G.I. in this series was 81.36; S.D.19.70. The minimum value was 63.7 and the maximum 128.0.

MacLagan (5, 1940) gives 68 as the average value for normal persons. From this point of view, 9 out of 10 cases of normal pregnancy had more than normal average G.I. In none of these patients, however did the G.I. exceed the normal maximum. The values obtained in these cases are given below.

1.	M.	1 Grav.	36 weeks	Galactose Index -	69.7
2.	S.	1 "	38 "	" "	85.5
3.	McN.	2 "	37 "	" "	63.7
4.	H.	6 "	Full term	" "	71.6
5.	A.	1 "	39 weeks	" "	128.0
6.	McD.	4 "	Full term	" "	76.4
7.	G.	3 "	36 weeks	" "	86.9
8.	C.	1 "	39 "	" "	80.5
9.	McL.	2 "	38 weeks	" "	85.4
10.	P.	1 "	Full term	" "	70.9

2. PRE-ECLAMPSIA

Galactose index was determined in 38 cases of pre-eclampsia. There was considerable difference between the values obtained in individual cases. The mild and severe toxaemias will therefore be presented separately.

1. Mild Toxaemia.

This series consists of 13 cases. The average galactose index was 105.66; S.D. 19.06. The minimum and maximum values were 69.1 and 136.9 respectively. In all cases the value exceeded/

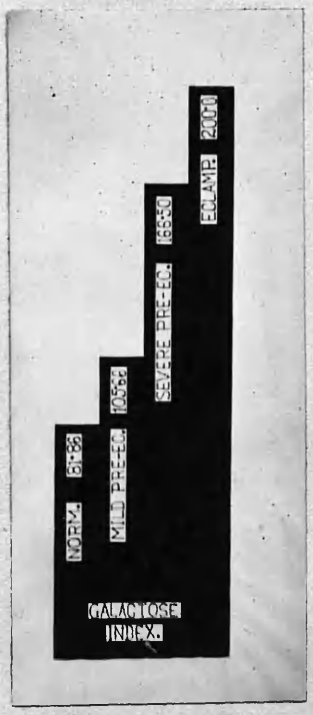

Fig. 73.

Galactose index in normal pregnancy, pre-eclampsia and eclampsia.

exceeded the normal average (MacLagan), but in none was the normal maximum exceeded. In 77 per cent. (10 cases) the G.I. was more than the average of normal pregnancy, but in only 1 patient it was more than the maximum of our series of normal cases. (Figure).

11. Severe Toxaemia.

Galactose index was determined in 25 cases of severe pre-eclampsia. The minimum G.I. in this series was 100.6, and the maximum 214.6. The average value was 166.5; S.D. 29.50. In all cases the G.I. was more than the average for normal persons (MacLagan) as well as that in normal pregnancy. In 44 per cent. (11 cases) it was higher than the normal maximum and in 64 per cent. (16 cases), it exceeded the maximum observed by us in normal pregnancy (Figure 73).

The increase of G.I. observed in mild and severe toxaemia is found to be statistically significant when compared with the value obtained in normal pregnancy. The difference in galactose index between mild and severe pre-eclampsia also shows statistical significance.

In order to provide comparison of data in normal pregnancy and toxaemia the frequency distribution of the values is presented in Table 112.

There appears to be a gradual change in the G.I. from normal pregnancy to severe pre-eclampsia. The distribution of values in the latter condition is in striking contrast to that of either of the other two groups of cases. Mild pre-eclampsia also shows a slight shift of the values to the

right/

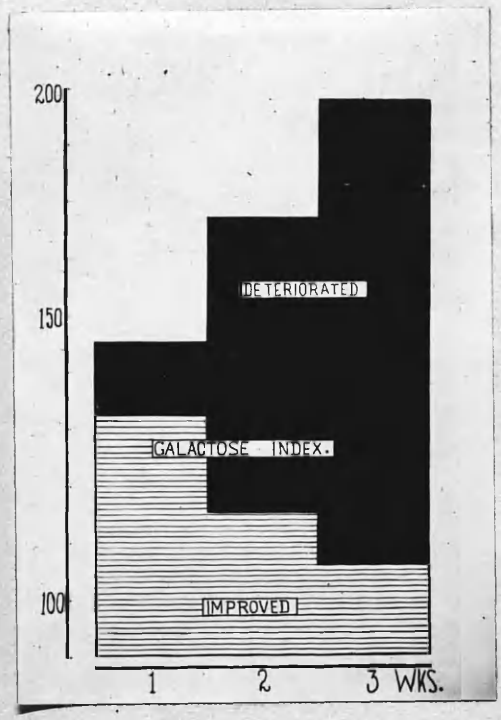

Fig. 74. Galactose index in pre-eclampsia in relation to the clinical course of the disease.

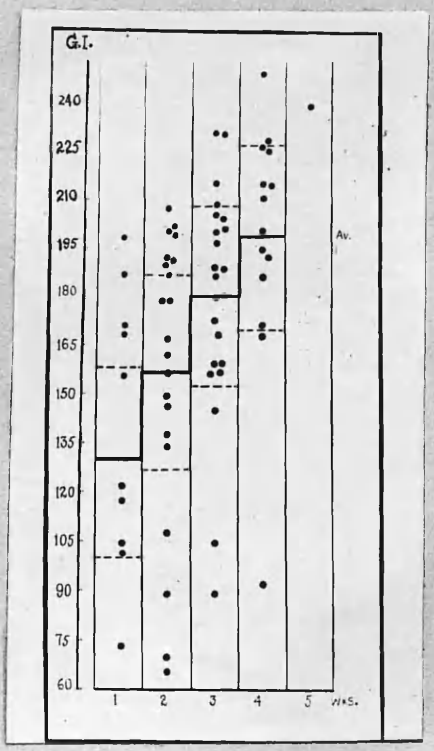

Fig. 75. Galactose index in pre-eclampsia in relation to the duration of the toxaemia.

Table 113

	Improved (11 cases)			Deteriorated (27 cases)		
Weeks	1	2	3	1	2	3
Minimum	71.8	72.1	80.7	69.1	89.4	91.6
Maximum	190.7	148.6	121.0	214.6	248.7	238.0
Average	132.2	115.2	105.8	145.4	167.5	188.1
S.D.	19.9	16.3	16.8	20.5	17.9	19.6

both series appears to be statistically significant. In those patients who were cured of the toxaemia the improvement was most noticeable in the maximum values. During the second stage of study none of the patients had a G.I. exceeding the maximum normal value (G.I. = 160, MacLagan). The minimum values in this series did not show any consistent change. However, when the state of toxaemia became worse the average values demonstrated a progressive deterioration. In order to determine the nature of this change these cases were further analysed in relation to the total duration of toxaemia. The results, presented in figure reveal that the increase in the G.I. in these cases bears a distinct relationship to the duration of toxaemia. It will be evident that the incidence of abnormal values (i.e., 160+) increases progressively from 40.0 per cent. in the first week of toxaemia to 52.4, 78.2 and 92.8 per cent. during the following three weeks. The average shows a steady increase which is statistically significant, and the scatter reveals

a/

a distinct shift to the right during each successive period of investigation.

IV. Galactose Index and Blood Pressure.

As in the previous tests the G.I. obtained from 113 tests performed on 38 cases of pre-eclampsia were studied in relation to the level of blood pressure at the time of the experiments. The results are shown in Table 114 and illustrated in figure 76.

Table 114

Systolic B.P. mm. Hg.		Systolic B.P. mm. Hg.		Diastolic B.P. mm. Hg.	
>150	111.9±10.7	176-180	193.9±10.3	>90	108.1±11.7
151-155	133.1±16.1	181-185	201.8±12.7	91-95	117.0±7.6
156-160	144.6±11.6	186-190	222.8±14.7	96-100	121.8±15.5
161-165	188.6±9.7	191-195	178.0	101-105	163.5±12.6
166-170	186.2±17.5	196-200	185.1±10.8	106-110	178.8±7.0
171-175	190.2±11.4	200+		111-115	200.1±6.5
All results are pexressed as average ± P.E.				116-120	220.7-5.9

The galactose index varies in a direct manner with the blood pressure. The changes in relation to systolic blood pressure, however, are not consistent but an increase of the diastolic pressure, causes a progressive rise in the value of the G.I. It is only slight and not beyond the normal limits (i.e., less than 160) until the pressure exceeds 100 mm. Hg. The first definitely abnormal value for the/

the G.I. is observed when the diastolic pressure reaches 105 mm.Hg. From this stage onwards the increase is progressive. The co-efficient of variation steadily decreases. The maximum G.I. was observed when the diastolic pressure was highest.

3. ECLAMPSIA

For obvious reasons the galactose tolerence test employed by us was not feasible during the stages of active convulsions and coma. The test was performed on 7 cases of eclampsia as soon as the patients had regained a state of consciousness suitable for the performance of the test.

The average G.I. in these cases was 200.0; S.D.21.9, with a range of variation between 166.9 and 224.3. In 3 patients the value exceeded 200 (212.5, 220.5 and 224.3), in the remaining 4 cases the G.I. was 185.2, 183.6, 175.5 and 166.9.

Thus, apart from the fact that all cases of eclampsia had an abnormal G.I., it is evident that the extent of the increase in value (25 per cent. above the normal maximum) is much greater than that observed in severe pre-eclampsia. In only one case did we succeed in doing galactose tolerence tests during the pre-eclamptic state. The G.I. was 158.6, & 160.4, eight and three days, before the onset of convulsions. As a result of the eclampsia the G.I. increased to 183.6. This represents a gain of 14.5 per cent. above the highest value obtained during the pre-eclamptic stage. In all cases in this series the test was repeated on the tenth day of convalescence/

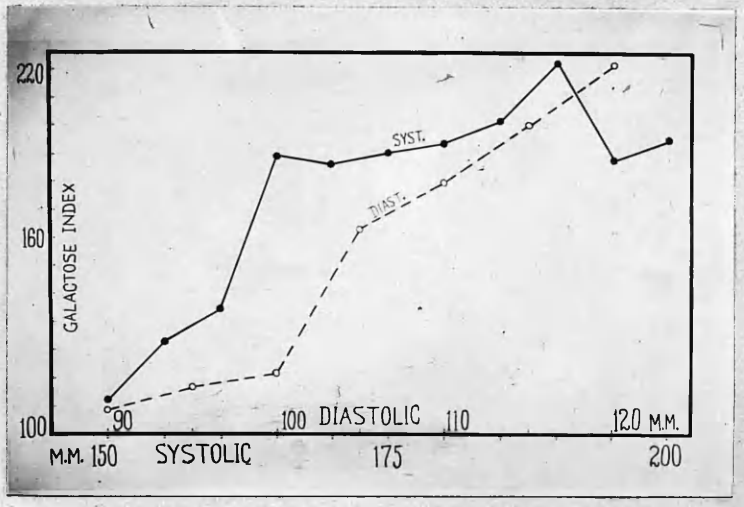

Fig. 76. Galactose index in relation to the systolic and diastolic blood pressure in pre-eclampsia.

convalescence. The average G.I., at this stage was 74.8; S.D. 22.8, with a maximum and minimum range of 104.6 and 50.7. These figures scarcely vary from the normal values given by MacLagan.

B. FORCED GALACTOSURIA

After a period of overnight fasting, each patient received a graded test meal of galactose (Rowe et al, 3a, 1936) dissolved in 150 to 250 ml. of water. Prior to the test the bladder was emptied and urine was collected at hourly intervals for 5 hours after the administration of galactose. Each sample of urine was tested qualitatively for galactose and a positive result was recorded only when a definite reducing reaction was obtained. For each test adequate controls of urine (obtained before the test), yeast (used for fermentation), standard galactose solution and mixture of galactose and yeast were also examined. The dose of galactose employed was 15 to 40 gms., increasing by 5 gms. at each stage.

Thirty cases of normal pregnancy between 36 weeks and term were tested in order to obtain normal values. Fifty cases of pre-eclampsia of varying severity and 10 cases of eclampsia were studied. The results obtained from this investigation are shown in Table 115 and figure 77.

It will be evident that, 20 gms. of galactose were tolerated by all cases of normal pregnancy, but 40 gms. produced galactosuria. In the intermediate stages the rate of utilisation of galactose decreased progressively with the

increase/

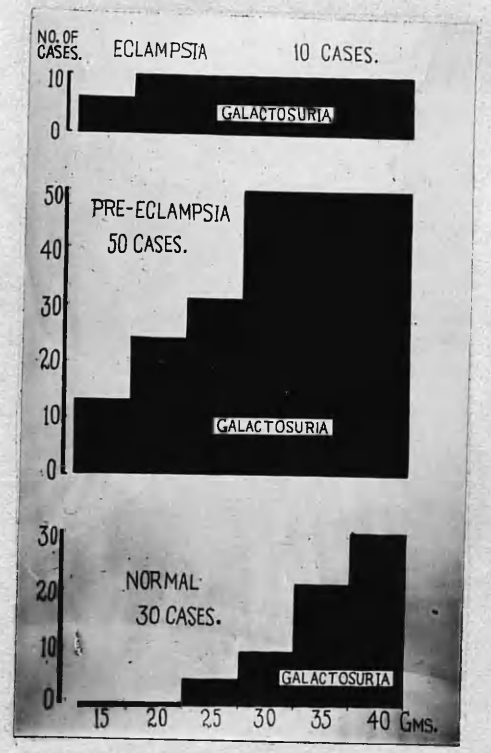

Fig. 77. Forced galactosuria in normal pregnancy, pre-eclampsia and eclampsia.

Table 115

Galacose gms.	Normal (30 cases)		Pre-eclampsia (50 cases)		Eclampsia (10 cases)	
	No. of cases (Galactosuria)					
	+	-	+	-	+	-
15	0	30	3	47	6	4
20	0	30	14	36	10	0
25	4	26	31	19	-	-
30	9	21	50	0	-	-
35	21	9	0	0	-	-
40	30	0	0	0	-	-

increase in dosage. Most normal cases tolerated 30 gms. of galactose, but with 35 gms. 70 per cent. of the patients shows signs of intolerence. Galactosuria appeared in 28 per cent. of the pre-eclamptics after 20 g. of galactose. With 30 gms., which produced galactosuria in 30 per cent. of cases of normal pregnancy, all pre-eclamptic patients developed galactosuria. Seventy-two per cent. of patients suffering from toxaemia could tolerate only 20 gms. of galactose (c.f. normal pregnancy, 30 gms.). It is of interest to note that 14 out of 19 cases of pre-eclampsia who tolerated more than 20 gms. of galactose without developing galactosuria were suffering from a mild degree of toxaemia. No patient who had a diastolic blood pressure of 110 mm.Hg. or more, remained without galactosuria after 25 gms. of galactose.

The limit of galactose tolerence was found to drop further in cases of eclampsia. Less than 15 gms. appeared to/

to be the limit of tolerence in this series.

COMMENTS

Galactose tolerence tests reveal only a slightly reduced tolerence for this sugar in normal pregnancy. The individual values for galactose index obtained by us in pregnancy do not appear to be grossly different from those obtained by MacLagan (5a, 1944) in normal "controls". The average G.I. in normal pregnancy is to some extent higher than that in non-pregnant individuals and in normal students (5a, 1944). The difference however, is of little statistical significance. The results of forced galactosuria are more striking. Dietel (7, 1936) observed galactosuria in 14 per cent. of normal pregnant women after the ingestion of 20 gms. of galactose. Rowe and co-workers (3a, 1936) found that the limit of tolerence for galactose at term was between 20 and 30 gms., and that the incidence of decreased tolerence increases with the advancement of pregnancy. Our figures, which were obtained from cases between 36 weeks and term are in fairly close agreement with these observations. Compared with non-pregnant individuals, normal pregnancy appears to cause a slight decrease in the tolerence for galactose.

This, however, need not necessarily be considered as an evidence of hepatic dysfunction (c.f. alkaline phosphatase, prothrombin and thymol turbidity). We are of the opinion that this slightly decreased tolerence is only an expression of/

of the altered carbohydrate metabolism during gestation.

In toxaemia of pregnancy conditions appear to be different. The results of both G.I. and forced galactosuria suggest a marked inability on the part of the liver to utilise galactose for building up the glycogen reserve. In 'non-nephritic' toxaemia of pregnancy Rowe et al (3a, 1936) found that the limit of tolerence was less than 30 gms. in 87 per cent. of cases. In our series 25 gms. of galactose was tolerated by only 62 per cent. of cases, and 30 gms. caused galactosuria in all patients. The results of the G.I. also demonstrate a markedly decreased tolerence for galactose in toxaemia, which is especially manifested in severe pre-eclampsia and in eclampsia. The behaviour of the G.I. in relation to the clinical course and progress of the disease also suggest that this abnormal G.I. is directly related to the severity of toxaemia. It is possible that the disturbed carbohydrate metabolism which is aggravated in toxaemia (Pt.1, Sc.2) may explain this decreased tolerence for galactose. In this connection, it is interesting to find that Rowe (3b, 1935) observed a depressed tolerence for galactose in hyperfunctional states associated with the anterior lobe of the pituitary.

The study of the G.I. in relation to blood pressure, demonstrates that an increase of vascular spasm (diastolic hypertension) predisposes to high levels of G.I. This brings the results of the galactose tolerence tests in conformity with other tests of hepatic functions already

described/

described. King (6, 1940) observed a decreased tolerence for galactose in experimental hepatic poisoning. In 10 cases of "toxic jaundice" with, or without cirrhosis of the liver, MacLagan (1a, 1940) found the G.I. to vary from 197 to 584. The values obtained by us are not so high but MacLagan's figures refer to conditions which are known to produce damage to the hepatic parenchyma. Nevertheless, the G.I. is undoubtedly abnormal in both severe pre-eclampsia and eclampsia. The relation which exists between hypertension and the G.I. suggests that interference with the hepatic functions may be one of the factors responsible for the high values observed in these cases. In the present state of our knowledge it is difficult to decide to what extent these abnormal values are due to a generally disordered state of carbohydrate metabolism.

CONCLUSIONS

Normal pregnancy gives rise to a slightly decreased tolerence for galactose. This does not appear to be of a grossly pathological nature.

In toxaemia of pregnancy, the metabolism of galactose is markedly interfered with. This is shown by the high levels of galactose in the blood and the frequent incidence of galactosuria. This reduced tolerence for galactose may be a manifestation of a depressed hepatic function. The possibility of the disturbed carbohydrate metabolism in toxaemia and the possible role of endocrines require

investigation/

investigation before the results of galactose tolerence tests can be interpreted in terms of functional efficiency of the liver.

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CHAPTER 3

A REVIEW OF HEPATIC FUNCTION TESTS IN NORMAL PREGNANCY AND IN PREGNANCY TOXAEMIA

Opinions on the state of hepatic efficiency in normal pregnancy are divided. All investigators have found a certain percentage of "positive results" with various tests employed during normal pregnancy. Consequently, the sensitivity of these tests have been doubted and different authors have advocated different selective tests for estimating the dysfunction which is believed to exist during an uncomplicated gestation. Thus, Drill and Ivy (1, 1944) consider that bromsulphthalein test is most selective in detecting liver injury. Soffer (2, 1933), Sullivan et al (3, 1934) Cantarow and co-workers (4, 1935) place most reliance on the bilirubin excretion test. Estimation of alkaline phosphatase is strongly advocated by Freeman (5, 1933). Takata-ara reaction by Dexter and Weiss (6, 1941), Hippuric acid test by Hirsheimer (7, 1939), Galactose tolerence test by Dietel (3, 1936), and Amino acid tolerence by Botella Llusia (9, 1936).

In the interpretation of these tests, however, very little consideration has been given to the anatomical, physiological and metabolic changes which normally accompany the state of pregnancy. Allowance must be made for the physiological demands of the foetus, the onset of a new status of endocrine equilibrium, and mechanical factors created by the distension of the uterus and a consequent displacement of/

of the abdomino-thoracic organs, before the values obtained from the liver-function-tests in pregnancy can be declared as abnormal. This subject has been discussed in connection with alkaline phosphatase and bilirubin retention. Both these tests have been found to give results, which are normally indicative of hepatic dysfunction. It has however been pointed out that when the normal changes caused by pregnancy are taken into account, these apparently "abnormal" results need not be regarded as manifestations of liver injury. This receives confirmation from the thymol turbidity tests and estimation of prothrombin. The changes in plasma fibrinogen, albumin:globulin ratio and carbohydrate metabolism have also been shown to be caused by a state of altered metabolism probably related to the new endocrine status which develops during pregnancy. To regard all these findings as manifestations of hepatic dysfunction, as has been done by some of the investigators (10, 1933) would amount to treating pregnancy as a "pathological" condition. When the results of the hepatic function tests are considered in the light of the normal changes during pregnancy, the available evidence does not suggest the existence of a gross dysfunction of the liver during uncomplicated gestation. Histological study of the liver by Rolleston and McNee (11, 1929), and liver biopsy studies made by Ingerslev and Teilum (12,1945) provide ample support for this belief.

Toxaemia of pregnancy however presents a different proposition. The results of our own investigations as well

as/

as those of most other investigators demonstrate that the values obtained in pre-eclampsia and eclampsia are abnormal. This is most strikingly observed with bilirubin retention test, and estimation of plasma alkaline phosphatase. Prothrombin concentration and response also show a similar deterioration, but to a less marked degree. Of all the tests employed, thymol turbidity showed the least positive results, although even with this test strongly positive reactions were obtained when the toxaemia was of severe degree. The results of our studies suggest that the gross metabolic disturbance in severe toxaemia and eclampsia are associated with variations in the functional capacity of the liver. The importance of these findings is enhanced by the fact that both the metabolic studies and hepatic function tests were carried out on the same patients and at the same time. We have not been able to trace any other investigation in the literature where a simultaneous study of functional and metabolic tests were carried out on the same subjects over a period of time. This has provided us with the opportunity of comparing the results obtained from the various investigations undertaken. As the thymol turbidity test yielded theleast number of positive results, the results of all other tests were compared against this. The result of this study is given in Table 116 and figure 78.

This comparative analysis indicates that there is some parallelism between the results obtained by the various tests for/

Table 116

Thymol Turb. Units	0-1.0	1.1-2.0	2.1-3.0	3.1-4.0	4.1-5.0	5.1-6.0
Alk. Phosph. Units	14.23-0.95 12.5 -20.5	15.33-1.56 12.9 -25.6	13.52-2.55 13.2 -29.5	20.93-2.66 13.4 -29.8	26.81-2.03 13.4 -30.0	31.56-0.78 30.4 -32.5
Bil. Pet. Percent.	5.31-2.63 0.4 -13.6	3.33-2.54 1.3 -23.7	11.60-1.90 2.9 -26.3	16.61-3.44 6.7 -28.6	23.51-2.12 13.4 -33.9	27.75-0.95 25.6 -28.9
Proth. Resp. Percent.	70.83-3.83 34.0 -90.0	60.74-3.43 37.2 -38.0	55.17-7.42 30.8 -32.9	43.92-5.73 29.7 -63.0	34.26-5.31 28.6 -43.4	34.17-0.23 28.6 -24.7
Sugar Mobl. mgms./100 ml.	19.37-0.72 16.5 -23.0	19.03-1.39 15.0 -22.0	17.07-2.09 8.6 -21.4	15.16-2.13 7.6 -21.5	10.63-1.67 6.8 -13.0	6.94-0.55 6.0-3.5
T : E Cholesterol	1.49-0.05 1.38-1.39	1.52-0.07 1.44-1.90	1.58-0.08 1.47-1.94	1.69-0.10 1.48-1.97	1.80 -0.08 1.52 -1.97	1.93-0.05 1.80-1.93
Amino Acid N. mgms./100 ml.	6.62-0.53 5.5 -9.7	7.46-0.54 6.2 -9.2	8.01-0.61 6.4 -10.6	8.65-0.65 7.2 -11.4	12.21-1.69 8.1 -18.8	17.93-1.41 14.4 -23.0

Figures represent average - P.E., minimum - maximum.

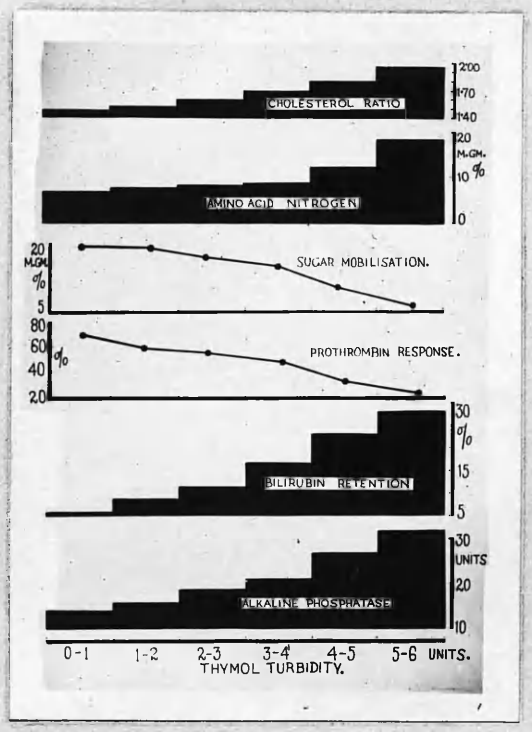

Fig. 78. Comparison of the metabolic and functional tests of the liver in pre-eclampsia. All findings have been correlated to the results of the thymol turbidity test.

for hepatic efficiency. The gradient of the change and statistical significance are, however, not uniform. Statistical significance was present at all stages only with alkaline phosphatase and bilirubin retention. With other tests this appeared only at higher levels of thymol turbidity. Least significant changes were present in the results of prothrombin response and sugar mobilisation. Cholesterol ester ratio showed definitely abnormal values only when the thymol turbidity was also high (4+ units). Galactose tolerence is not included here, as the test was not done on all patients in this series.

The significance of this analysis lies in the fact that all hepatic function tests do not seem to reveal signs of dysfunction in the same order. Thordarson (13, 1941) has suggested that there is a selective interference with hepatic functions at different stages of the disease. This implies that in early stages of pre-eclampsia several hepatic function tests must be employed before the functional status of the liver can be determined. In this respect we have observed bilirubin excretion test to be most satisfactory. However, when the toxaemia is severe and of long duration the results of all the tests showed consistent abnormality.

The cause of the hepatic dysfunction in toxaemia of pregnancy is less easy to understand. The hypothetical toxin, would have explained the condition, but it still waits to be discovered. Bilirubin excretion test clearly demonstrates that the degree of hepatic dysfunction which is present in

pre/

pre-eclamptis and eclampsia is not evident in nephritis and early stages of essential hypertension complicating pregnancy. It has been demonstrated that the changes observed in the different investigations showed no significant relationship to the degree of oedema and albuminuria. There was, however, a definite correlation with blood pressure, especially diastolic pressure when it was abnormal. This latter is an expression of arterial tension, and it is evident that as the vascular spasm increases, the functional efficiency of the liver suffers with it. It is reasonable to conclude that a long-continued spasm of the vessels, especially those supplying the liver, can give rise to a state in which functions of this organ commence to suffer. There is adequate evidence to support this hypothesis. Although both hepatic artery and portal vein carry blood to the liver, the organ depends upon the hepatic arterial supply for 30 per cent. (Barton-Opitz, 15, 1910, 1911) of the total blood flow and 40 per cent. (Schwiegk, 16, 1932) of the total oxygen supply. It has been shown by Blalock and Mason (17, 1936) that constriction of the hepatic artery causes a marked reduction of the oxygen content of the hepatic venous blood and the hepatic venous outflow is reduced by almost 30 per cent. These authors also point out that the compensatory increase of the portal venous flow under these conditions is inadequate and is of a short duration.

The significance of these observations is obvious in

pre/

pre-eclampsia and eclampsia. Persistent vascular spasm naturally creates a state of oxygen deficit in the organ, and the experimental study of Engel, Harrison and Long, (18, 1946) demonstrates that the liver cells may suffer irreversible damage if anoxaemia persists for a long time. The viviperfusion experiments of Frank, Seligman and Fine (19, 1946) also point out the importance of an adequate arterial supply for the maintenence of the normal hepatic functions.

The importance of vascular spasm in toxaemia of pregnancy is therefore, obvious. In the next section of the thesis, are presented the results of investigation into the nature and origin of this spasm affecting the blood vessels.

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SECTION 2.

CHAPTER 1.

PRELIMINARY STUDIES ON VASCULAR SPASM IN TOXAEMIA OF PREGNANCY

Introduction.

Studies on both metabolism and hepatic function tests suggest that a dysfunction of the liver is associated with toxaemia of pregnancy and that this functional derangement is in a manner related to the level of the diastolic blood pressure. Hypertension is a characteristic feature of toxaemia of pregnancy and a high diastolic pressure under such conditions is indicative of a state of vascular spasm. Spasm of the blood vessels have long been believed to constitute an important manifestation of pregnancy toxaemia. Zangemeister (1, 1916) and Stroganoff (2, 1923) held this responsible for the eclamptic convulsions. Irving (3, 1936), Chesley (4, 1939) and other workers believe that albuminuria in pre-eclampsia is due to vascular spasm. Investigations of Baird and Dunn (5, 1933), Kellar, Arnott and Matthew (6, 1937) demonstrate thickening of the glomerular vessels which may be manifestations of a persistant spasm. Byrom (7,1937) demonstrated that the hepatic lesions of eclampsia could be reproduced in rats with injections of pituitrin which is known to be a vasospastic agent. Direct evidence of the existence of a state of vascular spasm in toxaemia is however scanty. Increased response to pituitrin (de Valera & Kellar, 6a, 1933; Browne, 8, 1943; Mukherjee, 9, 1941) and cold pressor test (Dieckmann/

(Dieckmann, 10,1941) suggest that the vasomotor apparatus is abnormally sensitive to stimuli in pregnancy toxaemia, but this by itself does not show that a state of vascular spasm forms the basic feature of the condition. Direct visualisation of the arteries have been attempted. Baer and Reiss (11, 1924) using capillary microscope observed elongation and beading of the capillaries of the nail bed. Mussey (12, 1936) found similar changes in the capillaries in tissues obtained from the pectoral muscle biopsy. The retinal arteries are accessible to inspection, but Grace Jones (13, 1937) found "difficulty in recognising functional narrowing and constrictions" of the retinal arteries and Mussey and Mundell (14, 1939) agree with Jones and state that the functional spasticity of the retinal vessels in its incepiency may not be recognised.

It is therefore obvious that although vascular spasm is known to be the principal feature of toxaemia of pregnancy, clinical evidence in this respect is far from adequate. It, as has been stated that, the metabolic disturbances and hepatic functional disorders in toxaemia are related to vascular spasm, then the existance of such a state should be demonstrated by clinical means. In the following chapter the necessary data are presented to show that a state of vascular spasm exists in toxaemia of pregnancy and that there are means by which the extent of this can be judged in clinical practice. The writer feels that this/

this has an immense practical significance in assessing the course and prognosis of a case of toxaemia.

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STUDIES ON HYPERTENSION IN PREGNANCY TOXAEMIA

CHAPTER 2.

HYPERTENSION IN TOXAEMIAS OF PREGNANCY

A CLINICAL STUDY.

Hypertension is usually regarded as the most important manifestation of toxaemias of pregnancy. In the majority of cases it is the earliest symptom to appear. The standard of normal blood pressure during pregnancy, however, varies to some extent with different authors. Thus, Browne (1, 1946) states that a reading above 120/80 mm. Hg. should be regarded as abnormal. De Lee and Greenhill (2, 1948) and Stander (3, 1948) are of the opinion that 130/90 mm. should be reckoned as the maximum limit of normal blood pressure. Eden and Holland (4, 1948) consider the pressure high when it reaches 140/90 mm. McIlroy (5, 1936) gives 130/90 mm. Hg. as the highest limit of normal blood pressure during pregnancy.

Owing to this difference of opinion, it was considered that the standard of normal blood pressure during pregnancy for the cases seen in the Glasgow area should be known before the nature of hypertension in toxaemias could be studied. With this object the blood pressure readings of 480 cases of normal pregnancy attending the antenatal clinic were analysed. The personal factor of the/

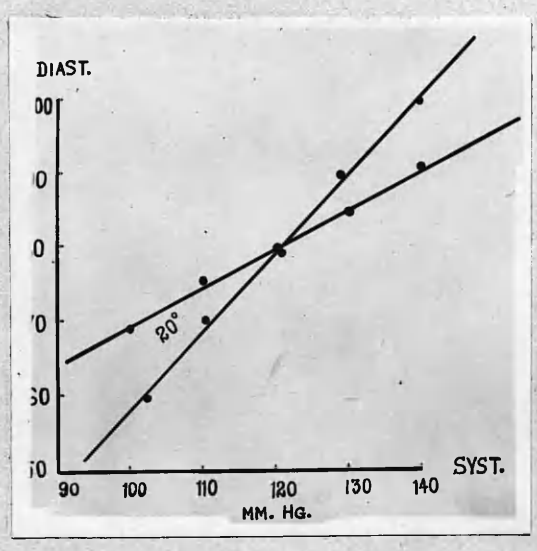

Fig. 84. Corelation between systolic and diastolic blood pressure in normal pregnancy. The extent of corelation is 0.939, which indicates a satisfactory aggreement between the systolic and diastolic pressure levels.

the physician plays an important role in the values for blood pressure obtained in a busy antenatal dispensary. Consequently, the values selected for examination needed verification. The systolic and diastolic blood pressures were subjected to mutual statistical correlation (Figure84). The extent of correlation was found to be 0.939, which indicates a high degree of agreement.

The range of blood pressures obtained in this analysis varied from 140 to 90 mm.Hg. systolic, and 94 to 55 mm.Hg. diastolic. The frequency distribution is given in Table 129.

Table 129

Syst. B.P. Mm.Hg.	No. of Cases	Per cent.	Diast. B.P. Mm.Hg.	No. of Cases	Per cent.
90	2	0.4	60	29	6.0
100	21	4.3	70	81	16.9
110	63	13.1	80	219	45.6
120	158	33.0	90	139	30.0
130	202	42.0	100	12	2.5
140	34	7.2	-	-	-

This table shows the frequency distribution of systolic and diastolic blood pressure in normal pregnancy.

It will be seen that 75 per cent. of these cases had a blood pressure between 111 and 130 mm.Hg. systolic, and 71 and 90 mm.Hg. diastolic. In 95 per cent. of all cases the blood pressure was within the ceiling level of 130/90 mm.Hg. For out study of hypertension, therefore, this figure has been accepted as the standard of <u>maximum</u> normal blood pressure during pregnancy.

The/

The analysis of hypertension is based upon the blood pressure readings in 346 cases of hypertensive toxaemia of pregnancy. As the systolic blood pressure only has been hitherto regarded as the measure of hypertension, the readings obtained at the time of the highest systolic blood pressure were used as materials for this study. The maximum and minimum values, in the whole series, were 240 and 132 (systolic), and 140 and 90 (diastolic) mm.Hg. respectively.

In recent years toxaemias of pregnancy have been regarded as functional disorders of the vascular system, which are manifested by increased tonicity and spasm of the arterioles of the body (Herrick, 6, 1933). The hypertension is due to the increased peripheral resistance to the blood flow. This necessarily implies a rise in the systolic blood pressure caused by a compensatory mechanism, whereby a powerful cardiac systole overcomes the resistance offered by the already distended aorta, and arterial trunks. In normal individuals, emotional and psychical states may give rise to a similar condition, owing to the stimulation of the splanchnic and visceral motor nerves, but in such a state, the normal pulse pressure: diastolic pressure: systolic pressure ration of 1:2:3 is usually maintained. An adequate/

adequate and proportional rise of the systolic blood pressure in response to a diastolic increase is extremely important from the point of view of an efficient circulation, and the normal functioning capacity of the organs. This subject has been adequately discussed by workers on essential hypertension (Hay, 7, 1931; Pickering, 8, 1939; Lyon, 9, 1940; Gilchrist, 10, 1941). In this connection, Laubry (11, 1935) pointed out that, in presence of arteriolar hypertension, the systolic blood pressure should be 1.7 times that of the diastolic pressure. As long as this ratio is maintained the hypertension has been called harmonious or balanced hypertension. Failure of the maintenance of this ratio is usually due to an abnormal state of the systolic pressure, whereby the pulse pressure becomes disproportionately high or low, the former causing a divergence of the values and the latter a convergence. Divergent hypertension is usually seen in younger people, as a result of nervous influences, or hyperthyroidism, while a convergent hypertension often indicates a diminishing efficiency of the heart.

It is thus, obvious that, in any analysis of hypertension the mutual relationship which exists between systolic and diastolic blood pressures is of considerable importance. In all our cases, the systolic: diastolic ratio was determined, and studied in relation to the clinical condition and course of the disease. The patients have been divided into four groups, and the results are presented below.

ANALYSIS OF DATA

Group 1. Hypertension in early pregnancy, without any "toxaemia" during the last trimester. This group consisted of 191 cases, all of whom had a blood pressure of more than 130-90 mm.Hg. on at least two antenatal visits between the third and fifth months of pregnancy. The hypertension persisted throughout the period of gestation, but there was never any albuminuria and oedema. The systolic blood pressures observed at different levels of diastolic pressure are given in Table 130.

Table 130

Diast. B.P. mm.Hg.	Av.Syst. B.P. mm.Hg.	Stand. Dev.	Min. - Max.	Ratio
90	155.2	14.3	140 - 180	1.73 ± 0.13
100	171.6	17.2	144 - 190	1.72 ± 0.11
110	187.0	19.7	150 - 210	1.70 ± 0.14
120	207.5	21.7	170 - 234	1.73 ± 0.10
130	218.0	23.6	186 - 240	1.68 ± 0.16
140	237.6	20.0	210 - 262	1.70 ± 0.11
150	255.5	16.6	230 - 275	1.70 ± 0.11

This table shows the blood pressure and the systolic: diastolic ratio in hypertension unassociated with toxaemia.

It will be evident that, inspite of high levels of systolic blood pressure, the ratio of the systolic and diastolic pressures remained fairly constant. The advancement of pregnancy in these cases did not upset the balance between the peripheral resistance and the cardiac output, and provided a state of harmonious hypertension.

The/

The absence of clinical symptoms of toxaemia, notwithstanding the high blood pressure, is interesting and is in striking contrast to the conditions in the following groups.

Group 2. Hypertension in early pregnancy with "toxaemia" during the last trimester. There were 164 patients in this group, all of whom had some degree of albuminuria and/or oedema during the last three months of pregnancy. The initial blood pressure was the same as in Group 1. The blood pressure readings were subjected to a similar analysis and the results are presented in Table 131.

Table 131

Diast. B.P.	Av. Syst. B.P.	S.D.	Min. - Max.	Syst.: Diast.
90	146.1	14.0	134 - 168	1.62 ± 0.14
100	161.4	16.3	140 - 190	1.61 ± 0.12
110	175.0	13.4	150 - 200	1.59 ± 0.10
120	186.0	16.0	162 - 210	1.55 ± 0.11
130	191.2	19.1	165 - 218	1.51 ± 0.09
140	208.5	17.1	180 - 232	1.49 ± 0.12
150	222.1	15.5	200 - 250	1.43 ± 0.12

This table shows the blood pressure and the systolic: diastolic ratio in hypertension associated with toxaemia.

The obvious difference between this and the preceding group is the comparatively low levels of systolic at equivalent levels of diastolic pressure. The effect of this is seen in the ratio which in the first group was 1.71 and in the present group 1.57. The difference between these ratios is statistically significant. It must be pointed/

pointed out, however, that the systolic: diastolic ratio in the present group of cases is not grossly abnormal. Nevertheless there is a marked tendency for this ratio to decrease. This is even more evident from a study of the ratios at each individual level, for as the diastolic pressure ascends the ratio progressively declines.

Group 3. "Toxaemia" in the last trimester without any hypertension in early pregnancy. This group consisted of 491 patients. There was no hypertension or albuminuria in early pregnancy in any of these patients. In the latter part of gestation, however, they developed hypertension and all but 9 albuminuria. The relation between the systolic and diastolic pressures is shown in Table 132.

Table 132.

Diast. B.P.	Av. Syst. B.P.	S.D.	Min. - Max.	Syst.: Diast.
90	138.7	12.5	130 - 170	1.54 ± 0.10
100	153.0	16.1	134 - 190	1.53 ± 0.12
110	171.3	17.3	150 - 200	1.56 ± 0.10
120	179.8	19.2	160 - 200	1.50 ± 0.09
130	191.0	14.3	170 - 220	1.47 ± 0.09
140	203.3	15.4	185 - 240	1.45 ± 0.10

This table shows the blood pressure and the systolic: diastolic ratio in true pregnancy toxaemia.

The average systolic blood pressure values in the present group compares satisfactorily with those of Group 2, where toxaemia was superimposed on pre-existing hypertension. The ratio of systolic and diastolic pressures, average 1.53, is less than that of either of the two preceding/

preceding groups of cases. However, both the average and the individual ratios at different levels of diastolic pressure are close to the values observed in normal non-pregnant individuals, except at the high levels of diastolic blood pressure, when the ratio inclines to fall below the normal limit, and reveals the tendency to a convergence of the systolic and diastolic pressure readings. It will be seen that the individual values as well as the average for the ratio are considerably less than the value regarded as optimum for an harmonious hypertension.

Group 4. Blood pressure during the eclamptic state.

Blood pressure readings from 90 cases of eclampsia during the stage when convulsions persisted were also submitted to a similar analysis. The most useful information would have been that obtained from readings immediately preceding the convulsions, but for obvious reasons, this was not practicable. All blood pressure readings taken within a quarter of an hour after the cessation of a convulsion were excluded in order to avoid the disproportionate systolic rise which occurs during a severe muscular effort, viz. convulsions. The results are presented in Table 133.

These figures leave little doubt as to the diastolic pressure exceeding the normal limit of proportion. The ratio of systolic: diastolic pressure at all stages lies below the value obtained in normal persons and is considerably less than that observed in balanced or harmonious hypertension. The tendency to a convergence of the

systolic/

systolic and diastolic pressure readings is more obvious in this, than in any of the preceding groups of cases. In only 1 patient (1.1 per cent.) in this series the ratio was 1.7. In 24 (26.7 per cent.) it was just above 1.5, while in 65 cases (72.2 per cent.) the ratio was between 1.28 and 1.49.

Table 133

Diast. B.P.	Av.Syst. B.P.	Stand. Dev.	Min. - Max.	Ratio
100	144.5	13.4	130 - 160	1.44 ± 0.09
110	156.1	16.1	140 - 185	1.42 ± 0.08
120	174.2	15.9	155 - 194	1.45 ± 0.09
130	185.0	17.0	162 - 205	1.42 ± 0.09
140	196.3	18.1	174 - 220	1.40 ± 0.10
150	205.5	18.4	190 - 230	1.37 ± 0.10

This table shows the blood pressure and the systolic: diastolic ratio in eclampsia.

COMMENTS

Most text books on obstetrics lay considerable stress on the importance of the systolic blood pressure in the prognosis and treatment of pre-eclampsia and eclampsia. In some of the communications (M.R.C.Sp.Rep. 12, 1927), the data provided do not even include the readings of the diastolic blood pressures. Yet, the importance of vascular spasm in toxaemia, and especially in eclampsia, was pointed out by investigators (Zangemeister, 13, 1916; Stroganoff, 14, 1923) even in the early part of this century, and the only clinical method is the determination of the diastolic pressure level.

The effect of the increase in the tone of the vessel wall/

wall is felt immediately by the heart. The rise in the peripheral resistance leaves the aorta and arterial trunks full and distended. In order to overcome this, and maintain an efficient circulation, the stroke volume must increase causing the systolic blood pressure to be elevated. The blood pressure study presented above clearly demonstrates that the hypertension which is associated with toxaemia of pregnancy is not of a pure systolic nature. The efficiency with which the circulation can be maintained in diastolic hypertension depends upon the compensatory increase in the level of the systolic blood pressure. As long as the continued vascular spasm and hypertension does not give rise to organic changes in the vessel wall, balanced or harmonious hypertension is not likely to interfere with the functions of the vital organs of the body to any appreciable degree. This has been adequately discussed by Gallavardin (15, 1920), Gilchrist (10, 1941) and several other investigators in connection with essential hypertension.

In hypertensive toxaemia of pregnancy two types of cases can be clearly differentiated. 1) Those in which hypertension exists in a balanced state. This is usually confined to the cases of pre-existing ("Essential") Hypertension. A small number of cases of true hypertensive toxaemia of pregnancy also come into this category. Of the pre-existing-hypertension group 53.7 per cent. of cases had a balanced hypertension whilst in only 19.6 per cent. of/

of cases of toxaemia of pregnancy did the systolic blood pressure adequately compensate the diastolic hypertension. In the former group none developed albuminuria or oedema; in the latter the amount of albuminuria varied from a trace to 0.2 per cent. and the oedema was only slight. 2) Cases with uncompensated diastolic hypertension. These constituted the majority of cases in our series, and whether they had pre-existing hypertension or not, all of them had albuminuria varying from 0.15 to 1.8 per cent. Oedema was also present in 97.2 per cent. (636 out of 655 cases) of cases in this group.

It is therefore evident, that the manifestations which constitute pre-eclampsia do not depend directly on the absolute level of the blood pressure, either systolic or diastolic, but on the relative balance which exists between these two pressure levels. This is best observed in the blood pressure study of the cases of eclampsia presented above. During the stage of repeated convulsions the systolic pressure although raised falls far below the level required for the maintenence of adequate compensation. The importance of abnormally high diastolic pressure in eclampsia has also been pointed out by Vaczy (16, 1946).

One of the immediate effects of vascular spasm is a reduction of the effective blood supply to organs. This can only be counteracted by maintaining the systolic pressure high enough to overcome the peripheral resistance caused/

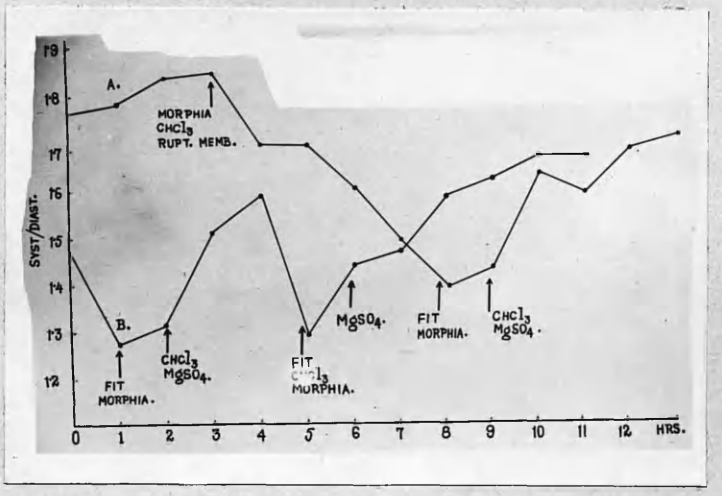

Fig 86.

Two illustrative cases showing the change in the ratio of systolic and diastolic blood pressures which accompanies eclamptic convulsions. The extent to which the ratio drops in eclampsia varies in different cases, depending upon the degree of pre-existing compensation, and especially oedema. In presence of marked oedema a small drop would produce the same effect as a comparatively bigger fall in the ratio in a non-oedematous hypertensive patient.

caused by the vascular spasm. When this is not so, the effects of the vascular spasm remain uncompensated and ultimately a stage developes when organs like the brain, kidney, and liver commence to suffer from a state of deficient oxygenation. Convulsions and coma, albuminuria and oliguria, and hepatic functional derangements follow as a natural sequence. The severity of symptoms preduced in pre-eclampsia and eclampsia appears to be related to the manner in which the diastolic hypertension (vascular spasm) is balanced by the systolic pressure.

EFFECTS OF HYPERTENSION IN TOXAEMIA

1. Blood Pressure and Albuminuria. It is generally accepted that the organic lesions which are usually observed post mortem in the kidneys of patients suffering from toxaemia are not wholly responsible for the degree of albuminuria present. Investigations of Chesley (17, 1939) and co-workers show that albuminuria of pre-eclampsia and eclampsia is of functional origin and is related to vascular spasm. It was therefore considered that an analysis of our data in relation to the degree of albuminuria might prove interesting. The results based on 390 systolic and diastolic pressure ratios obtained from 186 cases of pre-eclampsia are presented in Table134. In all the cases the blood pressures were taken by the writer himself and entered only when two consecutive readings were similar.

It will be evident that in over 75 per cent. of the readings/

Table 134

Syst: Diast.	Albuminuria per cent.								
	0-0.2	0.2-0.4	0.4-0.6	0.6-0.8	0.8-1.0	1.0-1.2	1.2-1.4	1.4+	Total
1.7+	3(18.7)	12(12.2)	10(12.8)	8(10.8)	3(4.9)	0	0	0	36
1.7	12(75.0)	54(55.0)	41(52.6)	29(39.2)	21(34.5)	2(4.6)	0	0	159
1.6	1(6.2)	28(28.6)	27(34.6)	28(37.9)	26(42.7)	29(67.5)	0	0	139
1.5	0	4(4.1)	0	9(12.1)	11(18.0)	11(25.6)	7(43.7)	0	42
1.4	0	0	0	0	0	1(2.3)	9(56.3)	2(50.0)	12
1.3	0	0	0	0	0	0	0	2(50.0)	2

readings the systolic: diastolic ratio was between 1.5 and 1.7. But in this group nearly 90 per cent. of cases were associated with less than 1.0 per cent. albumin in the urine. When the ratio was less than 1.5, 61.5 per cent. of the readings were accompanied by more than 1 per cent. albumin in the urine. The effect of the ratio on the degree of albuminuria is also evident from the disposition of the figures shown in the table, which shows that among individual groups the incidence of marked albuminuria increases only when the ratio descends below the normal levels. With slight albuminuria an abnormal ratio was rarely observed.

COMMENTS

Chesley, Markowitz and Wetchler (18, 1939) studied cold pressor tests in relation to albuminuria. They found that albuminuria occurred or increased in quantity whenever the pressure response was marked. Reiser and Ferris (19, 1948) investigated the nature of the cold pressor test, with the help of T.E.A.C. and observed that the mechanism by which the blood pressure is raised is of neurogenic origin. The effect of sympathetic stimulation is an increase in the tone of the arterioles, which if excessive becomes equivalent to a state of spasm. It is obvious that the effects of this increased tonus or spasm of the renal arterioles is related to the degree of albuminuria which is present in a case of eclampsia or pre-eclampsia. Mukherjee (20, 1942) demonstrated that injections of small doses of pitressin aggravates albuminuria in these cases. The response of the renal blood vessels

to/

Table 135

Ref. No.	More than 48 hours			Less than 12 hours		
	Syst.	Diast.	S.D.	Syst.	Diast.	S.D.
1. M.	165	100	1.65	175	118	1.48
2. D.	200	115	1.74	200	130	1.53
3. P.	150	90	1.64	180	124	1.45
4. B.	155	100	1.55	150	116	1.29
5. McI.	184	108	1.70	160	115	1.39
6. McV.	178	105	1.69	180	122	1.47
7. O'R.	160	100	1.60	165	112	1.47
8. McK.	160	95	1.68	190	125	1.52
9. McG.	170	102	1.67	160	120	1.33
10. W.	165	100	1.65	180	130	1.38
11. McC.	190	118	1.61	175	125	1.40

of the ratio before the onset of the accidental haemorrhage. This change in the ratio is independent of the manner in which the systolic blood pressure reacts, for in 7 cases in this series it was actually increased by 5 to 30 mm., in 1 patient it was stationary and in 3 it fell slightly below the initial level. The convergence of the two pressures as shown by a decrease in the ratio is caused by a rise in the diastolic pressure and may be accompanied by a disproportionate increase or even by a slight fall in the systolic pressure. The ratio itself was below normal in all cases except in 2, where it was at the lowest limit of normality.

It is therefore evident the vascular spasm which exists in/

in toxaemia of pregnancy suffers from a lack of adequate compensation before retroplacental haemorrhage occurs. Whatever may be the exact mechanism underlying the haemorrhage it is obvious that in a certain proportion of these cases the interference with the circulation in the decidua, due to the unbalanced state of vascular spasm is the primary cause.

3. Blood Pressure and Ocular Symptoms. Onset of visual disturbance is regarded as an evidence of grave toxaemia. In our series 37 patients developed dimness of vision and amblyopia. The relation of blood pressure to these symptoms is presented below. Detailed reports of ophthalmoscopic examination of the fundi were available in only 12 cases in this series. Patients with minor ocular symptoms have not been considered.

In all of the 37 cases who complained of varying degrees of amblyopia, there was a fall in the systolic: diastolic pressure ratio. In 26 patients the ratio was less than 1.5, in 9 it was between 1.5 and 1.6 and in 2 it exceeded 1.6. The maximum ratio in this series was 1.64. In 5 patients in this series, ophthalmoscopy revealed the presence of small "cotton-wool" patches. The ratio of systolic and diastolic pressure in these patients varied from 1.28 to 1.39, values which can be considered as indicative of intense vascular spasm and marked disturbance of circulation. In the remaining 7 cases the findings revealed the presence of "retinal vascular spasm and some congestion of the retinal veins"./

veins". The blood pressure ratio in these patients varied from 1.47 to 1.55. Considering that the level of blood pressure varied from 170 to 200 mm. (systolic) and 118 to 130 mm. (diastolic), these ratios are also below the optimum level. The correlation between the state of the retina and the blood pressure ratios provide further evidence for the existence of a state of active vascular spasm in toxaemia of pregnancy.

CONCLUSION

Hypertensive toxaemias of pregnancy are associated with a diastolic hypertension. When this is balanced or harmonious, pre-eclamptic manifestations are as a rule not severe. An unbalanced diastolic hypertension in pregnancy toxaemia indicates danger and usually precedes convulsions or retroplacental haemorrhage. Such a state points to intense vascular spasm with consequent interference with the delicate functions of the organs supplied by these blood vessels. The importance of the blood pressure readings in pregnancy toxaemias does not lie as much in the absolute values of pressure as on the mutual relationship between the diastolic and systolic values. In this respect a careful determination of the diastolic pressure is of considerable prognostic significance. Comparative study of "toxaemic" and "non-toxaemic" hypertensive patients during pregnancy suggests that satisfactory compensation exists as long as the systolic: diastolic pressure ratio is about 1.70.

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POSTSCRIPT.

Since this chapter on vascular spasm was written we have been able to obtain careful data on the behaviour of the blood pressure in a small number of individual cases of eclampsia and accidental haemorrhage. These data present an interesting study and support the statements made above. A short analysis of these cases is given below.

1. Mrs. McArdle.

Admitted in a pre-eclamptic state on 26. 1. 50. Antenatal B.P. upto 37 weeks 120/75 (ratio = 1.60). On admission, B.P. 150/100 (ratio = 1.50) ; albuminuria trace ; oedema of ankles slight.

B.P. and the syst. : diast. ratio on 27. 1. 50. were as follows :-

12.30 P.M.	155/100	ratio =	1.55.
2 P.M.	170/110	"	1.54.
3.40 P.M.	165/110	"	1.55.
5.30 P.M.	170/120	"	1.42.
7.30 P.M.	165/115	"	1.43.
9.10 P.M.	170/120	"	1.42.
12 M.N.	140/105	"	1.33.

An eclamptic convulsion occured at 12.20 A.M. on 28. 1. 50.

2. Mrs. Marynicz.

Sent in by the patient's own doctor as a case of hypertensive toxaemia. Admitted on 31. 1. 50. B.P. immediately before admission, 190/115 (ratio = 1.67).

On admission, B.P. 200/120 (ratio = 1.67) ; albuminuria trace : no oedema (8 P.M.).

On the following morning ((9 A.M., 1. 2. 50.) the B.P. was 130/100 (ratio = 1.30).

An eclamptic convulsion occured at 9.40 A.M.

3/ Mrs. Martin.

Admitted as a case of eclampsia with a history of 4 fits outside. On/

On admission (3. 2. 50.) the B.p. was-

2.50 A.M.	170/105	ratio =	1.62.
8.30 A.M.	160/110	"	1.60.
Eclamptic fit at 9 A.M.			
9.25 A.M.	140/100	"	1.40.
Eclamptic fit at 9.35 A.M.			
11 A.M.	148/100	"	1.48.
12 Noon	150/105	"	1.43.
1 P.M.	150/110	"	1.36.
Eclamptic fit at 1.30 P.M.			

4. Mrs. Scott.

Admitted as a case of hypertensive toxaemia on 13. 2. 50.
Oedema, moderate ; albuminuria, 0.6 %.

B.P. before admission :-

9.2.50	180/100	ratio =	1.80.
12.2.50	220/110	"	2.00.
On admission, 13. 2. 50.			
10 A.M.	220/110	"	2.00.
2 P.M.	208/128	"	1.63.
Eclamptic convulsion at	2.20 P.M.		

5. Mrs. McCartney.

Admitted on 12. 3. 50. with symptoms of pre-eclampsia.

Before admission, B.P. was :-

1.3.50	130/70	ratio =	1.86.
oedema, moderate ; albuminuria, trace.			
2.3.50	135/70	"	1.93.
oedema, and albuminuria - same.			
11.3.50	160/80	"	2.00.
oedema, marked ; albuminuria, 0.2 %.			

On admission, 12. 3. 50., B.P. was -

3 P.M.	150/100	"	1.50.

Eclamptic convulsion at 3.15 P.M.

NOTE. In presence of oedema a high systolic : diastolic ratio is essential in order to maintain an effective cerebral circulation and oxygenation. This is because of the raised intracranial pressure which accompanies oedema of the brain. When the ratio falls due to lack of compensation, eclampsia develops in these patients at a higher level of the ratio than in the non-oedematous subjects. Comparatively slight loss of compensation is sufficient to precipitate eclampsia in presence of marked oedema. In this respect oedema and vascular spasm are complementary.

6. Mrs. Smith.

Admitted on 31. 10. 49. in a state of coma after 4 eclamptic fits outside. Oedema, slight ; albuminuria 0.5 %. The B.P. recorded during the days after admission is given below :-

31.10.49.	145/115,	ratio =	1.26,	comatose.
1.11.49.	138/95 ,	"	1.45,	drowsy, and and restless.
2.11.49.	170/120,	"	1.41,	conscious, and restless.
3.11.49.	190/160,	"	1.18,	ECLAMPTIC FIT& COMA.

7. Mrs. Mulligan.

Admitted in a pre-eclamptic state on 16. 2. 50. Albuminuria, 0.5 % ; oedema present in the ankles and legs.

Antenatal B.P. :-

18.1.50. (6 months)	130/86	ratio =	1.50.
15.2.50.	168/104	"	1.61.

The morning B.P. after admission is given below.

16.2.50.	175/105	ratio =	1.67.
17.2.50.	162/100	"	1.62.
18.2.50.	158/90	"	1.75.
19.2.50.	168/105	"	1.60.
20.2.50.	160/100	"	1.60.
21.2.50.	155/100	"	1.5.5
22.2.50.	150/100	"	1.50.
23.2.50.	138/90	"	1.53.
24.2.50.	138/90	"	1.53.
25.2.50.	140/105	"	1.33.

Concealed accidental haemorrhage 10 hours after the last B.P. was recorded.

8. Mrs. Alden.

Admitted as a case of hypertensive toxaemia on 18. 4. 50. No oedema, and no albuminurial.

B.P. one week before admission 175/110, ratio = 1.58.

On admission :-

18.4.50.	190/120	ratio =	1.58.
19.4.50.	170/120	"	1.42.

Mixed accidental haemorrhage 8 hours after the last blood pressure was recorded.

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20./

CHAPTER 3.

THE NATURE OF VASCULAR SPASM. VASOMOTOR AND HUMORAL FACTORS.

The results of investigations described in the previous chapter shows that the essential feature of the hypertension in toxaemia of pregnancy is a vascular spasm, which increases the peripheral resistance, raises the diastolic pressure and causes a compensatory increase of the systolic blood pressure. It is therefore evident that the cause of hypertension in pre-eclampsia and eclampsia can be found only when the cause of the vascular spasm is known.

Normally arteriolar tonus is maintained to a great extent by the neurogenic or vasomotor mechanism in which the vasomotor centre, the carotid sinus, splanchnic and visceral autonomic nerves are involved. However, completely denervated vessels are not fully dilated (Pickering, 1, 1939). Essex and co-workers (2, 1943) demonstrated in dogs that denervation of the femoral artery is followed by a hypertrophy of the medial muscular coat with an accompanying restitution of the arterial tonus. This "peripheral tone" of the arteries is obviously dependent upon a humoral or chemical mechanism. Thus in a normal individual the state of arterial tonus is under a dual control, nervous and chemical. It is therefore important to ascertain how these factors are affected in toxaemia of pregnancy.

Hyper-reaction of toxaemic patients to cold pressor tests/

tests has been observed by Dieckmann (3, 1941), and this has been confirmed also by several other investigators. Reiser and Ferris (4, 1948) demonstrated that this reaction is of neurogenic origin. Reaction to this test has been taken to indicate that (1) The activity of the vasomotor mechanism is raised in pregnancy toxaemia, and/or (2) the vascular system is more sensitive to vasoconstrictor impulses.

To ascertain the role played by the vasomotor tonus in toxaemias of pregnancy injections of tetraethylene ammonium bromide (T.E.A.B. - Boots) were employed. Given by intravenous injection T.E.A.B. is reputed to cause a temporary paralysis of the sympathetic ganglia, thereby intercepting the nervous pathway between the centre and the peripheral blood vessels. The argument was that if the vasomotor nervous mechanism is hyperactive in toxaemia of pregnancy paralysis of the sympathetic ganglia would cause a fall of blood pressure proportional to the degree of activity of this nervous mechanism.

In the course of our preliminary experiments it was observed that T.E.A.B. caused an alarming fall of blood pressure in normal pregnant women, when even less than the full dose recommended by the manufacturers was employed. As our aim was to compare the reactions obtained in normal pregnancy and toxaemia, we decided to employ the smallest dose which caused a recognisable fall of blood pressure.

METHOD

Every/

Every patient was kept resting in bed for a period of at least an hour before the commencement of the experiment. Blood pressure readings were then obtained with a mercury manometer until three consecutive readings taken at half-a-minute intervals showed constant values for both systolic and diastolic pressure. One ml. of 10 per cent. T.E.A.B. was then injected intravenously in the cubital vein and blood pressures recorded every 30 seconds until the basal level was restored.

Nine cases of normal pregnancy and 27 cases of toxaemia were subjected to this experiment and the results obtained are presented below. No case with any evidence of renal lesion was included for this study.

RESULTS

1. Normal Pregnancy - All cases of normal pregnancy showed a fall in both systolic and diastolic pressures. The drop in the systolic blood pressure varied from 26 to 38 mm. with an average of 30.6 mm; S.D. 4.5. The average decrease in diastolic pressure was 26.2 mm.; S.D., 3.0, with a range of values from 22 to 30 mm.Hg. The manner in which the systolic and diastolic pressures were affected did not reveal any definite proportion, apart from the fact that the systolic decrease was in all cases less than what would be expected on account of the drop in the diastolic level.

Immediately after the injection most of the cases showed a slight (2 - 6 mm.) rise in both systolic and diastolic blood/

blood pressures. The effect of the drug however became manifested within 30 seconds of the injection, when both systolic and diastolic /blood pressures/started to fall almost simultaneously. The lowest level was reached between 3½ and 4 minutes after the injection. Then followed a phase of gradual increase of the pressure levels, in which both systolic and diastolic blood pressures were almost equally affected. Normal values were restored 10 to 12 minutes after the injection.

No untoward effect was observed during these experiments except for pallor, tingling sensation in the tongue and extremeties, slight interference with accommodation and a feeling of faintness when the fall of blood pressure exceeded 28 to 30 mm. systolic. These were however of short duration, except in one instance where the symptoms were severe enough to cause anxiety. Intramuscular injection of 0.5 ml. adrenalin restored the blood pressure almost immediately and the symptoms were relieved.

2. Toxaemia of Pregnancy - There were 22 cases of pre-eclampsia and 4 cases of eclampsia in this series. The results obtained can be conveniently classified into two groups.

Group 1 -'Reactors'- Nine patients reacted to the injection of T.E.A.B. by a fall of blood pressure. One of them was a case of post-partum eclampsia. The extent of the drop in blood pressure was to some extent similar to that observed in normal pregnancy. As a result of the injection, the blood pressure in 2 patients returned to normal/

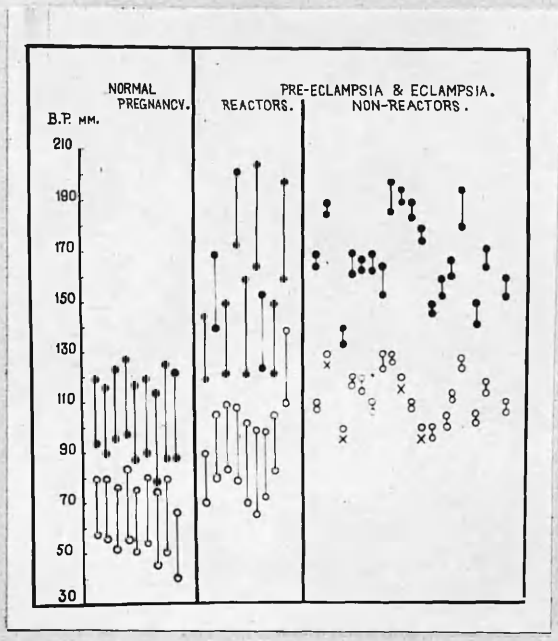


Fig. 87. A scatter diagram showing the hypo-tensive response of T.E.A.B. in normal and toxaemic pregnancy. The series does not include any case of 'nephritic toxaemia'. Cases of toxaemia of pregnancy fall mainly into two groups : Reactors and Non-reactors. Some cases in the former group react only partly in which the blood pressure is still maintained at a hypertensive level.

normal limits and persisted below the hypertensive level for more than one hour. In three other patients it returned to normal levels, but only for the duration of the test. In the remaining 4 cases, in spite of the fall the blood pressure was still maintained above normal.

In this group of reactors, the decrease in blood pressure caused by the T.E.A.B. was -

Systolic, average 31.2 mm.Hg.; S.D. 5.1.
maximum 40 mm. Minimum 25 mm.

Diastolic, average 27.3 mm.Hg.; S.D. 3.9.
maximum 35 mm. Minimum 22 mm.

The case of post-partum eclampsia in this series is particularly interesting.

Mrs. W.; aet. 30; primigravida; admitted with a diagnosis of pre-eclampsia; full term; on admission B.P. 145/90; oedema+ (ankles); urine contained 0.5 parts albumin (Esbachs); Past history presented no significant feature; obstetric examination revealed no abnormality; urea clearance was 115 per cent.; water excretion test showed 25 per cent. retention in two hours; plasma proteins 5.3 gms.per 100 ml.; hepatic function tests showed only an abnormal bilirubin retention (16.3 per cent.); T.E.A.B. test on 28.11.49 (2 days after admission) gave a positive reaction - the blood pressure dropping by 25/22 mm.Hg. On 30.11.49, during the third stage of labour the patient had an eclamptic convulsion. Blood pressure about half an hour before the fit was 150/105 mm.Hg. T.E.A.B. test was repeated one hour after the convulsion. The initial blood pressure was found to be

very/

very unsteady, varying between 155/110 to 145/100. The drug was injected when two readings of 143/102 were obtained. The fall caused by the injection was 30/26 mm.Hg. The systolic: diastolic pressure ratio, at the time of admission was 1.61, just preceding the eclamptic convulsion 1.43, at the time of the experiment 1.45, and after the sympathetic influence had been removed by the T.E.A.B. 1.55.

The level of the initial blood pressure appeared to have no relationship with the type of response obtained. Of 2 patients with an initial blood pressure of above 200 mm. Hg. (Systolic) one had a fall of 40 mm. and another 28. In this group there was a case of essential hypertension, who was admitted with a blood pressure of 198/140, with 11 parts albumin (Esbach) in the urine and marked oedema of the legs. T.E.A.B. produced a response of 38/30 mm.Hg. Pregnancy was artificially terminated in this patient and the blood pressure on the tenth day of puerperium was still 160/106 mm.Hg. The experiment was repeated and the hypotensive response was only 10/6 mm.Hg.

Group 2 - 'Non-reactors' - Of the 17 patients in this series there were 14 cases of pre-eclampsia and 3 of eclampsia. There was no fall of diastolic blood pressure in any of these patients which could be regarded beyond the margin of personal error (2-3 mm.). All, however, showed a drop in the systolic blood pressure which varied from 5 to 15 mm.Hg. (average 7.5 mm.; S.D.3.1).

The/

The initial blood pressure in this group varied from 140/98 mm. (a case of eclampsia) to 198/130 mm.Hg. Follow up during the puerperal period showed persistence of hypertension (? essential hypertension) 10 or more days after confinement in 3 patients in this group. The experiment was repeated on the tenth puerperal day on 4 cases of pre-eclampsia (blood pressure returned to normal level) and on 1 case where hypertension persisted. All 4 cases of pre-eclampsia had a reaction similar to that seen in normal individuals. The case where hypertension persisted in the puerperium reached poorly (10/4 mm.Hg.) to the injection.

COMMENTS

Brust, Assali and Ferris (5, 1948) using T.E.A.C. (tetra-ethylene ammonium chloride) in normal pregnancy and in a small series of toxaemias observed that the "floor" of blood pressure attained after the injection was higher in toxaemias than in normal pregnancy and concluded that a "humoral" mechanism was involved in toxaemic hypertension of pregnancy.

The results of this investigation indicate that although the hypertension is induced by a chemical agent in the majority of cases, there is a distinct group of patients in whom the high blood pressure is aggravated, if not actually maintained by the vasomotor system. In just over 33 per cent. of our patients the vasomotor effect on the blood pressure of pregnancy toxaemia was prominent. It is a common/

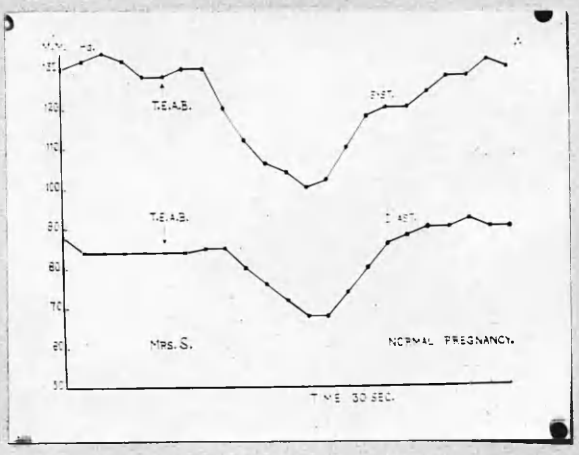
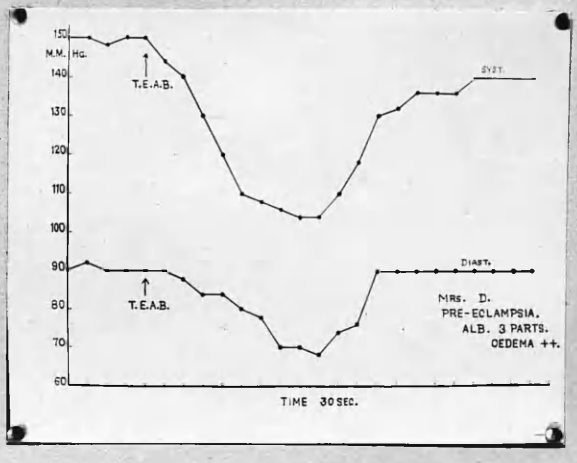


Fig. 88. Atypical case of of normal pregnancy, showing the behaviour of the blood pressure after the injection of T.E.AB.

Fig. 89. Blood pressure tracing of a case of pre-eclampsia after an injection of T.E.A.B. showing a normal fall of blood-pressure (Neurogenic hypertension).



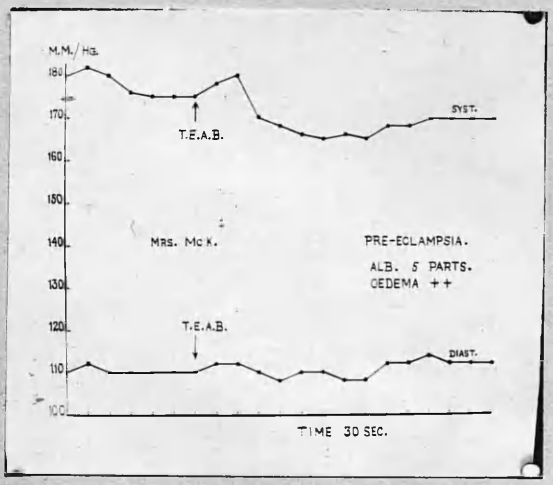


Fig. 90. Blood pressure tracing of a case of pre-eclampsia after T.E.A.B. Sympathicolysis is without effect(Humoral hypertension).

common experience in clinical obstetrics to find the hypertension subsiding spontaneously after the patient has been put to bed and when she gets used to the hospital environment. It is difficult to see how a "humoral" factor can undergo spontaneous resolution without any active treatment. However, it is not suggested that the hypertension found in these patients is wholly due to vasomotor hyperactivity, for should it be so, T.E.A.B. would be expected to cause the blood pressure to descend to normal limits in all patients. Reference to the data presented above will show that in only 5 cases belonging to the "reactor" group, sympathetic paralysis restored the normal blood pressure level for the time being. It is probable that in these patients the vasomotor mechanism was, to a very great extent, responsible for the maintenence of the hypertension. In the remaining 4 cases belonging to this group the blood pressure still remained above normal despite the fall produced by T.E.A.B. This suggests that the hypertension in these cases is only partly due to an overaction of the sympathetic and that there still remains a residual hypertension of humoral origin which is unaffected by T.E.A.B.

In a little over 66 per cent. of the patients studied by us removal of the vasomotor influence had no recognisable effect on the blood pressure. One can only conclude that, in these cases, the hypertension was due to some humoral agency or to organic changes in the vessel walls. It was obvious/

obvious however, from a repetition of our studies in the puerperium that in the majority of these patients a humoral factor was in action, and that it ceased to exist in the average case by the second week after confinement. Brust et al (1948) have suggested that this humoral factor is probably of endocrine origin.

In a few cases the blood pressure remained elevated after confinement, suggesting that the hypertension in these patients was partly due to organic disease of the vessels. Both the "reactor" and "non-reactor" groups were found to contain these cases.

It is obvious then that pre-eclampsia is a term which covers a number of different types of hypertension, any one of which may end in eclampsia. These types may be summarised as follows -

1. There is no pre-existing hypertension in early pregnancy, but due to a neuro-vascular disturbance the blood pressure is raised. These cases show a normal response to T.E.A.B.
2. There is no pre-existing hypertension, but owing to the abnormal humoral mechanism vascular spasm occurs causing the blood pressure to rise. These cases do not respond to T.E.A.B.
3. A vasomotor factor is superimposed on cases where the hypertension is initiated by a humoral mechanism. The height attained by the blood pressure in these cases may be considerable. T.E.A.B. causes a partial fall of blood/

blood pressure, but the lowest level attained is still above the limit of normal blood pressure.

4. Pre-existing hypertension (? essential) which is aggravated by an additional neurogenic factor. These cases also show a partial reaction to T.E.A.B.
5. Pre-existing hypertension, which is enhanced by the humoral agent responsible for the high blood pressure in true pre-eclampsia. These cases do not respond to T.E.A.B.
6. This classification, however, does not include cases of nephritic hypertension associated with pregnancy. Our investigation did not cover this complication of gestation.

From the point of view of isolation of the first 5 types of hypertension described above, the T.E.A.B. test is useful in differentiating type 1 from the rest. Types 2 and 5 which are both "non-reactors" can be separated at present only by noting the behaviour of the blood pressure during the puerperium. Types 3 and 4 which are "partial reactors" can also be differentiated in the puerperium. We have not been able to differentiate essential hypertension, unaccompanied with any organic change in the arteries, from cases of pre-eclamptic hypertension by means of T.E.A.B. As regards the severity of toxaemia none of these types of hypertension show any significant difference among themselves. It has been seen that a patient with neurogenic hypertension was subject to post-partum eclampsia, while in at least 18.5 per/

per cent. of cases of toxaemia in our series the neurogenic factor played a predominent role.

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FINAL CONCLUSIONS

An investigation of the nature described in the foregoing chapters does not provide for a conclusion with regard to the aetiology and nature of toxaemia of pregnancy. Nevertheless, it indicates that pre-eclampsia and eclampsia are associated with disturbances of metabolism affecting in general, protein, carbohydrate and fat. Study of hepatic dysfunction which was undertaken on the same patients and at the same time, and followed up in an identical manner demonstrates that the metabolic and functional disturbances in pregnancy toxaemia are related to each other. However, the mere presence of toxaemia does not always show marked disorder of metabolism and liver functions. These become evident when the toxaemia is of a severe degree. Follow up studies also, indicate that, improvement in the clinical condition is associated with an improvement in the metabolic and general functions of the liver, while, when the toxaemia deteriorates the metabolic and functional status of the liver follows a similar course. The results of the present investigation suggest that the metabolic disturbances are the effect and not the cause of toxaemia. For should it have been so, one would have reasonably expected the biochemical changes to precede the clinical manifestations. It has been pointed out that several authors have tried to isolate toxic metabolites in the blood, urine and placenta of/

of patients suffering from pregnancy toxaemia. Apart from the detection of some toxic amines, e.g. histamine, guanidine, tyramine in the circulation these searches have not met with any success. Moreover, in presence of a disordered metabolism, the nature of which has been described in the preceding pages, such findings do not seem unusual. No investigator has, as yet, been able to prove that these toxic metabolites are the cause of the toxaemia.

In the course of this study it has been suggested that the disturbances in the functional efficiency of the liver, especially with regard to its status in the control of metabolism, is brought about by vascular spasm. It has been demonstrated how decompensated vascular spasm constitutes the principal feature in the production of the more serious manifestations of toxaemia of pregnancy. The studies showing the relationship of blood pressure and metabolic functions (also liver functions in general) in pre-eclampsia indicate that high levels of diastolic pressure are associated with marked functional derangements. It has been observed in the section on hypertension that pre-eclampsia is not only associated with a comparatively low ratio of systolic: diastolic blood pressure but with a progressively increasing diastolic pressure the ratio becomes even lower. This undoubtedly indicates that with high levels of diastolic pressure a state of active uncompensated vascular spasm exists in pre-eclampsia. These provide/

provide indirect evidence in support of the view expressed above. Direct evidence of increase of renal arteriolar resistance in toxaemia of pregnancy has very recently been provided by Kenny, Lawrence and Millar (1, 1950). Evidence to show that the liver also suffers from the effects of anoxaemia caused by vascular spasm have been offered by Byrom (2, 1938), who succeeded in producing morphological degeneration of the liver cells and haemorrhage in the liver parenchyma with injections of pituitrin. These experiments have been confirmed by us in this laboratory. A study of the functional status of the liver in animals treated with pituitrin has however not been described.

This was done by us on 6 rabbits. While a repetition of the cytological changes in the liver of these animals (in view of agreement with Byrom's work) may appear unnecessary, the results of the biochemical findings were interesting and are given below. Each of these animals were given two injections of pitressin tannate in oil daily for 7 days. All injections were subcutaneous and the dose of pitressin employed for each injection was 10 units. Blood for the biochemical estimations was obtained from the marginal ear vein on the day just before the injections commenced and again 8 hours after the last injection. All animals were kept under standard laboratory conditions throughout the course of this experiment./

experiment. The methods of estimation and procedure employed were identical with those used for pre-eclamptic patients. The data obtained are shown in Table 136.

Table 136

	Plasma A.A.N. mg.		Alk. Phosph. units		Th. Turbidity units		Bilirubin Retention per cent.	
	Before	After	Before	After	Before	After	Before	After
R1	3.2	9.6	7.9	19.7	0.2	2.1	5.1	15.7
R2	3.0	11.4	4.6	21.0	0.3	4.5	3.2	18.6
R3	4.0	8.7	5.0	12.4	0.6	1.0	1.2	7.4
R4	3.6	6.9	5.0	14.0	1.0	1.9	1.0	7.0
R5	2.7	3.0	4.2	14.0	0.5	5.1	4.0	13.6
R6	3.1	10.4	4.0	17.8	0.5	4.9	3.5	14.0

It will be evident that continued treatment with pituitrin in rabbits produced changes in the metabolic (plasma amino-acid) and functional efficiency of the liver, which are similar to those already described in the human subjects in presence of pre-eclamptic and eclamptic toxaemia of pregnancy. In view of the fact that the only abnormal condition to which these animals were subjected between the first and the second estimations, was the injections (total number of injections 14) of pitressin and that the principal effect of this drug is vasoconstriction it seems reasonable to conclude that the functional dernagements observed during the period of this study have been caused by vascular spasm. It must be made clear however, that while/

while it is claimed that persistent vaso-spasm is the cause of the changes observed in toxaemia of pregnancy it is NOT suggested that an excess of pituitrin in the circulation is the cause of pre-eclampsia and eclampsia. The study of the nature of hypertension shows that in a small number of cases this vascular spasm may be of vaso-motor origin, but in the majority of cases of toxaemia the spasm of the blood vessels is caused by a humoral or endocrine factor. It should however be pointed out that vasomotor hypertension in pre-eclampsia need not imply a sympathetic over-activity. It does not seem out of place to mention that Hofbauar (2, 1941) and other workers have observed a reduced level of acetyl choline and a simultaneous increase of acetyl-choline-esterase in the blood and placenta of patients suffering from toxaemia. We have been able to confirm this finding in a small series of cases. It will therefore be proper, in the present state of our knowledge, to merely indicate that these cases of neurogenic vascular spasm and hypertension of pregnancy toxaemia are associated with a state of autonomic imbalance. Further study is required to understand the exact nature of the disturbance which upsets the equilibrium of the autonomic nervous system.

With regard to the humoral factor our knowledge is still inadequate. Considerable literature has accumulated contradicting the findings of Anselmino, Hoffmann and Kennedy/

Kennedy (3, 1932) who claimed the presence in the circulation of toxaemic patients of a pressor substance of probable posterior pituitary origin. It has also been suggested by several authors that the vascular system in toxaemia is sensitised by some unknown substance whereby the vasospastic effects are augmented. It is possible that the humoral substance provides the sensitising agent necessary for this purpose. Further investigations will show the nature and the manner of action of this humoral or endocrine substance which is active in toxaemia of pregnancy.

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A P P E N D I X.

PART I.

1. Analytical Methods in Biochemical Study.
2. Biochemical Data.
   a. General Biochemistry and Results of Hepatic function tests.
   b. Special Investigations.

BLOOD ANALYSIS

INTRODUCTION

Blood was obtained from the cubital vein in a dry syringe, without the use of a tourniquet, and transferred into

(i) Heparin tubes

(ii) Oxalated containers

(iii) Tubes not containing any anticoagulent (for serum).

For the estimation of carbon dioxide a separate syringe containing 0.5 ml. of liquid paraffin was used for drawing the blood, which wastransferred immediately into an oxalated tube under a layer of liquid paraffin. All estimations were done on plasma or serum. Plasma was separated within 5 minutes of the collection of the blood in a high-speed centrifuge. All haemolysed plasmas were discarded. The clear plasma was separated from the packed cells and transferred into marked tubes and set aside for estimation. All estimations were done on the day when the samples were obtained. Estimation of carbon dioxide and bicarbonates were done almost immediately after obtaining the samples.

METHOD

1. PLASMA PROTEINS. The method employed was that of King (1, 1947). Oxalated plasma was used. Proteins were precipitated with zinc hydroxide, digested with sulphuric acid (selenium dioxide, as the catalyst) and nitrogen estimated after nesslerisation. Globulin was precipitated with 40 per

cent. sodium sulphite. Fibrinogen was estimated from the fibrin clot obtained after re-constituting oxalated plasma with calcium chloride. The estimation of nitrogen was done on a "photo-electric absorptiometer", against a curve prepared from standard ammonium sulphate solution.

2. UREA. Urea was estimated by the method of Archer and Robb (2, 1925). Ammonia was liberated from urea with the help of urease and estimated by nesslerisation. Estimation was done on a "spekker" absorptiometer by comparing the readings with a curve obtained from a standard ammonium sulphate solution.

3. URIC ACID. Uric acid was estimated by Folin and Trimble's method (3, 1924). The colour produced by the reduction of the alkaline phosphotungstate by urate was read on a "spekker" against a curve prepared from a standard solution of uric acid.

4. CREATININE. The method employed was that of Folin and Wu (4, 1919), in which phosphotungstic acid filtrate is treated with alkaline picrate. The results were read from a "spekker" curve made from standard creatinine solution.

5. NON-PROTEIN NITROGEN. Non-protein nitrogen was estimated by the method described by King (1, 1947) using plasma instead of whole blood. Tungstic acid filtrate was digested with sulphuric acid - selenium dioxide mixture and nesslerised. The results were read on a "spekker curve"

prepared from standard ammonium choloride solution.

6. SUGAR. The method employed was that of Schaffer-Hartman, modified by Harding and co-workers (5, 1932). Sugar was estimated on the Somogyi (6, 1931) filtrate from the reduction of alkaline copper reagent. The reduced copper was estimated by re-oxidising with iodine and determining the iodine required in this process by titration with N/200 sodium thiosulphate.

7. GALACTOSE. Galactose estimation was done by the method described by King (1, 1947) in which the blood glucose is fermented with yeast and the non-fermentable galactose estimated by Harding's modification of Schaffer-Hartman's method. For each estimation blanks were tested. These consisted of

(i) Yeast suspension; (ii) Standard glucose solution and yeast suspension; (iii) Standard galactose solution and (iv) Standard galactose and yeast suspension.

8. CHOLESTEROL. The method employed was that of Sackett (7, 1925), in which the alcohol-ether extract of plasma is dried and the cholesterol estimated from the green colour produced by the Liebermann-Burchard reaction. The results were obtained from a "spekker" curve made with standard cholesterol solution.

9. CHOLESTEROL ESTER. Bloor and Knudson's method (8, 1916) was used, in which the alcohol-ether extract of

plasma is treated with alcoholic digitonin to precipitate the cholesteride. The evaporated extract is re-extracted with petroleum ether, in which digitonin cholesteride is insoluble. The petroleum-ether extract is then treated for the Liebermann-Burchard reaction.

10. LIPOID PHOSPHORUS. Lipoid phosphorus was determined by the method of Harnes (9, 1928), as described in Peters and Van-Slykes Quantitative Clinical Chemistry, Volume II. The phospholipoids are extracted with chloroform hydrolysed with sulphuric acid and estimated from the depth of the colour of the reduced molybdate formed during the reaction. The results were obtained by direct colorimetry against a standard phosphate solution.

11. AMINO-ACID NITROGEN. This was determined by Danielson's (10, 1933) and Sahyun's (11, 1938-39) modification of the original Folin's method. Tungstic acid filtrate was treated with alkaline naphthoquinone - sulphonic acid solution, and colour developed with heating. The estimation was done from a curve obtained with glycine - glutamic acid standard read on a photoelectric absorptiometer. The method allows a correct estimation up to 15 mgms. amino-acid nitrogen per 100 ml. (Hawk, Oser and Summerson). Whenever values above this level were obtained the analysis was repeated using half the quantity of the filtrate.

12. ALKALINE PHOSPHATASE. Phosphatase was determined

by the method of King and Armstrong (12, 1934), as modified by King, Haselwood, Delory and Baell (13, 1942). The method emplyed used disodium-phenyl phosphate as the substrate and the liberated phenol was estimated with alkaline Folin-Ciocalteau reagent. The unit of measurement is the enzyme necessary to liberate 1 mg. phenol from the substrate.

13. SULPHUR CONTENT OF PLASMA PROTEINS. The proteins of 0.2 ml of oxalated plasma were precipitated with 10 ml. of alcohol. The precipitate was washed in alcohol to remove the last traces of soluble sulphur in the plasma. The protein precipitate was then digested with Benedict's total sulphur reagent. The digested residue was taken up in dilute hydrochloric acid. The copper in the solution was precipitated with sodium hydroxide. The clear supernetant fluid containing the sulphates in proteins equivalent to 0.1 ml. of plasma was acidified and treated with barium chloride solution. The precipitate of barium sulphate was maintained in a uniform suspension by the addition of 5 per cent sulphur-free gelatin. Standard potassium sulphate solution containing 0.1 mg. sulphur per ml. was treated in an identical manner. Final comparison was done in a photo-electric absorptiometer by determining the density of the turbidity produced. The method was tried on various strengths of known sulphate solutions and was found to recover 98.5 per cent of the total sulphur.

14. Carb

15. CARBON-DIOXIDE AND BICARBONATES OF THE PLASMA. The carbon-dioxide combining power of the plasma was estimated by the method of Van-Slyke and Cullen. Blood was drawn in a syringe containing liquid paraffin and collected in an oxalated tube under a layer of liquid paraffin. The plasma was separated immediately after the sample of blood was obtained, transferred to another tube containing liquid paraffin, and the estimation was done at once. Van-Slyke's volumetric apparatus was used for this purpose. The results obtained were corrected for temperature and atmospheric pressure.

The carbon-dixide present as bicarbonates ($B.HCO_3$) was estimated by subtracting the free or dissolved carbon-dioxide (= mixture of anhydrous CO_2 and H_2CO_3) from the total carbon-dioxide content of the plasma. The free carbon-dioxide was calculated from the formula :-

Millimoles of CO_2 per litre = 0.0301p (Peters and Van-Slyke, 20, 1932).

The carbon-dioxide tension of the venous blood was estimated by the method described by Peters and Van-Slyke in 'Quantitative Clinical Chemistry', Vol. 2, 1932, p. 309.

16. PROTHROMBIN CONCENTRATION. Prothrombin concentration was calculated from the prothrombin time with the help of Quick's formula (21. 1939) :-

$c.t. = a - k/c.$ i.e., $c\ (conc.) = k \div c.t. - a.$

The values for the constants k and a were obtained from the data provided by Quick and Len (22,1937).

Prothrombin time was measured by the Fullerton's (24, 1940) modification of Quick's method, in which Russel's viper venom (Stypven, B.W. & Co.) is used as the thromboplastin. Each batch of Stypven was tested with normal plasma to give a prothrombin time of 10½ to 12 seconds.

ANALYSIS OF URINE AND FAECES.

1. URINARY NITROGEN. Urinary total nitrogen was estimated by the Folin-Farmer's Micro-Kjeldahl method as described by Hawk, Oser and Summerson in 'Practical Physiological Chemistry', 1947, p. 816. The non-protein nitrogen was estimated by precipitating the urinary proteins with trichloracetic acid and estimating the nitrogen in an aliquot portion of the filtrate.

2. FAECAL NITROGEN. Faeces were collected in a weighed sealed pan with sulphuric acid as the preservative. Until the time of estimation the pan was stored in a refrigirator. Digestion was carried out with sulphuric acid, aided by potassium persulphate (Wong, 23, 1923). The final estimation of nitrogen was done by nesslerisation.

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METHODS EMPLOYED FOR THE HEPATIC FUNCTION TESTS.

1. BILIRUBIN EXCRETION TEST. (Soffer and Paulson).

A total amount of bilirubin, equal to 1 mg. per kilogram of body weight, not exceeding 70 mg. was dissolved in 15 ml. of freshly prepared solution of M/10 sodium carbonate. The solution of sodium carbonate was sterilised by boiling and subsequently cooled to 80°C., before bilirubin was added to it.

A control sample of blood was collected in a dry syringe to prevent haemolysis. The bilirubin was rapidly cooled to body temperature and injected through the same needle which was left in situ after the withdrawal of the first blood sample.

Two further samples of blood were collected 5 minutes and 4 hours after the injection of bilirubin.

Two ml. of plasma from the control and 4 hour specimens were each treated with 2 ml. of acetone. One ml. of plasma from the 5 minute specimen was treated with 4 ml. of acetone. All specimens were centrifuged and the supernatant fluid decanted (filtered through ash free No. 44 Whatman filter paper when necessary). This supernatant fluid was compared with potassium dichromate standard (1:2,000 solution gives colour equivalent to 1 mgm. bilirubin per 100 ml. plasma). Heparinised plasma was used in all cases.

Calculation - Bilirubin retention per cent. =

200 X (mg. bilirubin 4 hrs. - mg. bilirubin control) ÷ (5 X mg. bilirubin 5 min.) - (2 X mg. bilirubin control).

2. PLASMA ALKALINE PHOSPHATASE.

The method employed was that King and Armstrong described in E.J.King's Micro-Analysis in Medical Biochemistry, J.A. Churchill, London, 1947.

3. PROTHROMBIN CONCENTRATION AND PROTHROMBIN RESPONSE

The estimation of prothrombin was done by the Fullerton's modification of Quick's method, 4.5 ml. of blood was drawn from the vein without compression and mixed with 10 mg. of potassium oxalate. This was centrifuged immediately and the plasma separated.

0.2 ml. of plasma was introduced into a narrow tube (0.5 cm. diameter) and to it was added 0.2 ml. of 1:10,000 solution of Russel viper venom (Stypven - B.W.& Co.). The tube was the immersed in a water bath at 37°C. to bring the temperature of the mixture to blood heat. 0.2 ml. of 1.11 per cent. calcium chloride was added to the tube and a stopwatch started. Prothrombin time was calculated from the time of addition of calcium chloride to the first appearance of fibrin fibrils. The prothrombin time was then calculated into prothrombin concentration according to Quick's formula, Proth. Conc. = $\frac{K}{c.t. - a}$ Quick gives the value of K as 302 and that of a as 8.7.

For the estimation of the prothrombin response a sample/

sample of blood as described above was obtained, and while the needle was in situ 20 mg. of Vitamin K (Synkavit) was injected intravenously. After 2 hours another sample of blood was obtained in the same manner as before.

The concentration of prothrombin was estimated in both the samples and the difference in concentration was expressed as the response of prothrombin to Vitamin K.

For all estimations undiluted plasma was employed.

4. THYMOL TURBIDITY TEST

Venous blood was placed in a dry test tube until serum had separated from the clot. 0.5 ml. of serum was pipetted and added to 3 ml. of MacLagans Thymol Buffer solution which was prepared according to the directions given by this author. The serum-buffer mixture in a narrow test tube was allowed to stand for half an hour. This was then compared with standard turbidity as advised by MacLagan in a comparator with a black line on a white background.

Calculation -

$$\text{Unit of Thymol Turbidity} = \frac{\text{Standard tube reading} \times \text{Final dilution of serum}}{600}$$

5. GALACTOSE TOLERENCE TEST

a. Galactose Index.

After a period of overnight fast the patient was given 40 g. of galactose dissolved in 250 ml. of water flavoured with lemon juice (in an empty stomach). Venous blood/

blood (2 ml.) was collected just before the administration of galactose (control) and ½, 1, 1½ and 2 hours after the galactose solution was drunk. Galactose was estimated in each of these samples by King's method already described. For all estimations of galactose blanks were put through, consisting of (i) reagents alone, and (ii) yeast, (iii) yeast and glucose, (iv) standard galactose, (v) standard galactose and yeast treated in the same manner as for the estimation of blood galactose. G.I. = sum total of galactose in mg. per 100 ml. in the 4 specimens of blood obtained after the administration of galactose.

b. Forced Galactosuria.

Preparation consisted of overnight fasting. Immediately before the test the bladder was emptied (control). Then a dose of galactose previously weighed and measured dissolved in from 150 - 250 ml. of water (depending upon the dose of galactose employed) was administered orally. The bladder was then emptied every hour for 5 hours. All five samples of urine were sent to the laboratory for the detecting the presence of galactose in the urine.

The first dose of galactose was 15 g. The test was repeated on each successive day, the dose of galactose being increased by 5 g. each day until galactosuria occurred following the ingestion of galactose. When this stage was reached the test was repeated once more on the following morning to confirm that the same amount of galactose/

galactose again gave rise to galactosuria. This dose was regarded as the limit of galactose tolerance.

Lactose was eliminated by the osazone test.

References to all authors quoted in this section have been mentioned in detail in the text.

ABBREVIATONS.

B.P	Blood Pressure in mm. Hg.
Alb.	Albumin - in Plasma - Gm. per 100 ml. in urine (Proteinuria) Gm. per 1,000 ml.
Glob.	Plasma Globulin, Gm. per 100 ml.
Fib.	Plasma Fibrinogen, Gm. per 100 ml.
T.P.	Plasma Total Protein, Gm. per 100 ml.
Urea	Plasma Urea, mg. per 100 ml.
A.A.N.	Plasma Amino Acid Nitrogen, mg. per 100 ml.
Sugar	Blood Glucose, mg. per 100 ml.
Sugar mobl.	Blood Glucose mobilisation as a result of adrenalin injection, mg. per 100 ml.
T.C.	Plasma Total Cholesterol, mg. per 100 ml.
E.C.	Plasma Ester Cholesterol, mg. per 100 ml.
Lip. P.	Plasma Lipoid Phosphorus, mg. per 100 ml.
Alk. Phos.	Plasma Alkaline Phosphatase, Units(King and Armstrong per 100 ml.
Proth. Conc.	Prothrombin Concentration, per cent of normal (Quick)
Proth. Resp.	Response of prothrombin (plasma) to vitamin K, per cent.
Th. T.	Thymol Turbidity (plasma), Units per 100 ml.(MacLagan)
Bil. Ret.	Bilirubin Retention , per cent, at the end of four hours after intravenous injection of bilirubin.

ALL BIOCHEMICAL DATA PRESENTED IN THIS PROTOCOL ARE BASED ON ESTIMATIONS DONE IN TRIPLICATE. THE MEAN VALUES ARE PRESENTED HERE. WHENEVER INDIVIDUAL VALUES VARIED BY MORE THAN 5 PER CENT THE ESTIMATION WAS REPEATED.

A UNIT. MIXED DIET. MILD TOXAEMIAS.

Cases 1 to 24.

1. Mrs. McCrimmon, aet. 24. Primigravida, 35 wks. Duration of Toxaemia 1 wk.

20. 1. 48. B.P. 140/100; Alb. 1; Oedema -; Urea 25.6; A.A.N. 6.5; T.P. 5.98; Alb. 3.24; Glob. 2.25; Fib. 0.49; Sugar- 81.0; Sugar. Mobl. 19.6; T.C. 228; E.C.153; Lip. P. 10.1; Alk. Phos. 14.2; Th. T. 0.4; Proth. Conc. 71.4; Proth. Resp. 78.8; Bil. Ret. 6.9.

27.1. 48. B.P. 140/95; Alb. 0.5; Oedema -; Urea 26.0; A.A.N. 6.5; T.P.- 5.60; Alb.- 2.98; Glob.- 2.23; Fib.- 0.39; Sugar- 93; Sugar Mobl. 19.8; T.C. 224; E.C.- 150; Lip. P.- 10.0; Alk. Phos. 14.6; Th. T. 0.5; Proth. Conc. 72.0; Proth. Resp. 78.8; Bil. Ret. 6.9.

2. Mrs. McClinchey, aet. 27. Primigravida 37 weeks. Duration of Toxaemia 1.5 wks.

21. 1. 48. B.P. 150/100; Alb. 2; Oedema - -; Urea 24.0; A.A.N. 6.5; T.P. 5.76; Alb. 3.05; Glob. 2.30; Fib. 0.41; Sugar- 96.2; Sugar Mobl. 18.5; T.C.- 236; E.C.- 160; Lip. P.- 11.3; Alk. Phos.- 15.0; Th.T.- 1.0; Proth. Conc.- 60.0; Proth. Resp. 79.6; Bil. Ret.- 4.4.

28.1.48. B.P. 160/100; Alb.- 2.5; Oedema -; Urea 24.5; A.A.N.- 6.7; T.P. 5.70; Alb.- 2.95; Glob.- 2.31; Fib.- 0.44; Sugar- 90.0; Sugar Mobl.- 18.0; T.C. 240; E.C.- 163; Lip. P.- 11.5; Alk. Phos.- 15.3; Th. T. 1.0; Proth. Conc. 60.0; Proth. Resp.- 74.7; Bil. Ret. 4.4.

4.2.48. B.P. 160/100; Alb. 5; Oedema - -; Urea 24.0; A.A.N.- 7.0; T.P.- 5.54; Alb. 2.73; Glob. 2.32; Fib.- 0.49; Sugar- 84.0; Sugar Mobl.- 18.0; T.C.- 252; E.C.- 166; Lip. P. 12.8; Alk. 17.8; Th.T. 1.0; Proth. Conc. 60.0; Proth. Resp.- 64.5; Bil. Ret.- 10.5.

12.2.48. B.P. 170/100; Alb. 6; Oedema - -; Urea- 22.6; A.A.N.- 8.6; T.P.- 5.49; Alb.- 2.42; Glob.- 2.20; Fib.- 0.37; Sugar- 91.5; Sugar Mobl.- 15.5; T.C.- 264; E.C.- 165; Lip. P.- 13.2; Alk. Phos.- 24.4; Th. T.- 3.5; Proth. Conc.- 48.7; Proth. Resp.- 50.5; Bil. Ret.- 15.9.

14.2.48. B.P. 175/120; Alb.- 6.5; Oedema - -; Induction of Labour/

Labour. Urea - 19.0; A.A.N.- 9.2; Sugar - 93.0; Sugar Mobl.- 14.3; T.C.- 260; E.C.- 158.

3. Mrs. Fox, Secondgravida, aet = 29 years.

35 weeks. Duration of Toxaemia 1 week.

5.3.48. B.P. 148/100; Alb. - 3; Oedema ++; Urea - 25.8; A.A.N.- 6.0; T.P.- 5.72; Alb.- 2.95; Glob.- 2.29; Fib.- 0.48; Sugar - 85.5; Sugar Mobl.- 17.0; Gal.In.- 116.4; T.C.- 248; E.C.- 164; Lip. P.- 11.8; Alk. Phos.- 13.9; Th. T.- 0.7; Pr. Conc.- 73.5; Pr. Resp.- 74.0; Bil. Ret.- 3.0.

12.3.48. B.P. 150/100; Alb.- 3; Oedema +; Urea - 25.0; A.A.N.- 7.2; T.P.- 5.71; Alb.- 2.73; Glob.- 2.29; Fib.- 0.49; Sugar - 89.0; Sugar Mobl.- 16.8; Gal. In.- 166.8; T.C.- 240; E.C.- 163; Alk. Phos.- 14.0; Th. T.- 0.75; Pr. Conc.- 72.8; Pr. Resp.- 69.5; Bil. Ret.- 4.9.

19.3.48. B.P. 160/100; Alb.- 5; Oedema +; Urea - 26.2; A.A.N.- 7.8; T.P.- 5.52; Alb.- 2.70; Glob.- 2.30; Fib.- 0.52; Sugar - 90.2; Sugar Mobl.- 17.8; T.C.- 239; E.C.- 160; Alk.Phos.- 16.5; Th. T.- 1.2; Pr. Conc.- 71.6; Pr. Resp.- 58.7; Bil. Ret.- 8.9.

24.3.48. B.P.- 160/110; Alb.- 6.5; Oedema +++; Spontaneous Labour. B.B.A.
Urea - 20.4; A.A.N.- 8.8; T.P.- 5.43; Alb.- 2.74; Glob.- 2.37; Fib.- 0.32; Sugar - 91.4; Sugar Mobl.- 14.5; Gal. In.-(21.3.48) - 188.0; T.C.- 25o; E.C.- 162; Alk. Phos.- 18.3; Th.T.- 3.0; Pr. Conc.- 61.0; Pr. Resp.- 50.0; Bil. Ret.- 14.7.

4. Mrs. Calder, Aet 26; Primigravida, 38 weeks.

Duration of toxaemia - 2 weeks.

5.3.48. B.P. 140/95; Alb.- 1.5; Oedema +; Urea - 29.5; A.A.N.- 6.0; T.P.- 5.81; Alb.- 3.08; Glob.- 2.25; Fib.- 0.48; Sugar - 80.6; Sugar Mobl.- 18.0; T.C.- 219.0; E.C.- 154; Lip. P.- 12.6; Alk. Phos.- 15.7; Th. T.- 0.4; Pr. Conc.- 68.4; Pr. Resp.- 66.0; Bil. Ret.- 3.2.

10.3.48. Spontaneous Labour. B.B.A. B.P.- 140/95; Alb.-2; Oedema +; T.P.- 5.77; Alb.- 2.93; Glob.- 2.34; Fib.- 0.50; Sugar - 84.0; Sugar Mobl.- 16.5; Alk. Phos.- 16.0; Th. T.- 0.5; Pr. Conc.- 69.0; Pr. Resp.-60.0; Bil. Ret.- 3.0.

5. Mrs. McBride, Aet 22. Primigravida, 37 weeks.

Duration of Toxaemia 2 weeks.

24.3.48. B.P.- 148/100; Alb.- 3.5; Oedema ++; Urea - 25.0; A.A.N.- 6.7; T.P.- 5.68; Alb.- 2.84; Glob.- 2.29; Fib.- 0.54; Sugar - 89.0; Sugar Mobl.- 20.0; Gal. In.- 118.3; T.C.- 266; E.C.- 176; Lip.P. - 12.3; Alk. Phos.- 15.9; Th. T.- 2.5; Proth. Conc.- 65.7; Proth. Resp.- 71.5; Bil. Ret.- 3.4.

1.4.48. B.P.- 150/110; Alb.- 5; Oedema +; Urea - 25.0; A.A.N.- 7.2; T.P.- 5.55; Alb.- 2.80; Glob.- 2.28; Fib.- 0.57; Sugar - 80.6; Sugar Mobl.- 17.5; Gal. In.(2.4.48) - 156.3; T.C.- 260; E.C.- 157; Alk.Phos.- 16.2; Th. T.- 3.0; Proth. Conc.- 65.0; Proth. Resp.- 68.0; Bil. Ret.- 4.4.

8.4.48. B.P.- 150/110; Alb.- 3.5; Oedema ±; Urea - 29.5; A.A.N.- 8.6; T.P.- 5.60; Alb.- 2.71; Glob.- 2.30; Fib.- 0.59; Sugar - 94.5; Sugar Mobl.- 20.7; Gal. In. (9.4.48) - 171.3; T.C.- 262; E.C.- 155; Alk. Phos.- 17.5; Th. T.- 3.3; Proth. Conc.- 66.2; Proth. Resp. 53.6; Bil. Resp.- 6.7.

15.4.48. B.P.- 150/110; Alb.- 3; Oedema ±; Urea - 28.0; A.A.N.- 8.5; T.P.- 5.60; Alb.- 2.71; Glob.- 2.30; Fib.- 0.40; Sugar - 86.8; Sugar Mobl.- 16.0; T.C.- 270; E.C.- 155; Alk. Phos.- 18.3; Th. T.- 3.7; Proth. Conc.- 64.8; Proth. Resp.- 47.6; Bil. Ret.- 12.4.

21.4.48. B.P. 150/100; Alb.- 2; Oedema ±; Spontaneous Labour; B.B.A.
Urea - 27.6; A.A.N.- 8.6; T.P.- 5.38; Alb.- 2.88; Glob.- 2.33; Fib.- 0.27; Sugar 86.0; Sugar Mobl.- 16.5; T.C.- 270; E.C.- 142; Alk. Phos.- 19.3; Th. T.- 3.5; Proth. Conc.- 65.0; Proth. Resp.- 45.3; Bil. Ret.- 8.3.

6. Mrs. Edmiston, Aet 34. Fourth gravida; 36 weeks.

Duration of Toxaemia 0.5 weeks.

19.3.48. B.P.- 140/90; Alb.- 1.5; Oedema +; Urea - 27.5; A.A.N.- 6.8; T.P.- 5.82; Alb.- 3.0; Glob.- 2.32; Fib.- 0.50; Sugar 87.8; Sugar Mobl.- 19.4; T.C.- 250; E.C.- 173; Lip. P.- 13.8; Alk. Phos.- 13.6; Th. T.- 1.0; Proth. Conc.- 70.8; Proth. Resp.- 68.6; Bil. Ret.- 7.4.

26.3.48. T.P.- 5.77; Alb.- 3.07; Glob.- 2.30; Fib.- 0.40; Sugar - 87.0; Sugar Mobl.- 21.0; Alk. Phos.- 14.0; Th. T.- 1.0; Proth. Conc.- 73.5; Proth. Resp.- 73.5; Bil. Ret.- 7.5.

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7. Mrs. Rennie, Aet 30; Second gravida, 32 weeks.

Duration of Toxaemia 1 week.

24.3.48. B.P.- 140/100; Alb.- 2; Oedema +; Urea - 24.5; A.A.N.- 6.0; T.P.- 5.81; Alb.- 2.97; Glob.- 2.34; Fib.- 0.50; Sugar - 91.0; Sugar Mobl.- 20.8; T.C.- 239; E.C.- 165; Lip. P.- 11.6; Alk. Phos.- 12.5; Th. T.- 1.0; Proth; Conc.- 67.8; Proth. Resp.- 63.4; Bil. Ret.- 2.3.

31.3.48. B.P.- 140/100; Alb.- 1.5; Oedema +; Urea - 24.0; A.A.N.- 6.9; T.P.- 5.81; Alb.- 2.97; Glob.- 2.34; Fib.- 0.50; Sugar - 94.6; Sugar Mobl.- 19.7; T.C.- 244; E.C.- 169; Alk. Phos.- 12.9; Th. T.- 1.2; Proth. Conc.- 70.6; Proth. Resp.- 70.3; Bil. Ret.- 2.35.

8. Mrs. Hughes, Aet 24. Primigravida; 37 weeks.

Duration of Toxaemia 2 weeks.

1.4.48. B.P.- 150/95; Alb.- 3; Oedema ++; Urea - 27.0; A.A.N.- 61; T.P.- 5.70; Alb.- 2.94; Glob.- 2.30; Fib.- 0.46; Sugar - 97.0; Sugar Mobl.- 18.0; Gal. In.- 136.9; T.C.- 260; E.C.- 174; Lip. P.- 13.3; Alk. Phos.- 16.3; Th.T.- 1.7; Proth. Conc.- 68.0; Proth. Resp.- 50.8; Bil. Ret.- 10.9.

8.4.48. B.P.- 150/110; Alb.- 3; Oedema +; Urea - 30; A.A.N.- 7.8; T.P.- 5.69; Alb.- 2.90; Glob.- 2.31; Fib.- 0.48; Sugar - 90.o; Sugar Mobl.- 19.7; Gal. In.- 144.2; T.C.- 250; E.C.- 167; Alk. Phos.- 17.5; Th. T.- 2.0; Bil.- 11.0.

15.4.48. B.P.-160/110; Alb.- 6; Oedema +; Urea - 30.0; A.A.N.- 9.2; T.P.- 5.47; Alb.- 2.64; Glob.- 2.30; Fib.- 0.53; Sugar - 87.6; Sugar Mobl.- 16.0; T.C.- 254; E.C.- 165; Lip. P.- 13.5; Alk. Phos.- 17.8; Th. T.- 2.0; Proth. Conc.- 58.5; Proth. Resp.- 40.0; Bil. Ret.- 13.0.

22.4.48. B.P. 180/120; Alb.- 10; Oedema - +++; Headache ++; Visual Disturbance +; Epigastric pain +; Surgical induction. S.B.
Urea - 30.0; A.A.N.- 14.4; T.P.- 5.12; Alb.- 2.54; Glob.- 2.34; Fib.- 0.24; Sugar - 87.0; Sugar Mobl.- 12.8; Gal. In.- (20.4.48) - 192.0; T.C.- 269; E.C.-15o; Lip. P.- 15.1; Alk. Phos.- 28.6; Th. T.- 4.8; Proth. Conc.- 41.9; Proth. Resp.- 24.0; Bil. Ret.- 19.6.

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9. Mrs. McKay, Aet 32; Third gravida; 30 weeks.

Duration of Toxaemia 1 week. Pre-eclampsia in first pregnancy.

2.4.48; B.P.- 150/100; Alb.- 2.5; Oedema - +; Urea - 24.5; A.A.N.- 60; T.P.- 5.72; Alb.- 2.95; Glob.- 2.28; Fib.- 0.49; Sugar - 90.0; Sugar Mobl.- 22.6; T.C.- 248; E.C.- 175; Lip. P.- 12.6; Alk. Phos.- 12.7; Th. T.- 0.3; Bil. Ret.- 2.3; Proth. Conc.- 70.7; Proth. Resp.- 51.0.

9.4.48. B.P.- 145/100; Alb.- 1.5; Oedema ±; Urea - 27.0; A.A.N.- 7.7; T.P.- 5.76; Alb.- 3.02; Glob.- 2.30; Fib.- 0.44; Sugar - 98.8; Sugar Mobl.- 23.0; T.C.- 244; E.C.- 172; Alk. Phos.- 12.9; Th. T.- 0.5; Proth. Conc.- 70.9; Proth. Resp.- 56.0; Bil. Ret.- 0.45.

16.4.48. B.P.- 145/100; Alb.- 1.5; Oedema ±; Urea - 27.2; A.A.N.- 8.2; T.P.- 5.80; Alb.- 3.09; Glob.- 2.31; Fib.- 0.40; Sugar - 81.0; Sugar Mobl.- 21.6; T.C.- 250; E.C.- 175; Alk. Phos.- 12.5; Proth. Conc.- 73.5; Proth. Resp.- 62.5; Bil. Ret.- 0.50.

23.4.48. B.P.- 140/90; Alb.- 0.5; Oedema - 0; Urea - 27.5; A.A.N.- 7.9; T.P.- 6.16; Alb.- 3.44; Glob.- 2.33; Fib.- 0.39; Sugar - 84.5; Sugar Mobl.- 20.5; T.C.- 231; E.C.- 168; Alk. Phos.- 14.6; Th. T.- 0.4; Proth. Conc.- 78.0; Proth. Resp.- 81.0; Bil. Ret.- 0.4.

10. Mrs. Slavin, Aet 23. Primigravida, 33 weeks.

Duration of Toxaemia 2 weeks.

Cystine - 5 gms. daily from 23.4.48 to 5.5.48.

8.4.48. B.P.- 150/100; Alb.- 5; Oedema ++; Urea - 25.5; A.A.N.- 6.1; T.P.- 5.53; Alb.- 2.76; Glob.- 2.28; Fib.- 0.49; Sugar - 87.6; Sugar Mobl.- 18.0; Gal. In.- 104.7; T.C.- 270; E.C.- 184; Lip.P.- 14.3; Alk. Phos.- 13.8; Th.T.- 0.9; Proth. Conc.- 65.5; Proth. Resp.- 67.2; Bil. Ret.- 8.5.

15.4.48. B.P.- 155/100; Alb.- 5; Oedema +; Urea - 25.0; A.A.N.- 6.8; T.P.- 5.55; Alb.- 2.68; Glob.-2.27; Fib.- 0.60; Sugar - 80.5; Sugar Mobl.- 17.6; Gal. In.- 129.6; T.C.-260; E.C.- 179; Alk. Phos.- 13.5; Th. T.- 1.0; Proth. Conc.- 65.0; Proth. Resp.- 64,3; Bil. Ret.- 8.0.

23.4.48. B.P.- 160/100; Alb.- 6.5; Oedema +; Urea-- 30.5; A.A.N./

A.A.N.- 8.2; T.P.- 5.40; Alb.- 2.56; Glob.- 2.30; Fib.- 0.54; Sugar - 93.0; Sugar Mobl.- 17.2; Gal. In.- 148.7; T.C.- 262; E.C.- 180; Alk. Phos.- 14.5; Th. T.- 1.4; Proth. Concn.- 65.0; Proth. Resp.- 59.0; Bil. Ret.- 8.0.

30.4.48. B.P.- 160/100; Alb.- 6; Oedema +: Urea - 28.6; A.A.N.- 8.4; T.P.- 5.48; Alb.- 2.49; Glob.- 2.29; Fib.- 0.50; Sugar - 90.0; Sugar Mobl.- 17.3; Gal. In.- 173.0; T.C.- 254; E.C.- 174; Alk. Phos.- 18.9; Th. T.- 2.0; Proth. Conc.- 50.0; Proth. Resp.- 50.0; Bil. Ret.- 8.96.

5.5.48. B.P.- 160/100; Alb.- 5; Oedema ±; Urea - 28.0; A.A.N.- 8.8; T.P.- 5.54; Alb.- 2.94; Glob.- 2.30; Fib.- 0.30; Sugar - 90.5; Sugar Mobl.- 17.5; T.C.- 266; E.C.-180; Alk. Phos.- 20.7; Th. T.- 3.5; Proth. Conc.- 64.7; Proth. Resp.- 43.6; Bil. Ret.- 8.17.

11. Mrs. Hastings, Aet 29. Third gravida; 34 weeks.

Duration of Toxaemia - 3 weeks.

Cystine - 5 gms. daily from 16.4.48 to 30.4.48.

8.4.48. B.P.- 150/100; Alb.- 5; Oedema ++; Urea 24.0; A.A.N.- 6.0; T.P.- 5,55; Alb.- 2.76; Glob.- 2.30; Fib.- 0.49; Sugar - 83.0; Sugar Mobl.- 18.9; Gal. In.- 96.7; T.C.- 244; E.C.- 165; Lip. P.- 16.1; Alk. Phos.- 15.7; Th. T.- 1.8; Proth. Conc.- 60.2; Proth. Resp.- 64.7; Bil. Ret.- 9.9.

16.4.48. B.P.- 150/100; Alb.- 3; oedema ++; Urea - 28.1; A.A.N.- 8.0; T.P.- 5.64; Alb.- 2.80; Glob.- 2.33; Fib.- 0.51; Sugar - 93.5; Sugar Mobl.- 21.5; Gal. In.- 119.6; T.C.- 240; E.C.- 160; Alk.Phos.- 16.3; Th. T.- 1.9; Proth. Conc.- 59.6; Proth. Resp.- 60.5; Bil. Ret.- 8.0.

23.4.48. B.P.- 150/100; Alb.- 3; Oedema +; Urea - 29.3; A.A.N.- 8.2; T.P.- 5.46; Alb.- 2.74; Glob.- 2.30; Fib.- 0.42; Sugar - 84.0; Sugar Mobl.- 20.8; Gal. In.- 144.5; T.C.- 240; E.C.- 161; Alk. Phos.- 160; Th. T.- 2.0; Proth. Conc.- 60.0; Proth. Resp.- 51.8; Bil. Ret.- 7.97.

30.4.48. B.P.- 150/90; Alb.- 3; Oedema ±; Urea - 29.5; A.A.N.- 8.2; T.P.- 5.37; Alb.- 2.70; Glob.- 2.28; Fib.- 0.39; Sugar - 80.0; Sugar Mobl.- 19.9; Gal. In.- 170.8; T.C.- 230; E.C.- 156; Alk. Phos.- 16.5; Th. T.- 2.1; Proth. Conc.- 62.7; Proth. Resp.- 37.2; Bil. Ret.- 6.93.

12. Mrs. Black, Aet 30; Second gravida; weeks.

Duration of Toxaemia - 1 week.

18.4.48. B .P.- 150/95; Alb.- 2.5; Oedema +; Urea - 29.5; A.A.N.- 7.5; T.P.- 5.70; Alb.- 2.97; Glob.- 2.30; - Fib.- 0.53; Sugar - 91.5; Sugar Mobl.- 19.0; T.C.- 252; E.C.- 174; Alk. Phos.- 12.9; Th. T.- 0.4; Proth. Conc.- 79.0; Proth. Resp.- 64.0; Bil. Ret.- 2.6; Lip. P.- 13.1.

26.4.48. B.P.- 145/90; Alb.-1; Oedema ±; Urea - 29.0; A.A.N.- 7.5; T.P.- 5.66; Alb.- 2.97; Glob.- 2.29; Fib.- 0.40; T.C.- 250; E.C.- 169; Alk. Phos.- 13.5; Th. T.- 1.8; Proth. Conc.- 81.2; Proth. Resp. - 68.0; Bil. Ret.- 2.6;

4.5.48. B.P.- 138/80; Alb.- 0.5; Oedema - 0; T.P.- 5.91; Alb.- 3.16; Glob.- 2.35; Fib.- 0.40; Alk. Phos.- 13.8; Th. T.- 0.5; Proth. Conc.- 88.8; Proth. Resp.- 80.6; Bil. Ret.- 2.6.

13. Mrs. Santi, Aet 23; Primigravida, 34 weeks.

Duration of Toxaemia - 2 weeks.

18.4.48. B.P.- 150/100; Alb.- 2; Oedema +; Urea - 24.5; A.A.N.- 6.4; T.P.- 5.71; Alb.- 2.82; Glob.- 2.35; Fib.- 0.54; Sugar - 82.6; Sugar Mobl.- 17.7; T.C.- 236; E.C.- 160; Lip. P.- 12.1; Alk.-Phos. - 12.5; Th. T.- 0.5; Proth. Conc.- 63.5; Proth. Resp.- 56.5; Bil. Ret.- 3.3.

26.4.48. B.P.- 145/100; Alb.- 2; Oedema ±; Urea - 24.0; A.A.N.- 6.9; T.P.- 5.72; Alb.- 2.85; Glob.- 2.32; Fib.- 0.55; Sugar - 80.5; Sugar Mobl.- 17.0; T.C.- 256; E.C.- 174; Alk. Phos.- 13.9; Th. T.- 0.5; Proth. Conc.- 66.7; Proth. Resp.- 66.0; Bil. Ret.- 3.0.

3.5.48. B.P. - 140/90; Alb.- 2; Oedema ±; Urea - 25.0; A.A.N.- 6.5; T.P.- 5.72; Alb.- 2.95; Glob.- 2.34; Fib.- 0.43; Sugar - 78.0; Sugar Mobl.- 19.7; T.C.- 244; E.C.- 165; Alk. Phos.- 13.0; Th. T.- 0.5; Proth. Concn.- 68.0; Proth. Resp.- 74.8; Bil. Ret.- 3.15.

14. Mrs. McEwan, Aet 32; Primigravida, 37 weeks.

Duration of Toxaemia - 1 week.

4.5.48. B.P.- 145/98; Alb.- 4; Oedema ++; Urea - 26.0; A.A.N. - 6.9; T.P.- 6.00; Alb.- 3.22; Glob.- 2.30; Fib.- 0.48; Sugar - 94.0; Sugar Mobl.- 18.9; T.C.- 230; E.C.- 157.5; Lip. P.- 15.5; Alk. Phos.- 16.5; Th. T.- 1.3; Proth. Conc.- 70.4; Proth. Resp.- 76.5; Bil. Ret.- 6.9.

11.5.48. B.P.- 150/100; Alb.- 5; Oedema +; Urea - 24.6; A.A.N.- 7.7; T.P.- 5.22; Alb.- 2.37; Glob.- 2.27; Fib.- 0.58; Sugar - 90; Sugar Mobl.- 18.0; T.C.- 238; E.C.- 161; Lip. P.- 15.9; Alk. Phos.- 17.0; Th. T.- 1.5; Proth. Conc.- 70.0; Proth. Resp.- 67.6; Bil. Ret.- 6.98.

18.5.48. B.P.- 160/110; Alb.- 9; Oedema ++; Urea - 19.3; A.A.N.- 9.0; T.P.- 5.20; Alb.- 2.36; Glob.- 2.28; Fib.- 0.60; Sugar - 92.0; Sugar Mobl.- 16.5; T.C.- 240; E.C.- 152; Lip. P.- 16.2; Alk. Phos; 22.8; Th. T.- 1.3; Proth. Conc.- 68.8; Proth. Resp.- 50.0; Bil. Ret.- 14.95.

22.5.48. B.P.- 175/115; Alb.- 12.5; Oedema +++; Headache ++; Dimness of Vision +; Epigastric pain +; Surgical induction; B.B.A.
Urea - 27.8; A.A.N.- 12.2; T.P.- 4.8; Alb.- 2.37; Glob.- 2.31; Fib.- 0.30; Sugar - 87.0; Sugar Mobl.- 15.0; T.C.- 235; E.C.- 127; Lip. P.- 13.2; Alk. Phos.- 24.6; Th. T.- 4.7; Proth. Conc.- 50.0; Proth. Resp.- 36.2; Bil. Ret.- 18.4.

15. Mrs. Daly, aet 37; Third gravida, weeks.

Duration of Toxaemia - 1 week.

3.6.48. B.P.- 150/90; Alb.- 5; Oedema ++; Urea - 25.5; A.A.N.- 6.7; T.P.- 5.57; Alb.- 2.80; Glob.- 2.27; Fib.- 0.50; Sugar, 89.2; Sugar Mobl.- 18.1; T.C.- 256; E.C.- 172; Lip. P.- 13.7; Th. T.- 1.0; Proth. Conc.- 78.0; Proth. Resp.- 78.0; Bil. Ret.- 3.2.
Confined on 9.6.48. B.B.A.

16. Mrs. Crawley, aet 30; Second gravida; 3o weeks.

Duration of Toxaemia - 1.5 weeks.

1.6.48. B.P.- 150/100; Alb.- 1; Oedema +; Urea - 26.5; A.A.N.- 6.5; T.P.- 5.99; Alk.- 3.18; Glob.- 2.21; Fib.- 0.54; Sugar - 87.7; Sugar Mobl.- 18.7; T.C.- 262; E.C.- 177; Lip. Phos.- 11.2; Alk. Phos.- 13.0; Th. T.- 1.8; Proth. Conc.- 73.4; Proth. Resp.- 71.9; Bil. Ret.- 2.8.

No follow-up because of skin infection.

17. Mrs. White, aet 23; Primigravida; 36/37 weeks.

Duration of Toxaemia - 1 week.

1.6.48. B.P.- 140/100; Alb.- 0.5; Oedema ±; Urea - 26.2; A.A.N.- 6.3; T.P.- 6.16; Alb.- 3.40; Glob.- 2.33; Fib.- 0.43; Sugar - 93.0; Sugar Mobl.- 19.3; T.C.- 249; E.C.- 168; Lip. P.- 13.1; Alk. Phosp.- 13.5; Th. T.- 0.8; Proth. Conc.- 70.7; Proth. Resp.- 68.0; Bil. Ret.- 12.9.

8.6.48. B.P.- 145/100; Alb.- 0.5; Oedema ±; Urea - 25.5; A.A.N.- 7.0; T.P.- 6.14; Alb.- 3.35; Glob.- 2.34; Fib.- 0.45; Sugar - 86.0; Sugar Mobl.- 19.0; T.C.- 257; E.C.- 175; Alk. Phos.- 13.6; Th. T.- 0.8; Proth. Conc.- 64.5; Proth. Resp.- 60.6; Bil. Ret.- 12.6.

16.6.48. B.P.- 145/100; Alb.- 0.5; Oedema ±; Urea - 24.0; A.A.N.- 7.0; T.P.- 5.83; Alb.- 3.04; Glob.- 2.30; Fib.- 0.49; Sugar - 89.6; Sugar Mobl.- 18.5; T.C.- 260; E.C.- 173.5; Alk.-Phos.- 14.8; Th. T.- 1.2; Proth. Conc.- 60.5; Proth. Resp.- 58.0; Bil. Ret.- 11.9.

23.6.48. B.P.- 150/110; Alb.- 1.5; Oedema ±; Urea - 24.4; A.A.N.- 7.8; T.P.- 5.81; Alb.- 2.99; Glob.- 2.29; Fib.- o.53; Sugar - 84.0; Sugar Mobl.- 15.0; T.C.- 2.64; E.C.- 163; Alk. Phos.- 16.8; Th. T.- 1.3; Proth. Conc.- 60.6; Proth. Resp.- 50.5; Bil. Ret.- 13.0.

30.6.48. B.P.- 150/110; Alb.- 1.5; Oedema 0; Spontaneous labour; B.B.A.
T.P.- 5.79; Alb.- 3.04; Glob.- 2.36; Fib.- 0.39; Sugar - 94.5; Sugar Mobl.- 15.0; Alk. Phos.- 22.5; Th. T.- 2.5; Proth. Conc.- 60.0; Proth. Resp.- 45.4; Bil. Ret.- 14.3.

18. Mrs. McElholm, aet 31; Second gravida; weeks.

Duration of Toxaemia - 1 week.

1.6.48. B.P.- 150/98; Alb.- 1.5; Oedema +; Urea - 27.5; A.A.N.- 6.2; T.P.- 5.81; Alb.- 3.08; Glob.- 2.21; Fib.- 0.52; Sugar - 90.0; Sugar mobl.- 18.7; T.C.- 268; E.C.- 181; Lip. P.- 14.5; Alk. Phos.- 14.4; Th. T.- 1.5; Proth. Conc.- 82.4; Proth. Resp.- 67.8; Bil. Ret.- 6.5.

7.6.48. B.P.- 145/90; Alb.- 0.5; Oedema ±; Urea - 27.9; A.A.N.- 6.0; T.P.- 5.73; Alb.- 3.13; Glob.- 2.20; Fib.- 0.40; T.C.- 265; E.C.- 180; Alk. Phos.- 14.0; Th. T.- 2.3; Proth. Conc.- 87.8; Proth. Resp.- 70.4; Bil. Ret.- 7.6.

19. Mrs. Sayers, aet 30; Primigravida; weeks.

Duration of Toxaemia - 1 week.

13.9.48; B.P.- 150/100; Alb.- 5; Oedema ++; Urea - 24.8; A.A.N.- 5.8; T.P.- 5.78; Alb.- 2.97; Glob.- 2.30; Fib.- 0.51; Sugar - 84; Sugar Mobl.- 19.1; T.C.- 188; E.C.- 130; Lip.P.- 15.2; Alk.-Phos.- 14.6; Th. T.- 1.8; Proth. Conc.- 70.4; Proth. Resp.- 69.0. Bil. Ret.- 9.6.

20.9.48. B.P.- 150/100; Alb.- 7; Oedema ++; Urea - 25.0; A.A.N./

A.A.N.- 6.8; T.P.- 5.67; Alb.- 2.88; Glob.- 2.29; Fib.- 0.50; Sugar - 80.6; Sugar Mobl.- 18.0; T.C.- 200; E.C.- 137; Alk. Phos.- 15.2; Th. T.- 1.5; Proth. Conc.- 69.5; Proth. Resp.- 63.0; Bil. Ret.- 10.2.
Spontaneous Labour on 21.9.48; B.B.A.

20. Mrs. McNair, Primigravida, aet 33; 38 weeks.

Duration of Toxaemia - 2 weeks.

2.10.48. B.P.- 150/100; Alb.- 6; Oedema +++; Urea - 25.0; A.A.N.- 6.0; T.P.- 5.80; Alb.- 3.00; Glob.- 2.31; Fib.- 0.49; Sugar - 78.5; Sugar Mobl.- 18.0; T.C.- 210; E.C.- 143; Lip. P.- 14.5; Alk. Phos.- 14.8; Th. T.- 1.5; Proth. Conc.- 63.5; Proth. Resp.- 68.0; Bil. Ret.- 8.5.

9.10.48. B.P.- 160/108; Alb.- 6; Oedema ++; Urea - 20.5; A.A.N.- 8.3; T.P.- 5.75; Alb.- 2.75; Glob.- 2.30; Fib.- 0.70; Sugar - 82.0; Sugar Mobl.- 16.0; T.C.- 216; E.C.- 137; Lip. P.- 17.3; Alk. Phos.- 18.9; Th. T.- 1.8; Proth. Conc.- 59.5; Proth. Resp.- 58.0; Bil. Ret.- 13.0.

16.10.48. B.P.- 175/115; Alb.- 8; Oedema ++; Urea - 18.6; A.A.N.- 9.2; T.P.- 5.40; Alb.- 2.75; Glob.- 2.31; Fib.- 0.34; Sugar - 82.0; Sugar Mobl.- 15.3; T.C.- 248; E.C.- 131; Lip.P. - 17.5; Alk. Phos.- 22.0; Th. T.- 2.0; Proth. Conc.- 50.8; Proth. Resp.- 50.6; Bil. Ret.- 19.

Surgical induction of labour on 17.10.48. S.B.

21. Mrs. Graham, Primigravida, aet 27; 38 weeks.

Duration of Toxaemia - 1.5 weeks.

8.10.48. B.P.- 148/98; Alb.- 3; Oedema ++; Urea - 27.8; A.A.N.- 6.3; T.P.- 5.77; Alb.- 2.96; Glob.- 2.32; Fib.- 0.49; Sugar - 88.2; Sugar Mobl.- 19.6; T.C.- 244; E.C.- 166; Lip. P.- 15.1; Alk. Phos.- 12.9; Th. T.- 1.0; Proth. Conc.- 78.6; Proth. Resp.- 75.0; Bil. Ret.- 5.0.

15.10.48. B.P.- 15o/100; Alb.- 2; Oedema +; Urea - 27.5; A.A.N.- 7.0; T.P.- 5.79; Alb.- 3.01; Glob.- 2.33; Fib.- 0.45; Sugar - 86.0; Sugar Mobl.- 19.0; T.C.- 250; E.C.- 170; Alk. Phos. - 13.2; Th. T.- 1.0; Proth. Conc.- 80.0; Proth. Resp.- 75.3; Bil. Ret.- 5.5.

22.10.48. B.P.- 150/98; Alb.- 2; Oedema $\pm$; Urea - 27.7; A.A.N.- 7.1; T.P.- 5.78; Alb.- 3.03; Glob.- 2.31; Fib.- 0.44; Sugar - 89.9; Sugar Mobl.- 19.0; T.C.- 247; E.C.- 168; Alk.Phos.- 13.4; Th.T.- 0.8; Proth. Conc.- 81.0; Proth. Resp.- 79.6; Bil. Ret.- 5.5.

22. Mrs. Grant, Primigravida; aet 24; 39 weeks.

Duration of Toxaemia - 1 week.

11.10.48. B.P.- 150/100; Alb.- 4; Oedema ++; Urea - 28.4; A.A.N.- 6.5; T.P.- 5.68; Alb.- 2.87; Glob.- 2.29; Fib.- 0.52; Sugar - 94.0; Sugar Mobl.- 18.0; T.C.- 228; E.C.- 154; Alk. Phos.- 13.4; Th. T.- 1.2; Lip. P.- 13.5; Proth. Conc.- 76.3; Proth. Resp.- 76.0; Bil. Ret.- 1.1.

18.10.48. B.P.- 140/90; Alb.- 1.5; Oedema +; Urea - 29.0; A.A.N.- 6.7; T.P.- 5.79; Alb.- 3.04; Glob.- 2.31; Fib.- o.44; Sugar - 97.0; Sugar Mobl.- 18.8; T.C.- 238; E.C.- 159; Alk. Phos.- 13.9; Th. T.- 1.0; Proth. Conc.- 80.0; Proth. Resp.- 78.6; Bil. Ret.- 1.6.

Spontaneous labour on 19.10.48; B.B.A.

23. Mrs. McKenzie, Third gravida; aet 34; weeks.

Duration of Toxaemia - 1.5 weeks.

21.10.48. B.P. 150/95; Alb.- 2; Oedema +; Urea - 29.6; A.A.N.- 6.1; T.P.- 5.71; Alb.- 2.91; Glob.- 2.30; Fib.- 0.49; Sugar - 91.6; Sugar Mobl.- 17.9; T.C.- 234; E.C.- 156.5; Lip. P.- 12.3; Alk. Phos. - 14.0; Th. T.- 1.0; Proth. Conc.- 69.7; Proth. Resp.- 65.4; Bil. Ret.- 1.0.

24. Mrs. McLaughlin, Second gravida; aet 32; 32 weeks.

Duration of Toxaemia - 1 week. Toxaemia in first pregnancy 4 years ago.

19.11.48. B.P. 145/100; Alb.- 2; Oedema +; Urea - 24.4; A.A.N.- 5.9; T.P.- 5.61; Alb.- 2.82; Glob.- 2.29; Fib.- 0.50; Sugar - 91.0; Sugar Mobl.- 18.2; T.C.- 219; E.C.- 143; Lip. P.- 13.2; Alk. Phos.- 13.0; Th. T.- 2.2; Proth. Conc.- 70.8; Proth. Resp.- 70.5; Bil. Ret.- 2.4.

+

26.11.48. B.P. 145/95; Alb.- 1; Oedema -; Urea - 23.0; A.A.N.- 6.6; T.P.- 5.71; Alb.- 2.94; Glob.- 2.31; Fib.- 0.46; Sugar - 91.7; Sugar Mobl.- 18.6; T.C.- 227; E.C.- 154.5; Alk. Phos.- 13.8; Th. T.- 2.0; Proth. Conc.- 74.4; Proth. Resp.- 72.8; Bil. Ret. 2.4.

A UNIT. MIXED DIET. SEVERE TOXAEMIAS.

Cases No. 25 to 42.

25. Mrs. Jones, Primigravida; aet 31; 37 weeks.

Duration of Toxaemia - 1 week.

13.1.48. B.P. 160/108; Alb.- 5; Oedema +; Urea - 19.7; A.A.N.- 8.5; T.P.- 5.68; Alb.- 2.77; Glob.- 2.30; Fib.- 0.61; Sugar - 88.5; Sugar Mobl.- 16.8; T.C.- 284; E.C.- 175.5; Lip. P.- 11.8; Alk. Phos.- 19.9; Th. T.- 3.0; Proth. Conc.- 67.5; Proth. Resp.- 47.8; Bil. Ret.- 13.9.

20.1.48. B.P. 150/100; Alb.- 4.5; Oedema ±; Urea 22.0; A.A.N.- 8.1; T.P.- 5.60; Alb.- 2.83; Glob.- 2.30; Fib.- 0.47; Sugar 87.9; Sugar Mobl.- 17.0; T.C.- 277; E.C.- 181; Lip. P.- 11.5; Alk. Phos.- 19.9; Th. T.- 3.0; Proth. Conc.- 68.0; Proth. Resp.- 47.0; Bil. Ret.- 13.9.

28.1.48. B.P. 150/100; Alb.- 4; Oedema ±; Urea - 21.6; A.A.N.- 7.1; T.P.- 5.62; Alb.- 2.83; Glob.- 2.30; Fib.- 0.49; Sugar - 89.5; Sugar Mobl.- 19.7; T.C.- 280; E.C.- 184; Lip. P.- 11.5; Alk. Phos.- 15.0; Th. T.- 2.0; Proth. Conc.- 68.0; Proth. Resp.- 47.0; Bil. Ret. 12.75.

2.2.48. B.P. 160/108; Oedema ±; Urea - 20.8; A.A.N.- 7.0; T.P.- 15.57; Alb.- 2.86; Glob.- 2.31; Fib.- 0.40; Sugar - 94.6; Sugar Mobl.- 15.7; T.C.- 240; E.C.- 15o; Alk. Phos.- 20.0; Th. T.- 1.5; Proth. Conc.- 64.8; Proth. Resp.- 44.6.

Spontaneous labour on 2.2.48. B.B.A.

26. Mrs. Smith, Primigravida; aet 28; 37 weeks.

Duration of Toxaemia - 1 week.

13.1.48. B.P. 165/110; Alb.- 9; Oedema +; Urea - 18.0; A.A.N.- 8.0; T.P.- 5.50; Alb.- 2.50; Glob.- 2.30; Fib.- 0.70; Sugar - 90.0; Sugar Mobl.- 14.6; Gal. In.- 167.8; T.C.- 278; E.C.- 169.5; Lip. P.- 14.9; Alk. Phos.- 20.5; Th. T.- 2.9; Proth. Conc.- 63.9; Proth. Resp.- 58.7; Bil. Ret.- 14.9.

20.1.48. B.P. 160/11o; Alb.- 11; Oedema +; Urea - 16.5; A.A.N.- 9.0; T.P.- 5.33; Alb.- 2.30; Glob.- 2.29; Fib.- 0.74; Sugar - 90.8; Sugar Mobl.- 12.4; Gal. In.-(19.1.48)- 189.3; T.C.- 292; E.C.- 172; Lip. P.- 19.4; Alk. Phos.- 22.0; Th. T.- 3.1; Proth. Conc.- 62.8; Proth. Resp.- 50.0; Bil. Ret.- 14.9.

26.1.48. B.P. 180/120; Alb.- 12; Oedema +; Headache +++; Epigastric pain +; Surgical induction - S.B. Urea - 28.8; A.A.N.- 16.0; T.P.- 4.97; Alb.- 2.29; Glob.- 2.32; Sugar - 90.0; Sugar Mobl.- 14.6; Gal. In.- 207.9; T.C.- 260; E.C.- 132; Lip. P.- 15.3; Alk. Phos.- 29.8; Th. T.- 3.9; Proth. Conc.- 49.3; Proth. Resp.- 30.8; Bil. Ret.- 23.5.

27. Mrs. Hill, Second gravida; aet 36; 38 weeks.

Duration of Toxaemia - 1.5 weeks. Pre-eclampsia in first pregnancy 3 years ago.

20.1.48. B.P. 170/110; Alb.- 9; Oedema ++; Urea - 18.3; A.A.N.- 9.0; T.P.- 5.29; Alb.- 2.41; Glob.- 2.29; Fib.- 0.59; Sugar - 81.5; Sugar Mobl.- 17.5; T.C.- 254; E.C.- 157; Lip. P.- 14.0; Alk. Phos.- 20.0; Th. T.- 3.4; Proth. Conc.- 57.8; Proth. Resp.- 50.3; Bil. Ret.- 13.1.

27.1.48. B.P. 150/90; Alb.- 9; Oedema +; Urea - 20.1; A.A.N.- 8.3; T.P.- 5.22; Alb.- 2.45; Glob.- 2.30; Fib.- 0.47; Sugar - 83.6; Sugar Mobl.- 14.3; T.C.- 260; E.C.- 162; Lip. P.- 15.8; Alk. Phos.- 17.6; Th. T.- 3.0; Proth. Conc.- 57.5; Proth. Resp.- 50.5; Bil. Ret.- 13.0.

3.2.48. B.P. 150/110; Alb.- 10.5; Oedema +; Urea - 19.7; A.A.N.- 9.0; T.P.- 5.10; Alb.- 2.41; Glob.- 2.30; Fib.- 0.39; Sugar 85.5; Sugar Mobl.- 9.7; T.C.- 276; E.C.- 169; Lip. P.- 16.2; Alk. Phos.- 19.3; Th. T.- 3.3; Proth. Conc.- 57.0; Proth. Resp.- 41.6; Bil. Ret.- 15.97.

7.2.48. B.P. 150/110; Alb.- 11; Oedema +; Urea - 20.5; A.A.N.- 9.5; T.P.- 5.02; Alb.- 2.41; Glob.- 2.32; Fib.- 0.29; Sugar - 92.7; Sugar Mobl.- 7.8; T.C.- 297; E.C.- 172; Lip. P.- 15.4; Alk. Phos.- 21.5; Th. T.- 4.7; Proth. Conc.- 50.5; Proth. Resp.- 34.0; Bil. Ret.- 15.46.

Spontaneous labour on 7.2.48. B.B.A.

28. Mrs. Sinclair, Third gravida; aet 39; 35 weeks.

Duration of Toxaemia - 2 weeks.

24.1.48. B.P. 160/110; Alb.- 5; Oedema ++; Urea - 19.9; A.A.N.- 9.0; T.P.- 5.76; Alb.- 2.85; Glob.- 2.30; Fib.- 0.61; Sugar - 91.7; Sugar Mobl.- 19.5; T.C.- 264; E.C.- 164; Lip. P.- 14.7; Alk. Phos.- 18.0; Th. T.- 1.8; Proth. Conc.- 65.0; Proth. Resp.- 48.7; Bil. Ret.- 12.9.

31.1.48. B.P. 140/90; Alb.- 0.5; Oedema - 0; Urea - 20.6; A.A.N.- 7.6; T.P.- 5.50; Alb.- 2.78; Glob.- 2.26; Fib.- 0.46; Sugar - 86.5; Sugar Mobl.- 19.0; T.C.- 252; E.C.- 169; Lip. P.- 13.4; Alk. Phos.- 15.0; Th. T.- 1.0; Proth. Conc.- 67.8; Proth. Resp.- 60.9; Bil. Ret.- 10.56.

7.2.48. B.P. 138/88; Alb.- ±; Oedema - 0; T.P.- 5.58; Alb.- 2.86; Glob.- 2.28; Fib.- 0.44; Sugar - 93.0; Sugar Mobl.- 21.2; Alk. Phos.- 15.0; Th. T.- 1.1; Proth. Conc.- 69.9; Proth. Resp.- 70.5; Bil. Ret.- 10.60.

29. Mrs. Campbell, Primigravida; aet 27; 32 weeks.

Duration of Toxaemia - 1 week.

26. 1.48. B.P. 160/100; Alb.- 9; Oedema ++; Urea - 21.7; A.A.N.- 8.75; T.P.- 5.41; Alb.- 2.74; Glob.- 2.27; Fib.- 0.40; Sugar - 79.7; Sugar Mobl.- 11.0; T.C.- 249; E.C.- 166.5; Lip. P.- 15.4; Alk.- Phos.- 16.7; Th. T.- 2.4; Proth. Conc.- 60.7; Proth Resp.- 54.0; Bil. Ret.- 8.9; Gal. In.- 155.0.

2.2.48. B.P. 160/110; Alb.- 10; Oedema +; Urea - 19.8; A.A.N.- 10.0; T.P.- 5.20; Alb.- 2.62; Glob.- 2.30; Fib.- 0.28; Sugar - 84.0; Sugar Mobl.- 11.5; T.C.- 2.58; E.C.- 164.5; Lip. P.- 17.1; Alk. Phos.- 17.5; Th. T.- 3.1; Proth. Conc.- 60.5; Proth. Resp.- 42.0; Bil. Ret.- 12.95; Gal. In.- 190.6.

9.2.48. B.P. 160/120; Alb.- 14; Oedema +++; Headache ++; Epigastric pain +; vomiting +; Urea - 29.5; A.A.N.- 15.9; T.P.- 4.82; Alb.- 2.32; Glob.- 2.32; Fib.- 0.18; Sugar - 87.0; Sugar Mobl.- 9.7; T.C.- 289; E.C.- 157; Lip. P.- 14.5; Alk. Phos.- 29.8; Th. T.- 4.9; Proth. Conc.- 56.2; Proth. Resp.- 31.0; Gal. In.- 230.0.

10.2.48. - Surgical induction of labour; S.B. B.P. 170/120. Urea - 36.0; A.A.N.- 18.6; Sugar 91.0; Sugar Mobl.- 7.5; T.C.- 251; E.C.- 128.5; Lip. P.- 12.3; Proth. Conc.- 44.1; Proth. Resp.- 24.0; Bil. Ret.- 23.48.

30. Mrs. McNeil, Primigravida; aet 25; 29 weeks.

Duration of Toxaemia - 0.5 weeks.

2.2.48. B.P. 210/100; Alb.- 8; Oedema +++; Urea - 22.5; A.A.N.- 8.1; T.P.- 5.42; Alb.- 2.83; Glob.- 2.28; Fib.- 0.31; Sugar - 86.5; Sugar Mobl.- 18.0; Gal. In.- 121.6; T.C.- 121.6; T.C.- 290; E.C.- 190; Lip. P.- 16.0; Alk. Phos.- 13.4; Th. T.- 4.2; Proth Conc.- 54.0; Proth. Resp.- 50; Bil. Ret.- 21.9.

9.2.48. B.P. 180/100; Alb.- 7; Oedema +; Urea - 20.0; A.A.N.- 7.2; T.P.- 5.23; Alb.- 2.65; Glob.- 2.21; Fib.- 0.37; Sugar - 84.9; Sugar Mobl.- 18.5; Gal. In.- 161.1; T.C.- 272; E.C.- 182.5; Lip. P.- 15.5; Alk. Phos.- 13.5; Th. T.- 3.8; Proth. Conc.- 55.2; Proth. Resp.- 57.6; Bil. Ret.-20.54.

16.2.48. B.P. 160/90; Alb.- 7; Oedema +; Urea - 24.4; A.A.N.- 7.2; T.P.- 5.51; Alb.- 2.86; Glob.- 2.26; Fib.- 0.39; Sugar - 92.0; Sugar Mobl.- 17.9; Gal. In. (18.2.48) - 170.8; T.C.- 270; E.C.- 183; Alk. Phos.- 12.8; Th. T.- 3.5; Proth. Conc.- 60.8; Proth. Resp.- 68.0; Bil. Ret.- 12.5.

31. Mrs. Irvine, Second gravida; aet 36; 32 weeks.

Duration of Toxaemia - 1 week. Pre-eclampsia in first pregnancy.

11.2.48. B.P. 155/110; Alb.- 3; Oedema ++; Urea - 18.5; A.A.N.- 9.1; T.P.- 5.82; Alb.- 3.00; Glob.- 2.32; Fib.- 0.50; Sugar - 87.9; Sugar Mobl.- 18.6; T.C.- 283; E.C.- 177; Lip. P.- 15.6; Alk. Phos.- 18.7; Th. T.- 1.8; Proth. Conc.- 60.8; Proth. Resp.- 49.7; Bil. Ret.- 12.7.

18.2.48. B.P. 150/90; Alb.- 2.5; Oedema +; Urea - 23.0; A.A.N.- 8.0; T.P.- 5.70; Alb.- 3.00; Glob.- 2.22; Fib.- 0.48; Sugar - 91.6; Sugar Mobl.- 21.0; T.C.- 264; E.C.- 174; Lip. P.- 15.0; Alk. Phos.- 13.5; Th. T.- 0.5; Proth. Conc.- 66.5; Proth. Resp.- 65.0; Bil. Ret.- 12.65.

25.2.48. B.P. 145/85; Alb.- 1.5; Oedema ±; Urea - 250; A.A.N.- 7.2; T.P.- 5.90; Alb.- 3.17; Glob.- 2.29; Fib.- 0.44; Sugar - 90.5; Sugar Mobl.- 21.4; T.C.- 260; E.C.- 177; Alk. Phos.- 13.5; Th. T.- 0.7; Proth. Conc.- 69.7; Proth. Resp.- 71.2; Bil. Ret.- 10.72.

32. Mrs. Hamilton, Primigravida; aet 26; 38 weeks.

Duration of Toxaemia - 1.5 weeks.

13.2.48. B.P. 168/112; Alb.- 7; Oedema ++; Urea - 19.2; A.A.N.- 9.8; T.P.- 5.72; Alb.- 2.99; Glob.- 2.33; Fib.- 0.29; Sugar - 90.6; Sugar Mobl.- 15.9; T.C.- 291; E.C.- 159; Lip. P.- 16.2; Alk. Phos.- 23.7; Th. T.- 4.0; Proth. Conc.- 48.7; Proth. Resp.- 39.0; Bil. Ret.- 19.1.

20.2.48. B.P. 168/110; Alb.- 8.5; Oedema +; Urea - 17.5; A.A.N.- 9.7; T.P.- 5.47; Alb.- 2.85; Glob.- 2.32; Fib.- 0.30; Sugar - 90.0; Sugar Mobl.- 15.3; T.C.- 290; E.C.- 161; Lip. P.- 17.1; Alk. Phos.- 20.6; Th. T.- 4.0; Proth. Conc.- 45.5; Proth. Resp.- 38.0; Bil.Ret.- 20.7.

28.2.48. B.P. 1'0/120; Alb.- 11.5; Oedema ++; Headache ++; Visual disturbance +; Induction of labour; B.B.A. Urea - 22.0; A.A.N.- 12.8; T.P.- 4.94; Alb.- 2.39; Glob.- 2.30; Fib.- 0.15; Sugar - 98.0; Sugar Mobl.- 10.5; T.C.- 277; E.C.- 142; Lip. P.- 15.6; Alk. Phos.- 28.3; Th. T.- 4.5; Proth. Conc.- 40.6; Proth. Resp.- 29.7; Bil. Ret.- 26.15.

33. Mrs. Lenox, Third gravida; aet 37; 36 weeks.

Duration of Toxaemia - 0.5 weeks. A case of recurrent Toxaemia.

16.3.48. B.P. 160/100; Alb.- 3.5; Oedema +; Urea - 20.0; A.A.N.- 7.0; T.P.- 5.57; Alb.- 2.90; Glob.- 2.30; Fib.- 0.37; Sugar 89.8; Sugar Mobl.- 17.6; T.C.- 273; E.C.- 179; Lip. P.- 16.6; Alk. Phos.- 17.7; Th. T.- 2.6; Proth. Conc.- 68.7; Proth. Resp.- 59.5; Bil. Ret.- 10.2.

23.3.48. B.P. 150/100; Alb.- 1; Oedema ±; Urea - 21.4; A.A.N.- 7.2; T.P.- 5.61; Alb.- 2.98; Glob.- 2.28; Fib.- 0.35; Sugar - 90.0; Sugar Mobl.- 20.6; T.C.- 270; E.C.- 175; Lip. P.- 16.0; Alk. Phos.- 17.8; Th.T.- 2.5; Proth. Conc.- 67.5; Proth. Resp.- 53.3; Bil. Ret.- 10.96.

30.3.48. B.P.-150/100; Alb.-1; Oedema ±; Urea - 21.0; A.A.N.- 7.2; T.P.- 5.61; Alb.- 2.98; Glob.- 2.28; Fib.- 0.35; Sugar - 87.6; Sugar Mobl.- 21.0; T.C.- 272; E.C.- 175; Lip. P.- 14.4; Alk. Phos.- 19.7; Th. T.- 2.8; Bil. Ret.- 10.08.

5.4.48. B.P. 150/100; Oedema ±; Spontaneous labour; B.B.A. T.P.- 5.56; Alb.- 2.90; Glob.- 2.29; Fib.- 0.37; Sugar.- 94.5; Sugar Mobl.- 17.6; Alk. Phos.- 19.5; Th. T.- 2.6; Proth. Conc.- 64.0; Proth. Resp.- 47.8; Bil. Ret.- 11.10.

34. Mrs. Wallace, Primigravida; aet 28; 37 weeks.

Duration of Toxaemia - 3 weeks.

27.3.48. B.P. 175/108; Alb.- 9; Oedema ++; Jaundice +; Urea - 16.6; A.A.N.- 8.5; T.P.- 5.32; Alb.- 2.73; Glob.- 2.28; Fib.- 0.31; Sugar - 78.8; Sugar Mobl.- 11.0; Gal. In.- 188.8; T.C.- 294; E.C.- 182.5; Alk. Phos.- 20.8; Th. T.- 4.5; Lip. P.- 17.0; Proth. Conc.- 42.0; Proth. Resp.- 34.0; Bil. Ret.- 28.6.

3.4.48. B.P.- 175/120; Alb.- 10; Oedema +; Jaundice +; Urea - 20.9; A.A.N.- 11.6; T.P.- 5.20; Alb.- 2.63; Glob./

Glob.- 2.28; Fib.- 0.29; Sugar - 80.0; Sugar Mobl.- 9.5; Gal. In.- 226.0; T.C.- 290; E.C.- 173.5; Lip. P.- 18.7; Alk. Phos.- 28.6; Th.T.- 4.8; Proth.Conc.- 40.6; Proth. Resp.- 29.5. Bilirubin excretion test not repeated because of evident jaundice. Bil.- 13 mgms.%.

10.4.48. B.P. 178/120; Alb.- 10.5; Oedema ++; Jaundice +; epigastric pain +; Surgical induction of labour; S.B. Urea - 39.0; A.A.N.- 18.2; T.P.- 5.07; Alb.- 2.58; Glob.- 2.29; Fib.- 0.20; Sugar 80.2; Sugar Mobl.- 7.0; Gal.In.- 238.0; T.C. 240; E.C.- 127; Lip.P.- 13.5; Alk. Phos.- 32.5; Th.T.- 5.1; Proth.Conc.- 38.9; Proth.Resp.- 24.7. Vandenberg test - biphesic reaction. Bilirubin 08.3 mgms.%.

35. Mrs. Little, Primigravida; aet 23; 32 weeks.

Duration of toxaemia - 1.5 weeks. Cystine - 5 gms.

daily from 8.4.48 to 23.4.48.

1.4.48. B.P. 168/110; Alb.- 5; Oedema ++; Urea - 17.7; A.A.N.- 8.7; T.P.- 5.60; Alb.- 2.80; Glob.- 2.29; Fib.- 0.51; Sugar - 84.2; Sugar mobl.- 19.6; T.C.- 280; E.C.- 182; Lip. P.- 16.4; Alk.Phos.- 19.7; Th.T.- 2.5; Proth.Conc.- 47.8; Proth. Resp.- 50.4; Bil. Ret.- 14.50.

8.4.48. B.P. 160/100; Alb.- 5.5; Oedema +; Urea - 19.5; A.A.N.- 8.3; T.P.- 5.47; Alb.- 2.70; Glob.- 2.27; Fib.- 0.50; Sugar - 90.0; Sugar mobl.- 20.5; T.C.- 288; E.C.- 185; Lip.P.- 16.0; Alk.Phos.- 18.5; Th. T.- 2.8; Proth. Conc.- 47.0; Proth. Resp.- 50.0; Bil. Ret.- 14.18.

16.4.48. B.P. 158/100; Alb.- 5; Oedema +; Urea - 20.8; A.A.N.- 7.8; T.P.- 5.45; Alb.- 2.69; Glob.- 2.28; Fib.- 0.48; Sugar - 87.2; Sugar Mobl.- 17.5; T.C.- 294; E.C.- 185; Lip. P.- 15.7; Alk. Phos.- 18.5; Th. T.- 2.6; Proth. Conc.- 47.5; Proth. Resp.- 48.5; Bil. Ret.- 14.76.

23.4.48. B.P.- 155/110; Alb.- 7; Oedema +; Urea - 20.0; A.A.N.- 8.0; T.P.- 5.39; Alb.- 2.62; Glob.- 2.30; Fib.- 0.47; Sugar - 86.4; Sugar Mobl.- 13.7; T.C.- 299; E.C.- 182; Lip. P.- 16.5; Alk. Phos.- 22.8; Th. T.- 2.5; Proth. Conc.- 44.8; Proth. Resp.- 40.0; Bil. Ret.- 15.12.

36. Mrs. McIntyre, Primigravida; aet 29; 37 weeks.

Duration of Toxaemia - 1 week. Cystine - 5 gms.

daily from 10.4.48 to 23.4.48.

3.4.48/

3.4.48. B.P. 180/120; Alb.- 9; Oedema +++; Urea - 16.2; A.A.N.- 8.7; T.P.- 5.50; Alb.- 2.90; Glob.- 2.32; Fib.- 0.28; Sugar - 89.0; Sugar Mobl.- 10.5; T.C.- 271; E.C.- 145; Lip. P.- 16.6; Alk. Phos.- 25.6; Th. T.- 1.5; Proth. Conc.- 45.0; Proth. Resp.- 39.0; Bil. Ret.- 23.7.

10.4.48. B.P. 172/110; Alb.- 8.5; Oedema ++; Urea - 21.7; A.A.N.- 10.0; T.P.- 5.31; Alb.- 2.75; Glob.- 2.30; Fib.- 0.26; Sugar - 93.0; Sugar Mobl.- 10.2; T.C.- 280; E.C.- 148; Lip. P.- 17.2; Alk. Phos.- 20.0; Th. T.- 1.3; proth. Conc.- 45.5; Proth. Resp.- 37.6; Bil. Ret.- 18.65.

17.4.48. B.P. 165/110; Alb.- 9; Oedema +; Urea - 21.0; A.A.N.- 12.2; T.P.- 5.14; Alb.- 2.60; Glob.- 2.29; Fib.- 0.25; Sugar - 90.6; Sugar Mobl.- 8.4; T.C.- 293; E.C.- 154; Lip. P.- 17.5; Alk. Phos.- 20.5; Th. T.- 1.0; Proth. Conc.- 43.8; Proth. Resp.- 34.0; Bil. Ret.- 18.65.

23.4.48. B.P. 175/120; Alb.- 11; Oedema +; Headache ++; Epigastric pain +; Surgical induction of labour - S.B. Urea - 31.0; A.A.N.- 18.5; T.P.- 4.97; Alb.- 2.45; Glob.- 2.32; Fib.- 0.20; Sugar - 91.0; Sugar Mobl.- 6.4; T.C.- 284; E.C.- 143; Lip. P.- 13.9; Alk. Phos.- 29.8; Th. T.- 4.8; Proth. Conc.- 39.0; Proth. Resp.- 24.1.

37. Mrs. McConnell, Primigravida; aet 31; 36/37 weeks.

Duration of Toxaemia - 1 week. Cystine - 5 gms. daily from 14.4.48 to 24.4.48.

7.4.48. B.P. 160/108; Alb.- 4; Oedema ++; Urea - 20.0; A.A.N.- 9.4; T.P.- 5.66; Alb.- 2.95; Glob.- 2.30; Fib.- 0.41; Sugar - 81.5; Sugar Mobl.- 17.0; Gal.In. - 170.6; T.C.- 262; E.C.- 161; Lip.P.- 13.2; Alk. Phos.- 18.5; Th. T.- 1.4; Proth. Conc.- 60.0; Proth. Resp.- 44.0; Bil. Ret.- 10.9.

14.4.48. B.P. 155/110; Alb.- 4; Oedema +; Urea - 26.0; A.A.N.- 10.0; T.P.- 5.60; Alb.- 2.85; Glob.- 2.29; Fib.- 0.46; Sugar - 89.0; Sugar Mobl.- 17.2; Gal. In.- 177.8; T.C.- 270; E.C.- 164; Lip. P.- 16.6; Alk. Phos.- 19.5; Th. T.- 1.0; Proth. Conc.- 60.0; Proth. Resp.- 42.5; Bil. Ret.- 10.1.

21.4.48. B.P. 150/110; Alb.- 3.5; Oedema ±; Urea - 24.0; A.A.N.- 11.8; T.P.- 5.68; Alb.- 2.84; Glob.- 2.28; Fib.- 0.56; Sugar - 84.5; Sugar Mobl.- 16.6; Gal. In.- 186.5; T.C.- 270; E.C.- 162; Lip. P.- 16.8; Alk. Phos.- 18.0; Th. T.- 1.0; Proth. Conc.- 60.5; Proth. Resp.- 40.5; Bil. Ret.- 13.18.

24.4.48/

24.4.48. B.P. 150/110; Spontaneous labour: B.B.A. Urea - 28.2; A.A.N.- 13.2; T.P.- 5.66; Alb.- 2.83; Glob.- 2.29; Fib.- 0.54; Sugar - 83.0; Sugar Mobl.- 16.2; Gal. In.- 194.2; T.C.- 275; E.C.- 162; Proth. Conc.- 60.0; Proth. Resp.- 35.0.

38. Mrs. Fraser, Primigravida; aet 24; 38 weeks.

Duration of Toxaemia - 3 weeks.

3.9.48. B.P. 178/110; Alb.- 10; Oedema +++; Urea - 19.6; A.A.N.- 8.5; T.P.- 5.38; Alb.- 2.47; Glob.- 2.32; Fib.- 0.59; Sugar - 90.5; Sugar mobl.- 16.8; T.C.- 240; E.C.- 144; Lip. P.- 17.8; Alk. Phos.- 20.4; Th. T.- 3.4; Proth. Conc.- 62.0; Proth. Resp.- 58.0; Bil. Ret.- 15.4.

9.9.48. B.P. 180/115; Alb.- 14; Oedema +++; Urea - 19.0; A.A.N.- 10.6; T.P.- 5.06; Alb.- 2.30; Glob.- 2.30; Sugar - 91.4; Sugar Mobl.- 14.0; T.C.- 240; E.C.- 144; Lip. Phos.- 17.7; Alk. Phos.- 22.6; Th. T.- 3.8; Proth. Conc.- 58.3; Proth. Resp.- 50.0; Bil. Ret.- 21.2.
Surgical Induction of Labour - B.B.A.

39. Mrs. Lefferty, Primigravida; aet 31; 37 weeks.

Twin pregnancy; Duration of Toxaemia - 2 weeks.

5.10.48. B.P. 160/100; Alb.- 4; Oedema +++; Urea - 20.0; A.A.N.- 7.2; T.P.- 5.32; Alb.- 2.60; Glob. - 2.33; Fib.- 0.39; Sugar - 80.3; Sugar Mobl.- 18.6; Gal. In.- 100.6; T.C.- 257; E.C.- 171; Lip. P.- 15.7; Alk. Phos.- 19.4; Th. T.- 3.0; Proth. Conc.- 67.8; Proth. Resp.- 70.0; Bil. Ret.- 8.6.

12.10.48. B.P. 160/100; Alb.- 4.5; Oedema ++; Urea - 20.6; A.A.N.- 84; T.P.- 5.21; Alb.- 2.40; Glob.- 2.31; Fib.- 0.50; Sugar - 88.0; Sugar Mobl.- 19.0; Gal. In.- 148.7; T.C.- 257; E.C.- 171; Lip.P.- 16.2; Alk. Phos.- 17.0; Th. T.- 2.5; Proth. Conc.- 65.0; Proth. Resp.- 63.0; Bil. Ret.- 8.9.

20.10.48. B.P. 170/105; Oedema +; Urea - 19.8; A.A.N.- 8.1; Sugar - 87.0; Sugar Mobl.- 18.0; Gal. In.- 168.6; T.C.- 276; E.C.- 179; Alk. Phos.- 17.9; Th. T.- 2.8; Proth. Conc.- 60.0; Proth. Resp.- 50.3; Bil. Ret.- 10.0.
Spontaneous Labour on 20.10.48. B.B.A.

40. Mrs. McLenan, Primigravida,;aet 24; 38 weeks.

Duration of Toxaemia - 1 week.

14.10.48/

14.10.48. B.P. 160/95; Alb.- 7; Oedema +++; Urea - 18.3; A.A.N.- 7.2; T.P.- 5.17; Alb.- 2.49; Glob.- 2.29; Fib.- 0.39; Sugar - 84.5; Sugar Mobl.- 18.5; Gal. In.- 139.6; T.C.- 239; E.C.- 162; Lip. P.- 13.0; Alk. Phos.- 14.4; Th. T.- 1.7; Proth. Conc.- 66.7; Proth. Resp.- 68.5; Bil. Ret.- 11.4.

21.10.48. B.P. 160/90; Alb.- 5; Oedema ++; Urea - 24.0; A.A.N.- 7.6; T.P.- 5.29; Alb.- 2.57; Glob.- 2.29; Fib.- 0.43; Sugar - 92.5; Sugar Mobl.- 19.6; Gal. In.- 130.4; T.C.- 244; E.C.- 163.5; Lip. P.- 12.6; Alk. Phos.- 13.9; Th. T.- 1.5; Proth. Conc.- 68.6; Proth. Resp.- 73.2; Bil. Ret.- 10.4.

28.10.48. B.P. 150/90; Alb.- 4; Oedema +; Urea - 25.2; A.A.N.- 7.2; T.P.- 5.33; Alb.- 2.60; Glob.- 2.29; Fib.- 0.44; Sugar - 90.2; Sugar Mobl.- 19.8; Gal. In.- 100.5; T.C.- 246; E.C.- 165; Lip. P.- 11.5; Alk. Phos.- 13.8; Th. T.- 1.5; Bil. Ret.- 10.6; Proth. Conc.- 73.1; Proth. Resp.- 80.0.

41. Mrs. Ozanne, Primigravida; aet 26; 36/37 weeks.

Duration of Toxaemia - 1 week.

22.10.48. B.P. 165/105; Alb.- 9; Oedema +++; Urea - 20.4; A.A.N.- 8.8; T.P.- 5.33; Alb.- 2.45; Glob.- 2.33; Fib.- 0.55; Sugar - 82.6; Sugar Mobl.- 16.5; T.C.- 280; E.C.- 171; Lip. P.- 16.8; Alk. Phos.- 17.8; Th. T.- 2.6; Proth. Conc.- 65.0; Proth. Resp.- 64.0; Bil. Ret.- 12.2.

30.10.48. B.P. 168/110; Alb.- 9; Oedema ++; Urea - 20.0; A.A.N.- 9.7; T.P.- 5.26; Alb.- 2.36; Glob.- 2.32; Fib.- 0.58; Sugar - 86.0; Sugar Mobl.- 15.0; T.C.- 288; E.C.- 172; Lip. P.- 17.5; Alk. Phos.- 20.0; Th. T.- 2.9; Proth. Conc.- 60.0; Proth. Resp.- 53.3. Bil. Ret.- 14.6.

1.11.48. B.P. 200/120; Oedema ++; Epigastric Pain +; Surgical induction. B.B.A.
Urea - 30.4; A.A.N.- 15.8; T.P.- 4.90; Alb.- 2.30; Glob.- 2.30; Fib.- 0.30; Sugar - 87.0; Sugar Mobl.- 10.0; T.C.- 296; E.C.- 156; Lip. P.- 15.3; Alk. Phos.- 26.5; Th. T.- 3.4; Proth. Conc.- 49.0; Proth. Resp.- 33.6; Bil. Ret.- 25.0.

42. Mrs. Muldoon, Primigravida; aet 22; 36/37 weeks.

Duration of Toxaemia - 1 week.

1.12.48. B.P. 160/105; Alb.- 3; Oedema ++; Urea - 20.7; A.A.N.- 8.9; T.P.- 5.40; Alb.- 2.55; Glob.- 2.32; Fib.- 0.53; Sugar - 93.0; Sugar Mobl.- 15.0; T.C.- 274; E.C.- 173; Lip. P.- 16.9; Alk. Phos.- 17.9; Th. T.- 2.8; Proth. Conc.- 62.7; Proth. Resp.- 60.0; Bil. Ret.- 12.0.

8.12.48/

8.12.48. B.P. 160/100; Alb.- 3.5; Oedema +; Urea - 22.2; A.A.N.- 8.7; T.P.- 5.27; Alb.- 2.48; Glob.- 2.30; Fib.- 0.49; Sugar - 90.2; Sugar Mobl.- 17.0; T.C.- 270; E.C.- 173; Lip. P.- 17.0; Alk. Phos.- 15.2; Th. T.- 2.0; Proth. Conc.- 63.0; Proth. Resp.- 54.6; Bil. Ret.- 12.0.

Induction of Labour for severity of Toxaemia on 20.12.48. S.B. Findings on the day of induction - B.P. 200/128; Alb.- 14; Oedema +++; Urea - 34.2; A.A.N.- 12.9; T.P.- 5.10; Alb.- 2.47; Glob.- 2.43; Fib. - 0.20; Sugar - 91.0; Sugar Mobl.- 11.0; Gal. In.- 204.6; T.C.- 240; E.C.- 132; Lip. P.- 13.4; Alk. Phos.- 22.6; Th. T.- 4.7; Proth. Conc.- 50.0; Proth. Resp.- 24.5; Bil. Ret.- 23.4.

B UNIT: HIGH PROTEIN DIET.

MILD TOXAEMIAS.

Cases No. 43 to 57.

Case No. 43. Mrs. Simmonds, Primigravida; aet 26;

33 weeks. Duration of Toxaemia - 1 week.

22.1.48. B.P. 150/98; Alb.- 2.5; Oedema ++; Urea - 30.6; A.A.N.- 6.9; T.P.- 5.80; Alb.- 3.03; Glob. 2.27; Fib.- 0.50; Sugar - 91.4; Sugar Mobl.- 19.1; T.C.- 178; E.C.- 122; Lip. P.- 11.6; Alk. Phos.- 14.5; Th. T.- 1.5; Proth. Conc.- 70.6; Proth. Resp.- 62.5; Bil. Ret.- 5.0.

29.1.48. B.P. 150/100; Alb.- 2; Oedema +; Urea - 28.8; A.A.N.- 7.1; T.P.- 5.66; Alb.- 2.99; Glob.- 2.26; Fib.- 0.41; Sugar 87.6; Sugar Mobl.- 19.0; T.C.- 196; E.C.- 196; Lip. P.- 11.5; Alk. Phos.- 14.0; Th. T.- 1.5; Proth. Conc.- 71.0; Proth. Resp.- 64.0; Bil. Ret.- 4.17.

5.2.48. B.P. 145/90; Alb.- 1.5; Oedema ±; Urea - 30.0; A.A.N.- 7.5; T.P.- 5.92; Alb. - 3.16; Glob.- 2.36; Fib.- 0.40; Sugar - 83.7; Sugar Mobl.- 19.5; T.C.- 198; E.C.- 136; Lip. P.- 12.0; Alk. Phos.- 14.3; Th. T.- 1.6; Proth. Conc.- 78.0; Proth. Resp.- 72.5; Bil. Ret.- 4.6.

13.2.48. B.P. 135/85; Alb.- ±; Oedema 0; Urea - 30.1; A.A.N.- 7.5; T.P.- 5.95; Alb.- 3.20; Glob.- 2.35; Fib.- 0.40; Sugar - 86.5; Sugar Mobl.- 19.0; T.C.- 200; E.C.- 138; Lip. P.- 10.8;;Alk. Phos.- 14.6; Th. T.- 1.0; Proth. Conc.- 88.1; Proth. Resp.- 85.0; Bil. Ret.- 4.5.

Case No. 44. Mrs. Sinclair, Second gravida; aet 29;

36/37 weeks. Duration of Toxaemia - 0.5 weeks.

Cystine - 5 gms. daily from 15.4.48 to 6.5.48.

8.4.48. B.P. 148/100; Alb.- 1.5; Oedema ++; Urea - 25.5; A.A.N.- 6.1; T.P.- 5.86; Alb.- 3.01; Glob.- 2.35; Fib.- 0.60; Sugar - 89.5; Sugar Mobl.- 20.4; Gal. In.- 72.7; T.C.- 230; E.C.- 155; Lip. P.- 11.4; Alk. Phos.- 13.7; Th. T.- 0.8; Proth. Conc.- 69.5; Proth. Resp.- 70.0; Bil. Ret.- 8.2.

15.4.48. B.P. 150/98; Alb.- 2; Oedema +; Urea - 28.0; A.A.N.- 7.9; T.P.- 5.75; Alb.- 3.0; Glob.- 2.35; Fib.-0.40; Sugar 92.5; Sugar Mobl.- 19.4; Gal. In. (16.4.48) - 65.0; T.C.- 238; E.C.- 161; Alk. Phos.- 14.2; Th. T.- 1.3; Proth. Conc.- 60.2; Proth. Resp.- 64.5; Bil. Ret.- 8.4.

22.4.48. B.P. 160/100; Alb.- 4.5; Oedema +; Urea - 27.4; A.A.N.- 8.0; T.P.- 5.69; Alb.- 2.87; Glob.- 2.34; Fib.- 0.48; Sugar - 80.0; Sugar Mobl.- 16.0; Gal. In.- (24.4.48)- 103.6; T.C.- 246; E.C.- 166; Alk. Phos.- 18.9; Th. T.- 3.0; Proth. Conc.- 60.4; Proth. Resp.- 50.0; Bil. Ret.- 10.6.

Salt free diet from 22.4.48 to

29.4.48. B.P. 160/110; Alb.- 5; Oedema ++; Urea - 27.5; A.A.N.- 8.6; T.P.- 5.70; Alb.- 2.87; Glob.- 2.34; Fib.- 0.49; Sugar - 80.5; Sugar Mobl.- 17.0; T.C.- 250; E.C.- 167; Alk. Phos.- 19.3; Th. T.- 3.5; Proth. Conc.- 60.0; Proth Resp.- 47.2; B il. Ret.- 10.8.

6.5.48. B.P. 150/100; Alb.- 4.5; Oedema +; Urea - 28.2; A.A.N.- 9.9; T.P.- 5.51; Alb.- 2.74; Glob.- 2.27; Fib.- 0;50; Alk. Phos.- 19.8; Proth. Conc.- 60.0; Proth. Resp.- 45.1; Bil. Ret.- 11.2.

Case No. 45. Mrs. Scott, Third gravida; aet 36; 34 weeks.

Duration of Toxaemia - 1 week. Recurrent toxaemia.

Cystine - 5 gms. daily from 17.4.48 to 30.4.48.

10.4.48. B.P. 140/100; Alb.- 4.5; Oedema +++; Urea - 25.0; A.A.N.- 7.0; T.P.- 5.70; Alb.- 2.85; Glob.- 2.33; Fib.- 0.52; Sugar - 83.0; Sugar Mobl.- 17.8; Gal. In.- 94.0; T.C.- 218; E.C.- 149; Lip. P.- 13.4; Alk. Phos.- 14.2; Th. T.- 0.5; Proth. Conc.- 76.5; Proth. Resp.- 69.8; Bil. Ret.- 3.0.

17.4.48. B.P. 140/90; Alb.- 3; Oedema ++; Urea - 27.8; A.A.N.- 7.0; T.P.- 5.71; Alb.- 2.96; Glob.- 2.34; Fib.- 0.41; Sugar - 83.0; Sugar Mobl.- 17.8; Gal. In. (19.4.48) - 87.8; T.C.- 210: E.C.- 144; Alk. Phos.- 13.6; Th. T.- 0.3; Proth. Conc.- 76.0; Proth. Resp.- 70.5; Bil. Ret.- 2.9.

24.4.48. B.P. 140/85. Alb.- 0.5; Oedema ±; Urea - 27.5; A.A.N.- 7.0; T.P.- 5.97; Alb.- 3.22; Glob.- 2.35; Fib.- 0.40; Sugar - 85.0; Sugar Mobl.- 22.0; Gal. In. (26.4.48) - 85.0; T.C.- 222; E.C.- 152; Alk. Phos..- 14.7; Th. T.- 0.3; Proth. Conc.- 87.2; Proth. Resp.- 75.0; Bil..Ret.- 2.91.

30.4.48. B.P. 140/90; Alb.- 0.5; Oedema ±; Urea - 27.0; A.A.N.- 6.5; T.P.- 5.98; Alb.- 3.23; Glob.- 2.35; Fib.- 0.40; Sugar - 88.2; Sugar Mobl.- 18.6; T.C.- 220; E.C.- 151; Alk.- Phos.- 14.0; Th. T.- 0.6; Proth. Conc.- 87.5; Proth. Resp.- 84.1; Bil. Ret.- 2.85.

Case No. 46/

Case No. 46. Mrs. Stevenson, Primigravida; aet 24;

36 weeks; Duration of Toxaemia - 1 week.

No follow up - patient treated with heparin.

10.4.48. B.P. 150/100; Alb.- 4.5; Oedema ++; Urea - 27.5; A.A.N.- 5.7; T.P.- 5.58; Alb.- 2.75; Glob.- 2.27; Fib.- 0.56; Sugar -87.5; Sugar Mobl.- 18.0; T.C.- 258; E.C.- 174; Lip. P.- 13.5; Alk. Phos. - 14.2; Th. T.- 1.0; Proth. Conc.- 70.5; Proth. Resp.- 68.6; Bil. Ret.- 1.2.

Case No. 47. Mrs. McNeil, Primigravida; aet 29;

39 weeks; Duration of Toxaemia - 2 weeks.

19.5.48. B.P. 150/90; Alb.- 1; Oedema +; Urea - 27.2; A.A.N.- 6.0; T.P.- 5.96; Alb.- 3.15; Glob.- 2.32; Fib.- 0.49; Sugar - 80.0; Sugar Mobl.- 20.6; T.C.- 249; E.C.- 170; Lip. P.- 15.2; Alk. Phos.- 13.8; Th. T.- 0.9; Proth. Conc.- 69.7; Proth. Resp.- 64.8; Bil. Ret.- 7.8.

26.5.48. B.P. 140/90; Alb.- ±; Oedema +; Urea - 27.0; A.A.N.- 6.7; T.P.- 6.0; Alb.- 3.25; Glob.- 2.36; Fib.- 0.39; Sugar - 84.0; Sugar Mobl.- 20.5; T.C.- 254; E.C.- 175; Alk. Phos.- 14.8; Th. T.- 1.0; Proth. Conc.- 82.5; Proth. Resp.- 81.0; Bil. Ret.- 7.75.

Case No. 48. Mrs. Dansmuir, Second gravida; aet 32;

38 weeks. Duration of Toxaemia - 2 weeks.

No follow up. Patient treated with heparin.

1.6.48. B.P.- 150/100; Alb.- 0.5; Oedema +; Urea - 24.6; A.A.N.- 6.2; T.P.- 6.19; Alb.- 3.26; Glob.- 2.35; Fib.- 0.58; Sugar - 92.6; Sugar Mobl.- 19.8; T.C.- 227; E.C.- 152; Lip. P.- 13.3; Alk. Phos.- 15.0; Th. T.- 0.5; Proth. Conc.- 65.8; Proth. Resp.- 65.6; Bil. Ret.- 10.3.

Case No. 49. Mrs. Leslie, Primigravida; aet 30;

38 weeks. Duration of toxaemia - 2 weeks.

No follow up. Patient treated with heparin.

15.6.48. B.P. 150/100; Alb.- 0.5; Oedema ±; Urea - 26.7; A.A.N.- 6.5; T.P.- 6.1; Alb.- 3.27; Glob.- 2.34; Fib.- 0.49; Sugar/

Sugar - 90.0; Sugar Mobl.- 20.4; T.C.- 234; E.C.- 154; Alk. Phos.- 13.4; Th. T.- 0.6; Proth. Conc.- 76.5; Proth. Resp.- 63.7; Lip. P.- 16.2; Bil. Ret.- 4.0.

Case No. 50. Mrs. Aslett, Primigravida; aet 24;

31 weeks; Duration of toxaemia - 1 week.

No follow up. Patient treated with heparin.

16.6.48. B.P. 148/98; Alb.- ±; Oedema ±; Urea - 25.4; A.A.N.- 6.8; T.P.- 6.45; Alb.- 3.47; Glob.- 2.39; Fib.- 0.59; Sugar - 94.5; Sugar Mobl.- 18.8; T.C.- 216; E.C.- 145; Lip. P.- 14.6; Alk. Phos.- 14.4; Th. T.- 1.0; Proth. Conc.- 71.2; Proth. Resp.- 69.7; Bil. Ret.- 6.9.

Case No. 51. Mrs. McAnaw, Primigravida; aat 27;

38 weeks. Duration of toxaemia - 2 weeks.

No follow up. Patient treated with heparin.

19.6.48. Urea - 25.2; A.A.N.- 6.4; T.P.- 5.56; Alb.- 2.77; Glob.- 2.25; Fib.- 0.54; Sugar - 80.0; Sugar Mobl.- 19.9; T.C.- 232; E.C.- 154; Lip. P.- 142; Alk. Phos.- 15.7; Th. T.- 1.0; Proth. Conc.- 72.5; Proth. Resp.- 70.2; Bil. Ret.- 8.8.

Case No. 52. Mrs. Thompson, Primigravida; aet 26;

36 weeks; Duration of Toxaemia - 1 week.

28.9.48. B.P. 150/100; Alb.- 6; Oedema ++; Urea - 24.8; A.A.N.- 6.0; T.P.- 5.58; Alb. - 2.71; Glob.- 2.30; Fib.- 0.57; Sugar - 87.5; Sugar Mobl.- 18.0; Gal. In.- 94.9; T.C.- 258; E.C.- 173; Alk. Phos.- 14.4; Th. T.- 1.8; Lip. P.- 13.2; Proth. Conc.- 74.2; Proth. Resp.- 70.6; Bil. Ret.- 5.4.

5.10.48. B.P. 150/100; Alb.- 6; Oedema +; Urea - 22.2; A.A.N.- 7.5; T.P.- 5.58; Alb.- 2.70; Glob.- 2.31; Fib.- 0.58; Sugar - 91.0; Sugar Mobl.- 18.0; Gal. In.- 90.6; T.C.- 250; E.C.- 166.5; Lip. P.- 13.0; Alk. Phos.- 15.2; Th. T.- 1.5; Proth. Conc.- 70.1; Proth. Resp.- 68.0; Bil. Ret.- 5.5.

12.10.48. B.P.- 150/100: Alb.- 4; Oedema +; Urea - 20.8; A.A.N.- 7.5; T.P.- 5.60; Alb.- 2.71; Glob.- 2.31; Fib.- 0.58 Sugar - 85.7; Sugar Mobl.- 18.3; Gal. In. (14.10.48)- 80.7; T.C.- 264; E.C.- 172.5; Lip. P.- Alk. Phos.- 16.5; Th. T/

Th. T.- 1.8; Proth. Conc.- 66.4; Proth. Resp.- 60.8; Bil. Ret.- 5.5.

Case No. 53. Mrs. Miller, Primigravida; aet 34; 36 weeks.

Duration of Toxaemia - 2 weeks.

5.10.48. B.P. 155/98; Alb.- 7; Oedema +++; Urea - 26.5; A.A.N.- 6.2; T.P.- 5.70; Alb.- 2.88; Glob.- 2.32; Fib.- 0.50; Sugar - 88.0; Sugar Mobl.- 18.4; T.C.- 246; E.C.- 164; Lip. P.- 12.8; Aslk. Phos.- 14.2; Th. T.- 2.0; Proth. Conc.- 72.6; Proth. Resp.- 68.8; Bil. Ret.- 8.0.

12.10.48. B.P. 155/105; Alb.- 7; Oedema ++; Urea - 21.4; A.A.N.- 7.4; T.P.- 5.70; Alb.- 2.80; Glob.- 2.30; Fib.- 0.62; Sugar - 89.0; Sugar Mobl.- 16.0; T.C.- 260; E.C.- 172.5; Lip. P.- 150; Alk. Phos.- 18.6; Th. T.- 2.6; Proth. Conc.- 63.5; Proth. Resp.- 60.2; Bil. Ret.- 11.4.

20.10.48. B.P. 160/110; Alb.- 7; Oedema ++; Urea - 20.0; A.A.N.- 8.1; T.P.- 5.60; Alb.- 2.60; Glob.- 2.30; Fib.- 0.70; Sugar - 89.3; Sugar Mobl.- 15.6; T.C.- 246; E.C.- 165; Lip. P.- 16.2; Alk. Phos.- 21.4; Th. T.- 3.4; Proth. Conc.- 60.2; Proth. Resp.- 57.3; Bil. Ret.- 14.0.

24.10.48. B.P. 160/110; Oedema +; Spontaneous Labour: B.B.A. Urea - 20.0: A.A.N.- 8.4; T.C.- 262; E.C.- 160; Alk. Phos.- 22.6; Th. T.- 3.4; Bil. Ret.- 17.4.

Case No. 54. Mrs. McNaughton, Primigravida, aet 23; 37 weeks. Duration of Toxaemia - 2 weeks.

12.10.48. B.P. 150/100; Alb.- 5; Oedema +; Urea - 24.6; A.A.N.- 6.1; T.P.- 5.89; Alb.- 3.05; Glob.- 2.33; Fib.- 0.51; Sugar - 84.2; Sugar Mobl.- 18.0; Gal. In. - 114.7; T.C.- 274; E.C.- 179; Lip. P.- 12.5; Alk.- Phos.- 14.9; Th. T.- 0.9; Proth. Conc.- 80.4; Proth. Resp.- 73.2; Bil. Ret.- 9.7.

19.10.48. B.P. 160/108; Alb.- 5; Oedema +; Urea - 20.6; A.A.N.- 7.4; T.P.- 5.89; Alb.- 2.91; Glob.- 2.30; Fib.- 0.68; Sugar - 83.7; Sugar Mobl.- 17.0; Gal. In.- 160.6; T.C.- 280; E.C.- 170.5; Lip. P.- 15.4; Alk. Phos.- 19.7; Th. T.- 1.9; Proth. Conc.- 62.3; Proth. Resp.- 60.0; Bil. Ret.- 10.6.

26.10.48. B.P. 170/115; Alb.- 12; Oedema +++; Urea - 19.3; A.A.N.- 8.3; T.P.- 5.04; Alb.- 2.41; Glob.- 2.32; Fib.- 0.31; Sugar - 82.5; Sugar Mobl.- 14.6; Gal. In.(25.10.48)- 218.7/

218.7; T.C.- 296; E.C.- 159; Lip.P.- 16.9; Alk. Phos.- 23.0; Th. T.- 2.6; Proth. Conc.- 55.0; Proth. Resp.- 49.4; Bil. Ret.- 19.9.
Surgical induction of labour on 26.1o.48. S.B.

Case No. 55. Mrs. McGough, Second gravida; aet 33;

31 weeks. Duration of Toxaemia - 1 week.

20.10.48. B.P. 150/95; Alb.- 2; Oedema +; Urea - 26.2; A.A.N.- 6.3; T.P.- 5.98; Alb.- 3.17; Glob.- 2.34; Fib.- 0.47; Sugar - 88.0; Sugar mobl.- 19.4; T.C.- 198; E.C.- 133; Lip. P.- 13.4; Alk. Phos.- 12.9; Th. T.- 0.7; Proth. Conc.- 80.2; Proth. Resp.- 78.6; Bil. Ret.- 4.1.

25.10.48. B.P. 150/100; Oedema ±; Spontaneous Labour, B.B.A. Urea - 27.0; A.A.N.- 7.5; Sugar - 97.2; Sugar mobl.- 16.5; T.C.- 183; E.C.- 124; Alk. Phos.- 14.0; Th. T.- 0.7; Proth. Conc.- 80.2; Proth. Resp.- 70.0; Bil. Ret.- 10.5.

Case No. 56. Mrs. McCrea, Primigravida; aet. 27;

35 weeks. Duration of Toxaemia - 1.5 weeks.

12.11.48. B.P. 150/100; Alb.- 4; Oedema ++; Urea - 24.9; A.A.N.- 6.9; T.P.- 5.77; Alb.- 2.93; Glob.- 2.30; Fib.- 0.54; Sugar - 92.5; Sugar Mobl.- 19.6; T.C.- 239; E.C.- 158; Lip. P.- 12.4; Alk. Phos.- 14.0; Th. T.- 1.2; Proth. Conc.- 73.6; Proth. Resp.- 74.0; Alk. Phos.- 14.0; Th. T.- 1.2; Bil. Ret.- 8.4.

20.11.48. B.P. 150/105; Alb.- 4; Oedema +; Urea - 21.5; A.A.N.- 7.1; T.P.- 5.75; Alb.- 2.88; Glob.- 2.30; Fib.- 0.59; Sugar - 90.0; Sugar Mobl.- 17.8; T.C.- 238; E.C.- 155; Alk. Phos.- 17.5; Th. T.- 1.5; Bil. Ret.- 10.0.

26.11.48. B.P. 160/110; Alb.- 7; Oedema +; Spontaneous labour: B.B.A.
Urea - 19.6; A.A.N.- 7.6; T.P.- 5.55; Alb.- 2.56; Glob.- 2.26; Fib. - 0.73; Sugar - 90.8; Sugar Mobl.- 16.8; T.C.- 246; E.C.- 151; Alk. Phos.- 21.2; Th. T.- 1.5; Bil. Ret.- 13.6.

Case No. 57. Mrs. Paul, Primigravida; aet 32;

38 weeks. Duration of Toxaemia - 2 weeks.

25.11.48. B.P. 150/95; Alb.- 3; Oedema ++; Urea 26.0; Fib.- 0.51; Sugar - 85.5; Sugar Mobl.- 18.7; T.C.- 241; E.C.- 162; Lip. P/

Lip..P.- 13.6; Alk. Phos.- 14.7; Th. T.- 1.3; Proth. Conc.- 70.5; Proth. Resp.- 72.0; Bil. Ret.- 2.4.

30.11.48. B.P. 150/105; Alb.- 5; Oedema +; Spontaneous Labour; B.B.A.
Urea - 24.2; A.A.N.- 7.4; T.P.- 5.78; Alb.- 2.80; Glob.- 2.30; Fib.- 0.68; Sugar - 88.3; Sugar Mobl.- 17.9; T.C.- 255; E.C.- 167; Alk. Phos.- 17.2; Th. T.- 2.9; Proth. Conc.- 68.8; Proth. Resp.- 70.0; Bil. Ret.- 9.7.

B UNIT: HIGH PROTEIN DIET

SEVERE TOXAEMIA.

Cases No. 58 to 75.

Case No. 58. Mrs. Harrison, Primigravida; aet 28;

37 weeks. Duration of toxaemia - 3 weeks.

7.1.48. B.P. 175/115; Alb.- 11; Oedema ++; Urea - 18.5; A.A.N.- 9.6; T.P.- 5.07; Alb.- 2.40; Glob.- 2.29; Fib.- 0.38; Sugar 90.2; Sugar Mobl.- 11.4; T.C.- 277; E.C.- 147; Lip. P.- 15.9; Alk. Phos.- 21.2; Th. T.- 3.5; Proth. Conc.- 42.6; Proth. Resp.- 39.6; Bil. Ret.- 18.8.

13.1.48. B.P. 150/100; Alb.- 6; Oedema +; Urea - 19.6; A.A.N.- 8.0; T.P.- 4.94; Alb.- 2.36; Glob.- 2.25; Fib.- 0.33; Sugar - 90.0; Sugar Mobl.- 12.0; T.C.- 270; E.C.- 168; Lip. P.- 14.3; Alk. Phos.- 16.0; Th. T.- 2.9; Proth. Conc.- 72.0; Proth. Resp.- 71.0; Bil. Ret.- 14.6.

19.1.48. B.P. 150/100; Alb.- 1; Oedema ±; Urea - 24.0; A.A.N.- 7.0; T.P.- 4.88; Alb.- 2.34; Glob.- 2.14; Fib.- 0.40; Sugar - 87.0; Sugar Mobl.- 15.5; T.C.- 278; E.C.- 180; Lip. P.- 13.8; Alk. Phos.- 15.5; Th. T.- 1.9; Proth. Conc.- 52.7; Proth. Resp.- 55.2; Bil. Ret.- 8.9.

31.1.48. B.P. 130/80; Alb.- 0; Oedema - 0; Urea - 26; A.A.N.- 6.6; T.P.- 5.42; Alb.- 2.82; Glob.- 2.20; Fib.- 0.40; Sugar - 89.0; Sugar Mobl.- 20.0; T.C.- 280; E.C.- 182; Lip. P.- 12.3; Alk. Phos.- 14.5; Th. T.- 0.9; Proth. Conc.- 61.9; Proth. Resp.- 62.0; Bil. Ret.- 8.98.

Case No. 59. Mrs. Wilson, Primigravida; aet 31;

29 weeks. Duration of toxaemia - 1.5 weeks.

9.1.48. B.P. 160/100; Alb.- 4; Oedema +; Urea - 21.4; A.A.N.- 7.8; T.P.- 5.60; Alb.- 2.63; Glob.- 2.30; Fib.- 0.67; Sugar - 80.5; Sugar Mobl.- 7.6; T.C.- 284; E.C.- 185.5; Lip. P.- 11.4; Alk. Phos.- 15.5; Th. T.- 3.0; Proth. Conc.- 68.3; Proth. Resp.- 50.0; Bil. Ret.- 10.2; Gal. In.- 145.8.

15.1.48. B.P. 168/108; Alb.- 4.5; Oedema ±; Urea - 21.0; A.A.N.- 9.8; T.P.- 5.51; Alb.- 2.59; Glob.- 2.31; Fib.- 0.51; Sugar - 89.5; Sugar Mobl.- 7.0; T.C.- 280; E.C.- 170; Lip. P.- 15.3; Alk. Phos.- 20.0; Th. T.- 4.0; Proth. Conc.- 65.8; Proth. Resp.- 44.4; Bil. Ret.- 13.94; Gal. In.- 168.2.

20.1.48. B.P. 195/120; Alb.- 11; Oedema ++; Epigastric pain +. Urea - 17.0; A.A.N.- 10.2; T.P.- 4.98; Alb.- 2.48; Glob.- 2.30; Fib.- 0.20; Sugar - 87.8; Sugar Mobl.- 7.0; Gal. In.- 225.2; T.C.- 296; E.C.- 156; Lip. P.- 17.1; Alk. Phos.- 30.4; Th. T.- 4.3; Proth. Conc.- 50.4; Proth. Resp.- 24.4; Bil. Ret.- 25.3.

Induction of Labour on 21.1.48. B.B.A. B.P. 194/120; Urea - 37.0; A.A.N.- 24.8.

Case No. 60. Mrs. McGlinchey, Second gravida; aet 30;

37 weeks. Duration of Toxaemia - 2 weeks.

First pregnancy - abortion 2 years ago.

13.1.48. B.P. 210/120; Alb.- 3; Oedema ++; Urea - 16.5; A.A.N.- 9.8; T.P.- 5.70; Alb.- 2.92; Glob.- 2.30; Fib.- 0.58; Sugar - 90.0; Sugar mobl.- 12.7; T.C.- 280; E.C.- 144; Lip. P.- 17.9; Alk. P.- 28.0; Th. T.- 2.6; Proth. Conc.- 51.6; Proth. Resp.- 41.5; Bil. Ret.- 24.2.

20.1.48. B.P. 190/110; Alb.- 3; Oedema ++; Urea - 16.5; A.A.N.- 10.6; T.P.- 5.57; Alb.- 2.95; Glob.- 2.34; Fib.- 0.28; Sugar - 87.5; Sugar Mobl.- 10.6; T.C.- 275; E.C.- 162.5; Lip. P.- 16.5; Alk. Phos.- 28.7; Th. T.- 2.8; Proth. Conc.- 53.0; Proth. Resp.- 36.8; Bil. Ret.- 24.3.

29.1.48. B.P. 210/115; Alb.- 5; Oedema ++; Headache +. Urea - 16.0; A.A.N.- 11.4; T.P.- 5.48; Alb.- 2.90; Glob.- 2.39; Fib.- 0.19; Sugar - 87.7; Sugar Mobl.- 6.0; T.C.- 260; E.C.- 138; Lip. P.- 14.1; Alk. Phos.- 29.8; Th. T.- 4.0; Proth. Conc.- 52.4; Proth. Resp.- 29.7; Bil. Ret.- 25.55.

Induction of Labour on 30.1.48. S.B. B.P. 210/120. Urea - 36; A.A.N.- 23.0; Alk. Phos.- 31.2.

Case No. 61. Mrs. Cheaney, Primigravida; aet 28;

38 weeks; Duration of toxaemia - 1 week.

15.3.48. B.P. 170/108; Alb.- 6; Oedema +++; Urea - 19.8; A.A.N.- 9.0; T.P.- 5.49; Alb.- 2.52; Glob.- 2.31; Fib.- 0.66; Sugar - 91.0; Sugar Mobl.- 16.7; Gal. In.- 161.6; T.C.- 250; E.C.- 153; Lip. P.- 16.9; Alk. Phos.- 19.6 ; Th. T.- 2.8; Proth. Conc.- 56.4; Proth. Resp.- 69.0; Bil. Ret.- 13.5.

24.3.48. B.P. 150/95; Alb.- 1; Oedema +; Urea - 22.0; A.A.N.- 7.0; T.P.- 5.24; Alb.- 2.49; Glob.- 2.28; Fib.- 0.47; Sugar - 84.5; Sugar Mobl.- 21.6; Gal. In.- 96.7; T.C.- 264; E.C./

E.C.- 176; Alk. Phos.- 16.0; Th. T.- 1.5; Proth. Conc.- 58.0; Proth. Resp.- 71.7; Bil. Ret.- 10.5.

1.4.48. B.P. 140/82; Alb.- 0.5; Oedema ±; Urea - 24.2; A.A.N.- 7.0; T.P.- 5.31; Alb.- 2.60; Glob.- 2.28; Sugar - 87.0; Sugar Mobl.- 22.0; Gal. In.- 119.2; T.C.- 260; E.C.- 177; Alk. Phos.- 15.0; Th. T.- 1.5; Proth. Conc.- 62.0; Proth. Resp.- 78.0; Bil. Ret.- 10.17.

Case No. 62. Mrs. Peckett, Second gravida; aet 33;

38 weeks. Duration of Toxaemia - 1 week.

First pregnancy normal.

No follow up: patient treated with heparin.

20.3.48. B.P. 170/110; Alb.- 2.5; Oedema +; Urea - 19.0; A.A.N.- 9.8; T.P.- 5.73; Alb.- 2.85; Glob.- 2.29; Fib.- 0.59; Sugar - 81.7; Sugar Mobl.- 17.3; T.C.- 248; E.C.- 150; Lip. P.- 16.4; Alk. Phos.- 20.8; Th. T.- 2.9; Proth Conc.- 70.0; Proth. Resp. - 61.0; Bil. Ret.- 4.9.

Case No. 63. Mrs. McGinnes, Primigravida; aet 28;

31 weeks. Duration of Toxaemia - 3 weeks.

Jaundice - 1 week.

18.3.48. B.P. 175/110; Alb.- 5.5; Oedema ++; Urea - 18.3; A.A.N.- 8.9; T.P.- 5.60; Alb.- 2.71; Glob.- 2.31; Fib.- 0.58; Sugar - 78.5; Sugar Mobl.- 10.7; Gal. In.- 146.0; T.C.- 290; E.C.- 173.5; Lip. P.- 16.9; Alk. Phos.- 19.4; Th. T.- 4.0; Proth. Conc.- 49.0; Proth. Resp.- 40.5; Bil. Ret.- 21.2; Vandenberg - direct immediate positive. Bilirubin - 9.6 mgms. per cent.

20.3.48. B.P. 175/118; Alb.- 7; Oedema ++; Jaundice +; Urea - 16.0; A.A.N.- 9.5; T.P.- 5.40; Alb.- 2.67; Glob.- 2.30; Fib.- 0.49; Sugar - 84.5; Sugar Mobl.- 10.9; T.C.- 298; E.C.- 157; Lip. P.- 18.6; Alk. Phos.- 26.5; Th. T.- 4.3; Proth. Conc.- 48.5; Proth. Resp.- 44.0;

26.3.48. B.P. 150/100; Alb.- 5; Oedema +; Jaundice ±; Urea - 18.5; A.A.N.- 8.2; T.P.- 5.45; Alb.- 2.75; Glob.- 2.30; Fib.- 0.40; Sugar - 84.0; Sugar Mobl.- 11.3. Gal. In. (25.3.48)- 127.1; T.C.- 292; E.C.- 171; Lip. P.- 19.4; Alk. Phos.- 16.6; Th. T.- 4.0; Proth. Conc.- 48.0; Proth. Resp.- 50.2.

31.3.48. B.P. 145/96; Alb.- 2; Oedema ±; Jaundice ±; Urea/

Urea 20.0; A.A.N.- 7.0; T.P.- 5.43; Alb.- 2.76; Glob.- 2.29; Fib.- 0.38; Sugar - 86.0; Sugar Mobl.- 15.5; Gal. In.- (1.4.48) - 100.1; T.C.- 282; E.C.- 184; Lip. P.- 17.0; Alk. Phos.- 16.5; Th. T.- 3.4; Proth. Conc.- 59.7; Proth. Resp.- 60.6.

9.4.48. B.P. 120/80; Alb.- 0; Oedema - 0; Jaundice - 0; Urea - 21.4; A.A.N.- 6.7; T.P.- 6.29; Alb.- 3.59; Glob.- 2.33; Fib.- 0.37; Sugar - 86.2; Sugar Mobl.- 21.4; T.C.- 270; E.C.- 180; Lip. P.- 14.6; Alk. Phos.- 15.8; Th. T.- 2.6; Proth. Conc.- 72.4; Proth. Resp.- 79.0.

Case No. 64. Mrs. Calderwood; Primigravida; aet 24;

34 weeks; Duration of Toxaemia - 1 week.

No follow up: Patient treated with heparin.

2.4.48. B.P. 160/110; Alb.- 5; Oedema ++; Urea - 20.6; A.A.N.- 10.2; T.P.- 5.87; Alb.- 2.97; Glob.- 2.30; Fib.- 0.60; Sugar - 88.8; Sugar Mobl.- 18.8; T.C.- 244; E.C.- 152.5; Lip. P.- 12.7; Alk. Phos.- 14.7; Th. T.- 1.0; Proth. Conc.- 59.7; Proth. Resp.- 55.6; Bil. Ret.- 12.6.

Case No. 65. Mrs. Traynor, Second gravida; aet 34;

33 weeks. Duration of Toxaemia - 1 week.

Cystine - 5 gms. daily from 2334.48 to 16.5.48.

8.4.48. B.P. 160/100; Alb.- 5; Oedema ++; Urea - 23.7; A.A.N.- 7.5; T.P.- 5.58; Alb.- 2.77; Glob.- 2.31; Fib.- 0.50; Sugar - 83.6; Sugar Mobl.- 19.1; Gal. In.- 104.1; T.C.- 237; E.C.- 158; Lip. P.- 13.9; Alk. Phos.- 16.0; Th. T.- 1.6; Proth. Conc.- 60.7; Proth. Resp.- 57.5; Bil. Ret.- 6.9.

16.4.48. B.P. 160/100; Alb.- 3.5; Oedema ++; Urea - 22.8; A.A.N.- 7.7; T.P.- 5.63; Alb.- 2.86; Glob.- 2.31; Fib.- 0.46; Sugar - 84.5; Sugar Mobl.- 19.0; Gal. In.- (17.4.48)- 107.4; T.C.- 242; E.C.- 159; Lip.P.- 15.1; Alk.- Phos.- 16.0; Th. T.- 1.6; Proth. Conc.- 60.0; Proth. Resp.- 55.0; Bil. Ret.- 8.7.

23.4.48. B.P. 160/96; Alb.- 2.5; Oedema +; Urea - 25.8; A.A.N.- 7.8; T.P.- 5.66; Alb.- 2.96; Glob.- 2.31; Fib.- 0.39; Sugar - 91.0; Sugar Mobl.- 22.0; Gal. In. (25.4.48)- 179.3; T.C.- 246; E.C.- 162; Lip. P.- 16.8; Alk. Phos.- 17.0; Th. T.- 1.5; Proth. Conc.- 61.2; Proth. Resp.- 52.0; Bil. Ret.- 12.85.

29.4.48. B.P. 155/100; Alb.- 1; Oedema +; Urea - 24.0; A.A.N.- 9.4; T.P.- 5.60; Alb.- 2.92; Glob.- 2.29; Fib.- 0.38; Sugar - 83.6; Sugar Mobl.- 18.8; T.C.- 245; E.C.- 159; Lip. P.- 14.8; Alk.-Phos.- 18.5; Th. T.- 1.9; Proth. Conc.- 60.0; Proth. Resp.- 48.1; Bil. Ret.- 13.56.

8.5.48. B.P. 160/100; Alb.- 1; Oedema +; Urea - 22.8; A.A.N.- 10.2; T.P.- 5.61; Alb.- 2.92; Glob.- 2.29; Fib.- 0.40; Sugar - 87.0; Sugar Mobl.- 18.0; T.C.- 250; E.C.- 161; Lip. P.- 16.6; Alk. Phos.- 18.7; Th. T.- 2.3; Proth. Conc.- 60.0; Proth. Resp.- 44.0; Bil. Ret.- 13.55.

Case No. 66. Mrs. Clelland; Primigravida; aet 26;

30 weeks. Duration of Toxaemia - 1 week.

No follow up. Patient treated with heparin.

5.6.48. B.P. 160/100; Alb.- 9.5; Oedema ++; Urea - 23.8; A.A.N.- 7.9; T.P.- 5.90; Alb.- 3.08; Alb.- 2.33; Fib.- 0.49; Sugar - 80.8; Sugar Mobl.- 17.4; T.C.- 262; E.C.- 170; Lip. P.- 15.5; Alk. Phos.- 14.0; Th. T.- 1.0; Proth. Conc.- 61.7; Proth. Resp.- 54.8; Bil. Ret.- 6.8.

Case No. 67. Mrs. Currie; Primigravida; aet 25;

37 weeks. Duration of Toxaemia - 1 week.

10.9.48. B.P. 160/110; Alb.- ; Oedema ++; Urea - 22.0; A.A.N.- 9.4; T.P.- 5.86; Alb.- 2.80; Glob.- 2.33; Fib.- 0.63; Sugar - 91.5; Sugar Mobl.- 14.7; Gal. In.- 146.6; T.C.- 268; E.C.- 167; Lip. P.- 15.8; Alk. Phos.- 19.9; Th. T.- 2.8; Proth. Conc.- 77.5; Proth. Resp.- 80.2; Bil. Ret.- 14.0.

17.9.48. B.P. 150/90; Alb.- 2; Oedema +; Urea - 25.8; A.A.N.- 8.5; T.P.- 5.60; Alb.- 2.85; Glob.- 2.26; Fib.- 0.49; Sugar - 93.0; Sugar Mobl.- 15.1; Gal. In.- 140.0; T.C.- 270; E.C.- 175; Alk. Phos.- 15.2; Th. T.- 2.0; Proth. Conc.- 80.4; Proth. Resp.- 80.5; Bil. Ret.- 10.7.

24.9.48. B.P. 140/90; Alb.- 1; Oedema $\pm$; Urea - 27.6; A.A.N.- 7.2; T.P.- 5.65; Alb.- 2.90; Glob.- 2.29; Fib.- 0.46; Sugar - 92.0; Sugar Mobl.- 18.7; Gal. In.- 120.7; T.C.- 270; E.C.- 181; Lip. P.- 13.1; Alk. Phos.- 14.8; Th. T.- 2.0; Proth. Conc.- 80.5; Proth. Resp.- 81.5; Bil. Ret.- 10.8.

Case No.68/

Case No. 68. Mrs. Thomson; Secondgravida; aet 31;

36/37 weeks. Duration of Toxaemia - 1 week.

First pregnancy normal.

28.9.48. B.P. 168/110; Alb.- 7.5; Oedema ++; Urea - 21.0; A.A.N.- 9.0; T.P.- 5.70; Alb.- 2.75; Glob.- 2.34; Fib.- 0.61; Sugar - 83.5; Sugar Mobl.- 15.9; T.C.- 285; E.C.- 170; Lip. P.- 16.7; Alk. Phos.- 20.2; Th. T.- 3.2; Proth. Conc.- 60.2; Proth. Resp.- 60.0; Bil. Ret.- 15.0.

5.10.48. B.P. 160/100; Alb.- 6; Oedema +; Urea - 22.5; A.A.N.- 8.8; T.P.- 5.49; Alb.- 2.70; Glob.- 2.29; Fib.- 0.50; Sugar - 80.5; Sugar Mobl.- 17.6; T.C.- 280; E.C.- 170; Lip. P.- 15.9; Alk. Phos.- 17.3; Th. T.- 2.2; Proth. Conc.- 60.7; Proth. Resp.- 63.8; Bil. Ret.- 14.0.

12.10.48. B.P. 150/95; Alb.- 3; Oedema ±; Urea - 24.0; A.A.N.- 7.5; T.P.- 5.55; Alb.- 2.80; Glob.- 2.31; Fib.- 0.44; Sugar - 81.2; Sugar Mobl.- 18.2; T.C.- 291; E.C.- 192; Alk. Phos.- 15.0; Th. T.- 2.0; Proth. Conc.- 65.7; Proth. Resp.- 71.4; Bil. Ret.- 12.6.

19.10.48. B.P. 140/90; Alb.- 1; Oedema ±; Urea - 26.6; A.A.N.- 7.0; Sugar - 84.2; Sugar Mobl.- 20.0; T.C.- 290; E.C.- 196; Lip. P.- 13.0; Alk. Phos.- 15.1; Th. T.- 1.6; Proth. Conc.- 78.6; Proth. Resp.- 86; Bil. Ret.- 12.8.

Case No. 69. Mrs. Smith; Primigravida; aet 27;

38 weeks. Duration of Toxaemia - 3 weeks.

7.10.48. B.P. 190/115; Alb.- 11; Oedema +++; Urea - 19.2; A.A.N.- 9.9; T.P.- 5.10; Alb.- 2.47; Glob.- 2.34; Fib.- 0.29; Sugar - 78.6; Sugar Mobl.- 12.7; Gal. In.- 203.4; T.C.- 257; E.C.- 137; Lip. P.- 16.7; Alk. Phos.- 23.7; Th. T.- 3.8; Proth. Conc.- 53.8; Proth. Resp.- 47.2; Bil. Ret.- 20.6.

12.10.48. B.P. 160/105; Alb.- 4; Oedema +; Spontaneous Labour: B.B.A.
Urea - 20.0; A.A.N.- 9.0; T.P.- 5.37; Alb.- 2.68; Glob.- 2.30; Fib.- 0.39; Sugar - 89.5; Sugar Mobl.- 16.0; Gal. In.- 200.0; T.C.- 266; E.C.- 165; Lip. P.- 15.6; Alk. Phos.- 18.0; Th. T.- 3.5; Proth. Conc.- 54.0; Proth. Resp.- 53.9; Bil. Ret.- 15.5.

Case No. 70/

Case No. 70. Mrs. Crawford; Primigravida; aet 30;

30 weeks; Duration of Toxaemia - 1 week.

7.10.48. B.P. 160/100; Alb.- 9; Oedema +; Urea - 22.8; A.A.N.- 8.0; T.P.- 5.51; Alb.- 2.70; Glob.- 2.32; Fib.- 0.49; Sugar - 82.7; Sugar Mobl.- 17.5; T.C.- 249; E.C.- 165; Lip. P.- 15.6; Alk. Phos.- 14.9; Th. T.- 2.0; Proth. Conc.- 70.0; Proth. Resp.- 73.0; Bil. Ret.- 3.9.

14.10.48. B.P. 160/100; Alb.- 1; Oedema ±; Urea - 22.0; A.A.N.- 7.8; T.P.- 5.47; Alb.- 2.70; Glob.- 2.30; Fib.- 0.47; Sugar - 84.0; Sugar Mobl.- 17.0; T.C.- 258; E.C.- 173; Lip. P.- 14.2; Alk. Phos.- 14.9; Th. T.- 2.0; Proth. Conc.- 71.0; Proth. Resp.- 77.0; Bil. Ret.- 4.0.

Case. No. 71. Mrs. McMichael, Secondgravida; aet 31;

38 weeks. Duration of Toxaemia - 2 weeks.

First pregnancy - abortion 2 years ago.

10.10.48. B.P. 170/110; Alb.- 8; Oedema +++; Urea - 19.6; A.A.N.- 9.2; T.P.- 5.45; Alb.- 2.50; Glob.- 2.33; Fib.- 0.62; Sugar - 82.5; Sugar Mobl.- 15.6; Gal. In.- 190.7; T.C.- 293; E.C.- 176; Lip. P.- 15.0; Alk. Phos.- 20.7; Th. T.- 3.4; Proth. Conc.- 65.0; Proth. Resp.- 60.3; Bil. Ret.- 8.8.

17.10.48. B.P. 158/100; Alb.- 5; Oedema ++; Urea - 21.4; A.A.N.- 8.7; T.P.- 5.40; Alb.- 2.60; Glob.- 2.30; Fib.- 0.50; Sugar - 87.0; Sugar Mobl.- 17.9; Gal. In.- 170.6; T.C.- 290; E.C.- 181; Lip. P.- 14.0; Alk. Phos.- 15.3; Th. T.- 3.0; Proth. Conc.- 67.0; Proth. Resp.- 70.3; Bil. Ret.- 7.6.

24.10.48. B.P. 148/95; Alb.- 3; Oedema +; Urea - 25.5; A.A.N.- 7.5; T.P.- 5.39; Alb.- 2.65; Glob.- 2.29; Fib.- 0.45; Sugar - 86.0; Sugar Mobl.- 18.0; Gal. In.- 121.0; T.C.- 281; E.C.- 187; Lip. P.- 14.1; Alk. Phos.- 14.8; Th. T.- 2.5; Proth. Conc.- 69.7; Proth. Resp.- 78.0; Bil. Ret.- 8.0.

Case No. 72. Mrs. Pritchard; Primigravida; aet 25;

36 weeks. Duration of Toxaemia - 3 weeks.

26.10.48. B.P.- 170/115; Alb.- 6; Oedema ++; Urea - 18.4; A.A.N.- 11.4; T.P.- 5.23; Alb.- 2.62; Glob.- 2.34; Fib.- 0.27; Sugar - 88.2; Sugar Mobl.- 12.5; Gal. In.- 214.6; T.C.- 300; E.C.- 159; Lip. P.- 15.0; Alk. Phos.- 22.7; Th. T.- 4.0; Proth. Conc.- 57.6; Proth. Resp.- 49.0; Bil. Ret.- 19.7.

30.10.48. B.P. 200/120; Alb.- 12; Oedema +++; Headache +; Visual Disturbance +; Induction of Labour: S.B. Urea - 25.9; A.A.N.- 14.6; T.P.- 4.89; Alb.- 2.35; Glob.- 2.34; Fib.- o.20; Sugar - 80.5; Sugar Mobl.- 6.6; Gal. In.- 248.7; T.C.- 268; E.C.- 136; Lip.P.- 13.0; Alk. Phos.- 28.6; Th. T.- 4.8; Proth. Conc.- 50.6; Proth. Resp.- 38.7; Bil. Ret.- 24.0.

Case N o. 73. Mrs. Owans; Primigravida; aet 26;

37 weeks. Duration of Toxaemia - 1 week.

29.10.48. B.P. 160/100; Alb.- 4; Oedema +; Urea - 23.5; A.A.N.- 9.0; T.P.- 5.50; Alb.- 2.69; Glob.- 2.31; Fib.- 0.50; Sugar - 92.5; Sugar Mobl.- 17.8; T.C.- 289; E.C.- 186; Lip. P.- 14.0; Alk. Phos.- 15.7; Th. T.- 3.6; Proth. Conc.- 63.7; Proth. Resp.- 66.0; Bil. Ret.- 13.5.

2.11.48. B.P. 180/120; Alb.- 8; Oedema +++; Urea - 17.5; A.A.N.- 12.0; T.P.- 4.89; Alb.- 2.33; Glob.- 2.33; Fib.- 0.23 Sugar - 96.6; Sugar Mobl.- 7.0; T.C.- 294; E.C.- 156; Lip. P.- 16.8; Alk. Phos.- 29.1; Th. T.- 3.8; Proth. Conc.- 58.8; Proth. Resp.- 39.0; Bil. Ret.- 25.0.

Induction of Labour on 3.11.48. B.B.A.

Case.No. 74. Mrs. Thomson; Primigravida; aet 34;

36/37 weeks. Duration of Toxaemia - 3 weeks.

9.11.48. B.P. 175/105; Alb.- 6; Oedema ++; Urea - 20.8; A.A.N.- 10.9; T.P.- 5.36; Alb.- 2.49; Glob.- 2.32; Fib.- 0.55; Sugar - 90.0; Sugar Mobl.- 16.5; T.C.- 271; E.C.- 170; Lip. P.- 14.8; Alk. Phos.- 16.7; Th. T.- 3.5; Proth. Conc.- 60.0; Proth. Resp.- 60.0; Bil. Ret.- 10.2.

13.11.48. B.P. 200/120; Alb.- 12; Oedema +++; Epigastric pain +; Induction of Labour - B.B.A. Urea - 30.0; A.A.N.- 16.6; T.P.- 4.84; Alb.- 2.30; Glob.- 2.33; Fib.- 0.21; Sugar - 94.0; Sugar Mobl.- 6.8; T.C.- 290; E.C.- 148; Lip. P.- 18.9; Alk. Phos.- 28.8; Th. T.- 4.9; Proth. Conc.- 48.6; Proth. Resp.- 36.2; Bil. Ret.- 23.1.

Case No. 75. Mrs. George; Primigravida; aet 29;

37 weeks. Duration of Toxaemia - 3 weeks.

16.11.48. B.P. 180/115; Alb.- 11; Oedema +++; Urea - 18.4; A.A.N.- 10.0; T.P.- 4.80; Alb.- 2.30; Glob.- 2.32; Fib.- 0.18; Sugar - 87.6; Sugar Mobl.- 11.5; T.C.- 284; E.C.- 151; Lip. P.- 16.0; Alk. Phos.- 22.7; Th. T.- 3.8; Proth. Conc.- 55.7; Proth. Resp.- 56.0; Bil. Ret.- 19.8 .

21.11.48. B.P. 195/120; Alb.- 14; Oedema +++; Headache ++; Epigastric pain +; Induction of Labour - S.B.; Urea - 38.8; A.A.N.- 15.7; T.P.- 4.8; Alb.- 2.30; Glob.- 2.32; Fib.- 0.18; Sugar - 90.2; Sygar Mobl.- 6.2; T.C.- 270; E.C.- 137; Lip.P.- 10.4; Alk. Phos.- 29.0; Th.T.- 4.1; Proth. Conc.- 47.5; Proth. Resp.- 33.0; Bil. Ret.- 26.2.

C UNIT LOW PROTEIN DIET.

MILD TOXAEMIA.

Case No. 76 to 86.

Case No. 76; Mrs. McNicoll; Third gravida; aet 33;
32 weeks; Duration of toxaemia 1 week.
First pregnancy abortion at 3 months;
second pregnancy pre-eclampsia.

23.1.48. B.P. 140/100; Alb.- 1; Oedema +; Urea - 24.6; A.A.N.- 6.0; T.P.- 5.74; Alb.- 3.02; Glob.- 2.26; Fib.- 0.46; Sugar - 97.5; Sugar Mobl.- 21.0; T.C.- 246; E.C.- 161; Lip. P.- 12.6; Alk. Phos.- 13.7; Th. T.- 1.2; Proth. Conc.- 70.1; Proth. Resp.- 67.0; Bil. Ret.- 1.8.

30.1.48. B.P. 140/100; Alb.- 0.5; Oedema ±; Urea - 23.5; A.A.N.- 6.5; T.P.- 5.92; Alb.- 3.22; Glob.- 2.30; Fib.- 0.40 Sugar - 93.6; Sugar Mob.- 21.5; T.C.- 248; E.C.- 161.5; Lip. P.- 12.5; Alk. Phos.- 13.5; Th.T.- 1.0; Proth. Conc.- 72.0; Proth. Resp.- 71.0; Bil. Ret.- 2.90.

7.2.48. B.P. 135/90; Alb.- ± Oedema - 0; Urea - 19.4; A.A.N.- 6.0; T.P.- 5.92; Alb.- 3.22; Glob.- 2.30; Fib.- 0.40; Sugar - 90.9; Sugar Mobl.- 21.5; Alk. Phos.- 13.8; Th.T.- 1.0; Proth. Conc.- 71.8; Proth. Resp.- 71.5; Bil. Ret.- 2.90

Case No. 77; Mrs. Reid; Primgravida; aet 24;
37 weeks; Duration of toxaemia - 3 weeks.

9.2.48. B.P. 148/100; Alb.- 3; Oedema + ; Urea - 25.8; A.A.N.- 6.2; T.P.- 5.46; Alb.- 2.70; Glob.- 2.19; Fib.- 0.57; Sugar - 91.7; Sugar Mobl.- 20.8; T.C.- 268; E.C.- 179; Lip. Phos.- 14.5; Th.T.- 2.0; Proth. Conc.- 78.0; Proth. Resp.- 62.0; Bil. Ret.- 2.0; Alk. Phos.- 14.2.

16.2.48. B.P. 150/108; Alb.- 4.5; Oedema +; Urea - 24.0; A.A.N.- 7.5; T.P.- 5.31; Alb.- 2.61; Glob.- 2.20; Fib.- 0.50 Sugar - 90.0; Sugar Mobl.- 20.5; T.C.- 268; E.C.- 179; Lip. P.- 16.7; Alk. Phos.- 18.5; Th. T.- 2.3; Proth. Conc.- 67.6; Proth. Resp.- 55.8; Bil. Ret.- 8.42.

22.2.48/

22.2.48. B.P. 150/110: Alb.- 4; Oedema + ; Urea - 22.4; A.A.N.- 7.2; T.P.- 5.32; Alb.- 2.55; Glob.- 2.20; Fib.- 0.57; Sugar - 83.7; Sugar Mobl.- 21.5; T.C.- 270; E.C.- 161; Lip. P.- 19.9; Th. T. 3.5; Proth. Conc.- 59.0; Proth. Resp.- 51.5; Bil. Ret.- 8.97.

2.3.48. B.P. 140/100; Alb.- 2.5; Oedema + ; Urea - 22.5; A.A.N.- 7.3; T.P.- 5.12; Alb.- 2.50; Glob.- 2.20; Fib.- 0.42; Sugar - 94.5; Sugar Mobl.- 20.0; T.C.- 275; E.C.- 173; Lip.P.- 13.0; Alk. Phos.- 15.0; Th. T.- 3.3; Proth. Conc.- 62.6; Proth. Resp.- 62.0. Bil. Ret.- 4.97.

Case No. 78; Mrs. Gilmore; Primigravida; aet 28;

37 weeks; Duration of toxaemia - 1 week.

6.3.48. B.P. 150/100; Alb.- 3; Oedema ++ ; Urea - 23.0; A.A.N.- 5.5; T.P.- 5.54; Alb.- 2.77; Glob.- 2.31; Fib.- 0.46; Sugar - 93.0; Sugar Mobl.- 18.6; Gal. In.- 89.7; T.C.- 257; E.C.- 173.5; Lip. P.- 13.6; Alk. Phos.- 14.8; Th. T.- 0.9; Proth. Conc.- 79.7; Proth. Resp.- 68.8; Bil. Ret.- 8.0.

13.3.48. B.P. 150/90; Alb.- 3; Oedema ± ; Urea - 24.5; A.A.N.- 6.1; T.P.- 5.52; Alb.- 2.79; Glob.- 2.30; Fib.- 0.43; Sugar - 89.5; Sugar Mobl.- 17.9; Gal. In. 83.0; T.C.- 262; E.C.- 178; Lip. P.- 12.4; Alk. Phos.- 14.5; Th. T.- 1.0; Proth. Conc.- 80.9; Proth. Resp.- 68.5; Bil. Ret.- 8.98.

20.3.48. B.P. 140/85; Alb.- 1.5; Oedema - 0; Urea - 24.0; A.A.N. - 6.0; T.P.- 5.60; Alb.- 288; Glob.- 2.32; Fib.- 0.40; Sugar - 91.5; Sugar Mobl.- 18.4; Gal. In. (21.3.48) - 87.1; T.C.- 260; E.C.- 177; Lip. P.- ; Alk. Phos.- 14.6; Th. T.- 1.0; Proth. Conc.- 80.9; Proth. Resp.- 71.0; Bil. Ret.- 8.98.

Case No. 79; Mrs. McIntosh; Second gravida; aet 34;

weeks; Duration of toxaemia - 1 week.

First pregnancy normal.

19.3.48. B.P. 148/90; Alb.- 0.5; Oedema ++ ; Urea - 30.0; A.A.N.- 6.0; T.P.- 5.71; Alb.- 3.08; Glob.- 2.16; Fib.- 0.47; Sugar - 87.0; Sugar Mobl.- 18.9; T.C.- 240; E.C.- 163; Lip. P.- 11.5; Alk. Phos.- 13.6; Th. T.- 0.8; Proth. Conc.- 71.6; Proth. Resp.- 64.0; Bil. Ret.- 8.9.

26.3.48./

26.3.48. B.P. 135/85; Alb.- 0.5; Oedema ± ; Urea - 26.0; A.A.N.- 6.3; T.P.- 5.70; Alb.- 3.10; Glob.- 2.20; Fib.- 0.40 Sugar - 91.0; Sugar Mobl.- 18.6; T.C.- 240; E.C.- 161.5; Alk. Phos.- 13.5; Th. T.- 0.5; Proth. Conc.- 78.9; Proth. Resp.- 64.0; Bil. Ret.- 8.85.

Case No. 80; Mrs. Harkness; Primigravida; aet 28;

37 weeks; Duration of toxaemia - 2 weeks.

20.3.48. B.P. 150/95; Alb.- 2.5; Oedema ++; Urea - 26.0; A.A.N.- 6.4; T.P.- 5.61; Alb.- 2.79; Glob.- 2.36; Fib.- 0.56; Sugar - 90.8; Sugar Mobl. 18.9; Gal. In.- 69.1; T.C.- 231; E.C.- 155 Lip. P.- 12.8; Alk. Phos.- 16.0; Th.T.- 2.4; Proth. Conc.- 68.5; Proth. Resp.- 60.0; Bil. Ret.- 10.90.

27.3.48. B.P. 160/110; Alb.- 8; Oedema ++; Urea - 26.5; A.A.N.- 7.9; T.P.- 5.30; Alb.- 2.51; Glob.- 2.30; Fib.- 0.47; Sugar- 83.6; Sugar Mobl.- 16.4; Gal.In. (29.3.48) - 172.0; T.C.- 249; E.C.- 162; Lip. P.- 15.5; Alk. Phos.- 19.6; Th. T.- 3.0; Proth. Conc.- 65.0; Proth. Resp.- 54.6; Bil. Ret.- 14.37.

3.4.48. B.P. 160/110; Alb.- 9.5; Oedema ++ ; Urea - 21.4; A.A.N.- 8.0; T.P.- 5.20; Alb.- 2.40; Glob.- 2.21; Fib.- 0.59 Sugar - 830; Sugar Mobl.- 18.0; Gal. In. (5.3.48) - 186.1; T.C.- 254; E.C.- 160; Lip. P.- 16.0; Alk. Phos.- 20.9; Th. T.- 3.3; Proth. Conc.- 65.0; Proth. Resp.- 50.0; Bil. Ret.- 15.8.

10.4.48. B.P. 165/115; Alb.- 10.5; Oedema ++ ;
Spontaneous labour - B.B.A.
Urea - 20.2; A.A.N.- 8.4; T.P.- 5.05; Alb.- 2.32; Glob.- 2.32 Fib.- 0.41; Sugar - 89.9; Sugar mobl.- 15.0; T.C.- 270; E.C.- 150; Lip. P.- 14.6; Alk. Phos.- 23.0; Th. T.- 3.8; Proth. Conc.- 54.7; Proth. Resp.- 42.6; Bil. Ret.- 18.88.

Case No. 81; Mrs. Barnett; Primigravida; aet 27;

34 weeks. Duration of toxaemia - 1 week.

Cystine - 5 gms. daily from 24.4.48 to 7.5.48.

17.4.48. B.P. 150/94; Alb.- 2.5; Oedema + ; Urea - 27.2; A.A.N.- 6.5; T.P.- 5.70; Alb.- 3.00; Glob.- 2.29; Fib.- 0.41; Sugar - 92.4;/

92.4; Sugar Mobl.- 19.3; T.C.- 226; E.C.- 155; Lip. P.- 13.2; Alk. Phos.- 14.7; Th. T.- 1.5; Proth. Conc.- 72.7; Proth. Resp.- 64.0; Bil. Ret.- 4.3.

24.4.48. B.P. 150/100; Alb.- 2; Oedema ± ; Urea - 30.0; A.A.N.- 7.4; T.P.- 5.74; Alb.- 3.04; Glob.- 2.30; Fib.- 0.40; Sugar - 94.4; Sugar Mobl.- 20.5; T.C.- 234; E.C.- 160; Lip. P.- 15.1; Alk. Phos.- 14.0; Th. T.- 1.5; Proth. Conc.- 73.0; Proth. Resp.- 60.4; Bil. Ret.- 6.25.

30.4.48. B.P. 150/100; Alb.- 2; Oedema ± ; Urea - 29.4; A.A.N.- 7.5; T.P. 5.72; Alb.- 3.0; Glob.- 2.31; Fib.- 0.41; Sugar - 90.0; Sugar Mobl.- 19.0; T.C.- 238; E.C.- 160; Lip. P.- 16.3; Alk. Phos.- 15.2; Th. T.- 1.8; Proth. Conc.- 72.6; Proth. Resp. 56.0; Bil. Ret.- 8.30.

7.5.48. B.P. 165/115; Alb.- 10.5; Oedema ++; Urea - 20.2; A.A.N.- 8.4; T.P.- 5.70; Alb.- 2.99; Glob.- 2.30; Fib.- 0.41; Sugar - 91.2; Sugar Mobl.- 18.5; T.C.- 235; E.C.- 157.5; Lip. P.- 15.8; Alk. Phos.- 15.8; Th. T.- 2.0; Proth. Conc.- 76.0; Proth. Resp.- 50.0; Bil. Ret.- 10.25.

Case No. 82; Mrs. McLeod; Primigravida; aet 31;

39 weeks; Duration of toxaemia - 2 weeks.

18.4.48. B.P. 150/100; Alb.- 4; Oedema ++; Urea - 24.4; A.A.N.- 6.2; T.P.- 5.61; Alb.- 2.88; Glob.- 2.29; Fib.- 0.44; Sugar - 86.6; Sugar Mobl.- 20.7; T.C.- 244; E.C.- 165; Lip. P.- 15.3; Alk. Phos.- 16.2; Th. T.- 1.8; Bil. Ret.- 2.40.

24.4.48. B.P. 150/100; Alb.- 3; Oedema + ; Urea - 25.0; A.A.N.- 6.4; T.P.- 5.70; Alb.- 2.90; Glob.- 2.31; Fib.- 0.46; Sugar - 89.0; Sugar Mobl.- 19.2; T.C.- 248; E.C.- 165; Lip. P.- 15.0; Alk. Phos.- 15.5; Th. T.- 1.8; Proth. Conc.- 61.0; Proth. Resp.- 53.1; Bil. Ret.- 4.45.

Case No. 83; Mrs. Cockburn; Second gravida; aet 32;

37 weeks; Duration of toxaemia - 2 weeks;

First pregnancy normal.

Cystine - 5 gms. daily from 24.4.48 to 9.5.48.

18.4.48./

18.4.48. B.P. 150/95; Alb.- 2.5; Oedema ++; Urea - 28.0; A.A.N.- 6.9; T.P.- 5.70; Alb.- 2.83; Glob.- 2.35; Fib.- 0.46; Sugar - 90.4; Sugar Mobl.- 19.9; Gal. In. (20.4.48) - 88.0; T.C.- 240 E.C.- 160; Lip. P.- 13.6; Alk. Phos.- 15.0; Th. T.- 1.4; Proth. Conc.- 61.4; Proth. Resp.- 69.0; Bil. Ret.- 2.0.

25.4.48. B.P. 150/100; Alb.- 3; Oedema + ; Urea - 30.2; A.A.N.- 7.6; T.P.- 5.70; Alb.- 2.86; Glob.- 2.30; Fib.- 0.54; Sugar - 97.2; Sugar Mobl.- 20.2; Gal. In.- 89.4; T.C.- 240; E.C.- 160; Lip. P.- 13.0; Alk. Phos.- 16.2; Th. T.- 1.5; Proth. Conc.- 61.0; Proth. Resp.- 62.0; Bil. Ret.- 2.9.

2.5.48. B.P. 150/95; Alb.- 2.5; Oedema ± ; Urea - 30.0; A.A.N.- 7.5; T.P.- 5.67; Alb.- 2.95; Glob.- 2.33; Fib.- 0.43; Sugar - 97.6; Sugar Mobl.- 20.2; Gal. In. (4.5.48) - 91.6; T.C.- 242; E.C.- 162.5; Lip. P.- 13.0; Alk. Phos.- 14.3; Th. T.- 1.5; Proth. Conc.- 60.0; Proth. Resp.- 55.2; Bil. Ret.- 4.32.

9.5.48. B.P. 150/90; Alb.- 2.5; Oedema ± ; Urea - 30.0; A.A.N.- 7.9; T.P.- 5.65; Alb.- 2.92; Glob.- 2.33; Fib.- 0.40; Sugar - 91.3; Sugar Mobl.- 18.0; T.C.- 248; E.C.- 164; Lip. P.- 13.0; Alk. Phos.- 14.0; Th. T.- 1.5; Proth. Conc.- 62.6; Proth. Resp.- 56.0; Bil. Ret.- 7.91.

Case No. 84; Mrs. Marshall; Primigravida; aet 23;

39 weeks; Duration of toxaemia - 1 week.

15.9.48. B.P. 150/100; Alb.- 5; Oedema +++ ; Urea - 24.5; A.A.N.- 6.0; T.P.- 5.62; Alb.- 2.84; Glob.- 2.31; Fib.- 0.47; Sugar - 90.9; Sugar Mobl.- 19.5; T.C.- 200; E.C.- 134; Lip. P.- 16.2; Alk. Phos.- 14.6; Th. T.- 1.5; Proth. Conc.- 71.3; Proth. Resp.- 65.6; Bil. Ret.- 4.97.

Spontaneous Labour on 18.9.48. B.B.A.

Case No. 85; Mrs. Bremner; Primigravida; aet 30;

38 weeks. Duration of toxaemia - 1.5 weeks.

15.9.48. B.P. 150/100; Alb.- 3; Oedema +++ ; Urea - 25.0; A.A.N.- 6.2; T.P.- 5.70; Alb.- 2.72; Glob.- 2.30; Fib.- 0.58; Sugar - 81.7; Sugar Mobl.- 18.1; T.C.- 235; E.C.- 163; Lip. P.- 10.8; Alk. Phos.- 13.6; Th.T.- 1.6; Proth. Conc.- 80.3; Proth Resp.- 80.0; Bil. Ret.- 3.8.

22.9.48/

22.9.48. B.P. 150/100; Alb.- 4; Oedema + ; Urea - 24.2; A.A.N.- 7.2; T.P.- 5.65; Alb.- 2.76; Glob.- 2.44; Fib.- 0.50; Proth.Conc.-88.6; Proth.Resp.- 18.0; T.C.- 238; E.C.- 165; Lip.P.- 10.6; Alk. Phos.- 13.9; Th.T.- 1.5; Proth. Conc.- 80.3; Proth. Resp.- 80.0; Bil. Ret.- 3.8.

29.9.48. B.P. 148/98; Alb.- 4; Oedema + ; Urea - 25.5; A.A.N.- 7.0; T.P.- 5.63; Alb.- 2.71; Glob.- 2.42;Fib.- 0.50; Sugar - 87.7; Sugar Mobl.- 16.5; T.C.- 242; E.C.- 168; Lip.P.- 10.3; Alk. Phos.- 13.8; Th.T.- 1.5; Proth. Conc.- 78.5; Proth. Resp.- 80.0; Bil. Ret.- 4.0.

86. Mrs. Gallaghar, Primigravida; aet 30; 34 weeks;

Duration of Toxaemia - 2 weeks.

7.10.48. B.P. 150/100; Alb.- 5; Oedema +++; Urea - 23.6; A.A.N.- 6.8; T.P.-5.65; Alb.- 2.75; Glob.- 2.30; Fib.- 0.60; Sugar - 98.4; Sugar Mobl.- 18.9; T.C.- 256; E.C.- 171.5; Lip.P.- 13.5; Alk.Phos.- 14.4; Th.T.- 1.5; Proth. Conc.- 70.0; Proth. Resp.- 67.6; Bil. Ret.- 5.6.

14.10.48. B.P. 160/100; Alb.- 7; Oedema ++ ; Urea - 22.0; A.A.N.- 7.4; T.P.- 5.59; Alb.- 2.60; Glob.- 2.31; Fib.- 0.68; Sugar - 90.2; Sugar Mobl.- 17.0; T.C.- 266; E.C.- 182; Lip.P.- 14.8; Alk. Phos. 15.2; Th.T.- 1.5; Proth. Conc.- 63.5; Proth. Resp-60.3; Bil. Ret.- 8.4.

19.10.48. B.P. 170/110; Alb.- 14; Oedema +++; Unduction of labour; B.B.A. Urea - 30.0; A.A.N.- 9.5; T.P.- 5.63; Alb.- 2.71; Glob.- 2.42; Fib.- 0.50; Sugar-88.7; Sugar Mobl.- 16.5; T.C. 282; E.C.- 172.5; Lip.P.- 13.0; Alk. Phos.- 19.9; Th.T.- 2.9; Proth. Conc.- 60.0; Proth. Resp.- 57.0; Bil. Ret.- 12.8.

C UNIT. LOW PROTEIN DIET.

SEVERE TOXAEMIA.

Case No. 87 to 100.

87. Mrs. McMenemy, Primgravida; aet 26; weeks;

Duration of Toxaemia - 2 weeks.

6.1.48. B.P. 184/110; Alb.-7; Oedema++ ; Urea - 18.2; A.A.N.-8.5; T.P.- 5.42; Alb.- 2.86; Glob.- 2.33; Fib.- 0-24; Sugar - 89.0; Sugar Mobl.- 16.7; Gal. In.- 156.1; T.C.- 286; E.C.- 170; Lip.P.- 16.8 Alk. Phos.- 19.7 Th.T.- 2.8; Proth. Cone.- 54.8; Proth. Resp.- 54.2; Bil. Ret.- 12.9.

13.1.48. B.P. 160/105; Alb.- 5; Oedema +; Urea - 17.6 A.A.N.- 8.3; T.P.- 5.39; Alb.- 2.60; Glob.- 2.30; Fib.- 0-49; Sugar - 91.5; Sugar Mobl.- 17-2; Gal. In.- 158.5; T.C.- 290; E.C.- 178: Lip.P.- 18.6; Alk. Phos.- 16.5; Th.T.- 2.8; Proth. Cone.- 50.0; Proth. Resp.- 50.5; Bil. Ret.- 12.87.

20.1.48. B.P. 160/110; Alb.- 7; Oedema +; Urea - 17.0; A.A.N.- 8.5; T.P.- 5.43; Alb.- 2.60; Glob.- 2.32: Fib.- 0.51; Sugar - 94.0; Sugar Mobl.- 16.2; Gal. In. (22.1.48) - 167.4; T.C.- 290; E.C.- 175: Lip.P.- 19.) ; Alk. Phos.- 20.5; Th.T.- 2.5; Proth. Cone.- 42.6; Proth. Resp.- 41.6; Bil. Ret.- 13.13.

24.1.48. B.P. 165/110; Oedema +; Spontaneous Labour; B.B.A. Urea - 17.5; A.A.N.- 9.3; T.P.- 5.22; Alb.- 2.62: Glob.- 2.33; Fib.- 0.27; Sugar - 97.0; Sugar Mobl.- 16.0; T.C.- 255; E.C.- 150; Lip.P.- 15.2; Alk. Phos.- 20.8; Th.T.- 3.0; Proth. Cone.- 40.0; Proth. Resp.- 33.7; Bil. Ret.- 14.48.

88. Mrs. Moore, Primigravida; aet 30; 33 weeks;

Duration of Toxaemia - 1 week.

11.1.48. B.P. 180/100; Alb.- 3.5; Oedema +; Urea - 19.9; A.A.N.- 7.4; T.P.- 5.57; Alb.- 2.90; Glob.- 2.34; Fib.- 0.33; Sugar - 93.4; Sugar Mobl.- 21.0; T.C.- 275: E.C.- 184.5; Lip.P.- 16.8; Alk. Phos.- 16.7; Th.T.- 3.0; Proth. Cone.- 58.9; Proth. Resp.- 44.6; Bil. Ret.- 13.1.

18.1.48. B.P. 180/120; Alb.- 5.5; Oedema +; Urea - 20.0; A.A.N./

A.A.N.- 7.7; T.P.- 5.60; Alb.- 2.98; Glob.- 2.32; Fib.- 0.40; Sugar - 90.0; Sugar Mobl.- 21.2; T.C.- 270; E.C.- 182; Lip.P.- 17.6; Alk. Phos.- 17.5; Th.T.- 3.0; Proth. Conc.- 60.8; Proth. Resp.- 58.0; Bil. Ret.- 13.1.

25.1.48. B.P. 170/100; Alb.- 2.5; Oedema 0; Urea - 20.2; A.A.N.- 7.5; T.P.- 5.60; Alb.- 2.97; Glob.- 2.33; Fib.- 0.40; Sugar - 86.5; Sugar Mobl.- 18.0; T.C.- 298; E.C.- 200; Lip.P.- 18.1; Alk. Phos.- 16.5; Th.T.- 2.8; Proth. Conc.- 68.5; Proth. Resp.- 53.0; Bil. Ret.- 12.9.

1.2.48. B.P. 160/90; Alb.- 2; Oedema - 0; Urea - 20.0: A.A.N.- 7.2; T.P.- 5.70; Alb.- 2.97; Glob.- 2.31; Fib.- 0.42; Sugar - 85.0; Sugar Mobl.- 18.0; T.C.- 292; E.C.- 196; Lip.P.- 15.3; Alk. Phos.- 16.3; Th.T.- 2.5; Proth. Conc.- 89.0; Proth. Resp.- 62.0; Bil. Ret.- 12.95.

9.2.48. B.P. 148/90: Alb.- 0.5; Oedema - 0; Urea - 18.5; A.A.N.- 8.0; T.P.- 6.13; Alb.- 3.40; Glob.- 2.32; Fib.- 0.41; Sugar - 91.0; Sugar Mobl.- 19.9; Alk. Phos.- 16.0; Th.T.- 2.3; Proth. Conc.- 91.5; Proth. Resp.- 82.9: Bil. Ret.- 12.68.

89. Mrs. Devlin, Primigravida; aet 33; weeks;

Duration of Toxaemia - 1 week.

14.1.48. B.P. 180/120; Alb.- 5; Oedema ++; Urea - 18.0; A.A.N.- 9.0; T.P.- 5.30; Alb.- 2.78; Glob.- 2.32; Fib.- 0.20; Sugar - 91.0; Sugar Mobl.- 12.7; Gal. In.- 197.6; T.C.- 281; E.C.- 155; Lip.P.- 16.0; Alk. Phos.- 28.3; Th.T.- 3.4; Proth. Conc.- 58.5; Proth. Resp.- 37.6: Bil. Ret.- 23.4.

22.1.48. B.P. 180/120; Alb.- 5.5; Oedema +; Urea - 24.5; A.A.N.- 12.5; T.P.- 5.30; Alb.- 2.78; Glob.- 2.32; Fib.- 0.20; Sugar - 90.7; Sugar Mobl.- 11.9; Gal. In.- (21.1.48)- 206.0; T.C.- 299; E.C.- 157; Lip.P.- 17.1; Alk. Phos.- 28;8; Th.T.- 3.0; Proth. Conc.- 49.5; Proth. Resp.- 30.8; Bil. Ret.- 26.30.

29.1.48. B.P. 190/120; Alb.- 11; Oedema ++; Headache +; Epigastric pain +; Induction of Labour - S.B.; Urea - 36.2; A.A.N.- 18.9; T.P.- 4.92; Alb.- 2.41; Glob.- 2.33; Fib.- 0.18; Sugar - 90.0; Sugar Mobl.- 9.6; Gal. In. (28.1.48)- 229.1; T.C.- 281; E.C.- 155; Lip.P.- 14.2; Alk. Phos.- 32.5; Th.T.- 3.5; Proth. Conc.- 40.2; Proth. Resp.- 28.0; Bil. Ret.- 28.96.

90. Mrs. Watson, Secondgravida; aet 29; weeks;

Duration of Toxaemia - 1.5 weeks.

First pregnancy abortion at 5 months.

9.2.48. B.P. 170/110; Alb.- 6; Oedema ++ ; Urea - 17.4; A.A.N.- 7.9; T.P.- 5.58; Alb.- 2.81; Glob.- 2.33; Fib.- 0.44; Sugar - 88.0; Sugar Mobl.- 17.0; Gal. In.- 160.8 T.C.- 256; E.C.- 160; Lip.P.- 15.8; Alk. Phos.- 18.8; Th.T.- 1.8; Proth. Cone.- 50.0; Proth. Resp.- 58.4; Bil. Ret.- 12.7.

16.2.48. B.P. 150/95; Alb.- 1.5; Oedema ±; Urea - 21.2; A.A.N.- 7.4; T.P.- 5.55; Alb.- 2.86: Glob.- 2.30; Fib.- 0.39; Sugar - 92.0; Sugar Mobl.- 19.7; Gal. In.- (17.2.48)- 130.3; T.C.- 264; E.C.- 172; Lip.P.- 14.4; Alk. Phos.- 16.5; Th.T.- 1.5; Proth. Cone.- 52.6; Proth. Resp.- 60.8; Bil. Ret.- 12.61.

23.2.48. B.P. 150/90; Alb.- 1.5; Oedema.- 0, Urea - 20.0; A.A.N.- 7.0; T.P.- 5.60; Alb.- 2.88; Glob.- 2.31; Fib.- 0.41; Sugar - 94.4; Sugar Mobl.- 21.5; Gal. In.- (24.2.48)- 111.3; T.C.- 266; E.C.- 178; Lip.P.- 14.0; Alk. Phos.- 16.5; Th.T.- 1.3; Proth. Cone.- 65.7; Proth. Resp.- 67.6;

1.3.48. B.P. 140/85; Alb. ±; Oedema ± 0; T.P.- 5.80; Alb.- 3.05; Glob.- 2.34; Fib.- 0.41; Sugar - 93.6; Sugar Mobl.- 21.9; Alk. Phos.- 15.3; Th.T.- 1.9; Proth. Cone.- 79.0; Proth. Resp.- 88.0; Bil. Ret.- 11.6.

91. Mrs. Small, Primigravida; aet 26; weeks;

Duration of Toxaemia - 1.5 weeks.

9.2.48. B.P. 152/100; Alb.- 6; Oedema ++; Urea - 19.0; A.A.N.- 7.0; T.P.- 5.48; Alb.- 2.86; Glob.- 2.32; Fib.- 0.30; Sugar - 90.4; Sugar Mobl.- 19.0; T.C.- 249: E.C.- 166; Lip.P.- 10.8; Alk. Phos.- 15.8; Th.T.- 3.0; Proth. Cone.- 61.7; Proth. Resp.- 59.8; Bil. Ret.- 9.9;

16.2.48. B.P. 150/95; Alb.- 1.5; Oedema ±; Urea - 21.2; A.A.N.- 7.4; T.P.- 5.50; Alb.- 2.84; Glob.- 2.30; Fib.- 0.36; Sugar - 94.3; Sugar Mobl.- 19.0; T.C.- 255; E.C.- 172; Lip.P.- 10.1; Alk. Phos.- 15.6; Th.T.- 1.5; Proth. Cone.- 64.0; Proth. Resp.- 68.0; Bil. Ret.- 9.9.

23.2.48. B.P. 136/80; Alb.- 0.5; Oedema -0; Urea - 21.5; A.A.N.- 7.0; T.P.- 5.62; Alb.- 2.95; Glob.- 2.31; Fib.- 0.36; Sugar - 87.9; Sugar Mobl.- 19.2; T.C.- 262; E.C.- 172; Lip.P.- 10.1; Alk. Phos.- 15.8; Th.T.- 2.3; Proth. Conc.- 64.0; Proth. Resp.- 74.0; Bil. Ret.- 9.9.

7.3.48. B.P. 130/80; Alb. -0; Oedema -0; T.P.- 5.68; Alb.- 2.98; Glob.- 2.30; Fib.- 0.40; Sugar Mobl.- 20.6; Alk. Phos.- 15.0; Th.T.- 1.4; Proth. Conc.- 64.2; Proth. Resp.- 81.2.

92. Mrs. Goodwin, Third Gravida, aet 32; 31 weeks; Duration of Toxaemia - 0.5 weeks; Both previous pregnancies were abortions at 3 and 5 months, respectively.

9.2.48. B.P. 160/100; Alb.- 6; Oedema ++ ; Urea - 21.2; A.A.N.- 7.6; T.P.- 5.50; Alb.- 2.86; Glob.- 2.30; Fib.- 0.34; Sugar - 104.0; Sugar Mobl.- 19.2; T.C.- 250; E.C.- 165; Lip.P.- 13.6; Alk. Phos.- 16.0; Th.T.- 1.8; Proth. Conc.- 67.5; Proth. Resp.- 52.6; Bil. Ret.- 10.9.

16.2.48. B.P. 150/100; Alb.- 4.5; Oedema + ; Urea - 20.6; A.A.N.- 7.5; T.P.- 5.41; Alb.- 2.76; Glob.- 2.26; Fib.- 0.39; Sugar - 97.7; Sugar Mobl.- 18.5; T.C.- 268; E.C.- 178; Lip.P.- 12.7; Alk. Phos.- 16.3; Th.T.- 1.5; Proth. Conc.- 68.0; Proth. Resp.- 52.0; Bil. Ret.- 10.97.

23.2.48. B.P. 150/90; Alb.- 3; Oedema ± ; Urea - 23.0; A.A.N.- 7.6; T.P.- 5.58; Alb.- 2.86; Glob.- 2.30; Fib.- 0.42; Sugar - 99.5; Sugar Mobl.- 19.0; T.C.- 260; E.C.- 175; Lip.P.- 11.8; Alk. Phos.- 14.5; Th.T.- 1.2; Proth. Conc.- 76.7; Proth. Resp.- 64.6; Bil. Ret.- 10.6.

2.3.48. B.P. 145/85; Alb.- 1; Oedema -0; Urea - 18.0; A.A.N.- 6.0; T.P.- 5.65; Alb.- 2.93; Glob.- 2.30; Fib.- 0.42; Sugar - 107.8; Sugar Mobl.- 20.4; Alk. Phos.- 14.2; Th.T.- 1.1; Proth. Conc.- 86.8; Proth. Resp.- 78.5; Bil. Ret.- 10.12.

93. Mrs. Flemming, Primigravida; aet 24; 36/37 weeks; Duration of Toxaemia - 2 weeks. Cystine 5 grms. daily from 26.3.48 to 9.4.48.

19.3.48. B.P. 180/105; Alb.- 10; Oedema -+++ ; Urea - 18.6; A.A.N./

A.A.N.- 8.7; T.P.- 5.37; Alb.- 2.57; Glob.- 2.30; Fib.- 0.50; Sugar - 83.7; Sugar Mobl.- 10.5; Gal. In. 170.4; T.C.- 261; E.C.- 162; Lip.P.- 17.0: Alk. Phos.- 17.4; Th.T.- 3.4; Proth. Cone.- 50.0; Proth. Resp.- 50.0; Bil. Ret.- 10.8.

26.3.48. B.P. 172/115; Alb.- 11; Oedema +++; Urea - 16.2; A.A.N.- 8.8; T.P.- 5.73; Alb.- 2.60; Glob.- 2.33; Fib.- 0.30; Sugar - 87.9; Sugar Mobl.- 13.1; Gal. In.- (25.3.48) - 201.1; T.C.- 270; E.C.- 153; Lip.P.- ; Alk.Phos.- 26.8; Th.T.- 4.0; Proth. Cone.- 50.2; Proth. Resp.- 47.5; Bil. Ret.- 18.75.

4.4.48. B.P. 175/115; Alb.- 11.5; Oedema ++ ; Urea - 18.9; A.A.N.- 9.8; T.P. 5.03; Alb.- 2.50; Glob.- 2.29; Fib.- 0.24; Sugar - 94.0; Sugar Mobl.- 13.6; Gal. In.- (2.4.48) - 200.5; T.C.- 276; E.C.- 147; Lip.P.- 18.9; Alk. Phos.- 27.3; Th.T.- 4.2; Proth. Cone.- 48.5; Proth. Resp.- 40.4; Bil. Ret.- 20.36.

9.4.48. B.P. 190/120; Alb.- 13; Oedema ++ ; Induction of Labour - S.B.; Urea - 16.0; A.A.A.- 10.0; T.P.; 4.90; Alb.- 2.45; Glob.- 2.32; Fib.- 0.13; Sugar - 91.0: Sugar Mobl.- 7.7; Gal. In.- (8.4.48) - 214.1; T.C.- 291; E.C.- 145; Lip.P.- 16.6; Alk. Phos.- 30.0; Th.T. 4.5; Proth. Cone.- 41.8; Proth. Resp.- 23.6; Bil. Ret.- 26.10.

94. Mrs. McCudden, Secondgravida; aet 36; 30 weeks; Duration of Toxaemia - 1.5 weeks; Twins; First pregnancy normal. Cystine 5 grns. daily from 25.4.48 to 9.5.48.

18.4.48. B.P. 160/100; Alb.- 4.5; Oedema +++ ; Urea - 20.9; A.A.N.- 7.3; T.P.- 5.36; T.P.- 2.64; Alb.- 2.64; Glob.- 2.30; Fib.- 0.42; Sugar - 96.3; Sugar Mobl.- 19.4; Gal. In.- 159.0; T.C.- 247; E.C.- 165; Lip.P.- 13.8; Alk. Phos.- 13.8; Th.T.- 2.5; Proth. Cone.- 60.0; Proth. Resp.- 52.0; Bil. Ret.- 6.9.

25.4.48. B.P. 155/100; Alb.- 3.5; Oedema ++; Urea - 24.1; A.A.N.- 8.1; T.P.- 5.23; Alb.- 2.60; Glob.- 2.33; Fib.- 0.30; Sugar - 90.0; Sugar Mobl.- 18.8; Gal. In.- 148.6; T.C.- 245; E.C.- 163; Lip.P.- 12.5; Alk. Phos.- 13.7; Th.T.- 2.6; Proth. Cone.- 60.4; Proth. Resp.- 59.0; Bil. Ret.- 3.0.

2.5.48. B.P. 150/100; Alb.- 3; Oedema + ; Urea - 21.7; A.A.N.- 8.9; T.P.- 5.26; Alb.- 2.63; Glob.- 2.27; Fib.- 0.36; Sugar - 97.0; Sugar Mobl.- 19.7; Gal. In.- 130.8; T.C.- 246; E.C.- 164; Lip.P.- 12.6; Alk. Phos.- 13.2; Th.T.- 2.4; Proth. Conc.- 65.0; Proth. Resp.- 65.5; Bil. Ret.- 2.94.

9.5.48. B.P. 142/90; Alb.- 1; Oedema ± ; Urea - 24.5; A.A.N.- 9.7; T.P.- 5.40; Alb.- 2.79; Glob.- 2.32; Fib.- 0.39; Sugar - 104.0; Sugar Mobl.- 20.4; Gal. In. (10.5.48) - 120.5; T.C.- 240; E.C.- 162; Lip.P.- ; Alk. Phos.- 13.4; Th.T.- 1.0; Proth. Conc.- 78.0; Proth. Resp.- 76.6, Bil. Ret.- 3.71.

95. Mrs. Murdoch, Second gravida, aet - 40; 39 weeks;

Duration of Toxaemia - 1 week. First pregnancy normal.

18.4.48. B.P. 162/100; Alb.- 6; Oedema++ ; Urea - 21.5; A.A.N.- 7.7; T.P.- 5.48; Alb.- 2.77; Glob.- 2.33; Fib.- 0.38; Sugar - 90.8; Sugar Mobl.- 17.9; T.C.- 265; E.C.- 178; Lip.P.- 13.9; Alk. Phos.- 14.5; Th.T.- 1.7; Proth. Conc.- 59.5; Proth. Resp.- 59.0; Bil. Ret.- 4.9.

24.4.48. B.P. 155/100; Oedema + ; Spontaneous Labour; B.B.A. Urea - 20.0; A.A.N.- 7.1; T.P.- 5.50; Alb.- 2.84; Glob.- 2.30; Fib.- 0.36; Sugar - 94.9; Sugar Mobl.- 19.5; T.C.- 270; E.C.- 180; Lip.P.- 14.0; Alk. Phos.- 14.8; Th.T.- 1.5; Proth. Conc.- 58.0; Proth. Resp.- 57.0; Bil. Ret.- 4.8;

96. Mrs. McDougal, Primigravida; aet 31; 39 weeks.

Duration of Toxaemia - 2 weeks.

1.9.48. B.P. 170/110; Alb.- 9; Oedema +++ ; Urea - 16.0; A.A.N.- 8.1; T.P.- 5.29; Alb.- 2.40; Glob.- 2.30; Fib.- 0.59; Sugar - 88.0; Sugar Mobl.- 17.0; Gal. In.- 191.7; T.C.- 290; E.C.- 178; Lip.P.- 15-0; Alk. Phos.- 20.0; Th.T.- 3.8; Proth. Conc.- 54.6; Proth. Conc.- 54.6; Proth. Resp.- 52.8; Bil. Ret. 18.9.

4.9.48. B.P. 170/120; Oedema ++ ; Spontaneous Labour; B.B.A.; Urea - 19.4; A.A.N.- 10.0; Sugar - 80.4; Sugar Mobl.- 10.2; Gal. In. (3.9.48)- 204.4; T.C.- 267; E.C.- 138; Lip.P.- 13.6; Alk. Phos.- 27.8; Th.T.- 3.9; Proth. Conc.- 49.4; Proth. Resp.- 34.0; Bil. Ret.- 23.7.

97. Mrs. McAlpine, Primigravida; aet 26; 35 weeks;

Duration of Toxaemia - 2 weeks.

25.9.48. B.P. 160/105; Alb.- 5; Oedema ++ ; Urea - 19.1; A.A.N.- 8.3; T.P.- 5.35; Alb.- 2.51; Glob.- 2.29; Fib.- 0.55; Sugar - 89.4; Sugar Mobl.- 16.8; Gal. In.- (26.9.48) - 186.6; T.C.- 282; E.C.- 176; Lip.P.- 14.3; Alk. Phos.- 17.0; Th.T.- 3.2; Proth.- Conc.- 60.4; Proth. Resp.- 60.5; Bil. Ret.- 11.5.

1.10.48. B.P. 160/110; Alb.- 8; Oedema ++ ; Urea - 17.0; A.A.N.- 8.5; T.P.- 5.32; Alb.- 2.35; Glob.- 2.30; Fib.- 0.67; Sugar - 90.6; Sugar Mobl.- 16.0; Gal. In. 199.7; T.C.- 280; E.C.- 173; Lip.P.; 16.8; Alk. Phos.- 19.6; Th.T.- 3.6; Proth. Conc.- 56.6; Proth. Resp.- 51.3. Bil. Ret.- 12.6.

6.10.48. B.P. 160/110; Oedema ++ ; Urea - 18.2; A.A.N.- 8.9; Sugar - 92.0; Sugar Mobl.- 16.0; Gal. In. (5.10.48)- 211.8; T.C.- 293; E.C.- 177; Lip.P.- 15.1: Alk. Phos.- 20.8: Th.T.- 3.8; Proth. Conc.- 50.0; Proth. Resp.- 40.1; Bil. Ret.- 13.8.

98. Mrs. McGregor, Secondgravida; aet 36; weeks;

Duration of Toxaemia + 1 week; Precelaupsia in first pregnancy.

2.10.48. B.P. 180/115; Alb.- 11; Oedema +++ ; Urea - 15.2; A.A.N.- 7.8; T.P.- 5.03; Alb.- 2.29; Glob.- 2.28; Fib.- 0.46; Sugar - 93.0; Sugar mobl.- 14.0; Gal. In.- 186.5; T.C.- 276; E.C.- 153; Lip.P.- 13.0; Alk. Phos.- 22.9; Th.T.-3.0; Proth. Conc.- 51.0; Proth. Resp.- 44.6; Bil. Ret.- 16.6.

6.10.48. B.P. 195/110; Oedema ++ ; Spontaneous Labour; B.B.A Urea - 17.5; A.A.N.- 9.0; Sugar - 96.0; Sugar Mobl.- 12.0; Gal. In.- 200; T.C.- 255; E.C.- 154; Lip.P.- 16.1; Alk. Phos.- 20.6; Th.T.- 3.0; Proth. Conc.- 47.8; Proth. Resp.- 35.0; Bil. Ret.- 22.4.

99. Mrs. McWinnè; Primigravida; aet 28; Full Term;

Duration of Toxaemia - 1.5 weeks; Spontaneous Labour on 19.10.48. B.B.A.

18.10.48. B.P. 200/120; Alb.- 10; Oedema +++; Urea - 16.4; A.A.N.- 9.0; T.P.- 4.82; Alb.- 2.30; Glob.- 2.30; Fib.- 0.22; Sugar - 90.8; Sugar Mobl.- 10.5; T.C.- 294; E.C.- 153; Lip.P. 17.8; Alk. Phos.- 29.5; Th.T.- 2.6; Proth. Conc.- 47.5; Proth. Resp.- 37.6; Bil. Ret.- 25.0.

100. Mrs. Dillon, Primigravida; aet 30; 30 weeks;

Duration of Toxaemia - 1 week.

22.11.48. B.P. 170/110; Alb.- 4 Oedema ++; Urea - 17.5; A.A.N.- 7.7; T.P.- 5.56; Alb.- 2.65; Glob.- 2.31; Fib.- 0.60; Sugar - 91.0; Sugar Mobl.- 16.8; T.C.- 288; E.C.- 175; Lip.P.- 16.61 Alk. Phos.- 20.5; Th.T.- 3.4; Proth. Conc.- 60.8; Proth. Resp.- 58.5; Bil. Ret.- 12.5.

1.12.48. B.P. 200/115; Alb.- 8; Oedema ++; Headache +; Epigastric pain +; Caesarian Section; B.B.A.; Urea - 16.0; A.A.N.- 9.3; T.P.- 5.19; Alb.- 2.40; Glob.- 2.32; Fib.- 0.47; Sugar - 93.0; Sugar Mobl.- 11.2; T.C.- 291; E.C.- 153; Lip.P.- 14.1; Alk. Phos.- 20.5; Th.T.- 3.4 Proth. Conc.- 58.5; Proth. Resp.- 48.4; Bil. Ret. 19.9.

ECLAMPSIA. (18 Cases.)

Case No. 1. Mrs. Dempster; Primigravida; aet 24;

Antepartum eclampsia; 5 fits;

Duration of toxaemia - 2 weeks.

Convulsive Stage.

19.1.48. B.P. 165/100; Alb.- 9; Oedema +++. Fits (before admission) - 4 (on admission) - 1; Coma ± ; Urea - 15.4; A.A.N.- 10.7; T.P.- 5.56; Alb.- 3.04; Glob.- 2.32; Fib.- 0.20; Sugar - 80.6; Sugar Mobl.- 4.1; T.C.- 240; E.C.- 110; Lip. P.- 13.0; Alk. Phos.- 24.8; Th.T.- 4.4; Proth. Conc.- 39.0; Proth. Resp.- 29.5; Bil. Ret.- 19.9.

Convalescence.

20.1.48. B.P. 160/100; Alb.- 9; Oedema +++. Coma ± Urea - 19.8: A.A.N.- 10.5; Sugar - 78.5; Sugar mobl.- 4.0; T.C.- 252; E.C.- 141; Lip. P.- 14.6; Alk. Phos.- 19.0; Th. T.- 4.4; Proth. Conc.- 40.0; Proth. Resp.- 29.0; Bil. Ret.- 17.9.

21.1.48. B.P. 155/95; Alb.- 6; Oedema ++. Coma - 0. Urea.- 19.0; A.A.N.- 9.0; Sugar - 84.0; Sugar Mobl.- 9.7; T.C.- 250; E.C.- 151; Lip. P.- 14.0: Alk. Phos.- 18.0; Th. T.- 4.0; Proth. Conc.- 40.0; Proth. Resp.- 33.0; Bil. Ret.- 17.5.

24.1.48. B.P. 150/90; Alb.- 6; Oedema ++ Urea - 18.2; A.A.N.- 8.2; Sugar - 83.0; Sugar Mobl.- 15.9; T.C.- 238; E.C.- 159; Lip. P.- 12.1; Alk. Phos.- 10.0; Th. T.- 2.9; Proth. Conc.- 46.0; Proth. Resp.- 48.6; Bil. Ret. 10.13.

31.1.48. B.P. 148/88; Alb.- 3; Oedema + . Urea - 17.5; A.A.N.- 6.1; Sugar - 82.6; Sugar Mobl.- 19.7; T.C.- 226; E.C.- 153; Alk. Phos.- 10.0; Th. T.- 2.9; Proth. Conc.- 52.0; Proth. Resp.- 60.4; Bil. Ret.- 8.1.

10.2.48. B.P. 140/80; Alb.- 0.5; Oedema - o; Urea - 20.0; A.A.N.- 5.9; Sugar - 81.7; Sugar Mobl.- 19.0; T.C.- 216; E.C.- 148; Lip. P.- 10.0; Alk. Phos.- 8.2; Th. T.- 1.8; Proth. Conc.- 81.2; Proth. Resp.- 84.7; Bil. Ret. 1.9.

Case/

Case No. 2. Mrs. Moore; Primigravida; aet - 29;

Intrapartum eclampsia; 2 fits;

Duration of toxaemia - 3 weeks.

Convulsive Stage.

19.1.48. B.P. 175/110; Alb.- 11; Oedema ++ ; Fits - 2; Coma - ± (Blood collected immediately after the second convulsion).
Urea - 15.0; A.A.N.- 7.6; T.P.- 5.0; Alb.- 2.47; Glob.- 2.30; Fib.- 0.23; Sugar - 81.7; Sugar Mobl.- 6.5; T.C.- 220; E.C.- 114; Lip. P.- 15.1; Alk. Phos.- 29.7; Th. T.- 4.8; Proth. Conc.- 37.6; Proth. Resp.- 34.2; Bil. Ret.- 14.9.

Convalescence.

20.1.48. B.P. 150/100; Alb.- 9; Oedema ++ ; Coma - o; Urea - 16.5; A.A.N.- 7.1; Sugar - 80.0; Sugar Mobl.- 6.0; T.C.- 200; E.C.- 118; Lip. P.- 16.0; Alk. Phos.- 27.5; Th. T.- 3.5; Proth. Conc.- 38.0; Proth. Resp.- 34.0; Bil. Ret.- 14.9.

21.1.48. B.P. 150/92; Alb.- 8.5; Oedema ++ ; Urea - 16.5; A.A.N.- 6.8; Sugar 84.0; Sugar Mobl.- 10.6; T.C.- 197; E.C.- 121; Lip. P.- 15.3; Alk. Phos.- 24.0; Th. T.- 2.6; Proth. Conc.- 38.2; Proth. Resp.- 40.5; Bil. Ret.- 14.3.

24.1.48. B.P. 145/85; Alb.- 6.5; Oedema + ; Urea - 17.0; A.A.N.- 6.3; Sugar - 89.0; Sugar Mobl.- 14.7; T.C.- 180; E.C.- 121; Alk. Phos.- 15.8; Th. T.- 1.8; Proth. Conc.- 44.0; Proth. Resp.- 48.6; Bil. Ret.- 10.9.

31.1.48. B.P. 140/80; Alb.- 4; Oedema ± ; Urea - 17.8; A.A.N.- 6.0; Sugar - 81.8; Sugar Mobl.- 19.8; T.C.- 168; E.C.- 115; Alk. Phos.- 10.0; Th. T.- 1.3; Proth. Conc.- 51.8; Proth Resp.- 59.7; Bil. Ret.- 6.9.

10.2.48. B.P. 140/80; Alb.- ± ; Oedema - o; Urea - 19.6; A.A.N.- 5.5; Sugar - 81.0; Sugar Mobl.- 21.0; T.C.- 170; E.C.- 116; Lip. P.- 9.8; Alk. Phos.- 6.8; Th. T.- 1.3; Proth. Conc.- 78.9; Proth. Resp.- 88.6; Bil. Ret.- 2.7.

Case/

Case No. 3. Mrs. McInalty. Primigravida; aet 25; Antepartum eclampsia; Fits - (before admission) 2 + (on admission) 1; Coma ± Duration of toxaemia - 3 weeks.

Convulsive Stage.

24.1.48. B.P. 140/110; Alb.- 11; Oedema++ ; Fits - 3; Coma ± (Blood sample obtained 30 minutes after the last convulsion).
Urea - 15.5; A.A.N.- 9.6; T.P.- 5.05; Alb.- 2.45; Glob.- 2.30; Fib.- 0.30; Sugar - 92-3: Sugar Mobl.- 4.0; T.C.- 250; E.C.- 127; Lip. P.- 14.8; Alk. Phos.- 20.2; Th. T.- 4.5; Proth. Conc.- 44.8; Proth. Resp.- 29.7; Bil. Ret.- 16.7.

Convalescense.

25.1.48. B.P. 150/100; Alb.- 10; Oedema++ ; Coma - o; Urea - 23.4; A.A.N.- 9.8; Sugar - 90.6; Sugar Mobl.- 4.3; T.C.- 230; E.C.- 133; Lip. P.- 14.8; Alk. Phos.- 18.5; Th. T.- 3.5; Proth. Conc.- 45.0; Proth. Resp.- 31.4; Bil. Ret.- 15.5.

26.1.48. B.P. 140/95; Alb.- 6; Oedema + ; Urea - 20.0; A.A.N.- 7.5; Sugar - 98.0; Sugar Mobl.- 6.9; T.C.- 221; E.C.- 137; Lip. P.- 15.5; Alk. Phos.- 18.2; Th. T.- 2.8 Proth. Conc.- 46.2; Proth. Resp.- 40.9; Bil. Ret. 15.0.

29.1.48. B.P. 138/90; Alb.- 3.5; Oedema ± ; Urea - 19.4; A.A.N.- 6.9; Sugar - 90.4; Sugar Mobl.- 15.7; T.C.- 204; E.C.- 135; Lip. P.- 14.4; Alk. Phos.- 11.0; Th. T.- 2.0; Proth. Conc.- 48.0; Proth Resp.- 54.5; Bil. Ret.- 12.9.

5.2.48. B.P. 135/80; Alb.- 1; Oedema - o; Urea - 19.5; A.A.N.- 6.1; Sugar - 86.5; Sugar Mobl.- 15.7; T.C.- 200; E.C.- 137; Alk. Phos.- 9.2; Th. T.- 1.8; Proth. Conc.- 60.7; Proth. Resp.- 67.8; Bil. Ret.- 7.9.

15.2.48. B.P. 130/80; Alb. ± ; Oedema - o; Urea - 19.5; A.A.N. 5.9; Sugar - 86.5; Sugar Mobl.- 18.8; T.C.- 202; E.C.- 138; Lip. P.- 10.5; Alk. Phos.- 7.0; Th. T. - 1.1; Proth. Conc.- 84.8; Proth. Resp.- 94.7.

Case/

Case No. 4; Mrs. Devlin; Primigravida; aet - 26;

Antepartum eclampsia; 4 fits;

Duration of toxameia - 2 weeks.

Convulsive Stage.

4.2.48. B.P. 168/110; Alb.- 5; Oedema ++; Fits (before admission) - 3; Coma ±; (Blood obtained one hour after the last convulsion).
Urea - 16.2; A.A.N.- 10.3; T.P.- 5.60; Alb.- 3.16; Glob.- 2.33; Fib.- 0.21; Sugar - 80.8; Sugar Mobl. - 7.6; T.C.- 280; E.C.- 142; Lip. P.- 16.7; Alk. Phos.- 20.2; Th. T.- 4.5; Proth. Conc.- 38.7; Proth Resp.- 30; Bil. Ret.- 15.9.

5.2.48. B.P. 165/100; Alb.- 6; Oedema ++; Fit - 1; Coma ± ; (Blood sample collected 3 hours after the convulsion).
Urea - 25.9; A.A.N.- 10.4; T.P.- 5.36; Alb.- 2.88; Glob.- 2.33; Fib.- 0.15; Sugar - 79.0; Sugar Mobl.- 2.5; T.C.- 203; E.C.- 100; Lip. P.- 13.0; Alk. Phos.- 30.8; Th. T.- 5.8; Proth. Conc.- 30.5; Proth. Resp.- 20.4; Bil. Ret.- 28.8.

Convalescence.

6.2.48. B.P. 165/100; Alb.- 6; Oedema ++; Coma - o; (24 hours after last fit).
Urea - 25.0; A.A.N.- 9.5; Sugar - 81.5; Sugar Mobl.- 4.0; Gal. In.- 212.5; T.C.- 200; E.C.- 109; Lip. P.- 13.0; Alk. Phos.- 22.0; Th. T.- 5.0; Proth Conc.- 37.8; Proth. Resp.- 20.0; Bil. Ret.- 20.7.

9.2.48. B.P. 150/95; Alb.- 4.5; Oedema + ; Urea - 20.0; A.A.N.-8.0; Sugar - 87.0; Sugar Mobl.- 7.8; T.C.- 200; E.C.- 132; Lip. P.- 15.2; Lip. Phos.- 13.0; Th. T.- 3.4; Proth. Conc.- 50.0; Proth Resp.- 56.7; Th. T.- 13.7.

16.2.48. B.P. 142/90; Alb.- 2.5; Oedema ± ; Urea - 19.6; A.A.N.- 6.8; Sugar - 85.0; Sugar Mobl.- 14.3; Gal. In.- 67.4; T.C.- 200; E.C.- 132; Lip. P.- 12.6; Alk. Phos.- 8.2; Th. T.- 3.0; Proth. Conc.- 59.5; Proth. Resp.- 71.8; Bil. Ret.- 8.9.

20.2.48. B.P. 135/80; Alb.- 0.5; Oedema ± ; Urea - 20.0; A.A.N.- 6.0; Sugar - 83.5; Sugar Mobl.- 19.7; T.C.- 186; E.C.- 128; Lip. P.- 10.1; Alk. Phos.- 7.0; Th. T.- 1.9; Proth. Conc.- 85.0; Proth. Resp.- 90.0; Bil. Ret.- 3.0.

Case No. 5; Mrs. Donaldson; Second gravida; aet - 33;

Post partum eclampsia; 5 fits;

Duration of toxaemia - 2 weeks.

Convulsive Stage.

4.2.48. B.P. 210/120; Alb.- 14.5; Oedema +++ ; Fits - 3; Coma + ; (Blood sample obtained ½ hour after the last fit.) Urea - 34.3; A.A.N.- 10.0; T.P.- 4.80; Alb.- 2.29; Glob.- 2.21; Fib.- 0.30; Sugar - 89.7; Sugar Mobl.- 4.5; T.C.- 228; E.C.- 116; Lip. P.- 18.0; Alk. Phos.- 30.8; Th. T.- 6.8; Proth. Conc.- 50.4; Proth. Resp.- 39.0; Bil. Ret.- 18.8.

5.2.48. B.P. 200/120; Alb. 14.5; Oedema +++; Fits - 2; Coma + (Blood sample obtained immediately after the last convulsion.) Urea - 42.5; A.A.N.- 10.9; T.P.- 4.95; Alb.- 2.45; Glob.- 2.30; Fib.- 0.17; Sugar - 80.8; Sugar Mobl.- 3.6; T.C.- 203; E.C.- 100; Lip. P.- 14.2; Alk. Phos.- 35.7; Th. T.- 7.5; Proth. Conc.- 40.0; Proth. Resp.- 24.6; Bil. Ret.- 29.1.

Convalescence.

6.2.48. B.P. 190/100; Alb.- 10.5; Oedema ++ ; Coma ± ; Urea - 40.0; A.A.N.- 9.2; Sugar - 80.5; Sugar Mobl.- 3.5; T.C.- 163; E.C.- 86; Lip. P.- 13.0; Alk. Phos.- 28.0; Th. T.- 5.0; Proth. Conc.- 40.2; Proth. Resp.- 25.0; Bil. Ret.- 28.30.

7.2.48. B.P. 160/95; Alb.- 9.5; Oedema ++ ; Coma - o; Urea - 31.5; A.A.N.- 8.4; Sugar - 89.0; Sugar Mobl.- 8.2; Gal. In.- 220.5; T.C.- 154; E.C.- 90; Alk. Phos.- 24.5; Th. T.- 3.9; Proth. Conc.- 44.0; Proth. Resp.- 31.1; Bil. Ret.- 19.9.

10.2.48. B.P. 150/95; Alb.- 8.5; Oedema + ; Urea - 27.2; A.A.N.- 7.6; Sugar - 87.5; Sugar Mobl.- 15.1; T.C.- 198; E.C.- 131; Lip. P.- 14.1; Alk. Phos.- 16.4; Th. T.- 3.0; Proth. Conc.- 58.7; Proth. Resp.- 63.8; Bil. Ret.- 8.2.

17.2.48. B.P. 140/90; Alb.- 3.5; Oedema ± ; Urea - 21.5; A.A.N.- 6.6; Sugar - 88.0; Sugar Mobl.- 18.7; Gal. In.- 101.2; Alk. Phos.- 10.8; Th. T.- 2.8; Proth. Conc.- 77.9; Proth. Resp.- 73.0; Bil. Ret.- 8.2.

28.2.48. B.P. 138/80; Alb.- 0.5; Oedema ± ; Urea - 21.0; A.A.N.- 6.1; Sugar - 83.4; Sugar Mobl.- 21.0; T.C.- 161; E.C.- 111; Lip. Phos.- 8.5; Th. T.- 2.0; Proth. Conc.- 89.1; Proth. Resp.- 90; Bil. Ret.- 2.8.

Case No. 6; Mrs. Anderson; Primigravida; aet - 29;

Intrapartum and Post Partum eclampsia -

Fits - 7.

Duration of toxaemia - 3 weeks.

Convulsive Stage.

1.4.48. B.P. 190/120; Alb.- 10; Oedema ++ ; Fits - 6; Coma + ; (Blood sample collected immediately after the last convulsion).
Urea - 14.6; A.A.N.- 18.0; T.P.- 5.12; Alb.- 2.73; Glob.- 2.31; Fib.- 0.18; Sugar - 84.0; Sugar Mobl.- 3.2; T.C.- 276; E.C.- 123; Lip. P.- 18.6; Alk. Phos.- 25.5; Th. T.- 5.8; Proth. Conc.- 32.7; Proth. Resp.- 25.0; Bil. Ret.- 21.8.

2.4.48. B.P. 190/115; Alb.- 10; Oedema ++ ; Fit - 1; Coma + ; (Blood sample collected one hour after convulsion).
Urea - 29.0; A.A.N.- 17.5; T.P.- 5.09; Alb.- 2.65; Glob.- 2.30; Fib.- 0.14; Sugar - 84.0; Sugar Mobl.- 2.9; T.C.- 219; E.C.- 95; Lip. P.- 12.1; Alk. Phos.- 30.4; Th. T.- 7.0; Proth. Conc.- 32.0; Proth. Resp.- 20.8; Bil.Ret.- 29.5.

Convalescence.

3.4.48. B.P. 170/110; Alb.- 10; Oedema ++ ; Coma - o; Urea - 39.0; A.A.N.- 14.0; Sugar - 84.5; Sugar Mobl.- 3.0; Gal. In.- 224.3; T.C.- 276; E.C.- 123; Lip. P.- 12.0; Alk. Phos.- 26.0; Th. T.- 6.0; Proth. Conc.- 32.6; Proth. Resp.- 20.6; Bil. Ret.- 24.0.

4.4.48. B.P. 150/100; Alb.- 8.5; Oedema + ; Urea - 29.4; A.A.N.- 10.0; Sugar - 89.0; Sugar Mobl.- 7.7; T.C.- 204; E.C.- 117; Lip. P.- 14.6; Alk. Phos.- 20.2; Th. T.- 4.8; Proth. Conc.- 34.0; Proth Resp.-30.8; Bil. Ret.- 17.7.

7.4.48. B.P. 142/95; Alb.- 4.5; Oedema ± ; Urea - 21.2; A.A.N.- 8.9; Sugar - 85.5; Sugar Mobl.- 13.8; T.C.- 198; E.C.- 131; Lip. P.- 14.5; Alk. Phos.- 14.5; Th.T.- 3.6; Proth. Conc.- 51.8; Proth. Resp.- 64.5; Bil. Ret.- 15.10.

14.4.48. B.P. 135/90; Alb.- 1.5; Oedema ± ; Urea - 20.7; A.A.N.- 7.0; Sugar - 84.2; Sugar Mobl.- 18.4; Gal. In.- 104.6; T.C.- 190; E.C.- 128; Alk. Phos.- 7.8; Th. T.- 2.7; Proth. Conc.- 68.7; Proth. Resp.- 72.6; Bil. Ret.- 9.3.

24.4.48. B.P. 130/92; Alb.- ± ; Oedema - o; Urea 20.0; A.A.N.- 6.2; Sugar - 82.6; Sugar Mobl.- 19.8; T.C. - 191 E.C. - 133; Lip. P.- 10.0; Alk. Phos.- 7.5; Th. T.- 1.4; Proth. Conc.- 74.0; Proth. Resp.- 87.8; Bil. Ret.- 3.0.

Case No. 7; Mrs. Bramston; Aet 25; Primagravida;

Intrapartum eclampsia; 3 fits.

Convulsive Stage.

8.4.48. B.P. 190/115; Alb.- 7; Oedema ++ ; Fits - 3; Coma ± ; (Blood obtained during the last convulsion). Urea - 13.9; A.A.N.- 8.8; T.P.- 5.30; Alb.- 2.46; Glob.- 2.33; Fib.- 0.21; Sugar - 83.7; Sugar Mobl.- 11.0; T.C.- 270; E.C.- 139; Lip. P.- 18.3; Ack. Phos.- 21.0; Th. T.- 5.7; Proth. Conc.- 32.7; Proth. Resp.- 25.0; Bil. Ret.- 15.6.

Convalescence.

9.4.48. B.P. 170/105; Alb.- 6.8; Coma - 0. Oedema ++; Urea - 18.5; Sugar - 81.5; Sugar Mobl.- 7.3; Gal. In.- 185.2; T.C.- 264; E.C.- 147; Lip. P.- 19.7; Ack. Phos.- 16.2; Th. T.- 4.5; Proth. Conc.- 32.0; Proth. Resp.- 20.8; Bil. Ret.- 15.0.

10.4.48. B.P. 150/95; Alb.- 4; Oedema + ; Urea - 18.0; A.A.N.- 7.8; Sugar - 89.6; Sugar Mobl.- 12.7; T.C.- 252; E.C.- 165; Lip. P.- 17.2; Ack. Phos.- 12.4; Th. T.- 3.0; Proth. Conc.- 57.9; Proth. Resp.- 38.4; Bil. Ret.- 14.2.

13.4.48. B.P. 148/90; Alb.- 2.5; Oedema ± ; Urea - 18.5; A.A.N.-/

A.A.N.- 7.0; Sugar - 91.4; Sugar Mobl.- 16.6; T.C.- 243; E.C.- 163; Alk. Phos.- 9.5; Th. T.- 1.9; Proth. Conc.- 53.2; Proth. Resp.- 58.8; Bil. Ret.- 10.0.

20.4.48. B.P. 138/90; Alb.- 0.5; Oedema ± ; Urea - 18.3; A.A.N.- 6.5; Sugar - 84.8; Sugar Mobl.- 19.5; Gal. In.- 78.7; T.C.- 240; E.C.- 164; Ack. Phos.- 7.5; Th. T.- 2.0; Proth. Conc.- 64.0; Proth. Resp.- 74.0; Bil. Ret.- 3.0.

30.4.48. B.P. 138/80; Alb.- ± ; Oedema - 0; Urea - 19.4; A.A.N.- 5.8; Sugar - 84.0; Sugar Mobl.- 20.7; T.C.- 240; E.C.- 165; Lip. P.- 9.3; Alk. Phos.- 6.5; Th. T.- 1.6; Proth. Conc.- 80.8; Proth. Resp.- 88.5.

Case No. 8; Mrs. Rough; aet 26; Primigravida;

Intrapartum eclampsia; Fits - 2;

Duration of toxaemia - 2 weeks.

Pre-convulsive Stage.

27.4.48. B.P. 168/110; Alb.- 9.5; Oedema +++ ; Urea - 18.8; A.A.N.- 8.0; T.P.- 5.28; Alb.- 2.84; Glob.- 2.26; Fib.- 0.68; Sugar - 87.8; Sugar Mobl.- 16.5; Gal. In.- (28.4.48) - 158.6; T.C.- 272; E.C.- 162; Lip. P.- 16.0; Alk. Phos.- 16.6; Th. T.- 3.0; Proth Conc.- 50.8; Proth. Resp.- 50.0; Bil. Ret.- 10.3.

3.5.48. B.P. 170/110; Alb.- 9.0; Oedema ++ ; Headache; epigrastic pain + ; surgical induction of labour. (Blood obtained 16 hours before convulsion).
Urea - 18.0; A.A.N.- 8.1; T.P.- 5.20; Alb.- 2.32; Glob.- 2.28; Fib.- 0.60; Sugar - 87.0; Sugar Mobl.- 12.5; Gal. In.- 160.4; T.C.- 312; E.C.- 182; Lip.P.- 16.6; Alk. Phos.- 18,6; Th. T.-3.6; Proth. Conc.- 50.0; Proth. Resp.- 48.8; Bil. Ret.- 19.3.

Convulsive Stage.

4.5.48. B.P. 180/115;/

4.5.48. B.P. 180/115; Alb.- 11; Oedema +++ ; Fits - 2; Coma ± ; (Blood obtained one hour after the last convulsion.)
Urea - 16.0; A.A.N.- 9.1; T.P.- 5.0; Alb.- 2.34; Glob.- 2.25; Fib.- 0.51; Sugar - 87.0; Sugar Mobl.- 7.0; Gal. In.- 183.6; T.C.- 237; E.C.- 122; Alk. Phos.- 26.8; Th. T.- 3.3; Proth. Conc.- 50.0; Proth. Resp.- 34.3; Bil. Ret.- 25.2; Lip. P.- 19.3.

Convalescence.

5.5.48. B.P. 170/110; Alb.- 11; Oedema +++ ; Coma ± ; Urea - 27.5; A.A.N.- 9.0; Sugar 84.0; Sugar Mobl.- 5.3; T.C.- 200; E.C.- 118; Alk. Phos.- 21.5; Th. T.- 3.0; Proth. Conc.- 46.2; Proth. Resp.- 30; Bil. Ret.- 24.9;

6.5.48. B.P. 150/100; Alb.- 8.5; Oedema ++ ; Coma - 0; Urea - 21.4; A.A.N.- 8.0; Sugar - 88.5; Sugar Mobl.- 10.7; T.C.- 197; E.C.- 128; Lip. P.- 14.1; Alk. Phos.- 18.7; Th. T.- 2.8; Proth. Conc.- 50.0; Proth Resp. - 39.0; Bil. Ret.- 20.8.

9.5.48. B.P. 142/95; Alb.- 6.5; Oedema + ; Urea - 20.2; A.A.N.- 7.4; Sugar - 85.4; Sugar - 16.5; T.C.- 194; E.C.- 130; Ack. Phos.- 10.5; Th. T.- 2.1; Proth. Conc.- 59.7; Proth. Resp.- 59.9; Bil. Ret.- 12.9.

16.5.48. B.P. 140/90; Alb.- 3; Oedema ± ; Urea- 20.5; A.A.N.- 6.8; Sugar - 84.0; Sugar Mobl.- 18.8; Gal. In.- 58.4; T.C.- 195; E.C.- 132; Alk. Phos.- 6.0; Th. T.- 1.8; Proth. Conc.- 71.0; Proth. Resp.- 79.8; Bil. Ret.- 10.7.

26.5.48. B.P. 135/82; Alb.- ± ; Oedema - 0; Urea - 20.4; A.A.N.- 5.9; Sugar - 83.7; Sugar Mobl- 20.6; T.C.- 196; E.C.- 132; Lip. P.- 9.6; Alk. Phos.- 6.0; Th. T.- 1.0; Proth. Conc.- 88.4; Proth. Resp.- 86.5; Bil. Ret.- 6.7.

Case/

Case No. 9; Mrs. Smith; Primigravida; aet - 24;

Antepartum eclampsia; Fits - 3.

Convulsive Stage.

4.6.48. B.P. 175/110; Alb.- 6.5; Oedema ++ ; Fits - 3; Coma + ; (Blood obtained 4 hours after the last con-:vulsion).
Urea - 15.4; A.A.N.- 9.8; T.P.- 5.38; Alb.- 2.88; Glob.- 2.30; Fib.- 0.19; Sugar - 80.0; Sugar Mobl.- 5.2; T.C.- 276; E.C.- 142; Alk. Phos.- 21.0; Th. T.- 4.0; Proth. Conc.- 45.0; Proth Resp.- 32.0; Bil. Ret.- 14.9; Lip. P.- 14.9.

Convalescence.

5.6.48. B.P. 160/100; Alb.- 6; Oedema ++ ; Coma - 0. Urea - 19.0; A.A.N.- 8.0; Sugar - 81.5; Sugar Mobl.- 4.5; Sugar Mobl.- 175.5; Gal. In.- 175.5; T.C.- 230; E.C.- 132; Lip. P.- 18.4; Alk. Phos.- 20.5; Th. T.- 3.4; Proth. Conc.- 44.2; Proth. Resp.- 33.0; Bil. Ret.- 14.2.

6.6.48. B.P. 150/100; Alb.- 5; Oedema + ; Urea - 20.0; A.A.N.- 7.3; Sugar - 87.6; Sugar Mobl.- 9.5; T.C.- 206; E.C.- 121; Alk. Phos.- 19.0; Th. T.- 2.8; Proth. Conc.- 46.8; Proth. Resp.- 39.7; Bil. Ret.- 10.3.

9.6.48. B.P. 140/90; Alb.- 3; Oedema + ; Urea - 19.5; A.A.N.- 6.8; Sugar - 87.0; Sugar Mobl.- 15.7; T.C.- 200; E.C.- 132; Lip. P.- 15.2; Alk. Phos.- 7.0; Th. T.- 1.6; Proth. Conc.- 49.0; Proth. Resp.- 57.6; Bil. Ret.- 8.0.

16.6.48. B.P. 138/82; Alb.- 0.5; Oedema ± ; Urea - 20.0; A.A.N.- 6.5; Sugar - 86.6; Sugar Mobl.- 17.8; Gal. In.- 62.4; T.C.- 176; E.C.- 119; Alk. Phos.- 7.0; Th. T.- 1.6; Proth. Conc.- 62.5; Proth. Resp.- 70.3; Bil. Ret.- 4.9.

26.6.48. B.P. 130/80; Alb.- ± ; Oedema - 0; Urea - 19.4; A.A.N.- 6.4; Sugar - 86.0; Sugar Mobl.- 19.8; T.C.- 170; E.C.- 116.5; Lip. P.- 10.4; Alk. Phos.- 6.3; Th. T.- 1.2; Proth. Conc.- 98.4; Proth. Resp.- 95.8; Bil. Ret.- 1.0.

Case/

Case No. 10; Mrs. McCabe; Primigravida; aet 29;

Antepartum eclampsia; 4 fits;

Convulsive Stage.

12.6.48. B.P. 180/120; Alb.- 10; Oedema +++ ; Fits - 3; Coma+ ; (Blood collected 1½ hours after last convulsion), Urea - 15.5; A.A.N.- 10.5; T.P.- 5.10; Alb.- 2.66; Glob.- 2.30; Fib.- 0.24; Sugar - 84.0; Sugar Mobl.- 4.8; T.C.- 243; E.C.- 125; Lip. P.- 17.8; Alk. Phos.- 27.4; Th. T.- 4.2; Proth. Conc.- 40.1; Proth. Resp.- 33.2; Bil. Ret.- 14.9.

13.6.48. B.P. 170/110; Alb.- 9; Oedema ++ ; Fits - 1 Coma ± ; (Blood collected immediately after the convulsion). Urea - 28.7; A.A.N.- 11.6; T.P.- 5.0; Alb.- 2.61; Glob.- 2.30; Fib.- 0.19; Sugar - 82.5; Sugar Mobl.- 2.5; T.C.- 203.0; E.C.- 99.0; Lip. P.- 18.2; Alk. Phos.- 28.8; Th. T.- 5.8; Proth. Conc.- 40.0; Proth. Resp.- 22.8; Bil. Ret.- 27.8.

Convalescence.

14.6.48. B.P. 150/105; Alb.- 7.5; Oedema ++ ; Coma - 0; Urea - 24.0; A.A.N.- 10.0; Sugar - 91.6; Sugar Mobl.- 3.8; Gal. In.- 166.9; T.C.- 188; E.C.- 109; Lip. P.- 18.0; Alk. Phos.- 22.0; Th.T.- 4.9; Proth. Conc.- 40.8; Proth. Resp.- 22.5; Bil. Ret.- 20.92.

17.6.48. B.P. 148/102; Alb.- 4; Oedema + ; Urea - 20.2; A.A.N.- 8.6; Sugar - 83.7; Sugar Mobl.- 10.7; T.C.- 189; E.C.- 116; Alk. Phos.- 12.0; Th. T.- 3.3; Proth. Conc.- 40.5; Proth. Resp.- 40.6; Bil. Ret.- 18.81.

24.6.48. B.P. 135/98; Alb.- 4; Oedema ± ; Urea - 20.0; A.A.N.- 7.1; Sugar - 85.9; Sugar Mobl.- 17.2; Gal. In.- 50.7; T.C.- 176; E.C.- 119; Alk. Phos.- 9.5; Th.T.- 2.1; Proth. Conc.- 63.4; Proth. Resp.- 67.8; Bil. Ret.- 12.98.

3.7.48. B.P. 138/88; Alb.- 0.5; Oedema ± ; Urea - 20.0; A.A.N.- 6.2; Sugar - 84.0; Sugar Mobl.- 19.8; T.C.- 175; E.C.- 120; Lip. P.- 10.0; Alk. Phos.- 7.5; Th. T.- 1.9; Proth. Conc.- 98.0; Proth. Resp.- 96.5; Bil. Ret.- 3.02.

Case No. 11; Mrs. McKenzie; Primigravida; aet 24;

Antepartum eclampsia; 10 fits.

Convulsive Stage.

27.7.48. B.P. 178/112; Alb.- 9.5; Oedema ++ ; Fits - 5; Coma + ; (Blood sample obtained ½ hour after last convulsion).
Urea - 43.0; A.A.N.- 15.9; T.P.- 5.18; Alb.- 2.52; Glob.- 2.25; Fib.- 0.40; Sugar - 70.5; Sugar Mobl.- 3.4; T.C.- 261; E.C.- 121; Lip. P.- 17.5; Alk. Phos.- 20.0; Th. T.- 4.6; Proth. Conc.- 39.5; Proth. Resp.- 27.6; Bil. Ret.- 18.9.

28.7.48. B.P. 185/125; Alb.- 12.5; Oedema ++ ; Fits - 2; Coma ++ ; (Blood sample obtained immediately after the last convulsion).
Urea - 142.5; A.A.N.- 21.2; T.P.- 4.91; Alb.- 2.58; Glob.- 2.33; Fib.- 0.10; Sugar - 70.0; Sugar Mobl.- 7.4; T.C.- 140; E.C.- 61.0; Lip. P.- 14.2; Alk. Phos.- 29.8; Th. T.- 6.3; Proth. Conc.- 39.0; Proth. Resp. 20.8; Bil. Ret.- 29.9.

28.7.48. (9 hours after the last estimation). B.P.- 98/?40; Anuria; Fits - 3; Coma +++ ; (Blood obtained half-an-hour after last convulsion and 4 hours before death).
Urea - 180; A.A.N.- 23.0; Sugar - 60.2; Sugar Mobl.- 10.2 T.C.- 87; E.C.- 10.5; Lip. P.- 9.4; Alk. Phos.- 39.4; Th. T. 10.1; Proth. Conc.- 38.5; Proth. Resp.- 0; Bil. Ret.- 44.1.

Case No. 12; Mrs. Henderson; Second gravida, aet 31;

Antepartum eclampsia; 18 fits.

Duration of toxaemia - 3 weeks.

Convulsive Stage.

9.9.48. B.P. 115/60; Alb.- 17; Oedema +++ ; Fits - 14; Coma ++; (Blood collected during the last convulsion).
Urea - 55.0; A.A.N.- 21.6; T.P.- 4.90; Alb.- 2.39; Glob.- 2.30; Fib.- 0.21; Sugar - 76.0; Sugar Mobl.- 0.0; T.C.-/

T.C.- 128; E.C.- 328; Lip. P.- 17.8; Alk. Phos.- 26.3; Th. T.- 7.6; Proth. Conc.- 30.4; Proth. Resp.- 26.2; Bil. Ret.- 25.7.

10.9.48. B.P. 100/?; Alb.- ?; (Anuria); Fits - 4; Coma - +++ ; (Blood collected ½ hour after the last convulsion). Urea - 296.0; A.A.N.- 22.6; T.P.- 4.80; Alb.- 2.38; Glob.- 2.34; Fib.- 0.08; Sugar - 60.0; Sugar Mobl.- 17.1; T.C.- 96; E.C.- 8.6; Lip. P.- 10.7; Alk. Phos.- 35.9; Th. T.- 9.2; Proth. Conc.- 20.1; Proth. Resp.- 17.3; Bil. Ret.- 33.7.

10.9.48. B.P. ?; Anuria; Coma +++ - 16 hours before death. (3 hours after the previous sample). Urea - 308 mgms.; A.A.N.- 23.8; Sugar - 50; T.C.- 90.0; E.C.- 0; Lip.- 6.5 P.- 10.7; Alk. Phos.- 39.5; Th. T.- 10.5; Proth. Conc.- 20.1; Proth. Resp.- 3.1; Bil. Ret.- 49.8.

Case No. 13; Mrs. Aird; Primigravida; aet 26;

Post partum eclampsia; 3 fits.

Pre-Convulsive Stage.

20.9.48. B.P. 160/100; Alb.- 7; Oedema ++ ; Urea - 17.5; A.A.N.- 7.9; T.P.- 5.11; Alb.- 2.82; Glob.- 2.29; Fib.- 0.50; Sugar - 88.0; Sugar Mobl.- 11.6; T.C.- 297; E.C.- 159.5; Lip.P.- 18.2; Alk. Phos.- 18.5; Th. T.- 2.8; Proth. Conc.- 69.7; Proth. Resp.- 57.2; Bil. Ret.- 17.3. (Convulsion after 21 hours).

Convulsive Stage.

21.9.48. B.P. 170/110; Alb.- 7; Oedema + ; Fits - 3; Coma ± ; (Blood obtained 4 hours after last convulsion). Urea - 13.0; A.A.N.- 9.0; T.P.- 4.93; Alb.- 2.83; Glob.- 2.30; Fib.- 0.30; Sugar - 80.6; Sugar Mobl.- 9.0; T.C.- 230; E.C.- 120; Lip. P.- ; Alk. Phos.- 21.8; Th. T.- 2.8; Proth. Conc.- 43.2; Proth. Resp.- 31.8; Bil. Ret.- 18.8.

Post-Convulsive Stage.

22.9.48. B.P. 160/98;/

22.9.48. B.P. 160/98; Alb.- 8; Oedema + ; Fits - 0; Urea - 24.5; A.A.N.- 8.5; Sugar - 88.8; Sugar Mobl.- 9.4; T.C.- 208; E.C.- 112; Lip. P.- 16.5; Alk. Phos.- 17.0; Th. T.- 2.4; Proth. Conc.- 43.5; Proth. Resp.- 35.1; Bil. Ret.- 16.2.

25.9.48. B.P. 150/95; Alb.- 8; Oedema + ; Urea - 25.8; A.A.N.- 8.0; Sugar Mobl.- 14.2; T.C.- 190; E.C.- 125; Lip. P.- 14.7; Alk. Phos.- 11.0; Th. T.- 1.3; Proth. Conc.- 50.0; Proth. Resp.- 55.3; Bil. Ret.- 12.7.

2.10.48. B.P. 140/80; Alb.- 3; Oedema ± ; Urea - 20.8; A.A.N.- 6.2; Sugar Mob,.- 18.3; T.C.- 182; E.C.- 123; Alk. Phos.- 11.0; Th. T.- 1.3; Proth. Conc.- 63.2; Proth. Resp.- 69.7; Bil. Ret.- 8.60.

12.10.48. B.P. 140/80; Alb.- ± ; Oedema - 0; Urea - 20.9; A.A.N.- 6.2; Sugar Mobl.- 20.2; T.C.- 180; E.C.- 121.5; Lip. P.- 9.9; Alk. Phos.- 8.8; Th. T.- 1.0; Proth. Conc.- 85.8; Proth. Resp.- 90.7; Bil. Ret.- 2.90.

Case No. 14; Mrs. Hughes; Primigravida; aet - 28;

Antepartum eclampsia; Fits - 8;

Pre-Convulsive Stage.

27.9.48. B.P. 150/105; Alb.- 6; Oedema +; Urea - 19.7; A.A.N.- 8.8; T.P.- 5.34; Alb.- 2.45; Glob.- 2.30; Fib.- 0.59; Sugar - 90.6; Sugar Mobl.- 16.5; T.C.- 271; E.C.- 171; Lip. P.- 15.9; Alk. Phos.- 18.6; Th. T.- 2.4; Proth. Conc.- 780; Proth. Resp.- 68.5; Bil. Ret.- 14.9.

4.10.48. B.P. 160/110; Alb.- 6; Oedema + ; Urea - 17.0; A.A.N.- 8.8; T.P.- 4.94; Alb.- 2.45; Glob.- 2.30; Fib.- 0.19; Sugar - 90.0; Sugar Mobl.- 16.0; T.C.- 301; E.C.- 167; Lip. P.- 17.5; Alk. Phos.- 20.2; Th. T.- 2.4; Proth. Conc.- 73.0; Proth. Resp.- 60.5; Bil. Ret.- 15.9.

Convulsive Stage.

5.10.48. B.P. 165/115; Alb.- 8; Oedema + ; Fits - 6; Coma + ; (Blood obtained 7 hours after the last convulsion). Urea/

Urea - 14.4; A.A.N.- 10.9; Sugar - 80.6; Sugar Mobl.- 3.5 T.C.- 254; Lip. P.- 10.0; E.C.- 114; Alk. Phos.- 26.0; Th. T.- 4.4; Proth. Conc.- 50.0; Proth. Resp.- 39.6; Bil. Ret.- 21.4.

6.10.48. B.P. 170/120; Alb.- 12; Oedema + ; Fits - 2; Coma + (Blood obtained 30 minutes after the last convulsion Urea - 47.0; A.A.N.- 205; Sugar - 80.0; Sugar Mobl.- 2.1; T.C.- 218; E.C.- 91; Lip.P.- 10.7; Lip. Phos.- 7.0; Alk. Phos.- 30.0; Th. T.- 5.7; Proth. Conc.- 30.0; Proth. Resp.- 17.0; Bil. Ret.- 26.6.

Post-Convulsive Stage.

7.10.48. B.P. 160/110; Alb.- 12; Oedema + ; Fits - 0; Coma + ; Urea - 40; A.A.N.- 18.6; Sugar - 80.0; Sugar Mobl.- 2.1; T.C.- 204; E.C.- 93; Lip. P.- 9.4; Alk. Phos.- 20.2; Th. T.- 5.0; Proth. Conc.- 41.6; Proth. Resp.- 27.7; Bil. Ret.- 19.6.

Case No. 15; Mrs. Ashcroft; Primigravida; aet - 30;

Intrapartum eclampsia; Fits - 2;

Convulsive Stage.

18.10.48. B.P. 170/110; Alb.- 8.5; Oedema ++ ; Fits - 2; Coma + ; (Blood obtained 1 hour after last convulsion). Urea - 15.7; A.A.N.- 11.2; Sugar - 85.8; Sugar mobl.- 8.0 T.C.- 288; E.C.- 149; Lip. P.- 13.8; Alk. Phos.- 23.0; Th. T.- 3.9; Proth. Conc.- 40.7; Proth. Resp.- 30.0; Bil. Ret.- 14.1.

Convalescence.

19.10.48. B.P. 150/100; Alb.- 7; Oedema + ; Fits - 0; Coma - 0; Urea - 23.3; A.A.N.- 10.0; Sugar Mobl.- 4.6; T.C.- 262; E.C.- 150; Lip. P.- 15.9; Alk. Phos.- 19.6; Th. T.- 3.6; Proth. Conc.- 42.0; Proth. Resp.- 27.0; Bil. Ret.- 14.0.

23.10.48. B.P. 140/86; Alb.- 3; Oedema ± ; Urea - 21.2; A.A.N.- 8.0; T.C.- 240; E.C.- 152; Alk. Phos.- 30.0; Th. T.- 5.7.

Case No. 16; Mrs. McLeod; Primigravida; aet - 30;
Antepartum eclampsia; 1 fit;
(Southern General Hospital; Blood obtained 3 hours after the convulsion).

1.2.49. B.P. 180/110; Alb.- 13; Oedema +++ ; Fit - 1; Coma + ;
Urea - 78.5; A.A.N.- 20.0; T.P.- 5.40; Alb.- 2.28; Glob.- 2.34; Fib.- 0.76; Sugar - 80.2; Sugar Mobl.- 9.21; T.C.- 277; E.C.- 141; Lip. P.- 20.7; Alk. Phos.- 23.6; Th. T.- 1.8; Proth. Conc.- 56.5; Proth. Resp.- 40.8; Bil. Ret.- 23.4.

4.2.49. B.P. 110/55; Alb.- 18; Oedema ++ ; Fits - 0; Coma +++:
Urea - 400.0; A.A.N.- 23.1; Sugar - 50.4; Sugar Mobl.- 10.0; T.C.- 124; E.C.- 21.5; Lip. P.- 13.4; Alk. Phos.- 39.7; Th. T.- 3.6; Proth. Conc.- 20.0; Proth. Resp.- 7.3; Bil. Ret.- 48.9.

Death from Anuria 16 hours after the blood sample was obtained.

Case No. 17; Mrs. Bryce; Primigravida; aet - 24;
Antepartum eclampsia; 3 fits.
(Bellshill Hospital; blood obtained 2 hours after last convulsion).

14.2.48. B.P. 240/150; Alb.- 14; Oedema - 0; Fits - 3; Coma + ;
Urea - 34.0; A.A.N.- 19.0; T.P.- 5.30; Alb.- 2.60; Glob.- 2.31; Fib.- 0.39; Sugar - 80.9; Sugar Mobl.- 7.8; T.C.- 247; E.C.- 126; Lip. P.- 12.0; Alk. Phos.- 23.6; Th. T.- 1.8; Proth. Conc.- 40.0; Proth. Resp.- 31.0; Bil. Ret.- 10.6.

Case/

Case No. 18; Mrs. Reid; Primigravida; aet - 29;
Antepartum eclampsia; 4 fits;
(Bellshill Hospital; Blood obtained
immediately after last convulsion).

21.2.49. B.P. 170/110; Alb.- 11; Oedema + ; Fits - 4;
Coma + ;
Urea - 32; A.A.N.- 11.0; T.P.- 5.01; Alb.- 2.50;
Glob.- 2.34; Fib. 0.17; T.C.- 279; E.C.- 138;
Lip. P.- 12.7; Alk. Phos.- 29.0; Th. T.- 2.7.

SPECIAL INVESTIGATIONS.

1. Cholesterol Feeding Experiments.

   Determination of esterification of Cholesterol.

2. Glucose - Insulin Experiments.

   Determination of Glycogen storage capacity.

3. Determination of Alkali-Reserve of the plasma.

4. Effects of Injection of Concentrated Human Plasma Protein in Toxaemia of Pregnancy.

CHOLESTEROL FEEDING EXPERIMENTS.

Each patient received 20 gm. of cholesterol suspended in 6 ounces of milk in empty stomach. Plasma cholesterol values immediately before the feed of cholesterol and 2 hours after are given below.

All results are expressed in mgms. per cent.

NORMAL PREGANCY.

(10 Cases).

No case with a B.P. above 130/80 m.m. Hg. was included in this series. No patient had albuminuria or oedema. All patients were between 32nd and 40th week of gestation.

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	Before			After		
	T.C.	E.C.	T.C/E.C.	T.C.	E.C.	T.C/E.C.
1.	230	160	1.49	318	222	1.48
2.	245	171	1.48	316	222	1.49
3.	212	145	1.46	300	202	1.48
4.	208	140.5	1.48	300	204	1.47
5.	207	139.8	1.48	306	206	1.49
6.	196	133	1.47	271	182	1.49
7.	218	146	1.49	302	202	1.49
8.	211	142	1.49	304	204	1.49
9.	234	157	1.49	313	213	1.47
10.	229	154	1.49	310	208	1.49

PRE-ECLAMPSIA

(15 Cases).

Serial No.	Name	Before			After		
		T.C.	E.C.	T.C/E.C.	T.C.	E.C.	T.C/E.C.
1.	Balfour	271	165	1.64	330	179	1.84
2.	Gibson	259	164	1.58	321	197	1.63
3.	Clark	263	154	1.71	339	170	1.99
4.	Gilliland	255	171	1.49	318	199	1.60
5.	Crammond	284	172	1.60	369	207	1.78
6.	Heron	260	172	1.51	342	208	1.64
7.	Currie	249	163	1.53	320	197	1.68
8.	Dunnipace	294	156	1.89	390	179	2.18
9.	Millar	248	149	1.66	331	166	1.99
10.	Paul	253	149	1.70	344	177	1.94
11.	Lochore	265	184	1.49	350	230	1.52
12.	Murray	259	162	1.60	336	191	1.76
13.	Wilkie	249	161	1.54	330	195	1.69
14.	Buchan	275	159	1.73	357	176	2.03
15.	Ferguson	290	156	1.86	378	172	2.20

DETERMINATION OF GLYCOGEN STORAGE

Preparation. High Carbohydrate diet on the day previous to the test. Glucose 10 gms. at bed-time in orange juice and water. Breakfast: Sweet tea, toast and jam. Test performed two hours after breakfast. Rest in bed for at least 24 hours before the test. Basal blood pressure reading: B.P. taken every minute until it is steady. Venepuncture done and blood collected for estimation of basal blood sugar (Fluoride tube). 10 ml. 50% glucose with 3 units insulin given I.V. without removing the needle. Blood from opposite antecubital vein collected 5 minutes and 20 minutes after injection. Bladder emptied before the test and again 30 minutes after injection. No patient with glycosuria included in this series.

All results are expressed in mgms. per 100 ml. blood.

NORMAL PREGNANCY.

	Name	Date	Condition of Pt.	Basal Sugar	5 min.	20 min.	Glucose storage differ-ence.
1.	Phillips	3.7.48	38/52; Pyelitis	70.4	129	64	65
2.	Moore	6.7.48	39/52; Breech	92.0	170	109	61
3.	Campbell	23.7.48	38/52; "	103.0	195	146	49
4.	Finne	19.7.48	40/52; C.P.	86.5	124	62	62
5.	Laird	1.8.48	40/52; "	90.0	154	132	22
6.	Patterson	10.8.48	42/52; Post.Mat.	94.0	152	106	46
7.	Thomson	14.8.48	36/52; Rh -	80.0	175	134	41
8.	Darrow	20.8.48	32/52; C.P.	72.6	126	74	52
9.	Trueman	22.8.48	34/52; "	65.0	102	47	55
10.	Cunningham	22.8.48	36/52; Pyelitis	62.0	108	52.5	55.5
11.	McGowan	22.8.48	32/52; C.P.	90.6	142	75	67
12.	Queen	26.8.48	34/52; Breech	90.0	118.4	74	44.4
13.	Harkins	26.8.48	36/52; C.P.	101.0	175	132.8	42.2
14.	Cunningham	29.8.48	40/52; -	92.5	168	140	28
15.	Stevenson	30.8.48	38/52; C.P.	80.0	119	81	38
16.	Nelson	1.9.48	36/52; "	80.5	140	94	46

Average glucose storage - 48.3; S.D. 14.19

PRE-ECLAMPSIA.

(25 Cases).

Name	Date	B.P.	Alb.	oedema	5 min.	20 min.	Glucose storage (difference)
1. McDougal	1. 9.48	170/110	9	+++	142.8	132.0	10.8
2. Fraser	3. 9.48	178/110	10	+++	150.7	143.0	7.7
3. Currie	10. 9.48	160/110	5	++	161.0	145.5	15.5
4. McAlpine	25. 9.48	160/105	5	++	106.7	89.0	17.7
5. Thomson	28. 9.48	168/110	7.5	++	139.5	121.1	18.4
6. McGregor	2.10.48	180/115	11	+++	109.9	98.2	11.7
7. Lefferty	5.10.48	160/100	4	+++	196.0	184.4	11.6
8. Smith	7.10.48	190/115	11	++	118.5	102.2	16.3
9. Crawford	7.10.48	160/100	3	+	129.7	109.1	20.8
10. Gallagher	7.10.48	150/100	5	+++	148.5	137.7	10.8
11. McNaughton	12.10.48	150/100	5	+	136.0	116.4	19.6
12. McMichael	10.10.48	170/110	8	+++	170.0	163.2	6.8
13. McLenan	14.10.48	160/95	7	+++	115.0	104.3	10.7
14. McWhinne	18.10.48	200/120	10	+++	160.0	157.2	2.8
15. Ozanne	22.10.48	165/105	9	+++	140.0	128.9	11.1
16. Dillon	22.10.48	170/110	4	++	139.0	126.0	13.0
17. Pritchard	26.10.48	170/115	6	++	187.0	173.9	13.1
18. Owans	29.10.48	160/100	4	+	140.4	124.9	15.5
19. Thompson	9.11.48	175/105	6	++	141.8	127.4	14.4
20. George	16.11.48	180/115	11	+++	160.0	155.5	4.5
21. Dunnipace	19.11.48	170/115	10	++	126.0	115.6	10.4
22. Murray	29.11.48	160/115	8	+++	170.0	160.3	9.7
23. Reilly	2.12.48	170/110	5	+++	150.5	136.6	13.9
24. Wilkie	21. 1.49	160/105	6	+++	138.3	130.0	8.3
25. Fairweather	16. 1.49	150/100	4	++	157.1	147.0	10.1

ECLAMPSIA

(3 Cases).

Name.	Oedema.	5 min.	20 min.	Glucose storage (Difference)
1. Aird		140.5	132.0	8.5
2. Hughes	6 fits	137.0	129.7	7.3
3. Ashcroft	2 fits	184.7	177.9	6.8

ALKALI RESERVE OF PLASMA

(All values are expressed as ml. of CO_2 per 100 ml. of plasma).

1. NORMAL PREGNANCY (14 Cases).

Name	1. Sharp	2. Donnelly	3. Reid	4. Gillan	5. Ross
Date	2.1.49	3.1.49	5.1.49	5.1.49	6.1.49
Total CO_2	51.98	50.35	51.2	52.2	49,8
B. HCO_3	49.5	48.0	48.8	49.7	47.2
H. HCO_3	2.48	2.35	2.40	2.50	2.36
$\frac{B}{H}$ CO_2	20.1	20.4	20.3	19.8	20.0

Name	6. Scott	7. Smith	8. Gallacher	9. McAvoy	10. Doherty
Date	7.1.49	8.1.49	9.1.49	9.1.49	10.1.49
Total CO_2	50.3	50.4	51.45	52.7	52.28
B. HCO_3	47.5	48.0	49.0	50.2	49.8
H. HCO_3	2.80	2.40	2.45	2.50	2.48
$\frac{B}{H}$ CO_2	19.9	20.0	20.0	20.0	20.1

Name	11. Richards	12. Kerr	13. Ashe	14. Curran
Date	10.1.49	9.1.49	8.1.49	6.1.49
Total CO_2	55.3	53.35	52.10	52.5
B. HCO_3	52.7	50.8	49.7	50.0
H. HCO_3	2.60	2.55	2.40	2.50
$\frac{B}{H}$ CO_2	20.3	19.9	20.4	20.0

ALKALI RESERVE OF PLASMA

2. TOXAEMIAS

(a) Mild Pre-eclampsia (15 Cases).

Name	1. Sayers	2. Clark	3. Marshall	4. Bremner	5. Thompson
Date	13.9.48	15.9.48	15.9.48	15.9.48	18.9.48
B.P.	150/100	150/100	150/100	150/100	150/100
Alb.	5	3	5	3	6
Oedema	++	+	+++	++	++
Total CO_2	48.9	53.8	46.4	49.1	51.4
B.HCO_3	46.6	51.1	44.0	46.8	49.0
H.HCO_3	2.3	2.7	2.4	2.3	2.4
$\frac{B}{H}$ CO_2	20.0	19.7	19.6	20.3	20.4

Name	6. Miller	7. Pattison	8. Graham	9. Grant	10. McNaughton
Date	5.10.48	1.10.48	8.10.48	11.10.48	12.10.48
B.P.	155/98	150/90	148/98	150/100	150/100
Alb.	7	4	3	4	5
Oedema	+++	++	++	++	+
Total CO_2	44.3	51.9	51.1	50.0	50.3
B.HCO_3	42.2	49.5	48.7	47.6	47.9
H.HCO_3	2.1	2.4	2.4	2.4	2.4
$\frac{B}{H}$ CO_2	19.8	20.6	20.2	20.0	19.9

Name	11. McGough	12. McCrea	13. Paul	14. Heron	15. Costello
Date	20.10.48	13.11.48	25.10.48	17.11.48	12.1.49
B.P.	150/95	150/100	150/95	150/100	150/100
Alb.	2	4	3	2	3
Oedema	+	++	++	+	+
Total CO_2	50.0	50.95	48.95	50.4	51.95
B.HCO_3	47.7	48.5	46.6	48.0	49.5
H.HCO_3	2.3	2.45	2.35	2.4	2.45
$\frac{B}{H}$ CO_2	20.7	19.8	19.8	19.9	19.8

(b) Severe Pre-eclampsia (15 Cases)

Name	1.McDougal	2.Currie	3.Fraser	4.McGregor	5.Lefferty
Date	1.9.48	10.9.48	3.9.48	2.10.48	5.10.48
B.P.	170/110	160/110	178/110	180/115	160/100
Alb.	9	5	10	11	4
Oedema	+++	++	+++	+++	+++
Total CO_2	46.7	49.8	46.0	47.2	46.4
B.HCO_3	44.5	47.4	43.8	45.0	44.2
H.HCO_3	2.2	2.4	2.2	2.2	2.2
$\frac{B}{H}$ CO_2	20.2	19.7	19.9	20.2	20.0

Name	6.Inglis	7.McAulay	8.McMichael	9.McLenan	10.Owans
Date	27.9.48	23.9.48	10.10.48	14.10.48	29.10.48
B.P.	160/115	170/115	170/110	160/95	160/100
Alb.	7	9	8	7	4
Oedema	++	+++	+++	+++	+
Total CO_2	50.9	44.2	46.55	46.75	50.8
B.HCO_3	48.5	42.1	44.3	44.5	48.4
H.HCO_3	2.4	2.10	2.25	2.25	2.4
$\frac{B}{H}$ CO_2	20.2	20.0	19.7	19.8	20.1

Name	11.Thompson	12.George	13.Muldoon	14.Crudrod	15.Sinclair
Date	9.11.48	16.11.48	1.12.48	1.12.48	24.2.49
B.P.	175/105	180/115	160/105	170/105	170/115
Alb.	6	11	3	5	4
Oedema	++	+++	++	++	++
Total CO_2	46.2	46.1	49.0	46.3	44.8
B.HCO_3	44.0	43.9	46.7	44.1	42.7
H.HCO_3	2.2	2.2	2.3	2.25	2.10
$\frac{B}{H}$ CO_2	20.0	19.9	20.3	19.6	20.2

(c) Eclampsia (10 Cases).

Name	1.Henderson		2.Aird	3.Hughes	4.Ashcroft
Date	9.9.48	10.9.48	22.9.48	5.10.48	18.10.48
Fits	16	18	1	6	2
Coma	+++	++++ 16 hrs. before death.	±	++	+
Total CO_2	20.8	14.2	40.8	30.2	38.6
B.HCO_3	17.4	11.1	38.4	28.0	36.3
H.HCO_3	2.6	3.1	2.4	2.2	2.3
$\frac{B}{H}$ CO_2	6.7	3.6	18.8	12.7	15.8

Name	5.McLeod	6.Morton	7.McAdam	8.Crawford	
Date	1.2.49	7.1.49	17.3.49	29.3.49	30.3.49
Fits	1	3	2	4	-
Coma	+++	++	+	++	+++
Total CO_2	30.7	37.0	38.0	37.8	30.0
B.HCO_3	28.9	34.65	35.8	35.6	27.9
H.HCO_3	1.8	2.35	2.2	2.2	2.1
$\frac{B}{H}$ CO_2	16.1	14.7	17.7	16.2	13.3

Name	9.Pardee		10.Ferguson	
Date	24.4.49	24.4.49 (5 hrs. later)	28.4.49	28.4.49 (3 hrs. later)
Fits	1	3	2	-
Coma	±	++	+	++
Total CO_2	43.0	34.2	40.1	36.6
B.HCO_3	40.8	32.1	37.7	34.4
H.HCO_3	2.2	2.1	2.4	2.2
$\frac{B}{H}$ CO_2	18.6	15.3	15.7	14.9

Numbers indicate the number of fits preceding the collection of blood.

Not included for the average.

EFFECTS OF INTRAVENOUS INJECTIONS OF CONCENTRATED HUMAN PLASMA PROTEIN IN TOXAEMIA OF PREGNANCY.

Each patient received a single concentrated plasma infusion.

1.	Clark	Plasma Protein	26.8 g.	in	200 ml.
2.	McAlpine	"	24.1 g.	"	180 ml.
3.	Thompson	"	30.9 g.	"	270 ml.
4.	McGregor	"	25.0 g.	"	195 ml.
5.	Clark	"	29.0 g.	"	220 ml.
6.	Smith	"	27.3 g.	"	200 ml.
7.	McWhinne	"	26.2 g.	"	195 ml.
8.	Donelly	"	28.7 g.	"	200 ml.
9.	Murray	"	26.0 g.	"	210 ml.

EFFECTS OF INJECTIONS OF CONCENTRATED PLASMA PROTEIN

1. Mrs. Clark, Pre-eclampsia, Primigravida, 37 weeks. 19.9.48 (Adm.15.9.48)

Days	0	1	2	3	4	5	6	7
Total Prot	5.30	6.0	5.57	5.46	5.38	5.35	5.30	5.26
Alb. Glob.	1.10	1.29	1.29	1.21	1.16	1.14	1.11	1.07
Fib.	0.49	0.46	0.31	0.39	0.45	0.47	0.47	0.49
Urea	18.0	18.6	14.8	23.5	22.6	20.5	18.5	16.7
A.A.N.	8.9	9.1	9.4	11.7	13.8	15.5	18.1	20.6
Oedema	+++	+++	++	±	±	+	+	++
Alb. (Esb.)	13	13	7	8	8	9	11	11
B.P.	170/105	160/105	165/105	170/105	175/105	175/110	175/110	180/110
Urine Vol.	790	850	1260	1005	935	970	800	745
Blood Vol.	35.0	34.6	58.0	50.0	47.0	40.0	38.0	34.5

2. Mrs. McAlpine, Pre-eclampsia, Primigravida, 36 weeks. 29.9.48 (Adm.25.9.48)

Days	0	1	2	3	4	5	6	7
Total Prot.	5.19	5.97	5.48	5.41	5.32	5.20	5.20	5.10
Alb. Glob.	1.05	1.29	1.26	1.28	1.13	1.10	1.06	1.06
Fib.	0.46	0.45	0.30	0.34	0.38	0.39	0.42	0.44
Urea	17.6	18.3	14.4	21.5	21.9	18.6	16.2	16.0
A.A.N.	9.5	9.5	9.8	10.9	14.5	15.8	18.6	19.3
Oedema	+++	+++	++	±	0	±	±	+
Alb.(Esb.)	12.5	12.5	11	9	7	9	12	14
B.P.	165/110	165/110	165/105	165/105	150/110	150/112	155/110	160/110
Urine Vol.	695	820	960	900	840	725	700	690
Blood Vol.	41.0	39.5	57.4	50.5	50.4	42.2	40.0	39.0

3. Mrs. Thompson, Pre-eclampsia, Primigravida, 34 weeks. 2.10.48 (Adm. 28.9.48).

Days	0	1	2	3	4	5	6	7
Total Prot.	5.27	6.21	5.59	5.50	5.41	5.37	5.30	5.30
Alb. Glob.	1.01	1.31	1.30	1.24	1.16	1.15	1.09	1.10
Fib.	0.66	0.48	0.36	0.44	0.48	0.48	0.54	0.40
Urea	20.0	19.2	17.6	22.6	18.5	16.0	16.2	16.0
A.A.N.	8.8	8.9	9.0	10.7	12.0	13.6	18.9	19.9
Oedema	+++	+++	+	0	0	0	±	+
Alb. (Esb.)	12	12	11	9	9	9	9	9
B.P.	160/108	150/100	150/100	150/105	155/105	160/105	160/110	160/110
Urine Vol.	680	670	940	925	880	770	700	700
Blood Vol.	39.5	40.2	59.6	55.5	50.4	48.6	40.0	36.5

4. Mrs. McGregor, Pre-eclampsia, Primigravida, 37 weeks. 4.10.48 (Adm. 2.10.48)

Days	0	1	2	3	4	5	6	7
Total Prot.	5.09	5.99	5.45	5.39	5.30	5.19	5.06	4.97
Alb. Glob.	1.02	1.29	1.29	1.21	1.15	1.08	1.02	0.98
Fib.	0.45	0.41	0.30	0.36	0.40	0.43	0.43	0.43
Urea	19.5	19.5	16.8	22.8	20.4	20.0	18.2	17.8
A.A.N.	8.5	8.4	8.0	10.6	12.8	14.6	18.2	18.4
Oedema	+++	+++	+	0	0	+	++	++
Alb. (Esb.)	11.5	12.0	11.0	10.0	10.0	10.0	13.0	13.0
B.P.	170/100	170/100	175/108	172/105	170/105	170/105	170/110	170/110
Urine Vol.	780	750	960	870	800	740	740	740
Blood Vol.	37.5	36.4	55.0	55.0	50.0	46.2	40.1	35.4

5. Mrs. Clark, Pre-eclampsia, Primigravida, 35 weeks. 7.10.48 (Adm. 4.10.48).

Days	0	1	2	3	4	5	6	7
Total Prot.	5.26	6.12	5.74	5.60	5.48	5.39	5.25	5.00
Alb. Glob.	1.04	1.26	1.27	1.23	1.17	1.14	1.13	0.96
Fib.	0.50	0.54	0.36	0.40	0.48	0.46	0.46	0.49
Urea	20.2	20.5	18.5	24.4	20.0	18.8	18.2	17.5
A.A.N.	7.9	8.1	8.3	11.0	13.2	14.6	15.8	18.9
Oedema	+++	+++	++	±	0	±	+	++
Alb.(Esb.)	11	11	11	9	8.5	9	9	10
B.P.	150/105	150/105	150/100	150/100	160/105	160/105	155/105	160/110
Urine Vol.	540	580	885	898	850	800	800	600
Blood Vol.	36.5	36.8	54.1	54.0	50.2	48.4	40.5	35.3

6. Mrs. Smith, Pre-eclampsia, Primigravida, 36 weeks. 10.10.48 (Adm. 7.10.48).

Days	0	1	2	3	4	5	6	7
Total Prot.	5.18	5.99	5.68	5.59	5.50	5.40	5.31	5.24
Alb. Glob.	1.03	1.28	1.28	1.25	1.20	1.16	1.12	1.08
Fib.	0.48	0.44	0.30	0.34	0.39	0.40	0.40	0.40
Urea	19.7	20.0	17.5	23.8	20.0	18.1	17.0	15.9
A.A.N.	7.9	8.3	8.3	11.8	14.6	14.8	18.5	19.2
Oedema	+++	+++	+	±	0	±	±	+
Alb.(Esb.)	10.5	11	11	10	9.5	9	9	9
B.P.	160/100	160/100	155/100	155/100	160/105	165/105	155/105	155/110
Urine Vol	620	635	848	850	800	742	695	650
Blood Vol.	35.6	36.0	49.0	49.2	40.0	38.2	35.0	34.4

7. Mrs. McWhinne, Primigravida,

Days	0	1	2	3	4	5	6	7
Total Prot.	5.32	6.18	5.76	5.62	5.50	5.44	5.35	5.28
Alb. Glob.	1.08	1.28	1.27	1.21	1.16	1.14	1.10	1.07
Fib.	0.47	0.48	0.40	0.44	0.46	0.49	0.50	0.50
Urea	18.8	19.0	17.0	23.5	20.0	17.4	16.2	15.8
A.A.N.	8.1	8.4	8.0	9.9	12.4	13.8	14.2	15.6
Oedema	+++	+++	+	0	0	0	+	+
B.P.	160/100	160/100	150/105	160/100	160/108	160/110	160/110	158/110
Alb. (Esb.)	12	11	11	8.5	9.5	10	10	11
Urine Vol.	610	660	900	890	820	750	710	645
Blood Vol.								

Case No. 8. Mrs. Donelly. Pre-eclampsia. 19. 7. 48.

Adm. 16.7.48.

Details presented in the body of the thesis,

Part 1, Page 135.

9. Mrs. Murray, Pre-eclampsia, Second gravida, 34 weeks. 2.12.48 (Adm. 29.11.48)
Plasma protein injected, 25.15 gms.

Days	0	1	2	3	4	5	6	7
Total Prot.	5.30	6.14	5.85	5.62	5.51	5.40	5.34	5.26
Alb. Glob.	1.08	1.27	1.30	1.21	1.17	1.14	1.11	1.08
Fib.	0.46	0.39	0.46	0.46	0.46	0.46	0.46	0.46
Urea	19.0	19.0	17.0	21.5	19.2	18.4	17.0	16.2
A.A.N.	8.9	8.8	9.0	12.0	13.9	15.2	16.8	17.5
Oedema	+++	+++	+	0	0	+	+	+
Alb.(Esb.)	12.5	12.0	11.0	11.5	10.5	11.0	11.0	11.0
B.P.	150/110	150/110	150/105	155/105	155/110	160/110	158/110	160/110
Urine Vol.	780	810	1,005	992	900	840	780	780
Blood Vol.	33.3	33.9	49.7	50.5	47.2	40.1	36.6	32.6

The results of plasma proteins are given in gms. per cent., Urea and A.A.N. in mg. per cent., Albuminuria in gms. per litre of Urine, Urine Volume in ml. per 24 hours and Blood Volume (plasma volume) in ml. per Kg. of body-weight.