A STUDY OF THE SERUM PROTEINS IN NORMAL AND TOXEMIC PREGNANCY

by

ROBERT E. RINEHART

A THESIS

Presented to the department of Biochemistry
and the Graduate Division of the University of Oregon Medical School
in partial fulfillment
of the requirements for the degree of
Master of Science

June 1942

APPROVED:

[redacted]

(Professor in Charge of Thesis)

[redacted]

(For the Committee)

PREFACE

This study was undertaken an attempt to satisfy a personal curiosity regarding the condition occasionally occurring during the latter part of pregnancy that is characterized by edema, hypertension, albuminuria, and sometimes coma and convulsions. Since the formation of edema has been ascribed to three fundamental mechanisms, each relatively easy to distinguish from the others, the serum proteins during pregnancy were selected for thorough investigation. Soon after the study was begun it became apparent that an at least superficial knowledge of the alterations in metabolism and physiology occurring during pregnancy, and their relation to experimentally induced changes in the functions of various organs, would be necessary in order to properly evaluate the findings. The information mentioned has not been collectively reviewed since Stander published his article on "The Toxemias of Pregnancy" in 1929, and for this reason the introduction to this paper contains sections covering the present day status of the toxemias of pregnancy and the pathology in normal and toxemic pregnancy. Since some readers of this article may be unfamiliar with recent progress in the field of protein metabolism another section of the introduction is devoted to a resumé of this topic. It is our hope that this review and work may be another step toward an understanding of the obscure syndrome that first aroused

our curiosity.

We wish to express our appreciation to the entire staff of the Department of Obstetrics and Gynecology, and in particular to Drs. Ronald Nielsen, Duncan Nielsen, James Whitely and Clifford Pearl, and Miss Johanna Eggers, for their generous cooperation in the clinical phase of this work. Without the criticism and encouragement of Dr. Edward S. West the laboratory studies could not have been completed. We are indebted to Mr. James Riley for several of the serum protein determinations, and to Miss Evelyn Packham for help in preparing the charts.

R.E.H.
Portland
April 2nd, 1942

INDEX

I. Introduction

A. Resumé of known facts concerning protein metabolism.

1. Sources of body protein.

It has been well known for many years that the protein needs of the body are derived primarily from ingested foodstuffs. It has been believed, but until recently not proven, that of these materials animal proteins are more efficacious than vegetable in supplying the needs of the organism. The work of Madden and co-workers ('40-'41), and Veech and Goettsch ('35'-'37-'38-'39), summarized by Madden and Whipple ('40), demonstrates that this is only relatively true if the rate of formation of plasma protein is used as a measure of the potency of the protein fed. These workers find that while the animal proteins, especially serum, can usually form new plasma proteins at a higher rate than vegetable proteins, there are exceptions.

Pommerenke and co-workers ('35), and Veech and Goettsch ('38-'39), have recently found that in dogs adequate food protein has a qualitative as well as a quantitative significance. Their experiments show that beef serum protein has three times the potency of beef heart, and five times that of beef stomach, in the regeneration of depleted plasma proteins.

Madden and co-workers ('41) have shown that when blood plasma proteins are depleted by plasmapheresis, "pure" proteins alone in the diet are ineffectual in replenishing the plasma proteins. When these

pure proteins are supplemented by certain amino acids they become relatively potent in protein formation. For instance, gelatin alone added to the basal liver diet causes very little if any extra plasma protein production. The addition to gelatin of cystine, or tyrosine, or tryptophane, or of both tyrosine and tryptophane has little or no effect on its potency for plasma protein formation. When gelatin is supplemented by cystine and either tryptophane or tyrosine, 25 to 40 per cent of the protein content of the combination is converted into plasma protein. This is an efficiency equivalent to the best of any of the natural proteins so far tested. Some of their preliminary work indicates that methionine cannot substitute for cystine nor can phenylalanine substitute for tyrosine in the efficient combination of gelatin plus cystine plus tyrosine.

Until the work of Rammerenko, mentioned above, evidence pointing to the fact that some food proteins favored specifically albumin or globulin production, was inconclusive. Using the method of plasmapheresis these workers have demonstrated that globulin formation is directly dependent on the diet. Quoting Madden's ('40) review of the work, " ---the same 100 grams of beef serum which produced 38 grams of total plasma protein, produced approximately 21 grams of albumin and 17 grams of globulin. The addition of 100 grams of bran flakes to a kidney basal diet results in the formation of about 12 grams of albumin and 11 grams of globulin. Since it has been shown that 100 grams of casein will yield only 5 grams or less of each, it becomes apparent that as measured by plasmapheresis diet regulates

globulin production equally as well as albumin formation."

It has long been known that there is an "endogenous" supply of protein whose existence is not apparent until the organism is placed on a diet restricted in protein or its protein reserves otherwise depleted. This supply has been demonstrated and its quantity estimated by the workers mentioned above, using two different approaches. One is by repeatedly bleeding the animal, separating the cells and plasma, and reinjecting the cells suspended in saline or Ringer-Locke solution. By this means, (known as plasmapheresis) it is possible to estimate the amount of protein which has to be removed to keep the plasma proteins at a constant level while the animal is on a basal diet. The other method is to place the animal on a diet deficient in protein until its plasma proteins have reached a basal level. Then the amount of dietary protein necessary to restore the plasma proteins to normal can be ascertained. The nature of this endogenous or reserve supply of protein is not fully known. It appears to be quite variable in amount, depending on the previous nutritional state of the animal. Meager data supplied by Borsook and Keighley ('35) indicate that the nitrogenous metabolites are stored as protein. Madden and Whipple conclude in their review that body protein is in equilibrium with plasma protein and vice versa. That this is not strictly true, and that the protein reserve of the body is separate and distinct from what we ordinarily think of as body protein, is proved by the fact that both they and other workers have been able to maintain animals in a state of hypoproteinemia on a basal low protein diets. If the proteins of the tissues could be converted to plasma protein surely the stimulus in these animals would be

sufficient to bring about this change. The concept that there is somewhere in the body, probably principally in the liver, a reserve store of potential protein-forming material, is more in keeping with the experimental evidence. This material may be of the nature of amino acids, polypeptides, or perhaps a hitherto undescribed form of protein, and it is this reserve which is depleted during the initial periods of plasmapheresis.

Of great interest both experimentally and therapeutically has been the demonstration by Madden and co-workers ('40) that a fasting dog can be indefinitely maintained in nitrogen equilibrium by the administration of plasma protein intravenously. This indicates that some body proteins are in a state of flux, with the plasma proteins playing much the same role as does the blood glucose in carbohydrate metabolism. It also demonstrates the rationale of plasma transfusion in primary and some types of secondary protein deficiency.

Madden and co-workers ('41) gave a casein digest by vein and subcutaneously to dogs that had had their plasma proteins diminished by plasmapheresis and found it to be effective in promoting abundant new plasma protein production. The ratio of new plasma protein production to protein intake was 20 to 25 per cent by both routes of administration. They found that this casein digest also gave the same response in plasma protein output when given by vein as when given by mouth. Another digest, obtained from a different source, required the addition of tryptophane and cysteine to be effective in plasma protein production. When these digests were given to normal dogs they were not utilized as

well as in dogs depleted of plasma protein.

2. Protein digestion and absorption.

This subject is well treated in many text books of biochemistry at present available and will not be discussed at length here. Suffice it to say that the ingested animal and vegetable proteins are broken down in the stomach and intestine into their constituent amino acids and absorbed as such. There is much speculation about the possibility of absorption of incompletely split proteins with accompanying allergic phenomena. This topic is of great importance to the field of allergy but is not well enough understood to discuss at this time.

3. Intermediate protein metabolism.

The amino acids absorbed into the blood stream from the intestinal mucosa are apparently transported directly or indirectly to the liver where most of the plasma protein synthesis takes place. This concept is well substantiated by experimental as well as clinical evidence. The work of Kerr and co-workers ('18), Emutti and co-workers ('37), Chemutin and co-workers ('38), and many others demonstrates that impairment of liver function, either by an Eck fistula, partial hepatectomy, or by injury with chloroform, phosphorous or other poison, results in lowering of the plasma proteins and impairment of protein metabolism. From this work it has been definitely proven that the liver is the sole site of albumin formation, and contributes at least a portion

of the globulin to the blood. Warner, Brinkhaus and Smith ('36) have proven that injury to the liver either by partial hepatectomy or by chloroform poisoning results in a marked decrease in the plasma prothrombin, an important constituent of the globulin fraction. This last phenomena, however, may be associated with faulty absorption of vitamin K rather than with impaired liver function.

We know very little concerning the actual processes concerned in linking one amino acid to another to form the huge protein molecule. We do know, however, that one of the important steps in the metabolism of these amino acids, the process of deamination and urea formation, takes place almost exclusively in the liver. The mechanism of this reaction has been worked out in detail by Krebs and Henseleit ('32), and by Krebs ('33). The experimental evidence to show that this process is confined to the liver has been excellently reviewed by Bollman and co-workers ('24).

Schoenheimer's work, discussed by Harrow ('40), using the nitrogen isotope N^{15} is of great interest. He finds that rats, fed isotopic ammonium citrate, utilized this nitrogen in the formation of glycine, glutamic acid, aspartic acid, proline, histidine, arginine and creatine, but not in the formation of lysine. In another experiment isotopic di-tyrosine was added to the diet. About one-half the isotope was retained in the tissues, nearly all of this in the tissue proteins. The above compounds were isolated from hydrolytic products of the liver and carcass and all contained N^{15} in quantities above the usual amount, again with the notable exception of lysine. In the case of arginine and histidine, dibasic amino acids, the isotopic N was found to be

present only in the alpha amino group. This work beautifully demonstrates the lability and exchangeability of the amino groups of various amino acids and creatine. This phenomenon is referred to as transamination.

The function of urea in acid-base equilibrium, the role of creatine and creatinine in muscle metabolism, and the functions of the purines are subjects too broad in themselves to be discussed in this paper.

4. Elimination of nitrogenous end-products.

Suffice it to say at this time, the principal end-product of protein metabolism is urea, and it is excreted in the urine where it is both an excretory waste and a substance intimately concerned with the preservation of fixed base. The remainder of the substances formed and excreted consist primarily of ammonia, creatine, creatinine, and uric acid. A discussion of their functions and excretion has no place here.

5. Factors influencing the level of the serum proteins.

It is evident from the above discussion that the proteins of the blood are in dynamic equilibrium with some tissue proteins on one hand and the protein constantly being synthesized in the liver on the other. As one would expect, any factor which affects the ingestion, digestion, absorption or synthesis of the building materials is bound to be reflected in the serum protein level. The studies of Peters and

Eisenman ('33), Veech ('35-'36-'37), and Dodd and Minot ('36), not to mention many others have shown that undernutrition from any cause will result in lowered values for serum proteins.

Cantarow ('38), Miller and Whipple ('40), Foley and co-workers ('40), Thompson, McQuarrie and Bell ('36), and Bollman ('35-'38), have shown that liver damage per se will cause a lowering of the serum proteins. Wiener and Wiener ('30) have followed the course of the serum protein levels in patients with liver disease and have found it of excellent prognostic value, as have Post and Patek ('42). Elman and Seifetz ('41) have studied the effect of experimental hypoalbuminemia on the morphology, function, and protein and water content of the liver. They found a fall of from 3.75 to 2.00 grams per cent in the plasma albumin of adult dogs maintained for 6 weeks upon a carrot protein deficient diet. Parallel microscopic changes in the liver were observed which consisted of a gradual loss in the stainable cytoplasm producing extensive vacuolization. This vacuolization was not due to the accumulation of fat or of glycogen, as shown by chemical analysis and stained sections of the livers. They found a fall in the protein content of the liver paralleling that of the plasma albumin, and assumed the histological changes in the livers to be due to loss of protein. This assumption was partly on the basis of an observed increase in the water content of the livers. They followed the liver function of these dogs by determining their ability to excrete iso-iodeikon and found that it fell with the fall of serum albumin.

In shock, both surgical and traumatic, a decrease in the plasma protein level is characteristic, apparently due in this instance to a leakage of protein through the damaged capillary membrane.

6. Functions of the serum proteins.

Authorities are unanimous in crediting Starling (1896) with recognition of the significance of the osmotic pressure of the serum proteins as a controlling factor in the distribution of fluid between plasma and tissue. A delicate balance normally exists between the hydrostatic formed due to blood pressure on one hand and the effective osmotic pressure of blood (due to plasma proteins) on the other, in their control of the flow of fluid through the capillary wall. The excellent reviews of this subject by Landis ('37) and Hend ('34) are well worth reading by anyone interested in the problem of fluid balance. It has been demonstrated by many experimenters that the osmotic pressure of the serum is related to its protein content. The exactitude of this relationship is in dispute because of the inherent difficulties in the measurement of the osmotic pressure of so complex a solution as serum. The reader is referred to the works of Krogh ('32), Govaerts ('28), and Schade and Claussen ('24) for a discussion of this relationship. One outstanding feature on which almost all agree is that the osmotic pressure of albumin per unit of weight is almost four times that of globulin, although the difference in their molecular weights is much smaller. Hend, in his review, has averaged the normal serum protein values obtained by several investigators. He gives the normal values

in grams per hundred cubic centimeters as follows: Total protein, from 6.2 to 8; albumin, from 3.6 to 5; globulin, from 2 to 3.5; albumin globulin quotient, from 1.2 to 2.2. Peters and his associates ('26) found that when the serum protein level, by reason of a deficit of albumin, fell below 5 grams per hundred cubic centimeters, edema was usually present. When the protein level was between 4 and 5 grams the edema could usually be eliminated by therapeutic measures, but when it fell below 4 grams, treatment was usually ineffectual. In a study of 75 cases of various types of nephritis, hemorrhagic, degenerative and arteriosclerotic, Moore and Van Slyke ('30) found that when the total protein content fell below 5.5 grams, or the albumin below 2.5 grams, or the specific gravity below 1.023, edema was usually present. While albumin seems to function chiefly in the maintainance of plasma osmotic pressure, globulin has had several additional functions attributed to it. Among these the production of specific antibodies and the provision of prothrombin to aid in the coagulation of blood arewell known. As our methods of analysis for plasma proteins have improved, specific functions have been attributed more and more to certain fractions. This will be discussed further under analytical methods.

7. Diseases characterized by a deficiency of serum proteins.

Until recently the "loss and lack" theory adequately explained the etiology and manifestations of all of the conditions that will be discussed. This was a simple and rational explanation of these phenomena, but based on insufficient evidence and overabundant speculation.

It maintained that all diseases accompanied by a deficiency in serum protein were due either to insufficient ingestion, or absorption, or to excessive loss in the urine or transudates. For the sake of clarity these conditions will be listed prior to discussion. They consist of deficiencies in: (1) Protein intake; (2) Protein digestion, (3) Absorption of protein digestion products, and (4) Protein synthesis in the body. It will be noted that the "loss" portion of the theory is not mentioned in this classification. It is the opinion of the writer that further evidence of plasma protein depletion by loss, other than through plasmapheresis, will have to be supplied before it can be judged more than a minor factor. The arguments for and against the "loss and lack" theory of protein deficiency have been well summarized by Bloomfield (33). Simply because there is a considerable loss of protein in the urine of the various forms of Bright's disease, and the amount of protein lost in an effusion such as ascitic fluid may at times be quite large, does not explain the changes in quality and quantity of serum proteins in these conditions. In the plasmapheresis experiments referred to above much larger quantities of protein are removed than are ever lost in these clinical states, and as long as the animals are maintained in a proper state of nutrition, at times even when they are undernourished, they show a surprising ability to regenerate their serum protein. The explanation is not yet clear, but probably lies in the disturbances of intermediary protein metabolism found in these conditions. More will be said of this later.

The most extensive work on deficiencies in protein intake, both clinical and experimental, has been done by Veech et al ('35-'36-'37-'38-'41). Other writers in this field are Peters and Eisenman ('35), Shelburne ('34), Dodd and co-workers ('36), and Bloomfield ('35). The majority of the work to date indicates that a hypoproteinemia may and does occur when the diet is deficient in protein, and the condition is promptly relieved by the ingestion of protein in adequate amounts. The problem still awaiting solution is whether or not the hypoproteinemia so produced can lead to sufficient damage to the protein synthesizing mechanism to institute a "vicious circle". Evidence is accumulating that dietary deficiency may cause impairment of liver function, and may possibly be the precursor of the Laennec type of cirrhosis. It has been shown by Messinger and Hawkins ('40), Schifrin ('32), and Miller and Whipple ('40), that experimentally damaged livers can be protected and caused to regenerate more rapidly by the feeding of a selected diet. These workers have in general found that protein and carbohydrate are protective to the damaged liver, and fat injurious. The demonstration by Elman and Heifetz ('41) of liver damage produced in dogs with experimental hypoproteinemia, which was discussed in the preceding section, seems conclusive. It appears that the liver is a site for both the formation and storage of albumin, and that a deficiency of serum albumin can cause liver damage which is demonstrable both anatomically and physiologically. To complicate our understanding of the effects of a deficiency in protein intake Bloomfield ('33) has found that rats maintained on a low

protein diet suffered only a small lowering of their serum proteins during the first ten days and thereafter for 147 days the concentration remained practically unchanged. Clinical cases can be cited which coincide with these findings. It appears that some other as yet unknown factor plays a role here.

Disorders of protein digestion have been studied less than any of the other causes of hypoproteinemia. For a review of this work the reader is referred to Keefer's ('33) article. The conditions in which digestive factors play a roll can be listed as follows: Chronic dysentery, tuberculosis of the intestine, celiac disease, diabetes mellitus, pernicious anemia, pregnancy, lactation, pellagra, chronic alcoholism, scurvy, and hookworm disease.

The problem of the absorption of the products of protein digestion has received little or no attention. Impairment of absorption has been associated with no specific disease states except in conditions with an increase in intestinal motility, and here only by speculation. When we have attained a better understanding of the hemodynamics of the portal circulation this should prove a fertile field for investigation.

Impaired protein synthesis has been definitely associated with a number of disease conditions, all related directly or indirectly to liver damage. A great mass of experimental data has accumulated (Williamson and co-workers ('22), Mann and co-workers ('29-'31), Rosenthal and co-workers ('26), Jones and Smith ('30), Whipple and Hurwitz ('11), Drury and Mc Master ('29), Kerr and co-workers ('18), Khutti and co-workers ('37), and Warner, Brinkhaus and Smith ('36)) to show that liver damage due to whatever cause results in depression

of plasma protein. Fibrinogen appears to be the first component to suffer, rapidly and somewhat in proportion to the liver injury. The blood fibrinogen values return to normal with liver regeneration and repair. The change in plasma albumin and globulin is a subject open to debate. The above mentioned workers, who are probably the best acquainted with the subject, attribute the production of albumin almost entirely to the liver. Globulin, as far as is now known, may arise in a variety of tissues. It is probable that the diversity of origin of the globulin fraction accounts for its complex nature. Madden and Whipple ('40) state that "the normal liver can (presumably) form and release into the blood stream albumin, globulin, and fibrinogen molecules, when given the proper mixture of amino acids". The contributions of Bergmann ('38) to our knowledge of the enzymatic processes concerned are of inestimable value but have not yet clarified the situation.

Cirrhosis and other chronic atrophic diseases of the liver have been known for many years to be accompanied by a lowered level of the serum proteins. One of the most completely studied series in the literature is that of Foley and co-workers ('37). They discuss the relationship of the total protein and albumin-globulin ratio to the clinical course of hepatic disease and find that it is a helpful guide in prognosis. Thompson and co-workers ('36) have reported a case of apparently congenital atrophic changes in the liver with associated hypoproteinemia. Rytand, ('42), Singer ('37), and Myers ('33) describe cases of hypoproteinemia accompanied by marked impairment of liver

function. Stadler and Stinger ('41) report a case of Pick's syndrome accompanied by a lowered level of the blood protein where the hypoproteinemia was of sufficient degree to contribute greatly to the formation of the accompanying ascites. Further studies along that line are indicated, since at autopsy considerable liver damage of the type usually associated with passive congestion was present in their case. Other writers on liver disease associated with changes in the serum proteins are Bollman ('38), Peters and Eisenman ('35), Cantarow ('38), Myers ('35), Snell ('35). Tumen and Bockus ('37) have compared the clinical significance of serum protein in hepatic disease with other liver function tests. They found that hypoalbuminemia was the most constant alteration noted, being present at some time in every case of chronic advanced liver disease and in most cases of obstructive jaundice. Elevation in the serum globulin and lowering of the albumin-globulin ratio, although usually present, was not as significant or constant as the reduction in serum albumin. They occasionally found minor serum protein changes in some cases of acute hepatocellular damage. They simultaneously determined the liver function with the galactose, urobilinogen, bromsulphthalein and Takata tests. Their data, as that of others, indicates that no one test of liver function can give significant results in every case. Studies of the serum proteins in cases of chronic hepatic insufficiency by the author have all supported the findings of a lowered total protein with a tendency to inversion of the albumin-globulin ratio discussed in the literature. One patient that we observed in the terminal stages of hepatic coma had

serum proteins containing thirteen per cent less nitrogen than is normally found. Abnormal nitrogen distribution and anomalous antigenic properties in the serum proteins of nephrosis have been described by Alving and Mirsky ('36), Goettsch ('36), and Widdowson ('33), but to date no abnormalities have been reported in cirrhosis, with the exception of the one mentioned below.

Butt, Snell and Keys ('39) have studied the colloid osmotic pressure of blood serum and of ascitic fluid in various diseases of the liver and attempted to correlate this with plasma protein levels and edema formation. They found a fair correlation between osmotic pressure and concentration of serum albumin, but in my opinion some of the differences found were so great that they indicate a considerable change in the properties of the so-called albumin molecule. In a case of cirrhosis that Iversen ('28) has reported, with ascites and edema, the serum protein value was normal but the colloid osmotic pressure was reduced.

B. The present-day status of the toxemias of pregnancy.

1. Classification.

The terms "toxemia of pregnancy" and "eclampsia" have many widely different connotations. Some believe them to be synonymous while others maintain that eclampsia is merely one of the many toxemias of pregnancy.

It is obvious that the term "toxemia" is derived from the roots "toxin" and "blood", implying the presence in the circulating blood of some toxin liberated from the products of conception or from the

maternal organism due to the changes produced during pregnancy. This conception has stimulated sporadic efforts to isolate and identify this toxin and to ascertain its source. Dieckmann (29) believes that the injection of tissue fibrinogen or lung extract into experimental animals will produce an atypical eclamptic lesion. Bartholomew ('32-'34) states that injections of Berkefeld filtrates of autolysed normal placenta will produce disturbances in guinea pigs clinically and pathologically similar to the human eclampsia. Hofbauer ('37) found that in both acute and chronic histamine poisoning in guinea pigs lesions were produced which were similar to those found in eclampsia. In another article Bartholomew ('36) states that he believes hypercholesterolemia to be the fundamental basis for the toxemias of pregnancy, through excessive deposition of cholesterol in the placental arteries with resulting rupture and inferction. Johnson ('40) believes that the syndrome may be on an allergic basis, and states, "(1) stasis in the intervillous spaces must be of sufficient duration to cause degeneration of chorionic tissue, with the production of tyrosine; (2) that only through infective processes with bacteria or enzymes circulating in the blood is the conversion of tyrosine to tyramine possible; (3) the absorption of the tyramine formed depends on the condition of uniform pressure as outlined------; (4) tyramine circulating in the blood in pregnancy produced only hypertension; and (5) in the sensitive or allergic patient, tyramine produces hypertension, plus capillary spasm which is the pathological unit of eclampsia." Titus ('32) states that "By experimental administration of guanidine compounds to animals

all of the ------clinical symptoms of eclampsia may be reproduced." Study of the papers of these authors leads one to believe that they have carried their conclusions farther than the experimental data warrants. Melville ('37) has devised a method for the quantitative extraction of posterior pituitary antidiuretic substance from blood. With this procedure he found that a similarly extractable substance could be detected as a normal constituent of dog and human blood. Applying his method to blood obtained from normal pregnancy and toxemic women he did not find any indication of a causal relationship between the presence of this substance in the circulating blood and the early symptoms (hypertension, edema, albuminuria) of toxemias of pregnancy. Page ('36) has studied the effect of eclamptic blood upon the urinary output and blood pressure of human recipients. His results do not support the contention that there is a markedly toxic substance in toxemic blood, nor the theory that there is a hypersecretion of the posterior pituitary gland in eclampsia. He could demonstrate no pressor substance in eclamptic blood. No experiments verifying the presence or absence of angiotonin in eclamptic blood have been reported to date. Browne and Dodds ('36) have studied the blood pressures of eclamptic mothers and their new-born babies. They were unable to detect an increased blood pressure in any of the infants. Further evidence is necessary before we can postulate the existence of a circulating toxin.

The term "eclampsia" is derived from the Greek <u>eklampsis</u>, meaning "a shining forth". At first used to designate a rapidly developing

fever, it was applied to the sudden occurrence of convulsions in pregnant women by Boissier de Sauvages in 1760. Today the word has no meaning other than of rapidly developing convulsions due to whatever cause in the latter part of pregnancy. Rather than to coin a new word to describe one of the conditions generally designated as "eclampsia" we shall retain it after attempting to give it a rigid definition.

Strauss ('30) has given us a rather workable classification of the toxemias of pregnancy by dividing this heterogeneous group of "toxemic" women into two main classes based upon the state of affairs antecedent and subsequent to the "toxemia". His studies show that "about 80 per cent of the women designated as having "toxemia" actually have chronic vascular or renal disease before and after the gravid state, and an additional 5 per cent have such disease in acute form". The remaining 15 per cent of cases, which have no demonstrable abnormality either before or after pregnancy, he designates as having "water-retention toxemia". His classification is given below.

"Essential hypertension"	60%
Chronic nephritis (including glomerulonephritis, pyelonephritis, and polycystic kidneys)	20%
Acute nephritis (usually pyelonephritis)	5%
Water-retention toxemia	15%

It is the groups of cases classed as "water-retention "toxemia" that we shall refer to in the remainder of this paper as "eclampsia", and to which we will devote the major portion of the discussion. "Pre-eclampsia" we will define as eclampsia without convulsions or coma, and consider the difference to be only one of degree.

No better description of this syndrome can be found than that

given by Strauss('30). To quote: "The clinical picture manifested by these women is characterized, first, by the absence of apparent abnormalities before gestation and after the puerperium and, second, by a fairly typical course. In the last trimester of pregnancy a rapid gain in weight, generally but nor always manifest as edema, is followed by a rising blood pressure, albuminuria, gastric pain, convulsions, and coma. The urine is generally of high specific gravity and does not contain red blood cells or white blood cells until the disorder has existed for some days at least. The non-protein nitrogen and the icteric index are always normal or lower than normal until the condition is far advanced. The retinal arteries never show the changes that are observed so commonly in women with chronic vascular or renal disease. It is to be emphasized that these cases comprise only one-sixth of the total so-called "toxemias", and that the typical clinical course is not necessarily diagnostic. Other conditions may simulate it closely."

In the discussion of the pathology of the toxemias will be presented the evidence on which this classification is based.

2. Frequency.

It must be realized that much of the statistical data given has been compiled from literature in which a proper classification of the type of toxemia was not made. However, these statistics are valuable when studied qualitatively without stressing exact ratios and percentages.

In 1929 Stander wrote an exhaustive review of the literature on the subject of toxemias of pregnancy. For references to much of the

earlier work the reader is referred to this article.

General incidence. The incidence is difficult to determine, being much higher in hospital patients than in those managed at home. This is undoubtedly due to the fact that many cases are transferred to the hospital with the development of symptoms. The only accurate statistics available are from Denmark and give the incidence of toxemia with convulsions as 1.74 per 1000 deliveries, (Hauch ('34)). This of course does not include the milder cases who do not progress to the convulsive stage. In a series of 718 pregnancies observed in this clinic, signs and symptoms of this condition, including even the mildest manifestations, were observed in 16 patients, an incidence of 22.2 per 1000 pregnancies. In a series of 512 hospital deliveries two cases of toxemia with convulsions were observed in which renal disease could be definitely excluded, an incidence of 3.9 per 1000.

Month of pregnancy. Although eclampsia is usually considered as a disease occurring only during the last half of pregnancy it is common knowledge that it may occasionally occur earlier. Kboler ('17) finds that the incidence of cases occurring before the fifth month is about one in every 500. When either eclampsia or pre-eclampsia occurs before the fifth month it is the rule to find an accompanying hydatidiform mole or multiple pregnancy (Page ('39)). Beck ('39) gives the following summary of the relationship of the disease to the period of gestation.

2-3 months----------1 case
5-6 months----------13 cases

6-7 months----------39 cases

7-8 months----------33 cases

8-9 months----------35 cases

9 months to term----------115 cases

That there must be a direct relationship to the duration of gestation is undeniable, and the accompanying hydatid mole or multiple pregnancy in many of the early cases implicates the enlarged uterus as an etiological factor. More will be said of this later.

Gravida. The incidence of convulsive toxemia in primigravidae is 3.7 per 1000 contrasted to 0.75 per 1000 multiparae, making the risk about five times greater than in primiparae. These figures were calculated from the data of Heuch ('34) and Lehman ('34), Büttner ('03), Hammerschlag ('04), and Meyer-Wirz ('04), and are subject to the errors of classification mentioned at the beginning of this section. In a series of 500 cases of eclampsia described by Falls ('35), 54 per cent occurred in primiparae.

Multiple pregnancy. According to Zangemeister ('19) about every fifteenth case of eclampsia occurs in a multiple pregnancy. White ('41) has reported a case of recession of toxemia following the intrauterine death of one dizygotic twin.

Season and climate. It is generally conceded that these factors seem to have some influence on the occurrence of pregnancy toxemias, although exact statistical analyses are few. It is our experience here that the few cases encountered occur as a rule between the months of September and March. Harrar ('05) in a study of the cases of the New

York Lying-In Hospital found that the frequency of the disease was at its highest during the month of April, and that unsettled, damp and cold weather, as usually occurs in the spring months, is accompanied by an increase in the number of eclamptic patients. It is well known that Glasgow and its surrounding country have a high incidence of eclampsia, and this has been attributed to the damp climate. Recently Fuerstner and Sargent ('40) have analyzed the incidence of the disease and compared the frequency with the passage of cold and warm fronts. They conclude that these have no etiological relationship but may have some influence on initiating convulsions. A more detailed discussion on initiating convulsions can be found in Stander's review ('29).

Diet. In Germany during the World War I blockade eclampsia was much less prevalent than formerly. The statistics on this subject have been well outlined and discussed by Warnekros ('16) and Varo ('20). No adequate explanation has ever been made of this phenomenon but it has been deduced by some that the increased use of vegetables was possibly a factor. Many of the older works on obstetrics recommend a vegetable diet during the latter part of pregnancy as a means of preventing the development of toxemia. Milk has always been regarded, on the basis of clinical experience alone, as the ideal food in impending eclampsia. The recent observations of Strauss ('38-'39), Dodge and Frost ('38), Harden and co-workers ('35), and Kooser ('41) on the benefits of diets high in protein in impending eclampsia are of great significance. Kooser finds that there does not seem to be any causative relationship

between the incidence of toxemia in the geographical region he studied and the current general diet, but there appears to be a direct relation between the seasonal incidence of toxemia and the seasonal scarcity of food. The other observers, on the basis of finding lowered plasma proteins in their toxemic patients, gave them diets high in protein with apparent benefit in many instances. Strauss's work on this subject is the most complete study in the literature.

3. Therapy.

a. Medical.

Until very recently the medical treatment of pre-eclampsia, and more particularly of eclampsia, has been based on two schools of thought. Both of these methods of treatment were entirely symptomatic and, in our opinion, based on erroneous concepts of the fundamental lesions in these conditions. They consisted of "eliminative" (Dublin), and "sedative" (Stroganoff), treatment. In addition to these two procedures many others have been advocated from time to time. These have been listed by Dieckmann ('37) as follows:

1. Elimination.

   a. Colon lavage
   b. Enemas
   c. Catharsis

2. Sedation

   a. Morphine
   b. Chloral hydrate
   c. Chloroform
   d. Ether
   e. Magnesium
   f. Barbiturates.

3. Venesection, including plasmapheresis

4. Parenteral fluids.

   a. Sodium bicarbonate
   b. Glucose solution

5. Spinal puncture

6. Dehydration

7. Diet

8. Veratrum viride

9. Termination of pregnancy

and to which we have added:

10. Adequate prenatal care

11. Replacement hormone therapy

Diechmann himself, in 1937, advocated the combined method of treatment then in use in the Chicago Lying-In Hospital. This involved sedation and elimination, with termination of pregnancy reserved for a last resort.

The eliminative procedures, which originated in the Rotunda Hospital in Dublin, were aimed at ridding the body of the accumulated "toxins" thought to be causing the patient's symptoms. To the original method of purgation and colonic irrigation was later added the parenteral injection of 1 per cent sodium bicarbonate solution and venesection, converting an innocuous procedure to one potentially very dangerous. Solomons ('22) has reviewed the results of treatment by this method.

The sedative procedures, originally popularized by Stroganoff ('23) rely mainly on the sedative action of magnesium sulfate, aided by barbituric acid derivatives and occasionally morphine. These undoubtedly aid in

controlling the convulsions and tend to decrease the hypertension, but can have no effect on the fundamental lesions. The original (Stroganoff) method utilized the intramuscular route for the administration of the magnesium sulfate. Since this occasionally resulted in the formation of abscesses which were difficult to treat most present-day workers give this drug intravenously. The occurrence of psychoses following the use of magnesium sulfate (2 per cent of 200 cases) has been reported by Stroganoff ('37). Since, however, psychoses are apt to occur following untreated eclampsia these figures are hard to evaluate.

The only series of cases encountered in which veratrum viride has been used was the one of Stevens ('22). He reports the use of this drug in twenty five cases, with a mortality of 4 per cent. The only adjunct employed was immediate artificial rupture of the membranes. Scattered reports of a few cases treated by this method are abundant in the literature. The conclusions reached are variable.

The use of intravenous glucose, with or without the addition of insulin, has many proponents. From our knowledge of the liver damage that accompanies this condition, and the known effect of glucose in aiding the repair of the damaged liver, this procedure is one of the few in general use that is distinctly indicated. The use of a parenteral solution of any salt can under no circumstances be condoned. The introduction of additional fluid and electrolyte into an organism that is already overloaded with these substances amounts to nothing less than a violation of fundamental biochemical principles, which can result only

in harm to the organism.

Spinal puncture, for the relief of the supposedly increased intracranial pressure, is at best only a symptomatic treatment.

Dehydration, which is obviously necessary for the relief of the edema, has in the past been attained by starvation and limitation of fluid intake. It is only recently that we have been aware of the dehydrating action of plain water, even when given with an adequate diet. The proponents of this course of action in pre-eclampsia have recently received experimental support through the work of Strauss ('37-'38-'39).

Termination of pregnancy, in most of the series reported, has led to no marked reduction in maternal or fetal mortality. It is probable that the customary reservation of this procedure for those cases "in extremis" is a factor in its inefficacy. No comparative studies of the mortality in early and late cases of eclampsia treated by this method are available. Stroganoff ('39) reports a series of 179 cases in which "early artificial rupture" of the membranes was performed, "early" referring to a cervical dilatation of less than 5 centimeters. The maternal mortality in this series was 9.5 per cent, a low rate when it is considered that the procedure was reserved for severe cases. Cesarean section in eclampsia is a formidable procedure and accompanied by a high mortality. This is understandable when the condition of the patient is taken into account. A pregnant woman, even under the best of conditions, is not an ideal surgical risk.

Probably the most marked reduction in the incidence, although not in the mortality, of eclampsia has been observed with the introduction of the modern system of prenatal care. True eclampsia, with coma and convulsions, has become a rare condition in most localities. In this clinic, during

the twelve month period of this study, not one case was observed. No accurate statistics are available on this decrease in incidence, which seems to occupy a position similar to that mysterious blood dyscrasia "chlorosis" in its rise and decline. Strauss ('39) and Dodge ('38) have demonstrated the influence of diet on the control of toxemic symptoms, and the effect of a salt free diet on the elimination of water. Anyone interested in the disturbances of salt and water balance occurring in pregnancy, and a rational means of restoring them to normal, is urged to read their articles. Fishberg ('39), who has studied hypertension and nephritis and their relation to the toxemias of pregnancy very thoroughly, whole-heartedly supports Strauss' recommendations. Simply stated, the principle of the treatment is as follows: Throughout pregnancy the patient is urged to eat an adequate diet, meaning one that contains sufficient calories to provide energy needs and sufficient protein to cover the increased demand of the fetus. At the first sign of hypertension, albuminuria, or edema the diet is modified by restricting the salt intake to a minimum and increasing the consumption of protein to 150-200 grams daily. With this regime, plus the administration of small daily doses of magnesium sulfate, we have never seen a patient fail to show an abatement of her toxemic symptoms. An important adjunct of this treatment is rest, secured if necessary by small doses of a barbiturate. Philipsborn et al ('41) have shown that a high protein diet does not have a deleterious effect on experimental renal hypertension.

The work of White and co-workers ('39-'40) with replacement hormone therapy in diabetic mothers is too recent to evaluate accurately. It is

discussed in the section on hormonal variations during pregnancy.

C. Pathology in normal and toxemic pregnancy.

1. Anatomical

Brain. The pathological findings in the brain have been best studied by de Vries ('31). He finds few gross lesions other than anemia of the cortex. Often, however, edema is present and multiple minute hemorrhages are common. On section, punctiform hemorrhagic spots frequently are distributed diffusely throughout the cortex and, in places where these are grouped, such areas may reach a diameter of 0.5 to 1 cm. These hemorrhages are shown microscopically to be associated with small foci of softening in which the arteries reveal evidence of degeneration. The arterial lumina often contain hyaline thrombi and in the walls of the vessels depositions of lipoid can be observed. At the periphery of these lesions there is an accumulation of red blood cells, which can also be seen in the perivascular spaces. Most of the ganglion cells have disappeared in the neighborhood of these foci, as have the glia cells. de Vries believes these lesions to be on the basis of arteriolar spasm.

Kidneys. The renal lesion in eclampsia has been a subject of debate for many years. The works of Fahr ('20), Keller ('27), and Bell ('32), are probably the most complete on this subject. Summarizing the results of these and other workers, we find that in eclampsia the kidney is enlarged, and on section its cortex is pale and cloudy. The tubules, particularly in their convoluted portions, show degener-

ative lesions which vary from simple cloudy swelling to complete necrosis. The epithelial swelling often is sufficient to obliterate the tubular lumina, which otherwise may be filled with precipitated albumin and desquamated necrotic epithelium. These changes are similar to those produced by poisonous chemicals but are thought by some to be caused by the anemia which follows spasm of the arterioles.

Changes in the glomerulus, on which fair agreement is obtained by most observers (Fahr ('20), Bell ('32), Zimmerman ('37), and Keller ('37),) appear to consist for the most part of increase in thickness of the glomerular basement membrane. This does not appear to them to be merely an edematous swelling but an actual increase in substance. The glomerular capillaries are practically empty. When stained to bring out the basement membrane, the capillary walls are found to be greatly altered due to an extensive and peculiar laminated thickening of this membrane. Because of these thick bands of homogeneously stained material between the rows of epithelial and endothelial cells, many of the capillary tufts have a hair pin or wire loop appearance. There is an absence of polymorphonuclear leucocytes, intracapillary fibers and epithelial crescents, such as are found in acute glomerulonephritis. Occasionally the syndrome of cortical necrosis is observed, with fatal termination. This has been well described by Keller.

Experimental renal hypertension and its relationship to pregnancy has been studied by Page ('41), Corbitt ('41), and Dill ('38). The former two investigators found that in rats and rabbits

rendered hypertensive by renal artery constriction, pregnancy tended to bring about a lowering of the blood pressure. This fall was more marked during the latter part of pregnancy and the blood pressure returned to its former hypertensive level following delivery. Dill observed an eclampsia-like syndrome occurring in pregnancy dogs and rabbits following renal artery constriction. The post-mortem findings revealed lesions very suggestive of those of human eclampsia. In a later paper Dill ('41) discussed the effect of renal injury produced by uranium nitrate, sodium oxalate, staphylococcus toxin and ureteral ligation in pregnant and non-pregnant rabbits. He concludes that "The pregnant animal seems to be minimally less susceptible than the nonpregnant one to uranium nitrate, slightly more susceptible to sodium oxalate, and demonstrates no significant difference to staphylococcus toxin or ureteral ligation."

The problem of whether or not the renal lesions of eclampsia are permanent has aroused much interest and controversy during recent years. In an excellent study and review Page and Cox ('38) found that recurring toxemias, hypertension and albuminuria were frequent sequelae of the toxemias of late pregnancy. From examination of the kidney tissue from 28 selected autopsies, thickened glomerular capillary membranes were demonstrated in the kidneys of eight patients dying during toxemias of late pregnancy. Seven women who were known to have had previous toxemias of varying severity, and who died of miscellaneous causes, uniformly showed similar changes in the glomerular capillary membrane. They found slight degrees of similar

glomerular changes in five out of eleven women who had had normal pregnancies and who died from various causes, demonstrating that the lesion is not specific for eclampsia. They conclude that "When a toxemia of late pregnancy is terminated, the swelling of the endothelial cells subsides and the tubular changes disappear, but our observations indicate that there is a persistence of the capillary membrane thickening. If this were severe, it might account for the residual hypertension observed in a large percentage of the cases which have been followed clinically. Marked lesions might result in a persistent albuminuria. Even though the patient may be normal clinically in the nonpregnant state, less severe lesions might be the basis for the constantly recurring hypertension and albuminuria in subsequent pregnancies. To establish these points would require more extensive studies." On the other hand Dieckmann and Brown ('39) in a statistical and clinical study conclude that eclampsia and pre-eclampsia do not cause permanent vascular and renal damage, and that where such damage occurs either the condition was not eclampsia or pre-eclampsia or that these diseases were superimposed on a patient with a predisposition to hypertensive arterial disease. Other recent writers on this subject have been Cheeley ('41), Williams, Nix and Mapes ('41), and Cheeley and Somers ('41).

Liver. It is in this organ that the principal and characteristic pathological changes of this disease are found. It is increased in size and softer than normal, and is usually a pale yellow color. The cut surface has a mottled appearance due to areas of hemorrhage

and necrosis which, on microscopic examination, are found to involve the periphery of the lobules. The almost universal finding of this lesion in this disease and its rarity in other conditions has led many observers to regard hemorrhage and necrosis of the periphery of the liver lobules as the characteristic lesion of eclampsia. (Schmorl ('02), Heinrichsdorff ('12), Ceelen ('10), and Konstantinowitsch ('07)). Although this necrosis is usually scattered throughout the liver substance there seems to be a predelection for the right lobe (Sison ('31) and Dieckmann('29). Theobald ('32) has shown that severe degenerative and necrotic changes in the livers of dogs, sometimes associated with hemorrhagic necrosis in the periphery of the lobules, may be caused by frequently raising the intra-abdominal pressure to between 60 and 100 cm. of saline solution for thirty seconds or longer. He concludes that "It is probable that the hepatic lesions associated with eclampsia and the coincident hemorrhages in the other organs of the body are more often caused by than are the cause of the convulsions which may be initiated by the onset of labor."

Uterus and placenta. Ogden, Hildebrand and Page ('40), and Page ('39), have studied the rise of blood pressure during ischemia of the gravid uterus, and the relation existing between hydatid moles, relative ischemia of the gravid uterus and the placental origin of eclampsia. In pregnant dogs and cats compression of the aorta by a clamp just below the origin of the renal arteries produced small rises in the carotid pressure. This was not found in non-pregnant control animals subjected to the same procedure. An extract of

placenta was prepared which when injected into unanesthetized animals produced a rise in blood pressure.

There has been much discussion about the relationship between placental infarction or necrosis and the liberation of toxic substances into the systemic circulation. This subject has been partially discussed at the beginning of the section on toxemias. In an excellent study of placental necrosis Clements ('34) has found that areas of necrosis measuring 1 cm. or more in diameter were observed in 69 per cent of a series of five hundred placentas. He believed that the amount of circulatory disturbance at the edge of the placenta as the result of such necrosis is so slight as to be negligible.. There appeared to be no apparent increased tendency to necrosis in the toxemias of pregnancy. Markedly toxic patients and pre-eclamptics were observed without apparent placental change while there were many placentas with advanced necrotic changes and a completely negative history.

Other workers have presented contradictory findings on the relationship of placental infarction, syncitial degeneration and placental degeneration. Tenney ('36) finds that there is a definite increase in amount and severity of syncitial degeneration in the toxemias, and that in the severe toxemias and eclampsia the syncitial degeneration is sufficiently marked to be of diagnostic value. Bartholomew ('32-'34-'36) believes that the toxemias of late pregnancy are directly due to placental infarction, brought about by a disturbance of placental circulation, resulting in a liberation of toxins from the infarcted area. Hunt, Patterson and Nicodemus ('40) believe

that placental infarcts and degenerating placental tissue liberates autolysates which if massive, or if renal function is poor, will produce severe late toxemia and eclampsia. These authors found placental infarcts of some kind in 53 per cent of their series of 180 patients, which included five eclamptics and fifteen pre-eclamptics. All of the placentas of the pre-eclamptic and eclamptic patients contained either acute or partially healed infarcts. Siddall ('26) found that "In 700 carefully examined placentas, which were delivered consecutively, there were infarcts of some kind in 67.7 per cent, there being no relationship of occurrence to age or number of pregnancies. All types were more frequent in placentas associated with toxemia of pregnancy, as was also extensive infarction. The presence of infarcts has little or no influence on the welfare of the child."

In the remainder of the organs of the body there appears to be a tendency toward the occurrence of petechial hemorrhages. An aspiration type of bronchopneumonia frequently occurs.

3. Biochemical

Studies of the biochemical pathology of pregnancy toxemias has been limited chiefly to a search for alterations in the chemical constitution of the blood. Studies on blood chemistry in normal and toxemic pregnancies will be discussed under the following headings: 1. Blood sugar, 2. Lipids, 3. Inorganic constituents, 4. Non-protein nitrogen, 5. Acid-base balance and 6. Plasma proteins.

<u>Urinalysis</u>. Since a slight to moderate albuminuria is a common accompaniment of the latter part of pregnancy, it is often difficult to decide whether or not this observation indicates impending

toxemia. In definite toxemia, however, the albuminuria often becomes massive. Studies on the absolute amount and nature of the urinary proteins in toxemic pregnancy are conspicuously lacking in the literature. Hynd, in 1925, investigated the urinary proteins in eclampsia with the methods then available. He concluded that the protein lost resembled lactalbumin more closely than it did serum albumin, and that perhaps the maternal organism had become sensitized to this protein. Hewitt ('29) finds no difference in the specific rotation of the serum and urinary proteins in eclampsia. Casts of various descriptions usually accompany the proteinuria. In most instances of the toxemia of pregnancy that we have observed the sediment contains few red cells, although these may at times be present in moderate numbers. Elden, Sinclair and Rogers ('36) found that the Addis count of casts, red cells, white cells, and epithelial cells increased in the acute stages of toxemia, a finding that we believe is accounted for by the oliguria. Oliguria is a common forerunner of eclampsia. Losee and Van Slyke ('17) find urinary ammonia and urea nitrogen ratios suggestive "of those which Nencki and Pavlov obtained from dogs from which the livers had been removed."

Blood sugar. On a theoretical basis many of the symptoms of eclampsia could be explained by finding a relative or absolute hypoglycemia before and during the convulsions. At autopsy sufficient liver damage is found to cause a hypoglycemia, and hypoglycemia is a well known cause of convulsions. Workers who have studied the blood sugar levels at frequent intervals during pregnancy and toxemias

make contradictory reports. Stander ('29) has been unable to discover any abnormalities in the blood sugar in eclampsia. In reporting his own work and that of others ('29) he summarizes the findings in the following table:

Author	No. of cases	Average	Limits
Stander	94	102	44-190
Lazard	12	115	87-166
Miller and Martinez	19	105	75-181

Mays and McCord ('35), studying the dextrose tolerance curve in toxemic pregnancy, state that they find no departure from normal. Examination of their data however discloses that the curves they obtained were nearly all of the type found in cases of impaired liver function, i.e. they show a delayed return to the initial value. Mietl ('36) studied the response of pregnant women to galactose and glucose. He found consistently normal responses to the galactose tolerance test but a diabetic type of dextrose tolerance curve. Blanco ('36), using the intravenous galactose test according to Althausen, found deviations from the normal in about 40 per cent of pregnant women and in six of seven toxemias. He believes that this may indicate impairment of liver function in normal pregnancy which is more marked in toxemia. Siegel and Wylie ('33) have studied blood sugar levels during normal pregnancy and the toxemias. They concluded from their investigations that while no characteristic changes could be found in the levels of the blood sugar, a certain instability was noted during the toxemias that suggested an unstable carbohydrate metabolism. In the light of the contradictory reports in the literature and the post mortem findings of severe liver

damage it is the author's opinion that their conclusion is probably right, and that the damaged liver is unable to carry on glycogenesis and glycogenolysis at a normal rate. It is improbable that hypoglycemia per se is the cause of any of the symptoms.

Lipids. Boyd ('34-'35-'36), who is today one of the most outstanding students of lipid metabolism, has made an exhaustive study of the lipid fractions of the blood during normal and toxemic pregnancies. He summarizes his work as follows: "In order to ascertain if there were any significant changes in the blood lipids in eclampsia, a quantitative estimation of all lipids, in whole blood, plasma, the red blood cells, and the white blood cells was made. It was found that the concentration of lipids varied greatly in eclamptic patients but no significant variation occurred in the value of any single lipid. The ratio of phospholipid to cholesterol in plasma was found, however, to be without exception higher in eclampsia than in other toxemias or in normal gestation. The mean minus the standard deviation for the ratio in eclampsia was higher than the mean plus the standard deviation in normal gravidas and other toxemias. Variations in the value of the ratio from one eclamptic patient to another were only one-third to one-fourth as great as the variation in single lipids, indicating that the ratio was also less variable than the component lipids. When the patients recovered from eclampsia, the ratio P/TC of plasma returned quickly to normal due chiefly to a fall in the value of phospholipid. Cessation of convulsions without termination of pregnancy left the ratio still high, indicating that

a high ratio did not result from convulsions but was associated with and possibly accounted for the eclamptic state. Only a small proportion of cases diagnosed as pre-eclampsia were found to have an elevated plasma P/TC ratio and, hence, were literally pre-eclamptic. The test is at present being used as a means of separating the pre-eclamptic group into true pre-eclamptics and non-convulsive cases."

In analyzing Boyd's data we find the following mean values:

	Total lipid	Neutral fat	Cholesterol total	Cholesterol ester	Cholesterol free	Phospho-lipid	Ratio P/TC
Blood plasma							
Eclamptic state	1018	368	216	132	84	345	1.61
Normal pregnancy	900	353	205	140	65	248	1.22
Normal	389	154	168	115	47	186	1.21
Whole blood							
Eclamptic state	829	219	187	90	97	361	1.96
Normal pregnancy	785	248	179	95	84	293	1.66
Blood cells							
Eclamptic state	638	78	146	40	106	367	
Normal pregnancy	584	89	135	16	121	361	

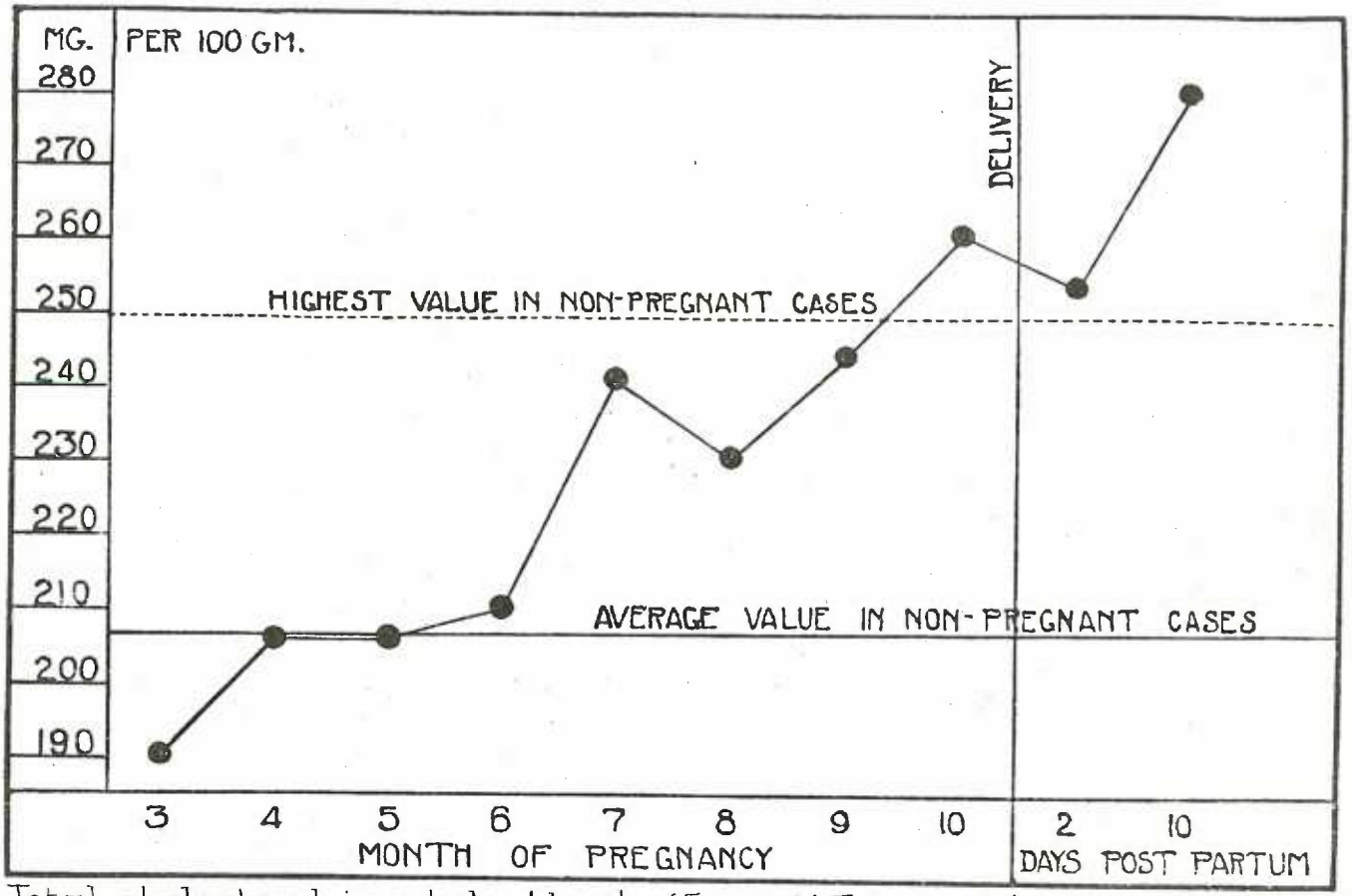
The significance of this increased ratio of P/TC is poorly understood. McQuarrie, Husted and Bloor ('33) found an increase of this ratio at, or about the time of, convulsions in epilepsy but did not attempt to explain it. An increase of plasma phospholipid could conceivably occur in the presence of an ineffecient liver, where these compounds were allowed to collect in the blood stream because of poor intermediary metabolism. The percentage of ester cholesterol, normally

between fifty and seventy, does not appear to be affected in eclampsia, a point against any severe degree of liver damage. It was in the lower limits of the normal in only one of Boyd's cases, all of the rest being well within the normal range.

Petterson, Hunt, and Nicodemus ('38) have studied the relationship between hypothyroidism, the hypercholesterolemia of pregnancy and the toxemias. On the basis of their experimental and clinical work they conclude that there exists in the toxemic mother a hypothyroidism not apparent until pregnancy, and that eclampsia is primarily due to a fetal hypometabolism secondary to a maternal hypothyroidism. Their experimental work is good but does not warrant the conclusions they have drawn. Stander ('29), in his review, concludes that the work done until that time failed to connect eclampsia with a disturbance of blood lipids. Tyler and Underhill ('25), corroborating the work of Simons and Stander ('23), showed that there is a definite increase in the total lipoids in the blood stream during normal pregnancy. The graphs on page 41 taken from their work illustrate this well, and also show that from the sixth to the ninth month there is a tendency for the percentage of cholesterol ester to fall, although it does not get below the average normal value. None of these workers could find any difference in the lipoids in the toxemias of pregnancy or in eclampsia. They noted the same increase in total blood lipids, in normal pregnant women as in those suffering from eclampsia.

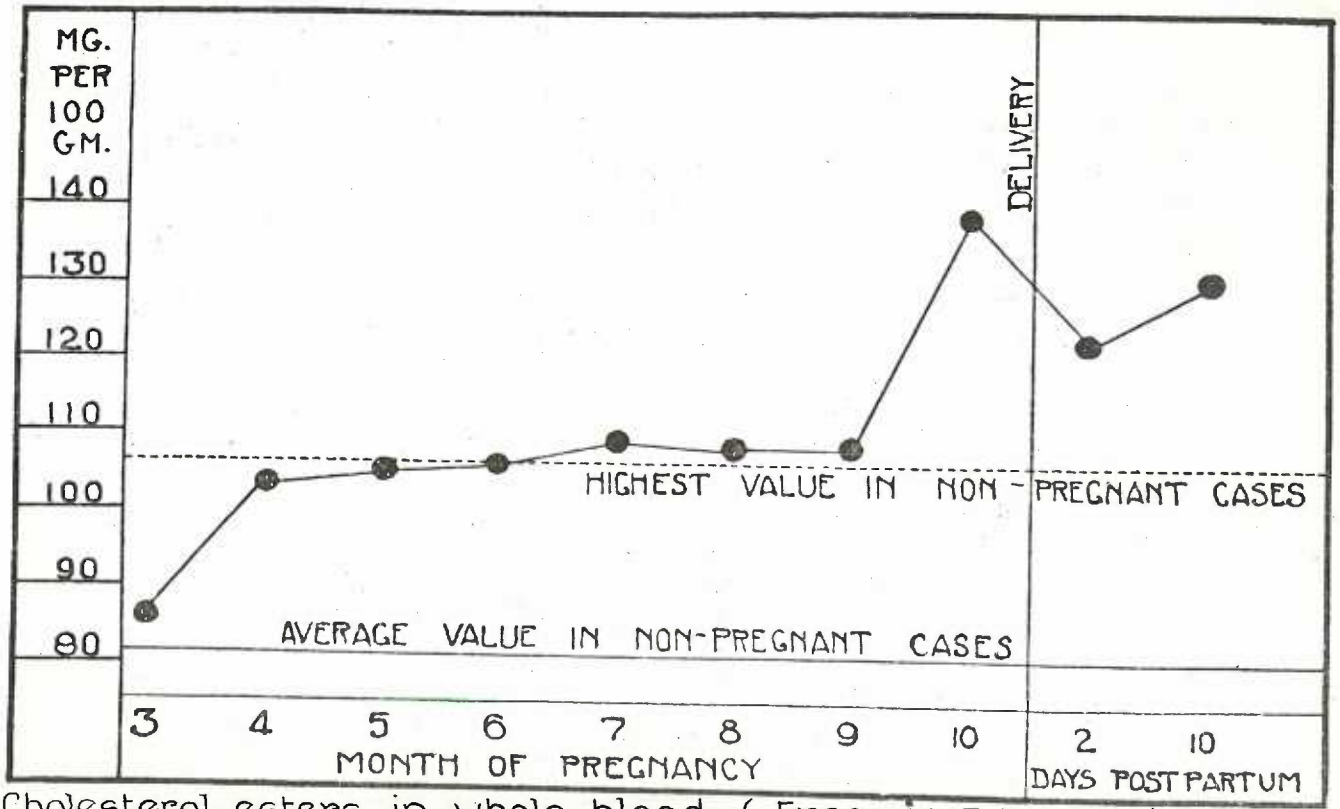
Inorganic constituents. This subject has been well reviewed by Stander ('29) and will not be discussed at length here. Studies have

GRAPH I



Total cholesterol in whole blood. (From M. Tyler and F.P. Underhill, J. Biol. Chem. 66 : 1, 1925

GRAPH II



Cholesterol esters in whole blood. (From M. Tyler and F.P. Underhill, J. Biol. Chem. 66 : 1, 1925)

been made of the sodium, potassium, magnesium, calcium, phosphorous, sulfate and chloride concentrations in the blood in this condition and no significant abnormalities detected except in the Ca/P ratio. Ivenyi, Rodecurt, and Linzenmeier ('26) found that in eclampsia the Ca/P ratio is definitely decreased; Ca/P = 3.51 in non-pregnant; 3.46 in early pregnancy; and 2.53 in late pregnancy; while in eclampsia it was 1.87. This decrease of Ca/P in eclampsia according to their figures is due to an increase in phosphorous. Stander, Duncan, and Sisson ('25) also noted a decrease in the Ca/P ratio or, as they expressed it, an increase in P/Ca, which is due to a high inorganic phosphorous value.

Non-protein nitrogen. Studies by Krebs ('32), Parr ('14), Harding ('24), Williams ('23), Bunker ('24), Caldwell ('21), Plass ('24), Simmons ('16) and Stander ('26) indicate that during normal pregnancy the total non-protein nitrogen of the blood falls within the lower limits of the normal range. It has been amply demonstrated that this reduction in the total is due primarily to a decrease in the urea fraction. The remainder of the non-protein nitrogenous constituents have been shown to remain well within the normal range throughout uncomplicated pregnancy. Losee ('17), and Morse ('17) have studied the amino nitrogen content of the blood in normal and toxemic pregnancy. They agree that in normal pregnancy the values remain within the normal range. Losee finds no appreciable change in this factor in toxemia, while Morse reports results that lead us to believe that it is distinctly increased in pre-eclampsia and

eclampsia, but not in the nephritic type of toxemia. Hellman ('39) finds a significant elevation of the blood lipid amino-nitrogen in eclamptic and pre-eclamptic women, paralleling the severity of the toxemia. Since Williams, in 1921, stated that uric acid is increased in toxemic pregnancy his findings have been confirmed by Caldwell ('21), Killian ('21), and King ('24). On the other hand, Bunker ('24), Harding ('24), and Plass ('24) do not find an appreciable deviation from the normal values. It has been demonstrated that the blood uric acid is elevated by starvation, adequately explaining its occurrence in toxemia.

Acid-base balance. In normal pregnancy Card and Peters ('20) found no change in inorganic phosphorous and chlorides. They found a reduction of about 5 per cent (8 mm.) of total base in the serum of pregnancy, almost entirely at the expense of sodium. This was accompanied by a concomitant and equal reduction of the anion content. The decrease was found in serum protein, serum bicarbonate, and organic acid, chiefly in the latter two. They state that "The pregnant organism appears to have a unique ability to tolerate a reduced concentration of serum electrolytes." Stander ('29) has thoroughly discussed the work that has been done on this subject in the toxemias. His conclusions follow. "Although the complete acid-base equilibria formula has not been worked out for eclampsia, the data up to date seem to indicate that there is a marked disturbance in the oxidative processes, and that this is associated with an acidosis which may often become "uncompensated". We are as yet unable to state that this disturbance is the cause or the effect of the eclamptic outbreak, but it undoubtedly

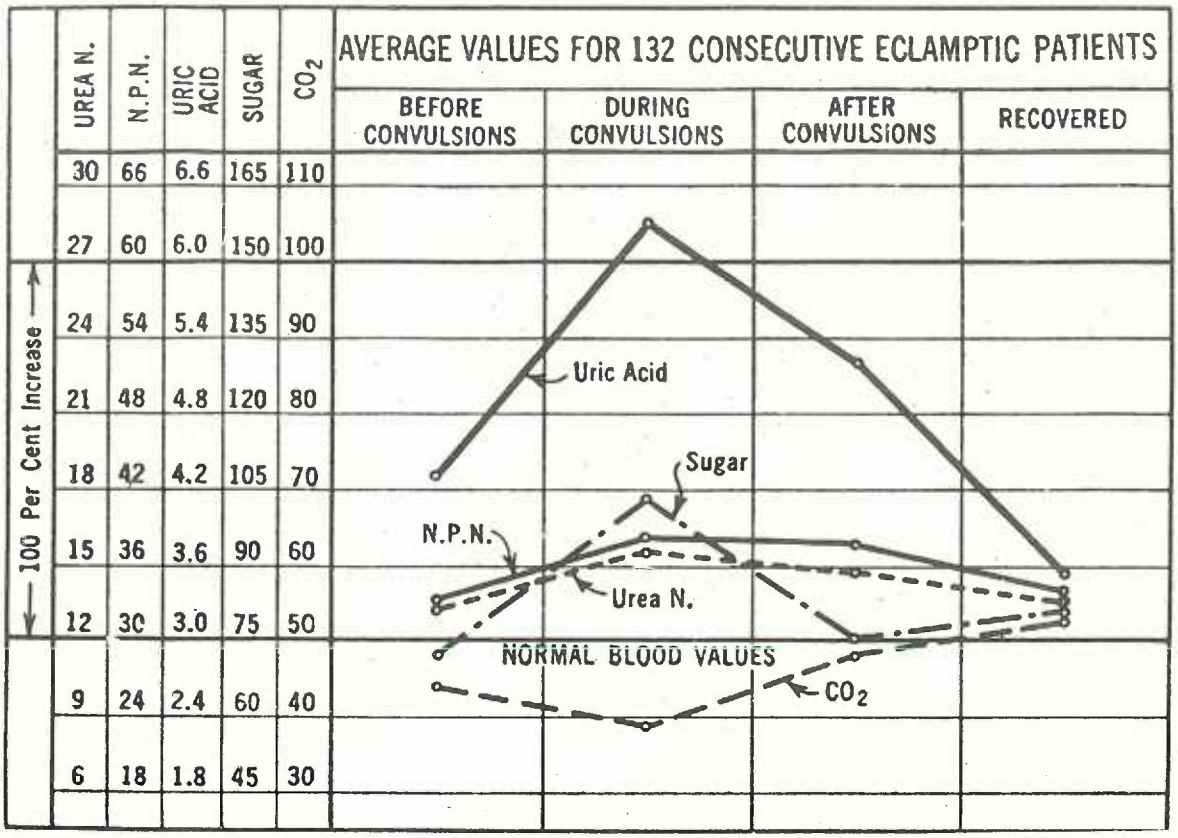
offers us one of the most promising fields for further work concerning the etiology of the disease." The charts on the following page from the works of Stander and Cadden, illustrate a great deal of the work that has been done on blood chemistry in eclampsia.

For a more detailed discussion of the changes in blood chemistry occurring in eclampsia and pre-eclampsia the reader is referred to Stander's ('34) review of this subject.

Plasma proteins. These are discussed under "The blood proteins during pregnancy" in section III.

3. Physiological.

The physiological changes during pregnancy involve too many systems to be discussed at length in this paper. The minor changes occurring in normal pregnancy will merely be mentioned since adequate references can be found in any textbook of obstetrics. When these changes appear to be associated with the toxemic states they will be discussed more fully and in that light. The changes in function encountered in the liver and kidney will be discussed at some length, because it is in these organs that the most marked histological changes have been described in the toxemias. The increase in blood pressure in the toxemias will be discussed in relation to the renal ischemia theory of hypertension. It may be said in passing that the correctness of the term "physiological" as we are using it here is questionable. Many authorities believe that pregnancy itself constitutes a "pathological" rather than a "physiological" state. This point will be left for the reader to decide.



Changes in the Concentration of Uric Acid and of Other Blood Constituents during Various States of Eclampsia. (After J.F. Cadden and H.J. Stander, Am. J. Obst. + Gyn. 37:37, 1939)

Condition	N.P.N. Mg. per 100 cc.	Urea N. Mg. per 100 cc.	Urea N. / N.P.N.	Uric Acid Mg. per 100 cc.	Sugar Mg. per 100 cc.	Chlorides Mg. per 100 cc.	CO_2 Vols. per cent
Eclampsia—before convulsions	33.1 (20)	13.4 (8)	0.405	4.2 (18)	70 (17)	508 (11)	43.0 (20)
Eclampsia—during convulsions	38.3 (74)	15.6 (28)	0.408	6.5 (61)	109 (50)	492 (23)	37.4 (70)
Eclampsia—before delivery	36.1 (70)	14.9 (31)	0.413	6.2 (62)	120 (45)	500 (11)	38.1 (71)
Eclampsia—recovered	33.6 (64)	13.6 (20)	0.405	3.5 (64)	81 (12)	483 (21)	52.7 (63)
Pre-eclampsia—before delivery	31.3 (30)	10.5 (14)	0.336	4.6 (30)	75 (23)	477 (25)	41.1 (29)
Pre-eclampsia—recovered	34.2 (31)	12.4 (15)	0.363	3.6 (31)	83 (28)	475 (29)	52.6 (30)

The figures in parentheses represent the number of patients studied.

Averages for 108 Eclamptic and 40 Pre-eclamptic Patients. (After Stander and Cadden, Am. J. Obst. + Gyn. 28:856, 1934)

Uterus. In the whole field of physiology is encountered no more remarkable instance of growth than that of the uterus during pregnancy. From an organ measuring about 7 x 5 x 2.5 cm., it develops into an enormous muscular sac, the dimensions of which are 35 x 25 x 22 cm. Its capacity, accordingly, is increased several hundred times---- to over 4,000 cc.

Pelvic vessels. The uterine and ovarian vessels are larger in diameter, elongated and more tortuous. Their lumina become enlarged to form large sinuses which are numerous and well developed in the region of the placental site.

Blood and circulation. There is a progressive increase in blood and plasma volumes during pregnancy which begins in the first trimester and reaches its maximum shortly before term when these volumes are nearly 25 per cent above the normal. Following delivery, the values decrease correspondingly and return to normal about eight weeks post-partum. Even when these volumes are calculated on the basis of body weight the increase, although not so great, is still observed. It must be remembered that the dye used in the determination of blood volume does not enter the fetal circulation, so that though the weights of fetus, placenta and amniotic fluid are included in the calculation, allowance is not made for the blood volume of the fetus.

The occurrence of a normocytic anemia is common during pregnancy. No adequate explanation has yet been offered for this, although it is well known that the majority of cases respond promptly to iron therapy. The results of much work indicate that the normocytic type of anemia is

is associated with the increase of blood volume discussed above. The other, and more uncommon, types of anemia occurring during pregnancy will not be discussed.

Ottenberg ('23) has reviewed the evidence for and against the theory that the toxemias of pregnancy may be caused by the passage of incompatable erythrocytes from the fetus to the mother through a defect in the placental circulation. He, as well as the other proponents of this theory, show an utter disregard for the widely different clinical picture seen in transfusion reactions and eclampsia. Most of the evidence in favor of this theory is the finding of methylene blue in the mother's urine after injection of the placental vessels with this dye between the second and third stages of labor. It is claimed that this occurs much more frequently in toxemias than in normal pregnancy, and also that toxemias are much more frequent when mother and child are of different blood groups. They neglect to consider the facts that methylene blue given to a normal non-pregnant individual either orally or parenterally appears in the urine in a very short time, and that the dye Congo Red used to determine the maternal blood volume during pregnancy never appears in the placental blood. Gruhzit ('23) believes that the mother's serum agglutinates the childs cells in vitro, thus giving rise to eclampsia.

Blood pressure. Anyone who has observed a large number of pregnancies cannot fail to be impressed by the fact that both the systolic and diastolic pressures tend to be moderately lowered during

the middle of gestation. There is a gradual increase toward the end of gestation, but the values still tend to be in the low normal range. The experimental data of Hare and Karn ('29), and Burwell et al ('38), demonstrate these facts clearly. In contrast to these mild and temporary changes in blood pressure in normal pregnancies we find the development of sudden and startling degrees of hypertension in the toxemias. The upper limits of normal blood pressure during pregnancy are usually considered to be 140 systolic and 90 diastolic. Any elevation above these levels for more than 24 to 48 hours is a danger sign to the obstetrician. One of the most striking findings in pre-eclampsia is the sudden rise in blood pressure from a normal value to 160/110 or higher. These points are too well known to warrant a lengthy discussion. The renal theory of the origin of hypertension will be discussed at some length, however, since it is of rather recent development and has not yet been specifically associated with eclampsia.

It has long been known that renal lesions are associated with hypertension in nephritis. The connection between the lesions and the hypertension remained obscure until the work of Goldblatt ('33-'34), which demonstrated that renal ischemia, produced by any means, results in an immediate and significant elevation in blood pressure. The findings in clinical and experimental hypertension of renal origin have been well correlated by Corcoran and Page ('41). The demonstration by Goldblatt ('34), Van Slyke ('36), and Corcoran ('38), that the rate of renal blood flow, as determined by clearance of urea,

phenol red, inulin and creatinine, is normal in many animals that are rendered experimentally hypertensive, casts some doubt on the renal ischemia theory. The experiments of Levy ('38), Schroeder ('40), and Kohlstaedt ('40), show that renal ischemia is not necessarily the cause of renal hypertension, and that merely a reduction of the pulse pressure in the renal artery, in the presence of a normal mean arterial pressure in the renal artery and a normal renal blood flow, will cause the liberation of renin into the renal venous blood and an increase in the peripheral arterial pressure. Corcoran and Page ('41) have discussed the possible mechanism by which a reduction in pulse pressure may lead to the establishment of hypertension, but are able to present only circumstantial evidence for their theory.

The humoral mediators in the production of the renal type of hypertension are considered by Corcoran and Page ('41) to be as follows: Renin, a substance present in normal kidneys but normally not liberated into the blood stream in detectable amounts, is produced in increased quantities by a kidney in which the hemodynamics have been upset. Renin alone in Ringer's solution, will not cause vasoconstriction when perfused through isolated blood vessels. There appears to be a substance in normal plasma, at the present time called "renin activator", which combines with renin to form a third substance termed "angiotonin". Angiotonin is a potent vasoconstrictor and appears to differ from most substances which cause a rise in blood pressure in that it does not lead to a decrease in cutaneous temperature. It also causes an increase in the force of the heart

beat. When this substance is given to normal dogs in successive doses they appear to develop a tolerance, a phenomenon known as tachyphylaxis. This tolerance does not occur to any great extent in dogs with both kidneys removed or severely damaged, indicating that there is perhaps a substance produced in the normal kidney which inactivates angiotonin. In a later article ('41) they conclude that: "The final origin of hypertension remains obscure, for the demonstration played by the renal pressor system clarifies some aspects of its etiology, but, at the same time, poses new problems." For other references to experimental hypertension the reader is referred to Blalock's ('40) review and Prinzmetal's ('40) discussion.

Renal function. Since the kidneys seem to be intimately associated with the development of the commoner forms of hypertension, and since hypertension is one of the cardinal symptoms of eclampsia, it seems advisable at this time to discuss briefly the results of renal function tests in normal and toxemic pregnancies. The variety of renal function tests in use at the present time is too great, and their interpretation too complicated, to be presented here. Gamble ('41) has written an excellent syllabus on water balance in which these tests and their significance are discussed at length.

Crabtree, Abramson and Robins ('40) have reported on the effect of pregnancy upon the excretion of intravenous diodrast in rabbits. Their only notable conclusion was that the urinary tract changes in quadrupeds during pregnancy cannot be compared to those

occurring in humans. Cheeley and co-workers ('38), who have investigated the renal function tests during pregnancy rather thoroughly, considered the specific gravity test to be the most sensitive. They found that when the specific gravity was as high as 1.022 there is apparently no indication for doing the other tests, since they were found to be normal. They have found that the urea clearance is the most generally applicable of all the tests studied (urea nitrogen/non-protein nitrogen, 2 hour and fractional excretion of intravenous phenolsulphonphthalein and the urea concentration ratio). In eclampsia, pre-eclampsia and hypertension they found levels comparable to those obtained in normal pregnant and non-pregnant women, as contrasted to an almost universal lowering of the clearance in cases of Bright's disease complicated by pregnancy. They specifically warn against attempting to interpret concentration tests performed on patients on a low-protein salt free diet, or urea clearance on oliguric patients. They find, that as measured by the diodrast clearance, the renal blood flow in eclampsia, pre-eclampsia and recurrent toxemia of pregnancy is charcteristically normal. In the section on anatomical pathology the contradictory evidence concerning the persistence of the renal lesions of eclampsia following recovery was presented. In an attempt to demonstrate this in the intact organism, Cheeley ('40) has ingeniously applied the tests of diodrast clearance in combination with either urea clearance or inulin clearance, to calculate what is known as the "filtration fraction", or the portion of plasma which is filtered into Bowman's

capsule as "pre-urine." He found that of 16 patients with normal filtration fractions during eclampsia only 6 per cent developed hypertension, while of 14 patients with abnormal filtration fractions, 50 per cent developed hypertension. He has also shown that this diminution of filtration fraction may be associated with the glomerular lesions described in eclampsia. Corcoran and Page ('41) have confirmed the findings of Cheeley, and further state that when the filtration fraction is increased the toxemia may be classified as essential hypertension, pre-existing or formerly latent. Homer Smith ('41) has recently published an excellent article on the significance of the inulin clearance, diodrast clearance and filtration fraction in normal and diseased kidneys which should be read by anyone interested in this field. Willie Smith ('40) has demonstrated that in women with pre-eclampsia the clearance of inulin is practically identical with that of various hexitols. This argues against a significant decrease in glomerular permeability in a disease where thickening of the glomerular membranes is frequently observed. He finds no reason to suspect that a precisely compensating increase in tubular permeability has obscured a decrease in glomerular permeability, since tubular function is apparently not disturbed. Welsh ('42), studying a significant number of normal pregnant and post-partum pregnant women, finds that the filtration rate (inulin clearance), effective renal blood flow (diodrast clearance), tubular excretory mass (diodrast Tm), and phenol red clearances are not altered in pregnancy or in the puer-

portum. Utilizing the same tests Welben ('42) finds that in the toxemias the tubular excretory mass is normal; the effective renal blood flow is normal or above normal; the glomerular filtration rate is somewhat reduced when referred to postpartum values; and that the filtration fraction is normal or low. These authors find further that following delivery the filtration fraction increases, in part because of a fall in diodrast clearance and in part because of an increase in inulin clearance. In the group they studied that appeared to be clinically well following the toxemia this increase in the filtration fraction remained within the normal range. In the group that developed a persistent hypertension the results of the functional tests were identical with those found in essential hypertension. Among their conclusions they mention that "The view that renal ischemia is an essential factor in the production of hypertension is opposed by the evidence that in the presence of the hypertension of toxemia there is a normal or even an increased renal blood flow". Elden, Sinclair and Rogers ('36) have found that the urea clearance is of no significance during pregnancy except that it may serve to differentiate true eclampsia and pre-eclampsia from Bright's disease. They found during the first three months postpartum that about 50 per cent of the cases of pre-eclampsia and 67 per cent of the cases of eclampsia had sustained evidence of renal damage as determined by the urea clearance test. Nice ('35) has found that during normal pregnancy there is a tendency for the urea clearance to be elevated, and suggests an association between this and the low blood urea normally found during pregnancy. It

would seem that the renal function, or better the renal blood flow, is disturbed during eclampsia and pre-eclampsia, when determined by suitable tests in the hands of competent observers. Such determinations, if done at infrequent intervals by untrained technicians, could only lead to confusion in the literature. In the absence of research facilities they are inapplicable to the differential diagnosis of hypertension during pregnancy.

The well known dilatation of the ureters during pregnancy renders valueless the phenolsulphonthalein excretion test of renal function.

The relationship between pregnancy and experimental hypertension, as it has been studied, has been discussed in the section on the anatomical pathology of the kidneys.

The albuminuria accompanying the toxemias of pregnancy is as obscure in origin as albuminuria occurring in other conditions. Fishberg ('39), in discussing his review of the subject of albuminuria in general, indicates that there are two mechanisms which can account for the appearance of protein in the urine. The first, which he designates as "renal albuminuria", he believes due to glomerular damage of sufficient extent to permit escape of the plasma proteins. The second, which he calls "humoral albuminuria", he believes to be due to the excretion of an abnormal protein present in the plasma. So far as we know the urinary proteins in eclampsia have not been studied by the precipitin method. Hewitt ('29), extending the work of Hynd ('25), has shown that the specific rotation of the proteins appearing in the urine in the pregnancy toxemias is the same as that of serum albumin. The nitrogen partition of

the urinary proteins in this condition has not been studied. A lifetime of research could profitably be devoted to this subject.

Venous pressure. Runge ('24) has found by direct manometric measurements that the pressure in the cubital vein and in the leg veins is the same in the non-pregnant woman. The pressure in the veins of the leg increases above that in the cubital vein during pregnancy, to return to a level slightly below that in the cubital vein following delivery. Burwell et al ('38) have confirmed the findings of Runge and presented other data which will be discussed at length later. Thomson, Reid and Cohen ('39) have found a diminution in venous pressure in the arm veins during normal pregnancy, although this never exceeded normal limits. They did not find extremely high pressures during pregnancy toxemias, although they did note a slight increase. Burwell ('38) et al studied the pulse rate, systemic blood pressure, vital capacity, arteriovenous difference, cardiac output, venous pressure and total blood volume. From this study, probably the most complete available, they conclude the following: "The chief alterations in the circulation of pregnant women are ---------: (1) An increased cardiac output per minute, (2) A decrease in the arteriovenous difference, (3) A rise in the pressure in the veins of the lower extremities, (4) An increase in pulse rate and pulse pressure, (5) A loud bruit over the site of the placenta, (6) An increase in total blood volume." They further state that: "The demonstrated phenomena of the circulation in pregnant women and pregnant animals, plus the available knowledge concerning the structure of the placenta, lead to the conclusion that the changes in

the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) an arteriovenous leak through the placenta and (2) an obstruction to venous return by the enlarged uterus." The findings of an increase of cardiac output varying from 45 to 65 per cent above the normal has also been reported by Weiss ('24), Gammeltoft ('26), Stander ('26), Schmidt ('32), Grollman ('32), and Haupt ('27). The decrease in arteriovenous difference has been noted by Weiss ('24) and Gammeltoft ('26). Burwell and his co-workers found that an increase of intra-abdominal pressure in pregnant dogs caused no change in venous pressure until the intra-abdominal pressure reached a point where the abdominal wall became tense. They state that this tenseness of the abdominal wall does not occur during pregnancy, a point which contradicts common observation in polyhydramnios and multiple pregnancy, practicularly in primiparae.

Experiments are now being planned in this laboratory to determine the effect of a femoral arteriovenous fistula on the experimental animal. Such a shunt should simulate rather closely the disturbed hemodynamics encountered during pregnancy.

Intra-abdominal pressure. Fasmore ('13-'21-'28-'37), as early as 1913, postulated that intra-abdominal pressure was increased during pregnancy and offered experimental evidence to prove his point. In his work published since that time he has confirmed his own investigations, and those of Theobald ('32), and attempted to establish a connection between this observed increase of pressure and the occurrence of eclampsia. In one interesting experiment he measured the rectal pressure of a woman in eclamptic coma before and after Cesarean section. With the

patient in the left lateral position, before operation, the pressure in the rectum was 35 mm. mercury, (normally 6 mm.). When the abdomen was opened, with the patient in the supine position, the pressure dropped to about 30 mm., where it had been 50 mm. before (normally 10 mm.). After removal of the child the pressure registered was 10 mm. Paramore is a strong proponent of the idea that the visceral lesions are the cause of the toxemia and that the increased pressure is the cause of the visceral lesions. In 1928 he reported a case of eclampsia which he treated with spinal anesthesia, because of the known action of this procedure in relaxing the abdominal musculature. The patient showed immediate symptomatic relief which persisted for about 24 hours. Six days later the foetal heart tones became inaudible and in two days further the patient gave birth to a dead fetus. Following the death of the fetus the blood pressure began to drop and following delivery it became normal and remained so. In 1937 Paramore devised instruments by means of which the intra-abdominal pressure could be measured with greater accuracy than with those he had used previously. His studies on normals and during pregnancy at this time confirmed his previous work. He deserves credit for being the first investigator to actually attempt to determine accurately the intra-abdominal pressure during pregnancy and to apply his findings to a rational explanation of the convulsive toxemias.

Reference has already been made to Theobald's work demonstrating that an increase of intra-abdominal pressure in dogs will produce hepatic lesions simulating those of human eclampsia. In the absence of any available means of measuring directly the intra-abdominal pressure in

humans he has studied the changes in this factor by introducing balloons into the stomach and rectum. By taking repeated measurements with the subject in various positions he believes that he has been able to obtain an average of pressures which is statistically significant. By means of such experiments he has demonstrated an increase in intra-abdominal pressure during pregnancy, which he believes is more marked in primipara, cases of polyhydramnios, and multiple pregnancy. Since he has studied this ordinarily neglected phase of physiology rather completely, a summary of his more recent work will be quoted in full here. He states that:

"1. The intraperitoneal pressure (P) of an anaesthetized dog or cat, tied on its back, with its hind legs extended, usually lies between 0.8 and 1.5 mm. of mercury.

"2. The pressure at any point in the peritoneal cavity of an animal at rest is equal to P plus the component of the weight of the viscera acting on that point. When, however, the intraperitoneal pressure is markedly raised the local differences in pressure become insignificant and P is approximately the same at whatever point it is measured.

"3. The introduction of saline into the peritoneal cavity increases the pressure in the peritoneal cavity and the stomach.

"4. The intra-abdominal pressure in cats and dogs is not increased by more than 2 mm. of mercury during pregnancy.

"5. The intra-abdominal pressure is probably not raised to any great amount in humans during pregnancy, except in the case of multiple pregnancy, especially if associated with hydramnios, in a primigravida.

"6. The pressure caused by the pregnant uterus on the abdominal viscera depends on its size and weight, and the distribution of its pressure components varies with the posture of the body and the build and musculature of the woman.

"7. The size and weight of the uterus, the elevation of the diaphragm and the position of lordosis associated with the latter weeks of pregnancy, render the woman liable to suffer from albuminuria.

"8. The increase in venous pressure affecting a considerable proportion of the blood of the body may lead to capillary dilatation and the diversion of blood from the extremities through the liver, and to an increase in the general blood pressure. (The renal theory of hypertension had not been published when Theobald wrote this. R.E.R.).

"9. The venous circulation in the smaller veins ceases when the surrounding pressure exceeds by one-tenth the pressure in the vein."

Paramore and Theobald have both performed experiments of a laborious and fundamental type. Their contributions to our knowledge of the pressure relationships in the various organs and cavities of the body during pregnancy is invaluable. It is regrettable that they were not familiar with our modern concepts of hepatic and renal function and the changes that might be produced in these organs by the altered dynamics they observed. At the present time we are attempting to discover if there is any relation between the intraperitoneal pressure and blood pressure in animals. If sufficient data becomes available it will be appended to this paper before completion.

Liver function. A great variety of liver function tests has been proposed for clinical use. It has been generally conceded by students

of this subject that no one test of function is capable of assessing accurately the ability of the liver to perform its normal duties. In competent hands the tests of pigment excretion, detoxification, ability to metabolize carbohydrate, and ability to form urea have given the most accurate results when compared with the microscopic appearance of the liver at biopsy or autopsy.

Kaufman ('31-'32) tested the liver function in normal pregnancy utilizing the tests of levulose tolerance, bile pigment excretion, and glycogen reserve. He found at least one function and sometimes all three impaired in the second half of pregnancy. Of especial interest is the fact that during the second and third months the glycogen content of the liver was lessened in all cases. Botelle-Lucia ('36), in an excellent investigation, found that during normal pregnancy the deaminizing and urea-forming powers of the liver are notably decreased. These disturbances are significantly more marked during the toxemias, especially eclampsia. He compared the findings mentioned above with those occurring in an Eck fistula dog. Neuweiler ('40) concludes that the hippuric acid excretion test, either oral or intravenous, gives increasingly lower values as the pregnancy progresses. In eclampsia and "Schwangerschaftsniere" he found even lower values than he noted in normal pregnant women during the same trimester. Cross ('29) has found that decrease in liver function as determined by a variety of tests is apt to occur during pregnancy. King ('24) has found that the bromsulphalein test is of definite value in differentiating between nephritis and the pre-eclamptic types of toxemia, and that the degree of retention seems to correspond with the clinical findings. He concludes, in part, that "the dye tests, as well as the

studies on the blood sugar and on the storage and mobilization of glucose and levulose, indicate that in the toxemias peculiar to pregnancy there is a definite impairment of liver function. Hirschenier ('35-'39), utilizing the intravenous hippuric acid excretion test, has confirmed the findings of the workers mentioned above, and also found this function to be depressed in one case of hyperemisis gravidarum. Sullivan, using the bilirubin excretion test, has found that in the first half of normal pregnancy liver function shows no impairment, but that during the second half there is a decrease in excretion in 30 per cent of cases. The test tended to return to normal following the termination of pregnancy. He believes that the test and its interpretation are too difficult to be useful in routine obstetric practice, although it may be of some value in differentiating between the nephritic and hepatic types of toxemia.

Stroebe ('32) investigated the liver function, utilizing a variety of tests, of 56 patients who had suffered from various toxemias. In 25 of these 56 patients he found that at least one of the tests indicated some impairment of liver function, and in several patients liver damage was indicated by two or more tests. Since he performed his determinations at varying periods following the abatement of the toxemia, and since he does not classify the toxemias according to type, the results are difficult to evaluate. It is obvious from his results, however, that the extent of liver damage suffered during toxemia must be greater than we have heretofore imagined. Hofbauer ('33), after a rather extensive study of the changes in the blood during pregnancy, comes to the following conclusion: "Die latente Leberschädigung der Graviden steht

in ursächlichen Zusammenhange mit den bekannten Veränderungen des Blutes: Steigerung der Blutkörperchensenkungsgeschwindigkeit, Änderung des Säure-Basengleichgewichtes, Änderung der Kolloidstabilität, Globulinvermehrung, Verminderung der Oberflächenspannung, hämoklasische Krise."

Hormonal variations. Smith and Smith ('35-'36-'39-'40), Frank ('31), and Rakoff ('39) have found that during normal pregnancy there is an increase in urinary excretion of estrogenic substances. Following delivery the amount excreted rapidly returns to normal. Cohen, Marrian and Watson ('35) have demonstrated that during pregnancy the free forms of estrone and estriol, normally constituting about 30 per cent of that appearing in the urine, are decreased to about one per cent. The maximum excretion of pregnandiol (as the sodium pregnandiol glucuronide) amounts to about 5 to 8 mg. per 24 hours and occurs about seven days before the onset of the menstrual period in the normal, menstruating woman. According to the studies of Stover ('39), Browne ('38), and Wilson ('38), a level of about 8 mg. per 24 hours in the fifth week of pregnancy occurs, and this excretion rises to about 18 mg. per 24 hours at term. The gonadotropic hormone, whose excretion forms the basis of the well known Aschheim-Zondek test, shows the most striking increase during pregnancy. Quantitative studies, because of the labor involved, have been few and not too reliable. They indicate, according to the Smiths ('36), that the peak of excretion of gonadotropic hormone seems to be during the second month of pregnancy.

The hormonal studies made during toxemia have been few. The Smiths ('35) have found that there is a marked decrease in the excretion of estrogenic substances in the toxemias. At term they found the average daily excretion to be 3600 rat units in 21 toxemic patients, compared to

7000 rat units for 15 normal patients. In these toxemic patients the level of serum estrogenic compounds also failed to show the rise that is characteristic for the normal pregnant woman. The composition of the estrogenic compounds also undergoes a change during the toxemias. According to the data obtained by the Smiths ('38) and Pincus ('37), the estrone fraction changes from about 50 per cent of the total serum estrogenic substances at the second missed period to about 6 per cent at term. The ratio of estriol to estrone is thus about 15 in the last months of a normal pregnancy; in pre-eclampsia and eclampsia this ratio is considerably lower. The excretion of pregnandiol has been found by the Smiths ('36) to fall sharply following the occurrence of toxemic symptoms. In one case the daily excretion fell from a level of about 80 mg. to 35 mg. following the onset of albuminuria, hypertension and edema.

A striking change has been found in the urinary excretion of chorionic gonadotropic hormone during the toxemias. As was mentioned above, during normal pregnancy this usually reaches a peak at about the second month, after which it falls to a constant level for the duration of pregnancy. The Smiths ('34) have found that in the sixth month the average excretion per 24 hours for the toxemic patient is 1600 rat units, and for normal patients 600 rat units. In the eighth month the average values were, respectively 6000 and 500 units. They also found the concentration of the serum gonadotropic hormone to be higher in the toxemic patient than in normals. Employing criteria too complicated to discuss here they concluded that the excessive amounts of gonadotropic hormone present in the blood and urine of toxemic patients originate in the placenta

and not in the pituitary.

A relationship between the normonal changes during pregnancy and the late pregnancy accidents occurring with diabetes has been established by the Smiths ('37) and White ('36-'40). These workers have shown that the diabetic mother is prone to have an abnormal rise in blood chorionic gonadotropin accompanied by a decrease in estrogen and progesterone during the latter part of pregnancy. Diabetics in whom these changes do not occur have uneventful pregnancies, but among twelve patients with abnormal values who received no therapy there were nine pre-eclamptic toxemias and three premature deliveries, with a fetal mortality of 42 per cent. In a series of thirteen cases with abnormal hormone values, treated with substitution doses of estrogen and progesterone, toxemia was controlled, premature deliveries did not occur, and fetal survival was 92 per cent. Whether these abnormal hormone concentrations are the cause or the result of the toxemia has not yet been demonstrated. Since the metabolism of sterols is thought to be mainly confined to the liver, the demonstrated derangements of liver function may be the cause of the upset in hormone metabolism. The concentration of the estrogenic compounds in placenta, liver, kidney and adrenal have been studied, the liver, either maternal or fetal, being found to contain a higher concentration of estrogenic compounds than did the placenta.

Other workers on the hormonal variations during toxemia, whose studies have not been as complete as those mentioned above, have been Robson ('37), Cope ('40), Weil ('38), Browne ('36-'38), and Siegler ('39). Their findings all confirm those that have been discussed. The work of

Payne ('41) on the excretion of gonadotropic and estrogenic hormones in the presence of hydatidiform mole and chorioepithelioma is of interest, in that his findings are similar to those observed in toxemia.

II. The Quantitative Determination of Serum Proteins

The earliest methods for determination of serum proteins involved acid and heat coagulation, followed by filtration and drying to constant weight. Since this procedure inevitably included a certain amount of the salts and lipids present in the serum, modifications have been added. Sierry and Vivaro ('25) and later Guillaumin, Wahl and Laurencin ('29), have used acetone precipitation and washing for the removal of lipids, followed by coagulation with acid and heat and washing with water. This prodedure did not remove the phospholipids, however, and by ashing the precipitate a variable amount of salts could be demonstrated. Robinson and Hogden ('41) have reviewed the literature on the gravimetric determination of proteins in serum, and present a method analysis which is both convenient and accurate. Their procedure involves heat and acid coagulation followed by washing with water, acetone and alcohol.

Since the introduction of the Kjeldahl method of analysis most studies have been based on this procedure. Because the determination assumes a constant nitrogen concentration for all proteins of the same type, an assumption that we and others have found to be incorrect for certain pathological sera, it is useful only when proteins of a known nitrogen content are being determined.

Because of the difficulties involved in the two procedures mentioned above, several indirect methods have been proposed for clinical use. The determination of the specific gravity of the serum, which Moore and Van Slyke ('30) have shown to be directly related to the protein content, has proved very unsatisfactory in our hands. The

direct determination of the specific gravity by weighing requires an inconveniently large amount of serum and the use of an analytical balance. The indirect determination by comparing the rate of fall of a drop of serum and a drop of a solution of known specific gravity through a mixture of brombenzene and xylene gives erroneous results on sera containing excess lipids or hemoglobin. Too, this method has never been adequately compared with either Kjeldahl or gravimetric determinations on pathologic sera.

Nephelometric determination of the serum proteins following the addition of a precipitating agent such as ammonium sulfate or sulfosalicylic acid, as proposed by Muszynak ('24) and Folin ('14), is subject to the inherent errors of all nephelometric determinations. These consist chiefly of inability to attain uniform particle size and even dispersion.

The phosphotungstic-phosphomolybdic acid reagent of Wu ('22) has been widely and successfully used for the determination of all types of protein. This procedure is based on the production of color when the reagent acts on the tyrosine portion of the protein molecule. Its chief source of error is the occasional formation of a precipitate during the development of the color. This does not result in a serious error when using the visual colorimeter but makes photocolorimetric determinations worthless.

Widdowson ('33) has used the criteria of specific rotation, osmotic pressure, ultraviolet absorption spectra, and other physical constants, as well as nitrogen distribution and racemization curves,

in studying the urinary and serum proteins in nephritis and nephrosis. Tuchman and Sobotka ('32) determined the tyrosine content of the serum and urinary proteins in the same conditions and found significant differences. Alving and Mirsky ('36) repeated their work, determining cystine however, instead of tyrosine. Their findings were similar. Goettsch and Reeves ('36) found that albumin and globulin isolated from nephrotic serum are not completely precipitated with the antisera developed against normal serum albumin and serum globulin.

Luetscher ('40-'41), and Longsworth ('39-'40), and others have recently begun to apply the "schlieren" diagram principle to the study of the proteins of the serum and urine in normal and pathological states. This field is virtually untouched, yet it has already yielded much new and interesting information.

Kingsley ('39-'40), Robinson ('40), and Pine ('35-'38), have recently proposed methods for the colorimetric determination of the proteins of plasma and serum utilizing the color produced when the protein is added to an alkaline solution of copper sulfate. This reaction is known as the biuret reaction because biuret, $NH_2CONHCONH_2$, a condensation product of urea, gives the test. The test is given by nearly all proteins and their hydrolysis products except the free amino acids, and also by a few non-protein substances such as biuret. The method was first applied to the quantitative determination of urinary protein by Autenrieth ('15-'17). It was not satisfactory as first proposed, because of the rapid deterioration of the protein solution used as standard. Hiller ('27) later modified the method,

employing pure biuret as a standard. This is satisfactory when the pure substance is obtainable, which is not always the case. With the advent of the photoelectric colorimeter, eliminating the necessity of having a standard for each individual determination, the method was popularized for the determination of serum proteins by Kingsley ('39-'40). Later Robinson found that dilute rabbit serum, preserved in the icebox with thymol, quantitatively retained its chromogenic properties over long periods of time. At the present time, then, the method is applicable to both the photoelectric and the visual colorimeter. Since this method is rapid, accurate, and may be used with small samples, it was selected for use in this study. The procedure of Kingsley was followed throughout for routine colorimetric determinations. It was checked by Kjeldahl analysis of aliquots of every tenth to fifteenth serum. For these routine checks the non-protein nitrogen was not determined, but was assumed to constitute 35 mgms. per cent of the total nitrogen and an appropriate correction made. The Klett-Summerson photoelectric colorimeter was used throughout this study.

Total protein. 0.1 ml. of serum is added to 4.0 ml. of 10 per cent NaOH from a pipette calibrated "to contain." The pipette is rinsed several times with the NaOH solution, which is then mixed with the serum by gentle rotation. 0.5 ml. of one per cent $CuSO_4 \cdot 5H_2O$ are added and mixed in the same manner. The resulting blue solution is then allowed to stand for 25 minutes, after which the color becomes quite stable, and is read in the photoelectric colorimeter. The colorimeter reading multiplied by a suitable factor, gives the protein content of the serum in grams per hundred ml. This factor is determined

for any given colorimeter by simultaneous Kjeldahl total and non-protein nitrogen determinations on aliquots of serums as shown in equation $f = \frac{C}{R}$

in which C is the concentration of serum protein, in any desired units, as determined by Kjeldahl analysis, and R is the colorimeter reading. When working in the narrow range of values encountered in serum protein determinations, a blank correction is unnecessary. After f has once been accurately ascertained it may be used throughout the life of the machine, provided of course that neither filters nor photocells have to be replaced. All Kjeldahl determinations were done either in duplicate or triplicate. Non-protein nitrogen was determined in the Folin-Wu filtrate. The table below gives the results of four typical determinations.

Kjeldahl nitrogen in mg./100 ml.			Protein (gms. per 100 ml.)	Colorimeter reading	f
Total	Non-protein	Protein			
1209	33	1166	7.22	318	227
1535	27	1508	8.18	360	225
1162	39	1123	7.03	310	226
985	30	955	5.70	253	227

Seventeen such determinations were made on different sera from normal pregnant women. The range of values for f lay between 225 and 230, average 227, with 95 per cent of the values being between 227 and 228. The factor 227 was used throughout this study. During the course of the investigation 27 determinations were made in which the non-protein nitrogen was assumed to be 35 mg. per 100 ml. These determinations gave values of f which fell between 230 and 235, averaging 227. The sera of six normal males and eight normal non-pregnant females gave values of f ranging between 226 and 232, averaging 228. There was no significance

difference between the two sexes.

Robinson ('40) has objected to this procedure on the grounds that the color produced is not linearly related to the protein concentration when the latter is high. Between the limits of 5.20 and 8.35 gms. of protein per 100 ml. of serum we have found a linear relationship. With sera in which the protein content had been artificially increased to 10-12 gms. per 100 ml. we found Robinson's objections to be valid.

Albumin. A great deal of work and speculation has been done on the significance of the albumin/globulin ratio in serum. Because of the multiplicity of procedures for the separation of these fractions, and the variable results obtained with the different procedures, many conflicting statements have been made. The fact remains, however, that a certain portion of the protein of the serum is precipitated by arbitrarily chosen concentrations of various salts. When determined by any one procedure this fraction remains relatively constant, within certain limits, for normal individuals. In certain pathological states abnormal values are consistently found. We selected Kingsley's modification of Howe's method for this study because of its simplicity and rapidity. In this procedure the serum (0.5 ml.) is half saturated with $Na_2SO_4 \cdot 10\ H_2O$ (7.5 ml. of 22.5%) and the mixture shaken with 2-3 ml. of ether in a 15 ml. centrifuge tube. It is then centrifuged for 15-20 minutes at moderate speed. The precipitated globulin fraction collects at the interface between the ether and sodium sulfate solution, the latter containing the dissolved albumin. Two ml. of the albumin solution are transferred to a colorimeter tube containing 2 ml. of 20

per cent NaOH. Copper sulfate is added as before and the remainder of the procedure is identical to that described above. We did not attempt to check this procedure with Kjeldahl analyses but did find that aliquots of serum gave results checking within plus or minus 2 per cent, over a range of 3.2 to 4.8 gms. of albumin per hundred ml. of serum.

III. The Blood Proteins During Pregnancy

The main objective of this work was to study the blood proteins during pregnancy, and considerable space will be devoted to a review of the findings of previous workers in this field. Following this will be a presentation of our original work and a discussion of the significance of the variations found. Since the normal values for blood proteins will vary with the analytical procedure used the results of any one worker should be considered alone, and compared with those of another only on a basis of relative changes. Howe, quoted by Plass ('26), remarks: "The evaluation and correlation of the various observations to show absolute differences in the distribution of the plasma proteins is difficult because of the variety of procedures which have been used in their estimation with accompanying variations in results." And later: "To single out definite values as representative of particular states, and especially the normal composition of blood plasma, is exceedingly uncertain." Examination of the works of Moore and Van Slyke ('30), Linder, Lundsgaard and Van Slyke ('24), Trevorrow ('42), and Osgood ('40), shows that for most purposes we can assign the following normal values to the serum proteins: Fibrin, 0.20-0.40 gms. per cent; globulin, 1.0-3.5; albumin 3.6-5.8; and total protein 6.0-8.0.

The average and extreme normal values obtained by our method on thirty-one non-pregnant nursing students expressed in gms. per hundred ml. were as follows: Total serum protein, average 6.94, extremes, 6.6-7.3; albumin, average 4.96, extremes 4.7-5.2; globulin, average 1.99, extremes 1.5-2.4. The narrow range of these normal values

can perhaps be explained by the facts that these individuals were all doing the same type of work, that their diet was identical in quality, that the determinations were all done over a short period of time, and that their previous immunological history, i.e. innoculations against contagious diseases, was identical, and that the determinations were all done according to one method and by one individual.

The average and extreme normal values obtained by this method on thirty normal medical students were as follows: Total serum protein, average 7.55, extremes 6.9-8.6; albumin, average 5.01, extremes 4.0-5.8; globulin, average 2.47, extremes 1.6-3.8. The spread of the extreme values here probably represents uncontrolled variations in environmental factors. It is however, quite clear that the average and extreme values for males tend to be significantly higher than those for females.

A. Review of previous studies.

A reduction of the total plasma proteins during pregnancy has been found by Zangemeister ('03), Zangemeister and Meisel ('06), Eckelt ('19), Landsberg ('10), Dienst ('18), Rusznyak, Berat and Kárthy ('24), Bergmann ('24), Coetzee ('25), Plass and Bogert ('24), Mahnert ('21), Rufinger ('29), Eastman ('30), Dieckmann and Wegner ('34), Mandelier, Meyer and Memon ('40), Bibb ('41), Strauss ('35-'38), and Plass and Matthew ('26). The study by Plass and Matthew ('26) is the most complete in the literature. They find that during normal pregnancy the plasma proteins begin to fall in the third lunar month, or occasionally even before that period, and decrease gradually to a minimum at the ninth month, after which there is a slight rise, with the values at the tenth month still

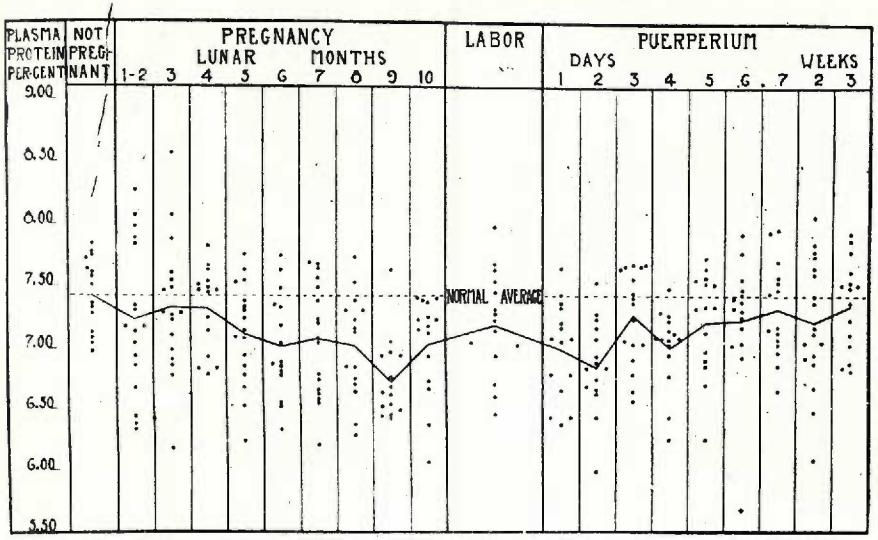
somewhat below normal. A further sharp rise occurs at the time of labor but in the next forty-eight hours the protein suffers an abrupt decrease, which is followed by a gradual rise to normal at the end of the first week. Fahraeus, according to Plass ('26), found the plasma proteins practically the same in five pregnant women as in six normal men. Hafner ('24), using a refractometric method of analysis and an arbitrary normal value, reports that the total proteins are definitely increased during gestation. His results, as has been shown under methods of analysis, are undoubtedly incorrect. Lewinsky ('03) found a higher protein value in four pregnant women than in one non-pregnant individual. The graphs on the following page, reproduced from the work of Plass and Matthew ('26), illustrate the changes which have been found by the great majority of workers.

Less work has been done on the protein fractions during pregnancy. Dienst ('18), Ruszynak, Barat and Kürthy ('24), Coetzee ('25), Plass and Matthew ('26), Plass and Bogert ('24), Dieckmann and Wegner ('34), Eastman ('30), Rufinger ('28), and Strauss ('35-'38), have found the albumin somewhat reduced, although Lewinsky ('03) reports a slight increase. Hafner ('24), without making comparisons with non-pregnant women, finds the albumin slightly lower after delivery than before parturition.

Dienst ('18) and Coetzee ('25) find the globulin decreased during gestation. Plass ('26) states that Fahraeus also noted this. Lewinsky ('03), Ruszynak, Barat, and Kürthy ('24), and Eastman ('30), report an increase, and Hafner ('24) finds a relative increase during pregnancy

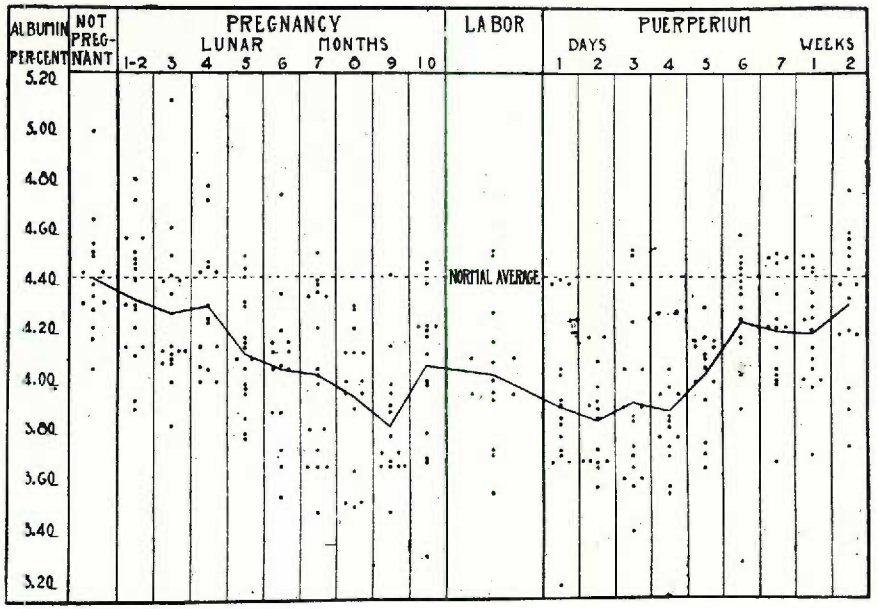
GRAPH III

Total Plasma Proteins During Pregnancy.



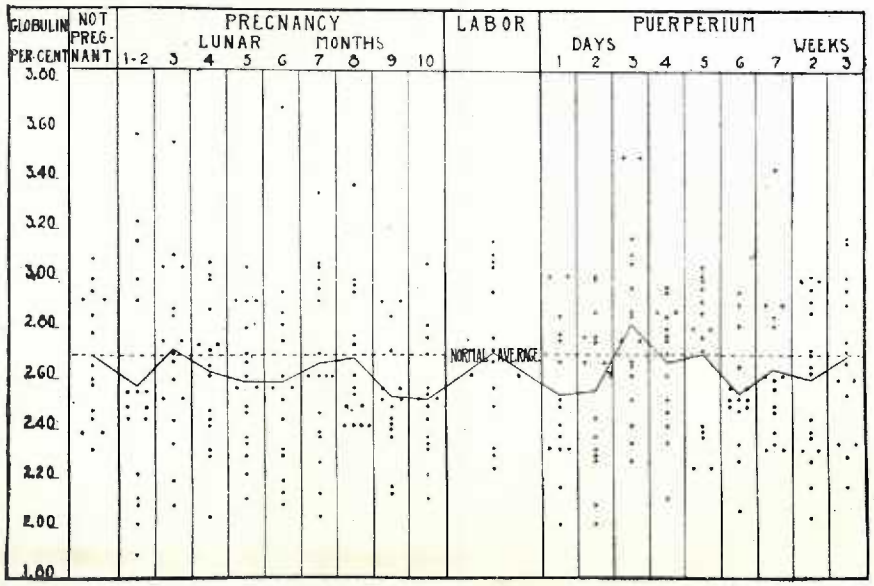
GRAPH IV

Plasma Albumin During Pregnancy.



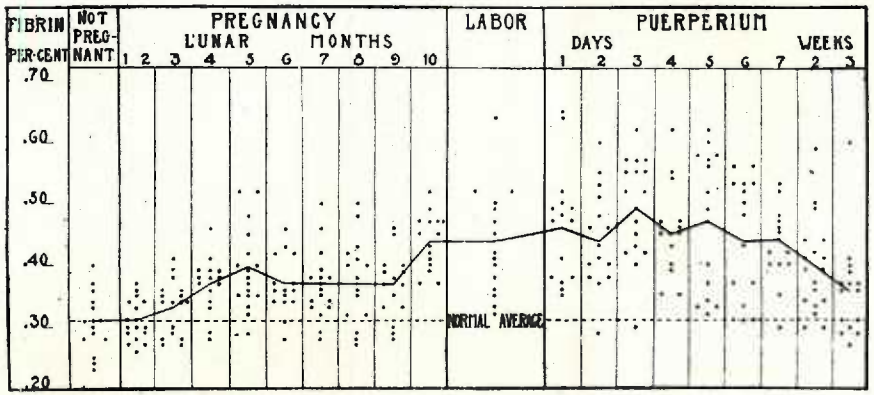
GRAPH V

Plasma Globulin During Pregnancy.



GRAPH VI

Plasma Fibrin During Pregnancy.



Plasma Protein Fractions in Normal Pregnancy, Labor and Puerperium. (After E.D. Plass and C.W. Matthew, Am. J. Obst. & Gyn. 12: 346, 1926)

with a rapid drop in the post-partum period. Plass and Matthew ('26) find no significant change in globulin during pregnancy.

General agreement has been obtained on the changes in fibrinogen during pregnancy. Dienst ('18), Foster ('24), Gram ('21), Lewinsky ('03), Kröeing ('11), Landsberg ('10), Ruznak, Berat and Kürthy ('24), Nasse (1876), de Wesselow ('22), Diechmann and Wegner ('34), Coetzee ('25), Plass and Matthew ('26), and Plass and Bogert ('24) all report that in pregnancy the plasma fibrinogen is augmented. The majority of these authors find a gradual increase during pregnancy with the highest values at the time of labor, although Gram reported his highest average at the eighth lunar month. Kröeing's figures would indicate a rather rapid fall during the early post-partum period.

Only one case of nutritional edema occurring during pregnancy, described as such, has been encountered in the literature. Maxwell ('23) states that this patient had many of the clinical features of eclampsia, including albuminuria and marked edema. This patient was placed on an adequate diet, recovered rapidly, and was subsequently delivered of twins. The blood pressure was not reported.

B. Results of this study.

For convenience our data has been treated on the basis of parity, season, and toxicity, (pre-eclampsia and eclampsia), and further subdivided under total protein, albumin, and globulin. Fibrinogen was not studied since the work in the past has been quite conclusive. All of the determinations were done by the photocolorimetric biuret method of Kingsley ('39-'40) described in the section on analysis, with slight modifications of our own.

The colorimetric determinations were checked at frequent intervals by Kjeldahl analysis of aliquot portions of serum. All dates have been calculated from the date of delivery, except in instances when this was unobtainable, when the calculated date of expectancy is used. All cases of systemic disease accompanying pregnancy, i.e. diabetes, tuberculosis, hyperthyroidism, hypertensive cardiovascular disease, acute or chronic nephritis, and similar conditions, have been excluded from the normal series. Cases included in the toxemic group have been divided into eclampsia and pre-eclampsia on the basis of the criteria of Strauss' ('39), referred to earlier. Specimens were obtained for analysis by venipuncture without prolonged stasis, since stasis has been shown to increase the concentration of serum protein.

Normal pregnancy. Altogether 251 determinations of serum total protein were done on 79 normal pregnant women. Table I and Chart I give the variations observed in this group. It will be noted that the average globulin value remains almost constant throughout, at all times being slightly higher than that of normal non-pregnant women. The total serum protein tends to fall to a minimum during the eighth and ninth month, rising rapidly toward normal following delivery. The values lie between 5.7 and 7.7, average 6.7 grams per hundred cubic centimeters. The lowest point on the entire curve represents a decrease of 7.1 per cent from the non-pregnant average, compared to a 9.3 per cent decrease noted by Plass and Matthew ('26). The most marked changes are found in the albumin fraction. This falls from an average of 4.7 at the beginning of the series (average non-pregnant normal 4.9) to 4.0 during the eighth and ninth months, a decrease of 18.3 per cent from the average non-pregnant normal. Plass and Matthew

Table 1. Serum Protein Variations During Normal Pregnancy

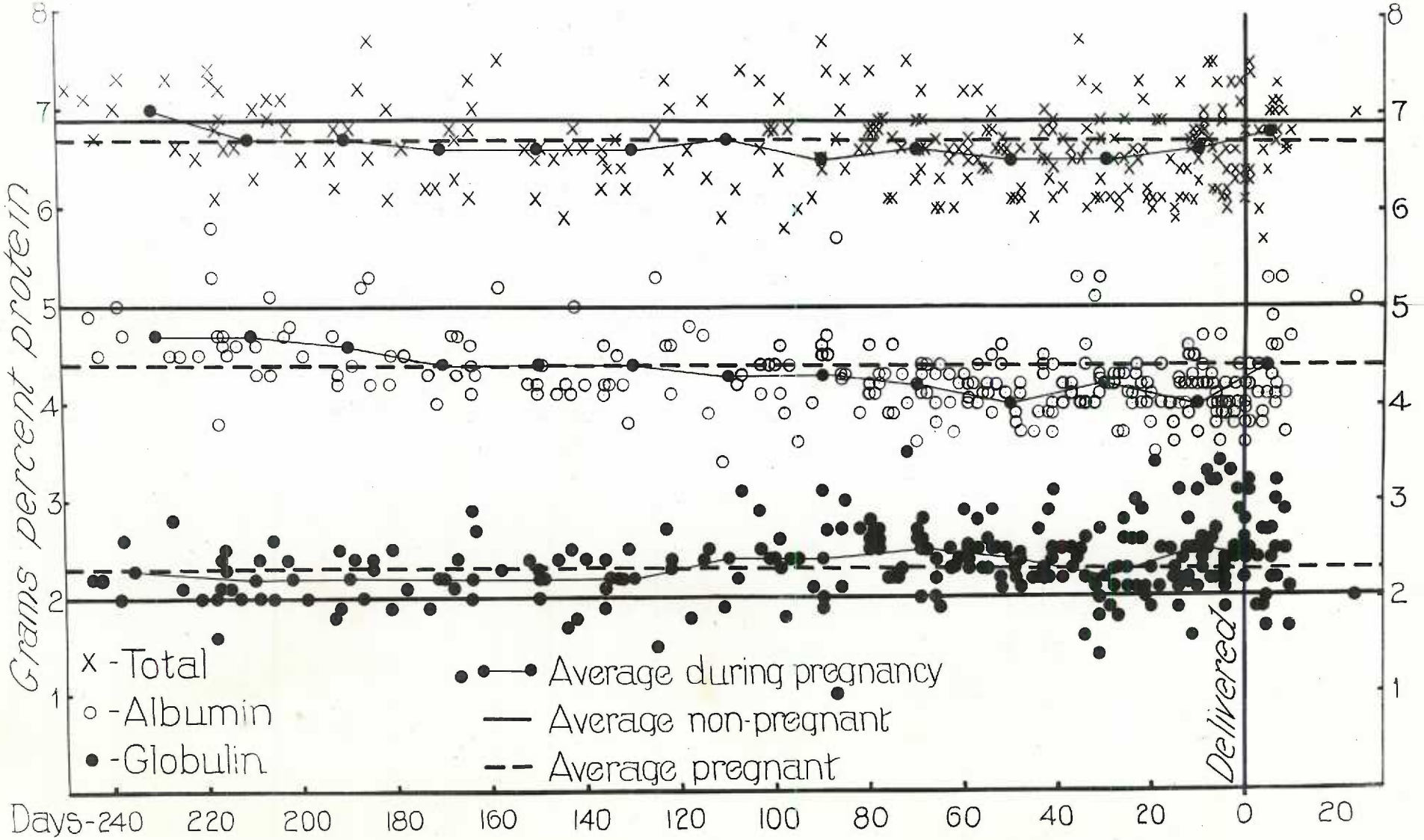
Period	No. of Determinations	Total Serum Protein		Serum Albumin		Serum Globulin	
		Extremes	Average	Extremes	Average	Extremes	Average
Postpartum	23	5.7-7.5	6.8	3.7-5.3	4.4	1.7-3.2	2.4
Delivery--20 days	46	5.9-7.3	6.6	3.5-4.7	4.0	1.6-3.4	2.5
21 days--40 days	34	6.0-7.7	6.8	3.7-5.3	4.2	1.4-3.0	2.2
41 " --60 "	31	5.9-7.2	6.5	3.7-4.6	4.0	2.1-3.1	2.4
61 " --80 "	25	6.0-7.3	6.6	3.6-4.6	4.2	1.9-3.5	2.5
81 " --100 "	18	5.8-7.7	6.5	3.6-4.7	4.3	1.0-3.1	2.4
101 " --120 "	10	5.9-7.4	6.7	3.4-4.8	4.3	1.8-3.1	2.4
121 " --140 "	11	6.2-7.3	6.6	3.8-5.3	4.4	1.5-2.7	2.2
141 " --160 "	10	5.9-7.5	6.6	4.1-5.2	4.4	1.7-2.5	2.2
161 " --180 "	10	6.1-7.5	6.6	4.0-4.7	4.4	1.2-2.9	2.2
181 " --200 "	10	6.1-7.7	6.7	4.2-5.3	4.6	1.6-2.5	2.2
201 " --220 "	14	6.1-7.4	6.7	3.8-5.8	4.7	1.6-2.6	2.2
221 " --250 "	8	6.5-7.3	7.0	4.5-5.0	4.7	2.0-2.8	2.3
Total	251	Average	6.7	Average	4.4	Average	2.3

Table 2. Seasonal Serum Protein Variations During Normal Pregnancy

Period	No. of Determinations	Total Serum Protein		Serum Albumin		Serum Globulin	
		Extremes	Average	Extremes	Average	Extremes	Average
Dec.-Jan.-Feb.	12	6.7-7.8	7.3	4.6-5.7	5.0	1.0-3.1	2.3
Mar.-Apr.-May	114	6.0-7.5	6.6	3.5-5.1	4.2	1.7-3.4	2.4
June-July-Aug.	109	5.5-7.5	6.6	3.4-5.8	4.3	1.3-3.5	2.3
Sept.-Oct.-Nov.	43	6.0-7.5	6.8	3.6-5.0	4.3	1.7-3.4	2.5
Total	278						

Chart I

SERUM PROTEINS DURING PREGNANCY



('24-'35) found a decrease of 13.5 per cent in this fraction. In the thirty-one nonpregnant women studied the albumin constituted 71.5 per cent of the total proteins, whereas at its lowest point in the pregnant series it constituted 61.5 per cent, a decrease of 14 per cent.

Since it seemed that the serum protein level of the subjects might be related to their parity the values obtained on the primipara of the series were plotted separately in chart II. It is obvious from the chart that the curves obtained coincide almost exactly with those plotted for the entire group. The serum proteins, in grams per hundred cubic centimeters, were as follows: total, average 6.7, extremes 5.8-7.7; albumin, average 4.4, extremes 3.6-5.9; globulin, average 2.3, extremes 1.0-3.3.

Since, as has been previously discussed, the serum proteins of the individuals in a given region tend to vary with the season, the values were replotted according to the month in which the specimens were taken without regard for the duration of the pregnancy. These are shown in table 8 and chart III. It is obvious here that, with the exception of the period December-January-February, the seasonal average is nearly constant. The small number of determinations in this December-January-February group decreases the significance of the apparently increased value for total serum protein and serum albumin observed here.

Toxemic Pregnancy. In the five cases of pre-eclampsia studied, a regrettably small number, we found the most marked changes in serum protein level observed in the entire series. If it were not that these findings agree so well with those reported by Ruffinger ('28), Plass ('28), Eastman ('30), and Strauss ('35-'38) we would be inclined to minimize their sig-

Chart II

SERUM PROTEINS DURING PREGNANCY IN PRIMIPARA

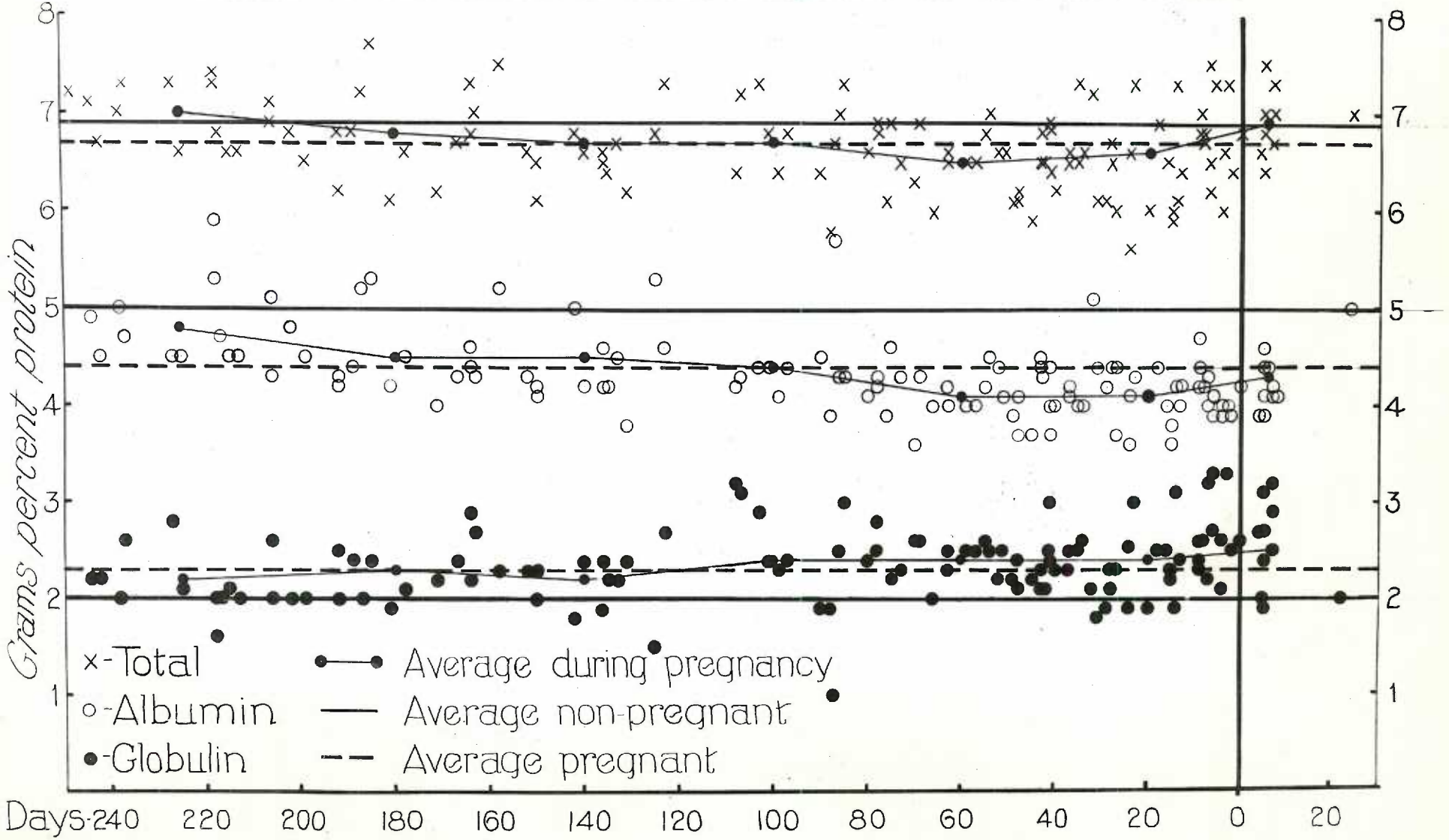
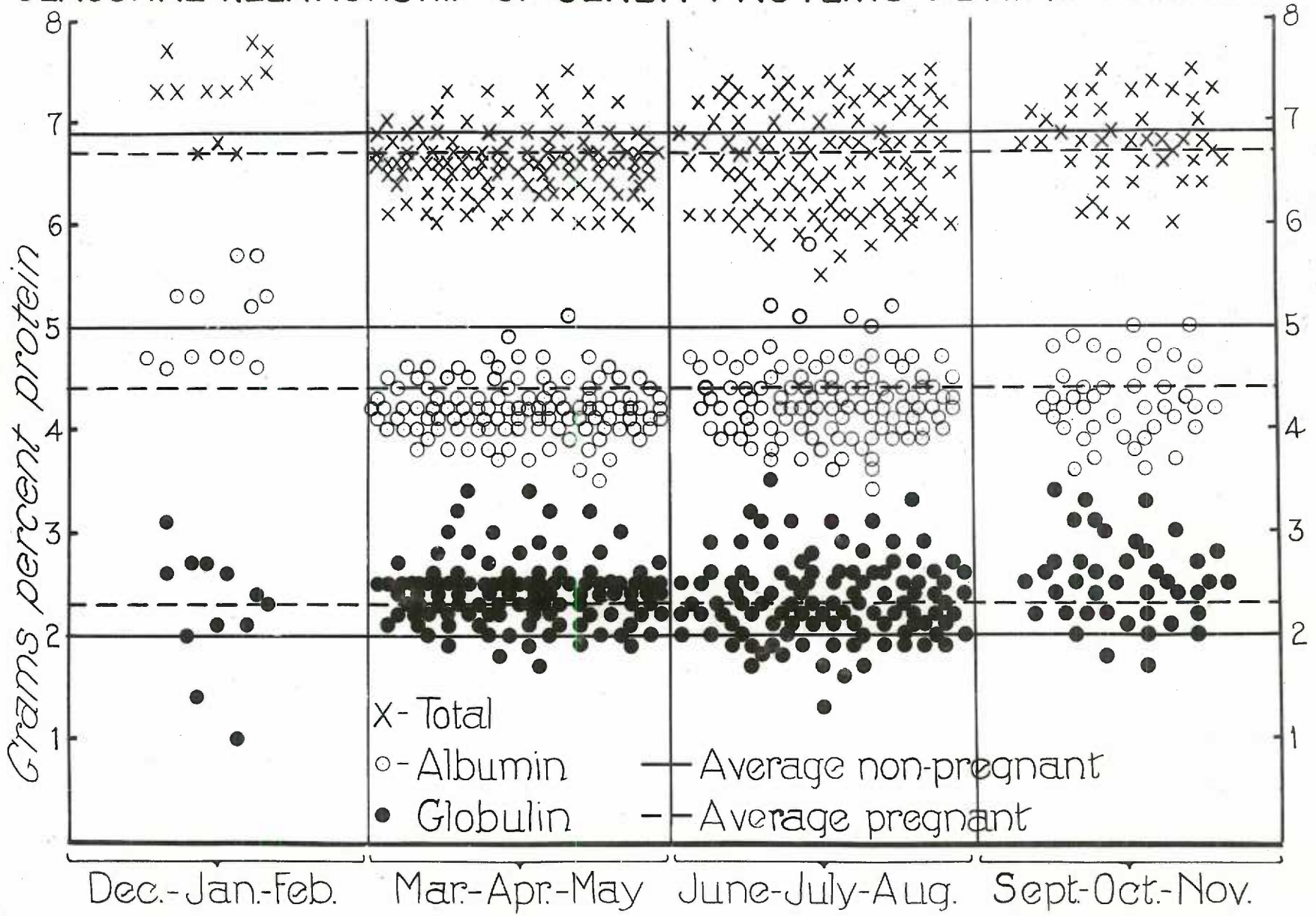


Chart III

SEASONAL RELATIONSHIP OF SERUM PROTEINS DURING PREGNANCY



nificance because of the paucity of cases. In view of the excellent correlation with the results of the above mentioned workers it is our opinion that they represent the true state of the serum proteins in pre-eclampsia. Presentation of the data obtained on these cases is difficult. Table 3 lists the findings statistically but provides no means of comparison. Chart IV gives some idea of the relationship between the serum protein values of these toxemic women and those of normal pregnant and non-pregnant women. The serum proteins in grams per hundred cubic centimeters, shortly before and at delivery, were as follows: total, average 5.6, extremes 4.8-6.4; albumin, average 3.5, extremes 3.0-4.0; globulin was not calculated since the values did not vary appreciably from those found in normal pregnancy. The fall in total protein from the average value obtained in normal non-pregnant women is 18.8 per cent, the fall in albumin according to the same standard is 33.3 per cent. The total protein is 13.8 per cent lower, and the albumin fraction is 12.5 per cent lower, than the lowest average values obtained at any time during normal pregnancy. In these cases the albumin constituted 62.5 per cent of the total protein, giving an albumin/globulin ratio of 1.65. Case number 4, which shows the least lowering of the albumin and total protein, was the mildest of the five cases observed. This patient had a labile blood pressure throughout pregnancy, showing changes in the diastolic pressure of 20-40 mm. of mercury over periods of a few hours. She was included in the series merely because of these border-line pre-eclamptic symptoms, and at no time appeared to be more than mildly "toxic". The cases are all discussed in detail in the attached protocol.

Newborn. In so far as we know no one has studied the serum proteins of maternal and cord blood at the time of delivery. Because of the availability

Table 3. The Serum Proteins in Toxemic Pregnancy

Case Number 1

Time (in days)	Serum Protein (in grams per 100 cc.) Total	Albumin	Globulin	Remarks
6 a.p.	5.2	2.7	2.5	Gained 6 lbs. in 1 wk. B.P. 120/68.
1 "	5.2	2.6	2.6	Headache, generalized edema, B.P. 145/100, low cervical section.
3 p.p.	4.8	3.8	1.0	
8 "	7.0	4.9	2.1	Asymptomatic, B.P. 120/60.
26 "	7.2	4.5	2.7	" " "

Case Number 2

Time (in days)	Serum Protein (in grams per 100 cc.) Total	Albumin	Globulin	Remarks
10 a.p.	6.7	4.3	2.4	B.P. 150/100, otherwise normal.
4 "	5.4	4.3	1.0	B.P. 140/95, albuminuria 3 plus.
2 "	5.6	3.4	2.2	Spontaneous labor, premature, B.P. dropping from 160/100 to 120/80 in 24 hrs.
3 p.p.	5.3	3.3	2.0	No further pertinent data available.
7 "	6.5	3.7	2.8	
11 "	6.1	3.9	2.3	

Case Number 3

Time (in days)	Serum Protein (in grams per 100 cc.) Total	Albumin	Globulin	Remarks
70 a.p.	6.7	4.2	2.6	
39 "	6.6	4.2	2.4	
17 "	6.0	3.7	2.3	B.P. 158/100, moderate edema, hospitalized.
10 "	6.1	3.9	2.1	Headache and epigastric pain.
2 "	6.1	3.6	2.5	Forceps delivery, B.P. 140/108.
1 p.p.	5.7	3.4	2.4	
4 "	6.1	3.9	2.2	B.P. 122/80, asymptomatic.
9 ""	6.4	4.0	2.4	" " "

Case Number 4

Time (in days)	Serum Protein (in grams per 100 cc.) Total	Albumin	Globulin	Remarks
161 a.p.	7.3	4.7	2.6	Blood pressure was labile throughout
140 "	6.4	4.2	2.3	pregnancy. Entered hospital 18 days

Table 3 continued.

Case Number 4 cont.

Time (in days)	Serum Proteins (in grams per 100 cc.) Total	Albumin	Globulin	Remarks cont.
119 a.p.	6.4	4.3	2.1	a.p. with B.P. 130/90 and mild pitting
98 "	6.1	3.6	2.4	edema. Delivered spontaneously with-
77 "	7.0	4.8	2.2	out difficulty, B.P. 175/80 with
56 "	6.5	4.4	2.3	occasional albuminuria. Clinically a
36 "	6.9	4.0	2.9	very mild case of pre-eclampsia.
11 "	6.9	3.6	2.4	
3 "	6.1	4.0	2.2	
5 p.p.	6.4	4.2	2.2	

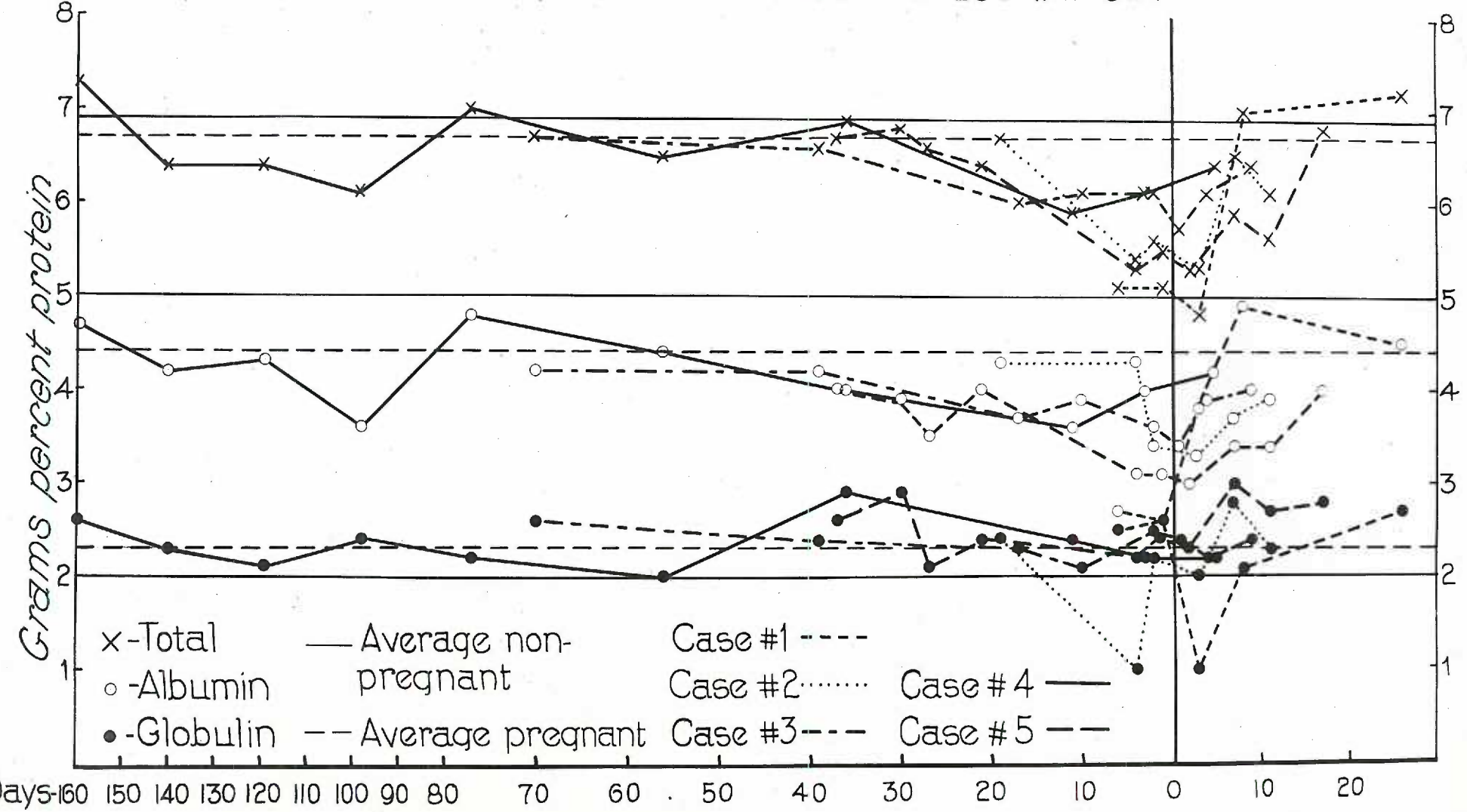
Case Number 5

Time (in days.)	(in grams per 100 cc.) Total	Albumin	Globulin	
37 a.p.	6.6	4.0	2.6	
30 "	6.8	3.9	2.9	B.P. gradually increased to 126/88
27 "	6.6	3.5	3.1	
21 "	6.4	4.0	2.4	Albuminuria 2-3 plus, B.P. 140/90
4 "	5.3	3.1	2.2	Semicomatose, very edematous.
11 "	5.5	3.1	2.4	" " "
2 p.p.	5.3	3.0	2.3	B.P. 126/86, no albuminuria, sympt- amatically much better.
7 "	6.4	3.4	3.0	
11 "	6.1	3.4	2.7	
17 "	6.8	4.0	2.9	Continued to have 1 plus albuminuria.

(a.p. = antepartum, p.p. = postpartum)

Chart IV

SERUM PROTEINS DURING PRE-ECLAMPSIA



of material during the period in which the preceding studies were being made, rather than the hope of obtaining any significant information, we performed 13 determinations of this type. The maternal blood was obtained by the usual method, immediately after delivery of the child. The cord blood was obtained immediately after the second stage of labor. The data obtained is presented in Table 4.

Table 4. The Serum Proteins, in Grams per Hundred Cubic Centimeters, of Maternal and Cord Blood at the Time of Delivery.

Case Number	Maternal			Cord		
	Total	Albumin	Globulin	Total	Albumin	Globulin
1	6.6	4.4	2.2	6.6	4.5	2.1
2	7.2	4.7	2.5	7.0	4.7	2.3
3	6.4	4.1	2.3	6.3	4.2	2.1
4	6.6	4.1	2.5	6.4	4.4	2.0
5	6.8	4.4	2.4	6.1	4.1	2.0
6	6.2	4.4	1.8	5.5	3.8	1.7
7	6.3	4.3	2.0	6.0	4.3	1.7
8	7.1	3.9	3.2	6.3	3.6	2.7
9	6.9	3.9	3.0	6.5	3.9	2.6
10	6.4	3.9	2.5	5.8	3.9	1.9
11	6.0	4.3	1.7	6.5	4.6	1.9
12	5.8	3.8	2.0	6.0	4.3	1.7
13	6.5	4.2	2.4	6.6	4.3	2.3
Average	6.5	4.2	2.3	6.3	4.2	2.1

The individual determinations show some variation, usually an increase in total protein and globulin in the maternal blood. The albumin values are nearly the same in both maternal and cord blood, and when the series is averaged they are exactly the same. The occurrence of a lower level of globulin in most of the cord bloods may be ascribed to the known deficiency of antibodies in the newborn. The most remarkable feature of the whole series is the close correlation between maternal and fetal albumin, indicating that a delicate osmotic balance is maintained across the placenta

IV. DISCUSSION

If the reader is unfortunate enough to have reached this point in this dissertation, he may be consoled by the fact that it is almost finished. We have attempted to present evidence, some admittedly circumstantial, that the so-called "toxemia of pregnancy" in its true form is nothing more than a clinically visible and exaggerated manifestation of the biochemical changes that accompany every pregnancy. It is our belief that the enlarged uterus with its dilated sinusoids introduces both static and dynamic factors interfering with the circulation to the abdominal viscera. By pressure, both direct and transmitted, on the mesenteric and portal vessels it interferes with the absorption and intermediate metabolism of carbohydrate, fat and protein. In shunting of a large portion of the blood in the abdominal aorta through the uterine arteries, sinusoids and veins to the inferior vena cava there is a diminution of the effective pulse pressure in the kidney, with resulting hypertension. This is of course abetted by the pressure of the uterus on the renal vessels. We have, then, the factors necessary for the production of hypertension, albuminuria and edema.

Interference with portal flow leads to an impairment of liver function, hindering an already overtaxed mechanism for the synthesis of protein. This in turn leads to a depletion of the serum proteins, particularly of albumin, with a disturbance of the delicately balanced osmotic relationship between the plasma and the extracellular fluid. This edema, which we see only on the surface of the body is simultaneously permeating all of the organs and tissues, resulting in further interference with their functions. Edema of the brain results in coma and convulsions, as it does

in other conditions. Renal edema is the cause of the cloudy swelling described by the pathologists, and probably accounts for a portion of the hypertension, albuminuria and oliguria. Edema of the intestinal mucosa results in impaired absorption of metabolites including amino acids. This leads to a greater protein deficiency and further edema, thereby instituting a "vicious circle" in the derangement of protein metabolism. Edema of the lungs interferes with aeration of the blood, which in turn slows metabolic processes and may give rise to an acidotic state.

The disturbance of renal hemodynamics results in the appearance of hypertension, with an accompanying increase in the filtration pressure available for forcing fluid through the capillary walls. The impaired renal function due to pressure, edema, and perhaps the action of the vasoconstricting agent present in the circulating blood, leads to salt retention. This retention of salt in turn requires that more water must be retained in the tissues to preserve the isotonicity of the extracellular fluid, causing an increase in the edema.

Obviously there must be predisposing factors present in the maternal organism, or eclampsia would be much more prevalent than it is. Some of these factors may be as follows: Multiple pregnancy, polyhydramnios and hydatid mole; a protein deficient diet; restriction of food and fluid, plus extraperenteral administration of salt solution; anatomical abnormalities of the abdominal viscera or bony pelvis.

The treatment of this condition, with its high fetal and maternal mortality and its predisposition toward hypertension in those who recover, lies not in treating the active disease but in preventing its occurrence. When this is impossible the most active therapeutic measures available

should be instituted as soon as the presence of the condition is discovered.

Prevention involves closely following the weight, blood pressure and urinalysis of every pregnant woman, of insisting on an adequate diet throughout pregnancy, and of doubling these precautions in cases with complications. Therapy always consists of combating water retention, rest and sedation, and sometimes of interruption of pregnancy, although this last is seldom necessary.

Combating water retention. This is best accomplished by elimination of sodium chloride from the diet and, in the presence of adequate urinary output, by allowing the patient to drink as much water as she desires. Any water which the patient takes into her system, if unaccompanied by salt, must be eliminated by the kidneys, and in so doing will remove salt which is already present in excess. This is one condition in which water is an excellent diuretic. We have found it advisable to administer magnesium sulfate, 3 grams daily in the morning, in a glass of water. This small dose does not have a cathartic action, but aids in dehydration, and acts as a mild sedative. As a further aid in combating water retention the feeding of a high protein diet, 100-200 grams per day, is advisable. If the patient's ability to form serum proteins is not appreciably impaired this will assist materially in increasing the colloid osmotic pressure of the blood and in eliminating edema fluid. The urea formed in amino acid breakdown acts as a diuretic. While no work has been done to date, the intravenous administration of human plasma would seem to be an ideal means of increasing the lowered colloid osmotic pressure.

Rest and sedation. This is easily attained by putting the patient to bed, in the hospital if deemed advisable, and administering a mild

sedative. Phenobarbital and chloral hydrate have provided sufficient sedation in the cases we have followed.

Interruption of pregnancy. This is the most important, and most difficult, question to decide in the management of a woman with early toxemia. In this locality it is seldom, if at all, considered before the period of viability. From the standpoint of the mother and of the fetus it is of paramount importance. Fetal mortality is high in toxemia of pregnancy. Moreover, the studies of Peckham ('33) show that fetal mortality increases in proportion to the severity of the toxemia, and that the highest fetal mortality occurs in the cases allowed to progress the longest time after the appearance of toxemia. From the maternal standpoint one must bear in mind the fact previously discussed that the proportion of women with toxemia who subsequently develop essential hypertension, and die prematurely as a result of it, is exceedingly high. Peckham ('41) has recently shown that the incidence of subsequent hypertensive disease is greater the longer and more severe the toxemia. It is my opinion that if the patient is definitely before or after the period of viability, and does not strikingly improve on the measures recommended above, the pregnancy should be terminated at once. The only excuse for delay is in cases where a short wait would bring the fetus to the period of viability.

V. SUMMARY

The object of this investigation was to discover whether or not the values reported in the literature for the serum proteins during normal and toxemic pregnancy were the rule rather than the exception, and if they were of common occurrence to investigate the factors that might give rise to them. The study involved a rather extensive review of the literature on metabolic disturbances occurring during pregnancy, which has been included in the introduction.

Normal subjects were selected at random from the patients presenting themselves at the Prenatal Clinic at the University of Oregon Medical School. All cases of toxemic pregnancy encountered in the clinic were referred to the author for study and treatment during the period of the investigation.

Venous blood was obtained without prolonged stasis at the time of the patient's regular visits to the prenatal clinic. The serum was removed and analyzed for total protein and albumin by the method described.

Normal serum protein values were obtained by analysis of sera from thirty-one healthy nursing students. These agree well with the values reported in the literature.

A total of 251 determinations on the sera of 79 normal pregnant individuals leads to the following conclusions:

1. The average value for serum globulin remains almost constant throughout pregnancy.

2. The average total protein tends to fall from the nonpregnant level at the beginning of pregnancy to a minimum during the eighth and ninth month, rising rapidly to normal following delivery. At its

lowest point this represented a decrease of 7.1 per cent from the non-pregnant average.

3. This decrease in total protein is confined primarily to the albumin fraction. The albumin decreased from a nonpregnant average value of 4.9, to 4.0 grams per hundred cubic centimeters, and represented a decrease of 13.5 per cent.

4. These variations in serum protein are not associated with parity or seasons.

A total of 30 determinations on the serum of 5 pre-eclamptic individuals leads to the following conclusions:

1. The value for serum globulin is normal in this condition.

2. The average value for total protein in these cases was 13.8 per cent below that of normal women in the same stage of pregnancy.

3. This decrease in total protein was confined to the albumin fraction, it being 12.5 per cent lower than the lowest average value obtained at any time during pregnancy, and 33.3 per cent lower than the normal nonpregnant average.

A total of fifteen determinations of serum proteins was performed on samples of maternal and cord serum obtained simultaneously. Slight differences were noted in the total protein content, which were chiefly due to variations in the globulin fraction. The albumin content of maternal and cord serum was nearly identical.

The significance of these changes, their relationship to the metabolism of the organism as a whole, and a scheme for the management of toxemia of pregnancy, are discussed.

VI. PROTOCOL

Case No. 1, unit No. 114608. An 18 year old primipara with a generally contracted pelvis. No history or renal disease. No familial history of hypertension. The pregnancy progressed without incident until the eighth lunar month, at which time there was a rapid increase in weight, albuminuria, headache, generalized edema, and epigastric pain. On a low salt diet in the hospital the visible edema receded and there was no further gain in weight. The blood pressure, however, steadily rose from 120/80 at the onset of her symptoms to 145/100 during the ninth month, at which level it remained until term. After a trial of labor she was delivered of a normal infant by low cervical section. The blood pressure dropped within 24 hours after delivery to 120/80 and remained there during her stay in the hospital. A mild degree of albuminuria persisted following pregnancy. The patient has not been seen since she left the hospital.

Case No. 2, unit No. 113914. A 19 year old primipara with no physical abnormalities. No history of renal disease or familial hypertension. She was perfectly well until late in the seventh lunar month, at which time she developed a feeling of discomfort in the upper abdomen accompanied by a mild degree of generalized edema. At this time her blood pressure was 100/60, there was no albuminuria. She was next seen early in the ninth lunar month, at which time her blood pressure had risen to 150/100 and there was a moderate albuminuria. She was placed on a salt free diet, bed rest and a mild sedation at home. After two weeks of this regime her blood pressure had dropped to 130/90, the other symptoms remaining unchanged. During the next week her blood pressure rose to 140/95. She presented no generalized edema, but there was massive albuminuria. She was hospitalized

and after five days with no change in her symptoms had a spontaneous premature labor. At this time the blood urea nitrogen was 16 mgms. per 100 cc., the alkali reserve 72 volumes per cent, blood dextrose 132 mgms. per 100 cc. and the blood sodium chloride 480 mgms. per 100 cc. Her blood pressure immediately dropped to 120/80 from 160/100, and remained at that level. Ten days following delivery the blood urea nitrogen was 20 mgms. per 100 cc. and the urea clearance, maximal, was 73.4 per cent of normal. On discharge from the hospital 18 days following delivery there was a slight albuminuria. She has not been seen since.

Case No. 3, unit No. 112874. An 18 year old primipara with no physical abnormalities. No history of renal disease or familial hypertension. Her pregnancy progressed normally until early in the ninth lunar month at which time her blood pressure rose from a normal level to 150/100, she developed a headache and epigastric pain, and there was a rapid gain in weight accompanied by generalized edema. At no time did she have any marked albuminuria. The blood pressure varied between 160/100 and 140/100 after a five day period of hospitalization on the regime we have recommended. Because of the persistent hypertension she was medically stimulated and delivered of a normal infant. Shortly before delivery the blood urea nitrogen was 11 mgms. per 100 cc., and the blood dextrose was 68 mgms. per 100 cc. Following delivery the blood pressure dropped to 122/80 accompanied by a disappearance of the other symptoms.

Case No. 4, unit No. 117665. A 22 year old primipara with no physical abnormalities. No history of renal disease. Mother had hypertension. Throughout the entire pregnancy the blood pressure was labile, varying over a wide range at hourly intervals. She had no albuminuria

at any time and no systemic symptoms. She was hospitalized late in the ninth lunar month because of a blood pressure of 138/90. After three days rest in bed on the recommended regime the blood pressure dropped to 120/80, but in view of the previous fluctuations little significance can be attached to this. She signed her own release, against our advice after a short period of hospitalization. She reentered the hospital again in a few days in active labor with a blood pressure of 175/80. Albuminuria varied from mild to moderate during the weeks immediately preceding and following delivery. Shortly before delivery the dilution and concentration test was normal, in spite of the low salt diet, and at the same time the urea clearance was 69 per cent of normal. On discharge from the hospital her blood pressure was 120/80, no albuminuria.

Case No. 5, unit No. 103339. A 30 year old primipara with no physical abnormalities. No history of renal disease or familial hypertension. Throughout pregnancy there was a gradual increase in the diastolic pressure, from 120/74 during the third month to 126/88 early in the ninth month. During the eighth and ninth months there was a moderate to severe albuminuria. Her weight increased very rapidly during this period and there developed marked generalized edema. At its maximum, shortly before delivery, the blood pressure was 160/96, but rapidly fell to 126/76 following delivery. Labor was induced a little before full term by rupture of the membranes. She continued to have mild albuminuria for two months following delivery, after which time the urine became normal.

BIBLIOGRAPHY

Addis, T., Poo. L.J., and Lew, W., Protein Loss From the Liver During a Two-day Fast. J. Biol Chem. 115: 117-118, 1936.

Alving, A.S., and Mirsky, A.E., The Nature of the Plasma and Urinary Proteins in Nephrosis. J. Clin Invest. 15: 215, 1936.

Autenrieth, W., Ueber Kolorimetrische Bestimmungsmethoden: Die Bestimmung von Serumalbumin und Globulin in Harn, in der Aszitesflussigkeit und im Blutserum. Münch. med. Woch., 64: 241, 1917.

Autenrieth, W., and Mink, F., Ueber Kolorimetrische Bestimmungsmethoden: die quantitative Bestimmung von Harneiweiss. Münch. med Woch., 62: 1417, 1915.

Bartholomew, R.A. and Krucke, R.R. The Relation of Placental Infarcts to Eclamptic Toxemia. Am. J. Obst & Gyn. 24: 797, 1932.

_____, The Probable Role of the Hypercholesteremia of Pregnancy in Producing Vascular Changes in the Placenta, Predisposing to Placental Infarction and Eclampsia. Am. J. Obst. & Gyn. 31: 549-562, 1936.

Bartholomew, R.A., and Parker, F., A Possible Derivation of Guanidine and Histamine in the Autolysis of Acute Placental Infarcts and Their Probable Relation to Eclamptic Toxemia. Am. J. Obst. & Gyn. 27: 67, 1934.

Beck, A.C., Obstetrical Practice. Williams & Williams Co., Baltimore, 1939.

Bell, E.T., Renal Lesions in the Toxemias of Pregnancy. Am. J. Path. 8: 1, 1932.

Bergmann, E., Serumiweiss und Erythrocytenbestimmung an gesunden und Hydropischen Schwangeren. Zentralbl. f. Gyn. 48: 1346-1351, 1924.

Bergmann, M., The Structure of Proteins in Relation to Biological Problems. Chem. Rev. 22: 425, 1938.

Bibb, J.D., Protein and Hemoglobin in Normal and Toxic Pregnancies. Am. J. Obst. & Gyn. 42: 103, 1931.

Bierry, H., and Vivario, R., Dosage des Albumins Globules du Plasma Sanguin. Compt. Rend. Soc. Biol. 89: 13, 1923.

_____, Etude Comparative des Proteines Plasmatiques chez l'Homme a l'etat Normal et a l'etat Pathologique. Compt. Rend. Soc. Biol. 89: 15, 1923.

Binger, M.W., and Keith, N.M., General Edema of Indeterminate Etiology. J.A.M. 109: 2-6, 1937.

Blalock, A., Experimental Hypertension. Physiol. Rev. 20: 159-193, 1940.

Blanco, J. T., Einege Besonderheiten des Kohlenhydratstoffwechsels in der Schwangerschaft in Verbindung mit der Leberfunktion. Arch. für Gynäk. 161: 243, 1936.

Bloomfield, A.L., The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat. J. Exp. Med. 57: 705, 1933.

Bogelmann, O., and Rether, J., Beitrag zur Frage der Neutralitätsregulation in der Schwangerschaft. Klin. Wchnschr. 7: 543, 1928.

Bollman, J.L., Some Experimental Observations Pertinent to Treatment of Hepatic Disease. Ann. Int. Med. 12: 2-5, 1938.

Bollman, J.L. and Mann, F.C. Studies of the Physiology of the Liver. XVIII. The Effect of Removal of the Liver on the Formation of Ammonia. Am. J. Physiol. 92: 92, 1930.

_____, Alterations in Hepatic Function Produced by Experimental Hepatic Lesions. Ann. Int. Med. 9: 617-624, 1935.

Bollman, J.L., Mann, F.C., and Magath, T.B., Studies on the Physiology of the Liver, VIII. Effect of Total Removal of the Liver on the Formation of Urea. Am. J. Physiol. 69: 371, 1924.

Borsook, H., and Keighley, G.L., The "Continuing" Metabolism of Nitrogen in Animals. Proc. Roy. Soc. 118B: 498, 1935.

Botella-Llugia, J., Stickstoffwechselveränderungen während der Schwangerschaft ihre Beziehungen zur Leberfunktion. Arch. fur Gynäk. 161: 254, 1936.

Boyd, E.M., Lipemia of Pregnancy. J. Clin. Invest. 13: 347, 1934.

_____, Blood Lipids in Eclampsia. Am. J. Obst. & Gyn. 30: 323, 1935.

_____, Blood Lipids in Pre-eclampsia. Am. J. Obst. & Gyn. 32: 937, 1936.

Boyd, E.M., and Fellows, M., Blood Lipids During Pregnancy in Guinea Pigs. Am. J. Physiol. 114: 635, 1936.

Boyd, E.M., and Wilson, K.M., The Exchange of Lipids in the Umbilical Circulation at Birth. J. Clin. Invest. 14: 7, 1935.

Browne, F.J., and Dodds, C.H., Cause of Hypertension in Pre-eclamptic Toxemia; Study of Blood Pressure in Mother and Infant. Lancet 1: 1059-1060, 1936.

Browne, J.S.L., Henry, J.S., and Venning, E.H., The Urinary Excretion of Prolan, Estrin, and Pregnandiol in Normal Pregnancy and in Early and Late Pregnancy Toxemia. J. Clin. Invest. 17: 503, 1938.

Bunker, C.W.D., and Mundell, J.J., The Value of Blood Chemistry in Pregnancy. J.A.M.A. 83: 836, 1924.

Burwell, C.S., Strayhorn, W.D., Flickinger, D., Corlette, M.B., Bowerman, E.P., and Kennedy, J.A., Circulation During Pregnancy. Arch. Int. Med. 62: 979, 1938.

Butt, H.R., Snell, A.M., and Keys, A., Plasma Proteins in Hepatic Disease: A Study of the Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of the Liver. Arch. Int. Med. 63: 143, 1939.

Büttner, O., Statistik und Klinik der Eclampsie im Grossherzogtum Mecklenburg-Schwerin. Arch. f. Gyn. 70: 322, 1903.

Caldwell, W.E., and Lyle, W.G., The Blood Chemistry in Normal and Abnormal Pregnancy. Am. J. Obst. & Gyn. 2: 17, 1921.

Cantarow, A., Changes in the Blood Following Repeated Withdrawal of Ascitic Fluid in Cirrhosis of the Liver. Am. J. Clin. Path. 8: 142, 1938.

Ceelen, W., Über Eklamptische Leberveränderungen. Virchow's Arch. f. Path. Anat. u. Phys. 201: 361, 1910.

Chanutin, A., Hortenstine, J.C., Cole, W.S., and Ludwig, S., Blood Plasma Proteins in Rats Following Partial Hepatectomy and Laparotomy. J. Biol. Chem. 123: 247-256, 1938.

Chesley, L.C., The Validity of the Calculation of Standard Urea Clearances from Low Urine Volumes. J. Clin. Invest. 16: 653, 1937.

_____, Certain Laboratory Findings and Their Interpretation in Eclampsia. Am. J. Obst. & Gyn. 38: 430, 1938.

_____, Urea Excretion at Low Urine Volumes. The calculation of "Minimal" urea Clearances. J. Clin. Invest. 17, 119, 1938.

_____, Renal Excretion at Low Urine Volumes and the Mechanism of Oliguria. J. Clin. Invest. 17: 591, 1938.

_____, Renal Function Tests in the Differentiation of Bright's Disease from the So-called Specific Toxemia of Pregnancy. Surg., Gyn., & Obst. 67: 481, 1938.

_____, An Analysis of Some Factors Associated with Post-toxemia Hypertension. Am. J. Obst. & Gyn. 41: 751-764, 1941

_____. The Question of Glomerular Damage Following Toxemia of Pregnancy. Am. J. Obst. & Gyn. 42: 229, 1941.

Chesley, L.C., Connell, E.J., Chesley, E.R., Katz, J.D., and Glissen, C.S., The Diodrast Clearance and Renal Blood Flow in Toxemias of Pregnancy. J. Clin. Invest. 29: 219-224, 1940.

Chesley, L.C., and Somers, W.H., Eclampsia and Post-eclamptic Hypertension. Surg., Gyn., & Obst. 72: 872, 1941.

Clements, A.B., Placental Necrosis. Am. J. Obst. & Gyn. 27: 84, 1934.

Coetzee, L.J., The Plasma Proteins in Normal and Abnormal Pregnancy. Proc. Roy. Soc. Med. 18: 28, 1925.

Cohen, S.L., Marrian, G.F., and Watson, M., Excretion of Oestrin During Pregnancy. Lancet, 1: 674, 1935.

Cope, C.L., Excretion of Pregnandiol in Toxemias of Pregnancy. Lancet, 2: 158-159, 1940.

Corbit, J.D., The Effect of Pregnancy Upon Experimental Hypertension in the Rabbit. Am. J. Med. Sci. 201: 876, 1941.

Corcoran, A.C., and Page, I.H., Observations on the Relation of Experimental Hypertension to Renal Clearance and Renal Ischemia. Am. J. Physiol. 123: 1938.

_____. Renal Function in Late Toxemia of Pregnancy. Am. J. Med. Sci., 201: 385, 1941.

_____. Arterial Hypertension. J.A.M.A. 116: 690-694, 1941.

_____. Renal Aspects of Experimental and Clinical Hypertension. J. Lab. & Clin. Med. 26: 1713-1728, 1941.

Corcoran, A.C., Smith, W.H., and Page, I.H., The Removal of Diodrast from Blood by the Dog's Explanted Kidney. Am. J. Physiol. 134: 333-337, 1941.

Crabtree, E.G., Abramson, D., and Robins, S.H., The Effect of Pregnancy on the Excretion of Intravenous Diodrast in Rabbits. Surg., Gyn. & Obst. 71: 60, 1940.

Cross, R.C., A Study of Various Liver Function Tests in Normal Pregnancy. Am. J. Obst. & Gyn. 18: 800, 1929.

De Vries, E., Acute Diseases of the Brain Due to Functional Disturbances of the Circulation. Arch. Neur. & Psych. 25: 227, 1931.

De Wesselow, O.L., Some Chemical Observations on the Toxemias of Pregnancy. J. Obst. & Gyn. Br. Emp. 29: 21, 1922.

Dieckmann, W.J., Further Observations on the Hepatic Lesion in Eclampsia. Am. J. Obst. & Gyn. 18: 757, 1929.

_____, Serum Colloid Osmotic Pressure in Normal Pregnancy. Proc. Soc. Exp. Biol. & Med. 32: 1127-1129, 1935.

_____, Blood and Plasma Volume Changes in Eclampsia. Am. J. Obst. & Gyn. 32: 927-936, 1936.

_____, Therapy of Eclampsia. Am. J. Obst. & Gyn. 33: 165-173, 1937.

_____, The Cold Presser Test in Pregnancy. Am. J. Obst. & Gyn. 36: 408, 1938.

_____, Therapy of Eclampsia. Am. J. Surg. 48: 101-111, 1940.

Dieckmann, W.J., and Brown, I., Do Eclampsia and Pre-eclampsia Cause Permanent Renal Vascular Damage. Am. J. Obst. & Gyn. 37: 762, 1939.

Dieckmann, W.J., and Kramer, S., Edema in Pre-eclampsia and Eclampsia. Am. J. Obst. & Gyn. 41: 1-16, 1941.

Dieckmann, W.J., and Wegner, C.R., Studies of the Blood in Normal Pregnancy. IV. Percentages and Grams per Kilogram of Serum Protein and Fibrin. Arch. Int. Med. 53: 353, 1934.

Dienst, A. Die Eiweissstoffe im Blutplasma unter Normalen Verhältnissen in der Schwangerschaft und bei der Eklampsie, zugleich ein Beitrag zur Fibrinogenfrage und zur Pathogenese der Eklampsie. Arch. f. Gynäk. 109: 669-702, 1918.

Dietl, H. Zur Funktion der Leber in der Schwangerschaft. Arch f. Gynäk. 161: 242, 1936.

Dill, L.V., and Erickson, C.C., Eclampsia-like Syndrome Occurring in Pregnant Dogs and Rabbits Following Renal Artery Constriction. Proc. Soc. Exp. Biol. & Med. 39: 362, 1938.

Dill, L.V., and Isenhour, C.E., The Effect of Pregnancy on Experimentally Produced Renal Injury. Am. J. Obst. & Gyn. 41: 675, 1941.

Dodd, K., and Minot, A.S., Edema in Infancy and Childhood as an Expression of Chronic Dietary Insufficiency. J. Pediat. 8: 442, 1936.

_____, The Occurrence of Moderately Reduced Serum Albumin in Five Hundred Children in a Southern Clinic. J. Pediat. 8: 452, 1936.

Dodge, E.F., and Frost, T.T., Relation Between Blood Plasma Proteins and Toxemias of Pregnancy. J.A.M.A. 111: 1698, 1938.

Drury, D.R., and McMaster, P.D., Liver as a Source of Fibrinogen. J. Exp. Med. 50: 569, 1929.

Eastman, N.J., The Serum Proteins in the Toxemias of Pregnancy. Am. J. Obst. & Gyn. 20: 343, 1930.

Ebeler, F., Ueber Früheklampsie. Ztschr. f. Geb. und Gyn. 79: 536, 1916-17.

Eckelt, K., Zur Genese der Symptome der Schwangerschaftsniere. Ztschr. f. Geb. und Gyn. 81: 1-29, 1919.

Elden, C.A., Sinclair, F.D., Jr., and Rogers, W.C., The Effect of the Toxemias of Pregnancy on Renal Function. J. Clin. Invest. 15: 317, 1936.

Elman, R., and Heifetz, C.J., Experimental Hypoalbuminemia. Its Effect on the Morphology, Function, and Protein and Water Content of the Liver. J. Exp. Med. 73: 417, 1941.

Eufinger, H., Die Kolloidstruktur des Plasmas während der Graviditat. Klin. Wchschr. 7: 492, 1928.

Fahr, T., Über Nierenveränderungen bei Eklampsie. Zentralbl. f. Gyn. 44: 991, 1920.

_____, Über die Nierenveränderungen bei der Eklampsie und ihre Abgrenzung gegen andere Formen des Morbus Brightii. Zentralbl. f. Gyn. 52: 474, 1928.

Falls, F.H., A critical Study of Five Hundred Cases of Eclampogenic Toxemia. Am. J. Obst. & Gyn. 29: 316, 1935.

Farr, C.B., and Williams, P.F., The Total NPN of the Blood in Pregnancy and Eclampsia. Am. J. Med. Sci. 148: 556, 1914.

Fine, J., The Biuret Method of Estimating Albumin and Globulin in Serum and Urine. Biochem. J., 29: 799, 1935.

_____, Determination of Fibrin by the Biuret Reaction. J. Lab. & Clin. Med. 21: 1084, 1936.

Fishberg, A.M., Hypertension and Nephritis. Lea & Febiger, Philadelphia, 1939.

Foley, H.F., Keeton, R.W., Kendrick, A.B., and Darling, D., Alterations in Serum Protein as an Index of Hepatic Failure. Arch. Int. Med. 60: 64-76, 1937.

Folin, O., and Denis, W., The Quantitative Determination of Albumin in Urine. J. Biol. Chem. 18: 273, 1914.

Foster, D.P., A Clinical Study of Blood Fibrin with Observations in Normal Persons, Pregnant Women, and in Pneumonia and Liver Disease. Arch. Int. Med. 34: 301-312, 1924.

Frank, R.T., Goldberger, M.A., and Spielman, F., A Method of Demonstrating Prepituitary Maturity Hormone in the Blood of Non-pregnant Women. Proc. Soc. Exp. Biol. & Med. 28: 999, 1931.

Fuerstner, P.G., and Sargent, F., Heteertropism in the Etiology and Pathogenesis of Eclampsia. J. Lab. & Clin. Med. 25: 779-788, 1940.

Gamble, J.L., Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid, a Lecture Syllabus. Spaulding-Moss Co., Boston, 1941.

Gammeltoft, S.A., Recherches sur le Debit Cardiaque par Minute Pendant la Grossesse. Compt. Rend. Soc. Biol. 94: 1099, 1926.

Goettsch, E., and Kendall, F.E., Analysis of Albumin and Globulin in Biological Fluids by the Quantitative Precipitin Method. J. Biol. Chem. 109: 221, 1935.

Goettsch, E., and Lyttle, J.D., Precipitin Studies of Nephrosis and Nephritis. J. Clin. Invest. 19: 9, 1940.

Goettsch, E., and Reeves, E.B., Observations on the Nature of Serum Proteins in Nephrosis. J. Clin. Invest. 15: 173, 1936.

Goldblatt, H., Studies on Experimental Hypertension. V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia. Ann. Int. Med. 11: 69, 1937.

Goldblatt, H., Lynch, J., Hanzal, R.F., and Summerville, W.W., The Production of Persistent Hypertension in Dogs. Am. J. Path. 9: 942, 1933.

Goldblatt, H., Lynch, J., Hanzal, R.F., and Summerville, W.W., Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia. J. Exp. Med. 59: 347, 1934.

Goldblatt, H., Weinstein, H., and Kahn, J.R. Studies on Experimental Hypertension. XIV. The Effect of Intermittent Renal Arterial Occlusion on the Blood Pressure of the Dog. J. Exp. Med. 37: 439, 1941.

Govaerts, P., Influence de la Teneur du Serum en Albumines et en Globulines sur la Pression Osmotique des Proteines et sur la Formation des Oedemes. Bull. Acad. Roy. de Med. de Belgique. 7: 356, 1927.

_____, Etude de la Composition du Liquide d'Oedeme dans un Cas "d'Oedeme de Quincke." Compt. Rend. Soc. Biol. 99: 339, 1928.

Gram, H.C., On the Causes of Variations in the Sedimentation of the Corpuscles and the Formation of the "Crusta Phlogista" (size, "Buffy coat") of the Blood. Arch. Int. Med., 28: 312-330, 1921.

Grollman, A., The Cardiac Output of Man in Health and Disease. Charles C. Thomas, Springfield, Ill., 1932.

Gruhzit, O.M., Toxemias of Pregnancy from a New Aspect. Am. J. Obst. & Gyn. 5: 400, 1923.

Guillaumin, C.O., Wahl, R., and Lauroncin, M.L. Sur le Dosage des Albumines Seriques. Comparison de Quelques Resultats Obtenus par Pesee, par Azotometrie, et par Refractometrie. Bull. Soc. Chim. Biol. 11: 387, 1929.

Hafnew, E.A., Ueber den Globulin und Albuminkoeffizienten des Serums Besonders Während der Schwangerschaft. Arch. f. Exp. Path und Pharmakol. 101: 335, 1924.

Hammerschlag, R., Die Eklampsie in Ostpreussen. Monatschr. f. Geb. und Gyn. 20: 475, 1904.

Hand, H.M., Concentration of Serum Proteins in Different Types of Edema. Arch. Int. Med. 54: 215-238, 1934.

Harden, B., McIlroy, W.S., and Huggins, R.R., Therapy of Eclampsia by Protein Feeding. Am. J. Obst. & Gyn. 30: 524-533, 1935.

Harding, V.J., Allin, K.D., and Van Wyck, H.B., NPN and Uric Acid Values in Blood in Pregnancy. J. Obst & Gyn. Br. Empire. 31: 595, 1924.

Hare, D.C., and Karn, M.N., An Investigation of Blood Pressure, Pulse-Rate, and the Response to Exercise During Normal Pregnancy and Some Observations after Confinement. Quart. J. Med., 22: 381, 1928-29.

Harrar, J.A., Concerning One Hundred and Fifty Cases of Eclampsia in the Lying-in Hospital of New York. Bull. Lying-In Hosp., N.Y. 2: 72, 1905.

Harrow, B., Textbook of Biochemistry. W.B. Saunders Co., Philadelphia, 1940.

Hauch, E., and Lehman, K., Investigations into the Occurrence of Eclampsia in Denmark During the Years 1918-1927. Acta Obstet. et Gyn. Scandinavia. 14: 425, 1934.

Haupt, W., Das Minutenvolumen des Herzens bei Wochnerinnen. Arch. f. Gyn. 132: 33, 1927.

Heinrichdorff, P., Die Anatomischen Veranderungen der Leber in der Schwangerschaft. Zeitschr. f. Geb. und Gyn. 70: 620, 1912.

Hellman, L., Reid, D.E. and Moore, R.A., The Lipid Amino Nitrogen in Eclampsia. Am. J. Obst. & Gyn. 38: 631, 1939.

Hewitt, L.F., Urine Proteins in Nephrosis, Pregnancy, and Myelomatosis. Lancet, 1: 66, 1929.

Hirschheimer, A., The Synthesis and Excretion of Hippuric Acid in Pregnancy. Am J. Obst. & Gyn. 29: 395, 1935.

_____, The Hippuric Acid Excretion Test in Pregnancy. Am. J. Obst. & Gyn. 37: 363, 1939.

Hofbauer, J., Therapy of Eclampsia. Am. J. Obst. & Gyn., 26: 311, 323, 1933.

_____, Hepatopathia Gravidarum und die Pathogenese der Eklampsie. Zentralbl. f. Gyn. 1: 35, 1933.

_____, Pathogenicity of Eclampsia. Zentralbl. f. Gyn. 61: 2482, 1937. Abstracted in Am. J. Obst. & Gyn. 37: 903, 1939.

Hiller, A., Determination of Albumin and Globulin in Urine. Proc. Soc. Exp. Biol. Med. 24: 385, 1927.

Hiller, A., McIntosh, J.F., and Van Slyke, D.D., The Excretion of Albumin and Globulin in Nephritis. J. Clin. Invest., 4: 235, 1927.

Holman, R.L. and Mebane, J.G., The Influence of Nitrogen Retention Upon the Regeneration of the Plasma Proteins. J. Exp. Med. 71: 299, 1940.

Howe, P.E., The Function of the Plasma Proteins. Physiol. Abst. 5: 439, 1925.

Hunt, H.F., Patterson, W.B., and Nicodemus, R.E., Placental Infarction in the Etiology and Pathogenesis of Eclampsia. Am. J. Clin. Path. 10: 319-331, 1940.

Hynd, A., On the Nature of Urinary Protein, with Special Reference to Eclampsia. Lancet, 2: 910, 1925.

Ivanyi, Rodecurt, and Linzenmeier. Blutalk- und Blutphosphorbestimmungen bein Normaler und Pathologischer Schwangerschaft. Zentralbl. f. Gyn. 50, 731, 1926.

Iversen, P., Untersuchungen uber die Ascites-Pathogenese. Klin. Wchnschr. 7: 2001, 1928.

Johnson, H.W., Role of Tyramine in Pathogenesis of Toxemias of Pregnancy. Surg., Gyn., & Obst. 70: 513-516, 1940.

Jones, T.B., and Smith, H.P., Blood Fibrinogen Level in Hepatectomized Dogs and an Outline of a Method for the Quantitative Determination of Fibrinogen. Am. J. Physiol. 94: 144, 1930.

Kaufmann, C., Uber die Schwangerschaftsleber. Zeitsch. f. Geb. und Gyn. 99: 562, 1931.

_____, Uber die Schwangerschaftsumstellung der Leberfunktion. Klin. Wchnschr. 11: 493, 1932.

Keefer, C.S. Edema--Its Pathologic Physiology and Clinical Significance. Internat'l. Clinics. 2: 85, 1933.

Kellar, R.J., Arnett, W.M., and Matthew, D., Observations of the Morbid Histology of the Kidney in Eclampsia and Other Toxemias of Pregnancy. J. Obst. & Gyn. Br. Emp. 44: 320, 1937.

Kerr, W.J., Hurwitz, S.H., and Whipple, G.H., III. Liver Injury Alone; Liver Injury and Plasma Depletion; the Eck Fistule Combined with Plasma Depletion. Am. J. Physiol. 37: 379, 1918.

_____, Regeneration of the Blood Serum Proteins. I. Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion. Am. J. Physiol. 47: 356, 1918.

_____, II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion. Am. J. Physiol. 47: 370, 1918.

Killian, J.A., and Sherwin, C.P., Some Chemical Studies in Normal and Abnormal Pregnancies. I. Significant Changes in the Blood of the Toxemias of Pregnancy. Am. J. Obst. & Gyn. 2: 6, 1921.

King, E.L., and Denis, W., Uric Acid in the Blood in the Toxemias of Pregnancy. Am. J. Obst. & Gyn. 7: 409, 1924.

_____, Liver Function Tests in the Toxemias of Pregnancy. Am. J. Obst. & Gyn. 12: 577, 1926.

Kingsley, G.R., The Determination of Serum Total Protein, Albumin and Globulin by the Biuret Reaction. J. Biol. Chem. 131: 197, 1939.

_____, A Rapid Method for the Seperation of Serum Albumin and Globulin. J. Biol. Chem. 133: 731, 1940.

Knutti, R.E., Erickson, C.C., Madden, S.C., Bakers, P.E., and Whipple, G.H., Liver Function and Blood Plasma Protein Formation. Normal and Eck Fistula Dogs. J. Exp. Med. 65: 455, 1937.

Kohlstaedt, K.G., and Page, I.H., The Liberation of Renin by Perfusion of Kidneys Following Reduction of Pulse Pressure. J. Exp. Med. 72: 201, 1940.

Konstantinowitsch, N., Beitrag zur Kenntnis der Leberveränderungen bei Eklampsie. Beitr. Z. Path. Anat. u.z. Allg. Path. 40: 482, 1907.

Kosser, J.H., Observations on the Possible Relationship of Diet to the Late Toxemia of Pregnancy. Am. J. Obst. & Gyn. 41: 888-94, 1941.

Krebs, A.K., Untersuchungen über den Stoffwechsel der Aminosäuren im Tierkörper. Z. Physiol. Chem. 217: 191, 1933.

Krebs, A.K., and Henseleit, K., Untersuchungen über die Harnstoffbildung im Tierkörper. Z. Physiol. Chem. 210: 33, 1932.

Krebs, C.S., and Briggs, A.P., Blood Studies in Normal Pregnancy. Am. J. Obstet. & Gyn. 5: 67, 1923

Krogh, A., Landis, E.M., and Turner, A.H., The Movement of Fluid Through the Human Capillary Wall in Relation to the Venous Pressure and to the Colloid Osmotic Pressure of the Blood. J. Clin. Invest. 11: 63, 1932.

Krösing, E., Das Fibrinogen im Blute von Normalen Graviden, Wochnerinnen und Eklamptischen. Arch f. Gyn. 94: 317-331, 1911.

Landis, E.M. The Passage of Fluid Through the Capillary Wall. Am. J. Med. Sci. 193: 297-313, 1937.

Landsberg, E., Untersuchungen über den Gehalt des Blutplasmas an Gesamteiweiss, Fibrinogen und Reststickstoff bei Schwangeren. Arch. f. Gyn. 92: 639-720, 1910.

Levy, S.E., Robinson, C.J., and Blalock, A., The Effect of Altering the Renal Blood Pressure and Blood Flow on the Glomerular Filtration of a Transplanted Kidney in Unanesthetized Dogs. Am. J. Physiol. 123: 383, 1938.

Lewinsky, J., Beobachtungen über den Gehalt des Blutplasmas an Serum-albumin, Serumglobulin und Fibrinogen. Pflüger's Arch. f. d. Ges. Physiol. 100: 611-133, 1903.

Linder, G.C., Lundsgaard, C., and Van Slyke, D.D., The Concentration of the Plasma Proteins in Nephritis. J. Exp. Med. 39: 867, 1924.

Longsworth, L.G. and MacInnes, D.A., An Electrophoretic Study of Nephrotic Sera and Urine. J. Exp. Med. 71: 77, 1940.

Longsworth, L.G., Shedlovsky, T., and MacInnes, D.A., Electrophoretic Patterns of Normal and Pathological Human Blood Serum and Plasma. J. Exp. Med. 70: 399, 1939.

Losee, J.R., and Van Slyke, D.D., The Toxemias of Pregnancy. Am. J. Med. Sci. 153: 194, 1917.

Luetscher, J.A. Jr., Electrophoretic Analysis of Plasma and Urinary Proteins. J. Clin. Invest. 19: 813, 1940.

_____, Electrophoretic Analysis of the Proteins of Plasma and Serous Effusions. J. Clin. Invest. 20: 99, 1941.

Madden, S.C., Finch, C.A., Swalbach, W.G., and Whipple, G.H., Blood Plasma Protein Production and Utilization. The Influence of Amino Acids and Sterile Abscesses. J. Exp. Med. 71: 283, 1940.

Madden, S.C. and Whipple, G.H., Plasma Proteins, Their Source, Production and Utilization. Physiol. Rev. 20: 194-217, 1940.

Madden, S.C., Turner, A.P., Rowe, A.P., and Whipple, G.H., Blood Plasma Protein Production as Influenced by Various Degrees of Hypoproteinemia and by Amino Acids. J. Exp. Med. 73: 571, 1941.

Madden, S.C., Zeldis, L.J., Hengerer, A.D., Miller, L.L. Rowe, A.P., Turner, A.P., and Whipple, G.H., Casein Digests Parenterally Utilized to Form Blood Plasma Protein. J. Exp. Med. 73: 727, 1941.

Mahnert, A., Ueber das Blutvolumen in der Schwangerschaft. Arch. f. Gyn. 114: 168, 1921.

Mann, F.C., and BollmanJ.L., Influence of Complete Removal of Liver on Factors Concerned in Coagulation of Blood. Proc. Staff Meet. Mayo Clinic. 4: 328, 1929.

Mann, F.C., Bollman, J.L., and Markowitz. A Study of the Relation of the Liver to the Process of Coagulation of Blood. Am. J. Physiol. 90: 445, 1929.

Mann, F.C., Fishback, F.C., Gay, J.G., and Green, G.F., I. Experimental Pathology of the Liver: III, IV, and V. Arch Path. 12: 878-793, 1931.

Maxwell, J.P., On Food Deficiency Disease Simulating Pregnancy Toxemia. J. Obst. & Gyn. Br. Emp. 30: 34, 1923.

Mays, C.R., and McCord, W.M., A Study of Blood Sugar Levels in Eclampsia. Am. J. Obst. & Gyn. 29: 405-414, 1935.

McQuarrie, I, Husted, C., and Bloor, W.R., Lipids of Blood Plasma in Epilepsy: Variations of Lipids in Relation to Occurrence of Seizures. J. Clin. Invest. 12: 255, 1933.

Melville, K.I., Antidiuretic Pituitary Substance in Blood, with Special Reference to the Toxemia of Pregnancy. J. Exp. Med. 65: 415, 1937.

Messinger, W.J., and Hawkins, W.B., Arsphenamine Liver Injury Modified by Diet, Protein and Carbo-Hydrate Protective, but Fat Injurious. Am. J. Med. Sci. 199: 216-225, 1940.

Meyer-Wirz, E., Klinische Studie über Eklampsie. Arch. f. Gyn. 71: 15, 1904.

Miller, L.L. and Whipple, G.H., Chloroform Liver Injury Increases as Protein Stores Decrease. Am. J. Med. Sci. 199: 204-216, 1940.

Moore, N.S., and Van Slyke, D.D., The Relationship Between Plasma Specific Gravity, Plasma Protein Contentand Edema in Nephritis. J. Clin. Invest. 8: 337, 1930.

Morse, A. The Amino-acid Nitrogen in the Blood in Cases of Normal and Complicated Pregnancy and also in the New-born. Bull. Johns Hopkins. Hosp. 28: 199, 1917.

Mundaliar, A.L., Nayar, S.M., and Menon, M.K.K., Clinical and Biochemical Study of Eclampsia. J. Obst. & Gyn. Br. Emp. 47: 291-306, 1940.

Myers, W.K., and Taylor, F.H.L., Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins. J.A.M.A. 101: 196, 1933.

Myers, W.K., and Keefer, C.S., Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver. Arch. Int. Med. 55: 349, 1935.

Nasse, H., Das Blut der Schwangeren. Arch. f. Gyn. 10: 315-385, 1876.

Neuweiler, W., Über die Hippursäure-Synthese in der Normalen Schwangerschaft und im Wochenbett. Klin. Wchnschr. 18: 1050, 1939.

_____, Über Hippursaresynthese bei Gestosen. Klin. Wchnschr. 19: 135, 1940.

Nice, M., Kidney Function During Normal Pregnancy. I. The Increased Urea Clearance of Normal Pregnancy. J. Clin. Invest. 14: 579, 1935.

Card, H.C., and Peters, J.P., The Concentration of Acid and Base in the Serum of Normal Pregnancy. J. Biol. Chem. 81: 9, 1929.

Ogden, E., Hildebrand, G.J., and Page, E.W., Rise of Blood Pressure During Ischemia of the Gravid Uterus. Proc. Soc. Exp. Biol. & Med. 43: 49-51, 1940.

Osgood, E.E., A Textbook of Laboratory Diagnosis, 3rd. Ed., P. Blakiston's Son & Co., Philadelphia, 1940.

Ottenberg, R., The Etiology of Eclampsia. J.A.M.A. 81: 295, 1923.

Page, E.W., The Relation Between Hydatid Moles, Relative Ischemia of the Gravid Uterus, and the Placental Origin of Eclampsia. Am. J. Obst. & Gyn. 37: 291, 1939.

_____, The Effect of Eclamptic Blood Upon the Urinary Output and Blood Pressure of Human Recipients. J. Clin. Invest. 17: 207, 1938.

Page, E.W., and Cox, A.J., Renal Changes Following Toxemias of Late Pregnancy. West. J. Surg. 46: 463, 1938.

Page, E.W., and Ogden, E., The Physiology of Hypertension in Eclampsia. Am. J. Obst. & Gyn. 38: 230-239, 1939.

Page, E.W., Patton, H.S., and Ogden, E., The Effect of Pregnancy on Experimental Hypertension. Am. J. Obst. & Gyn. 41: 53-60, 1941.

Paramore, R.H., The Intra-abdominal Pressure in Pregnancy. Proc. Roy. Soc. Med. 6: 291, 1913.

_____, Eclampsia and Its Incidence. Lancet, 2: 1147, 1921.

_____, Eclampsia and Its Treatment: An Experience with Spinal Anesthesia in One Case. Proc. Roy. Soc. Med. 21: 1334, 1928.

_____, The Intra-abdominal Pressure in Pregnancy Newly Considered. J. Obst. & Gyn. Br. Emp. 44: 1056, 1937.

Patterson, W.B., Hunt, H.F., and Nicodemus, R.E., The Etiology of Eclampsia. A Preliminary Report. Am. J. Clin. Path. 8: 120-135, 1938.

Payne, F.L., Hormone Studies in the Presence of Hydatidiform Mole and Chorioepithelioma. Surg., Gyn., & Obst. 73: 86, 1941.

Peckham, C.H., Fetal Mortality in Toxemias of Pregnancy. J.A.M.A. 101: 1608, 1933.

_____, Time of Onset and Duration of the Toxemias of Late Pregnancy in Relation to the Development of Permanent Vascular Damage. Am. J. Obst. & Gyn. 42: 638, 1941.

Peters, J.P., Eisenman, A.J., and Bulger, H.A., The Plasma Proteins in Relation to Blood Hydration. I. In Normal Individuals and in Miscellaneous Conditions. J. Clin. Invest. 1: 435, 1925.

Peters, J.P., Bulger, H.A., Lee, C., and Murphy, C.F., The Relation of Albuminuria to Protein Requirements in Nephritis. Arch. Int. Med. 37: 153, 1926.

Peters, J.P., Wakeman, A.M., Eisenman, A.J., and Lee, C., Total Acid-base Equilibrium of Plasma in Health and Disease. X. The Acidosis of Nephritis. J. Clin. Invest. 6: 517, 1929.

Peters, J.P., Wakeman, A.M., Eisenman, A.J., and Lee, C., Total Acid-base Equilibrium of Plasma in Health and Disease. XII. A Study of Renal Edema. J. Clin. Invest. 6: 577, 1929.

Peters, J.P., and Eisenman, A.J., The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys. Am. J. Med. Sci. 186: 808, 1933.

Peters, J.P., Lavietes, P.H., and Zimmerman, H.M., Pyelitis in Toxemias of Pregnancy. Am. J. Obst. & Gyn. 32: 911, 1936.

Philipsborn, H., Katz, L.N., and Redbard, S., The Effect of High Protein Diets on Experimental Renal Hypertension. J. Exp. Med. 74: 591, 1941.

Pincus, G., and Zahl, P.A., The Biogenesis of Primary Sex Hormones. I. The Fate of Estrins Injected Into the Rabbit. J. Gen. Physiol. 20: 679, 1936-37.

Plass, E.D., Nonprotein Nitrogenous Constituents of the Blood in Eclampsia and Allied Conditions. J. Am. Med. Assoc. 82: 266, 1924.

_____, NPN Retention During Eclampsia and Allied Conditions. Johns Hopkins Hosp. Bull. 35: 345, 1924.

Plass, E.D., and Bogert, L.J., Plasma Protein Variations in Normal and Toxemic Pregnancies. Johns Hopkins Hosp. Bull. 35: 361, 1924.

Plass, E.D. and Matthew, C.W., Plasma Protein Fractions in Normal Pregnancy, Labor and Puerperium. Am. J. Obst. & Gyn. 12: 346, 1926.

Pommerenke, W.T., Placental Interchange. I. On the Concentration of Certain Nitrogenous Substances in the Blood, Before and After Passing Through the Placenta. J. Clin. Invest. 15: 485, 1936.

Pommerenke, W.T., Slavin, H.B., Kariher, D.H., and Whipple, G.H., Blood Plasma Protein Regeneration Controlled by Diet. Systematic Standardization of Food Proteins for Potency in Protein Regeneration. Fasting and Iron Feeding. J. Exp. Med. 61: 261, 1935.

_____, Dog Plasma Protein Given by Vein Utilized in Body Metabolism of Dog. Horse Plasma and Dog Hemoglobin not Similarly Utilized. J. Exp. Med. 61: 283, 1935.

Post, J., and Patek, A.J., Serum Proteins in Cirrhosis of the Liver. I. Relation to Prognosis and to Formation of Ascites. Arch. Int. Med. 69: 67, 1942.

_____, Serum Proteins in Cirrhosis of the Liver. II. Nitrogen Balance Studies on Five Patients. Arch. Int. Med. 69: 83, 1942.

Prinzmetal, M., Lewis, H.A., and Leo, S.D., Etiology of Hypertension Due to Complete Renal Ischemia J. Exp. Med. 72: 763, 1940.

Rakoff, A.E., Studies on the Concentrations of Estrogenic and Gonadotropic Hormones in the Serum of Pregnant Women. Am. J. Obst. & Gyn. 38: 371. 1939.

Robinson, H.W., and Hogden, C.G., The Biuret Reaction in the Determination of Serum Proteins. J. Biol. Chem. 135: 707, 1940.

_____, The Gravimetric Determination of Blood Serum Proteins. J. Biol. Chem. 140: 853, 1941.

Robson, J.M., and Paterson, S.J., Progesterone in Pre-Eclamptic Toxemia. Br. Med. J. 1: 311, 1937.

Rosenthal, F., Licht, H., and Melchior, E., Weitere Untersuchungen am Leberlosen Saugetier. Arch. Exp. Path. und Pharmakol. 115: 138, 1926.

Runge, H., Über den Venendruck in Schwangerschaft, Geburt und Wochenbett. Arch. f. Gyn. 122: 142, 1924.

Rusnyak, S., Die Nephelometrische Bestimmung des Albumin-Globulinquotienten. Biochem. Z. 133: 370, 1922.

Rusznyak, S., Barat, I., and Kürthy, L., Untersuchungen über die Klinische Bedeutung der Eiweissfraktionen des Blutplasmas. Ztschr. f. Klin. Med. 98: 337, 346, 1924.

Rytand, D.A., Edema with Unexplained Hypoproteinemia. Arch. Int. Med. 69: 251, 1942.

Schade, H., and Clausen, F., Der Onkotische Druck des Blutplasmas un die Entstehung der Renalbedingten Odema. Ztschr. f. Klin. Med., 100: 363, 1924.

Schifrin, A., Der Einfluss Qualitativ. Verschiedener Erhährungsformen auf die durch Salvarsan Hervorgerugenen Lebernekrosen. Virchow's Arch. 287: 175, 1932.

Schmidt, R.H., Ueber die Herzarbeit in der Frühschwangerschaft in der Ruhe und nach Arbeitsversuchen. Monatschr. f. Geburtsh. und Gyn. 90: 83, 1932.

Schmorl, G., Zur Lehre von der Eklampsie. Arch. f. Gyn. 65: 504, 1902.

Schroeder, H.A., and Steele, J.M., Behavior of Renal Blood Flow after Partial Constriction of Renal Artery. J. Exp. Med. 72: 707, 1940.

Shelburne, A., Experimental Edema. Arch. Path. 17: 152, 1934.

Siddall, R.S., Hartman, F.W., Infarcts of the Placenta: A Study of Seven Hundred Consecutive Placentas. Am. J. Obst. & Gyn. 12: 683-699, 1926.

Siegel, I.A., and Wylie, H.B., Blood Sugar Findings in Eclampsia and Pre-eclampsia. Am. J. Obst. & Gyn. 26: 29-37, 1933.

Siegler, S.L., Estrogenic and Chorionic Gonadotropic Hormone in Normal Pregnancy and in Toxemia of Pregnancy. J. Lab. & Clin. Med. 24: 1277, 1939.

Sison, H., A Clinicopathologic Study of Eclampsia Based Upon Thirty-eight Autopsied Cases. Am. J. Obst. & Gyn. 22: 35, 1931.

Slemons, J.M., and Morriss, W.H., The NPN and Urea in the Maternal and the Fetal Blood at the Time of Birth. Bull. Johns Hopkins Hosp. 27: 343, 1916.

Slemons, J.M., and Hegert, L.J., The Uric Acid Content of Maternal and Fetal Blood. J. Biol. Chem. 32: 63, 1917.

Slemons, J.M., and Stander, H.J., The Lipoids of Maternal and Fetal Blood at the Conclusion of Labor. Johns Hopkins Hosp. Bull. 34: 7, 1923.

Smith, G. van S., and Smith O.W., Excessive Gonad-Stimulating Hormone and Subnormal Amounts of Oestrin in the Toxemias of Late Pregnancy. Am. J. Physiol. 107: 126, 1934.

_____, The Quantitative Determination of Urinary Estrin. Am. J. Physiol. 112: 340, 1935.

_____, Further Quantitative Determinations of Prolan And Estrin. Pregnancy with Especial Reference to Late Toxemia and Eclampsia. Surg., Gyn., & Obst., 61: 27, 1935.

_____, The Urinary Excretion of Estrogenic and Gonadotropic Hormones During Menstrual Cycles, the Period of Conception and Early Pregnancy. New Eng. J. Med. 215: 908, 1936.

_____, Observations Concerning the Metabolism of Estrogens in Women. Am. J. Obst. & Gyn. 36: 769, 1938.

_____, The Anterior Pituitary-like Hormone in Late Pregnancy Toxemia. Am. J. Obst. & Gyn. 38: 618, 1939.

_____, Estrogen and Progestin Metabolism in Pregnant Women. Am J. Obst. & Gyn. 39: 405, 1940.

Smith, G. van S., Smith C.W., and Pincus, G., Total Urinary Estrogen, Estrone and Estriol During a Menstrual Cycle and a Pregnancy. Am. J. Physiol. 121: 98, 1938.

Smith, H.W., Note on the Interpretation of Clearance Methods in the Diseased Kidney. J. Clin. Invest. 20: 631, 1941.

Smith, W.W., Finkelstein, N., and Smith, H.W., Renal Excretion of Hexitols (Sorbitol, Mannitol and Dulcitol) and their Derivatives (Sorbitan, Isomannide and Sorbide) and of Endogenous Creatinine-like Chromogen in Dog and Man. J. Biol. Chem. 135: 231, 1940.

Snell, A.M., The Effects of Chronic Disease of the Liver on the Composition and Physiochemical Properties of the Blood. Ann. Int. Med. 9: 690, 1935.

_____, Changes in the Proteins of the Blood in Hepatic Disease. Proc. Staff Meetings Mayo Clinic. 10: 489, 1935.

Solomons, B., The Results of the Treatment of Eclampsia by the Dublin Method. J. Obst. & Gyn. Br. Emp. 29: 416, 1922.

Stadler, H., and Stinger, D., A Case of Pick's Syndrome as the Basis for a Study of Hypoproteinemia. J. Ped. 18: 84, 1941.

Stander, H.J. and Duncan, E.E., The Use of Insulin in Eclampsia. Am. J. Obst. & Gyn. 10: 823, 1935.

Stander H.J., Studies in Anesthesia, Anoxemia, Anhydremia and Eclampsia, with Certain Deductions Concerning the Treatment of Eclampsia. Am. J. Obst. & Gyn. 12: 633, 1926.

_____, The Toxemias of Pregnancy. Med. 8: 1, 1929.

Stander, H.J., and Cadden, J.F., The Cardiac Output in Pregnant Women. Am. J. Obst. & Gyn. 24: 13, 1932.

_____, Therapy and Blood Chemistry of Eclampsia. Am. J. Obst. & Gyn. 28: 856-871, 1934.

_____, Uric Acid Metabolism in Eclampsia. Am. J. Obst. & Gyn. 37: 37, 1939.

Stander, H.J., Duncan, E.E., and Sisson, W.E., Chemical Studies on the Toxemias of Pregnancy. Johns Hopkins Hosp. Bull. 36: 411, 1925.

_____, Heart Output During Pregnancy. Am. J. Obst. & Gyn. 11: 44, 1926.

Stander, H.J., and Radelet, A.H., The Blood Chemistry in Eclampsia. Johns Hopkins Hosp. Bull. 38: 423, 1926.

Starling, E.H., On the Absorption of Fluids From the Connective Tissue Spaces. J. Physiol. 19: 312, 1895-96.

Stevens, T.G., Treatment of Eclampsia by Veratrum Viride. J. Obst. & Gyn. Br. Emp. 29: 426, 1922.

Stover, R.F., and Pratt, J.P., Progestin Studies: Pregnandiol Excretion. Endoc. 24: 29, 1939.

Strauss, M.B., Observations on the Etiology of the Toxemias of Pregnancy. Am. J. Med. Sci. 190: 811-824, 1935.

_____, Edema in Eclampsia. Am. J. Med. Sci. 194: 772-783, 1937.

_____, Edema in Eclampsia. Am. J. Med. Sci., 194: 772-783, 1937.

_____, Vitamin B_1 in Eclampsia. Am. J. Med. Sci. 195: 516-518, 1938.

_____, Plasma Proteins in Eclampsia. Am J. Med. Sci. 195: 723-728, 1938.

_____, Etiologic Relationship Between Water Retention and Arterial Hypertension. Am. J. Med. Sci., 196: 188-198, 1938.

_____, Types, Etiology and Treatment of Eclampsia. Am. J. Obst. & Gyn. 38: 199-210, 1939.

Stroebe, F., Latente Hepatopathie nach Schwangerschaftstoxikose. Klin. Wchnschr. 11: 495, 1932.

Stroganoff, W., My Improved Method of the Prophylactic Treatment of Eclampsia. J. Obst. & Gyn. Br. Emp. 30: 1. 1923.

Stroganoff W., and Davidovitch, O., Two Hundred Cases of Eclampsia Treatedwith Magnesium Sulfate: Preliminary Report. J. Obst. & Gyn. Br. Emp. 44: 289, 1937.

_____, Early Artificial Rupture of Membranes in Prophylactic Treatment of Eclampsia. Gyn. et Obst. 35: 220, 1937.

Sullivan, C.F., Tew, W.P., and Watson, E.M., The Bilirubin Excretion Test of Liver Function in Pregnancy. J. Obst & Gyn. Br. Emp. 41: 347, 1934.

Tenney, B., Jr., Syncitial Degeneration in Normal and Pathologic Placentas. Am. J. Obst. & Gyn. 31: 1024-1028, 1936.

Theobald, G.W., The Intraperitoneal Pressure and its Changes During Pregnancy. J. Obst. & Gyn. Br. Emp. 34: 854, 1932.

———————. The Hepatic Lesions Associated with Eclampsia and Those Caused by Raising the Intra-abdominal Pressure. J. Path. & Bact. 35: 843, 1932.

Thompson, W.H., McQuarrie, I., and Bell, E.T., Edema Associated with Hypogenesis of Serum Protein and Atrophic Changes of the Liver. J. Pediat. 9: 604-619, 1936.

Thomson, K.J., Reid, D.E., and Cohen, M.E., Studies on Circulation in Pregnancy. IV. Venous Pressure Observations in Normal Pregnant Women, in Pregnant Women with Compensated and Decompensated Heart Disease and in the Pregnancy "Toxemias." Am. J. Med. Sci., 198: 665, 1939.

Titus, P., Messer, F.C., and McClellan, R.H., Increase of Guanidine Compounds in Eclampsia: An Experimental Study. Am J. Obst. & Gyn. 24: 667, 1932.

Trevorrow, V., Kaser, M., Patterson, J.P., and Hill, R.M., Plasma Albumin, Globulin, and Fibrinogen in Healthy Individuals From Birth to Adulthood. II. Normal Values. J. Lab. & Clin. Med. 27: 471, 1942.

Tuchman, L.R., and Sobotka, H., A Comparison of the Wu and Kjeldahl Methods of Serum Protein Determinations. J. Biol. Chem. 98: 35, 1932.

Tumen, H., and Bodkus, H.L., The Clinical Significance of Serum Proteins in Hepatic Diseases. Am J. Med. Sci. 193: 786, 1937.

Tyler, M., and Underhill, F.P., The Influence of Pregnancy Upon the Lipoids of the Blood. J. Biol. Chem. 66: 1, 1925.

Van Slyke, D.D., Rhoads, C.P., Hiller, A.M., and Alving, A.S., Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption and Diuresis; the Mechanism of Urea Excretion. Am. J. Physiol. 109: 324, 1934.

Varo, B., Krieg und Eklampsie. Zentralbl. f. Gyn. 44: 522, 1920.

Warnekros, K., Kriegskost und Eklampsie. Zentralbl. f. Gyn. 40: 897, 1916.

Warner, E.D., Plasma Prothrombin: Effect of Partial Hepatectomy. J. Exp. Med. 68: 831, 1938.

Warner, E.D., Brinkhaus, K.M. and Smith, H.P., A Quantitative Study of Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions. Am. J. Physiol. 114: 667, 1936.

Weech, A.A., Nutritional Edema. Internat. Clinics, 46th Series, 2: 234, 1936.

_____, Puzzles of Protein Privation. J. Ped. 19: 608, 1941.

Weech, A.A., and Goettsch, E., Dietary Protein and the Regeneration of Serum Albumin. I. Method of Assay and Discussion of Principles. Bull. Johns Hopkins Hosp. 63: 154, 1938.

_____, Dietary Protein and the Regeneration of Serum Albumin, II. Comparison of the Potency Values of Beef Serum, Beef Muscle and Casein. Bull. Johns Hopkins Hosp. 63: 161, 1938.

_____, Dietary Protein and the Regeneration of Serum Albumin, III. The Potency Values of Egg White, Beef Liver and Gelatin. Bull. Johns Hopkins Hosp. 64: 425, 1939.

Weech, A.A., Goettsch, E., and Reeves, E.B., Development of Hypoproteinemia on a Diet Deficient in Protein. J. Exp. Med. 61: 299, 1935.

Weech, A.A., Vann, D., and Grillo, R.A., The Clearance of Bilirubin from the Plasma, A Measure of the Excreting Power of the Liver. J. Clin. Invest. 20: 323, 1941.

Weech, A.A., Wollstein, M., and Goettsch, A., Nutritional Edema in the Dog. J. Clin. Invest. 16: 719-728, 1937.

Weil, P.G., The Excretion of Pregnandiol in the Toxemias of Pregnancy. Sci. 87: 72, 1938.

Weiss, R., Ueber die Mehrleistung des Herzens während der Schwangerschaft. Klin. Wchnschr. 3: 106, 1924.

Wellen, I., Welsh, C.A., and Taylor, H.C., The Filtration Rate, Effective Renal Blood Flow, Tubular Excretory Mass and Phenol Red Clearance in Specific Toxemia of Pregnancy. J. Clin. Invest. 21: 63, 1942.

_____, The Filtration Rate, Effective Renal Blood Flow, Tubular Excretory Mass and Phenol Red Clearance in Normal Pregnancy. J. Clin. Invest. 21: 57, 1942.

Whipple, G.H., and Hurwitz, S.H., Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning. J. Exp. Med. 13: 136, 1911.

White, P., and Hunt, H., Prediction and Prevention of Pregnancy Accidents in Diabetes. J.A.M.A. 115: 2039-2040, 1940.

White, P., Titus, R.S., Jesli, E.P., and Hunt, H., Prediction and Prevention of Late Pregnancy Accidents in Diabetes. Am. J. Med. Sci. 198: 482-492, 1939.

White, W.A., Recession of Toxemia Following the Intrauterine Death of One of Zygotic Twins. Am. J. Obst. & Gyn. 41: 710, 1941.

Widdowson, E.M., A Comparative Investigation of Urine and Serum Proteins in Nephritis. Biochem. J. 27: 1321, 1933.

Wiener, H.J., andWiener, R.E.,.Plasma Proteins. Arch. Int. Med. 46: 236, 1930.

Williams, E.C.P., Investigation of the Constancy of the Chemical Composition of the Blood During Pregnancy. J. Obst. & Gyn. Br. Emp. 30: 189, 1923.

Williams, J.C., Increased Amount of Uric Acid in the Blood in the Toxemias of Pregnancy. J.A.M.A. 76: 1297, 1921.

Williams, T.J., Nix, H.G., and Mauzy, C.H., The Incidence of Hypertension After the Toxemias of Pregnancy. Am. J. Obst. & Gyn. 42: 98, 1941.

Williamson, C.S., Heck, F.J., and Mann, F.C., A Study of Fibrinogen Following Removal of the Liver. Am. J. Physiol. 59: 487, 1922.

Wilson, R.B., and Randall, L.M., Studies on Pregnandiol. II. The Excretion of Pregnandiol During Normal Pregnancy. Proc. Mayo Clin. 13: 813, 1938.

Wu., H., A New Colorimetric Method for the Determination of Plasma Proteins. J. Biol. Chem. 51: 33, 1922.

Zangemeister, W., Die Beschaffenheit des Blutes in Schwangerschaft und der Geburt. Ztschr. f. Geb. u. Gyn. 49: 92-103, 1903.

_____, Der Hydrops Gravidarum Sein Verlaus un Seine Beziehungen zur Nephropathie und Eklampsie. Ztschr. f. Geb. und Gyn. 81: 491, 1919.

Zangemeister, W., and Meisgl, T., Vergleichende Untersuchungen über Mutterliches Blut und Fruchtwasser nebst Bemerkungen über die Fetale Harnsekeretion. Munchen. Med. Wchnschr. 1: 673-678, 1903.

Zimmerman, H.M., and Peters, J.P., Pathology of Pregnancy Toxemias. J. Clin. Invest. 16: 397, 1937.