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TOXEMIA OF PREGNANCY: A DISEASE OF PROTEIN INSUFFICIENCY AND POOR UTERINE VASCULATURE

by

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B.S., Kansas State University, 1974

A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods and Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1975

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INTRODUCTION

Toxemia of pregnancy (TP) is a controversial and confounding disease syndrome. The exact etiology and pathophysiology are unresolved, and the prophylaxis and treatment are largely empirical. The only incontrovertible cause of toxemia is pregnancy and the only certain cure is the termination of pregnancy (1-3). The study of TP has been severely handicapped in the past by the lack of widely accepted definitions and agreed-upon criteria, which has lead to lack of uniformity in the diagnosis of the disease itself (2).

Toxemia, at least in Western countries, is the commonest formidable complication of pregnancy (4, 5). The death of the mother is uncommon with conventional therapy, but this disease continues to be an important cause of perinatal mortality (6, 7).

PHYSIOLOGICAL CHANGES IN NORMAL PREGNANCY

When discussing a disease unique to pregnancy it is important to realize that the physiology of the pregnant women is altered quite drastically, especially in the last two trimesters, from that of the nonpregnant state (8, 9). Table 1 lists some of the important physiological changes seen in normal pregnancy. These changed conditions must be used as a baseline in order to determine the additional changes peculiar to TP.

TABLE 1

Some important physiological changes in normal pregnancy
(Derived from 2, 8-10)

Area	Change from non-pregnant state	When
Liver	Increased plasma fibrinogen	Throughout
	Increased plasma angiotensinogen	Throughout
Kidneys	Increased renal plasma flow (around 25%)	1st half
	Increased renal plasma flow (30-50%)	2nd half
	Increased glomerular filtration rate (around 50%)	2nd half
	Decreased serum urea & creatinine concentration	2nd, 3rd trimester
	Increased ureteral, calyceal & pelvic pressure	3rd trimester
	Increased plasma renin activity	Throughout
Adrenals	Increased serum aldosterone	Throughout
Cardio-vascular	Increased blood volume (30-50%)	2nd, 3rd trimester
	Decreased hematocrit	2nd, 3rd trimester
	Decreased plasma albumin concentration	2nd, 3rd trimester
	Decreased total serum protein concentration	2nd, 3rd trimester
	Slight edema & sodium retention	2nd, 3rd trimester
	Increased coagulability of blood	Throughout
	Increased platelet agglutination	Throughout
	Increased fibrinolytic activity	Throughout
	Increased angiotensin activity	Throughout
	Increased angiotensinase activity	Throughout

DEFINITION AND CLASSIFICATION

Diagnosis

The American Committee on Maternal Welfare has currently classified toxemia of pregnancy from the assumption that TP must be defined by means of empiric description of the symptoms developi during pregnancy. Such symptoms are present only in women in the gravid state and can be objectively differentiated from other diseases characterized by the same signs and symptoms (10).

TABLE 2

Classification of Toxema (Derived from 10)

I Toxema of pregnancy

A. Preeclampsia

1. Mild

2. Severe

B. Eclampsia

II Chronic hypertensive vascular disease in pregnancy

A. Without hyperimposed toxemia of pregnancy

1. Hypertension known to exist before onset of pregnancy

2. Hypertension discovered in pregnancy before 24 weeks of gestation

B. With superimposed toxema of pregnancy

III Recurrent Toxemia

TP usually occurs in the last trimester of pregnancy or early in the puerperium, although there have been a few documented reports of true TP occurring before the 24th week of testation (11). TP may be defined as a clinical syndrome-the preeclampsia-eclampsia syndrome.

Preeclampsia, the first stage of the syndrome, is characterized by two of the triad of hypertension, proteinuria, and pathologic edema, or all three, developing after the 24th week of gestation (2, 10) Hypertension may be defined as a systolic blood pressure of 140 mm Hg or above, or a rise of 30 mm Hg or more above the known average normal level of the patient in question, and a diastolic blood pressure of 90 mm Hg or above or a rise of 15 mm Hg or more above the usual level. These pressures should be noted on at least two occasions at least 6 hours apart (2, 10). Proteinuria of a significant degree should be noted in clean urine specimens on two or more successive days. The edema should be of the face or hands, and should be persistent rather than transient (2, 10).

Preeclampsia is classified as severe when any of the following is evident: (a) systolic blood pressure of 160 mm Hg or above and diastolic of 110 mm Hg or above observed on two occasions at least 6 hours apart with patient at bed rest; (b) proteinuria of 5 g or more in 24 hours or a qualitative albumin of 3+ or 4+; (c) oliguria of 400 ml or less per 24 hours; (d) cerebral or viaual disturbances; or (e) pulmonar edema or cyanosia (2, 12).

Eclampsia is present by definition whenever a patient with antecedent preeclampsia of any degree of severity develops convulsions with or without coma (2, 10).

Chronic hypertensive vascular disease in pregnancy is diagnosed when the blood pressure is 140/90 or above prior to the 24th week of gestation and there is subsequent evidence that the hypertension persists indefinitely after delivery. This, of course, corresponds in all clinical respects to essential hypertension and is not, therefore, peculiar to pregnancy (2, 10). This disease entity has been found, however, to predispose one to the development of preeclampsia (1, 2, 10). Patients who are classified as having chronic hypertensive vascular disease with superimposed toxemia show the characteristic renal glomerular lesions of preeclampsia, as demonstrated by recent studies using electron microscopy (2).

Although the classification of TP by the American Committee on Maternal Welfare is so worded as to include the possibility of toxemia in a patient without hypertension, most authorities believe that toxemia should be excluded as a diagnosis when there is no rise in blood pressure (2, 10).

The diagnosis of recurrent toxemia is made if a patient with clinical evidence of TP has a history of one or more antecedent episides of toxemia in previous, but not necessarily consecutive,

pregnancies, and has been normotensive in the nonpregnant intervals (2, 10).

Signs of Mild Preeclampsia

Symptoms may be prevalent in patients with severe preeclampsia, but the early mild forms of the disease are essentially symptom free (2). It is for this reason that regular prenatal care by a physician is of the utmost importance in the prevention of the life-endangering forms of toxemia. Early recognition, prompt treatment, and proper surveilance of the woman with signs of preeclampsia in its mild early stages can usually avoid a worsening of the disease (13).

Sudden, excessive weight gain is often the first clue that the patient is developing preeclampsia because in most cases TP is associated with an abnormal water retention (1, 2, 14). Excessive weight gain tends to be demonstrable for several weeks before the appearance of clinical edema (12, 13). In an attempt to narrow down when this abnormal weight gain develops, Vedra and Pavlikove (13) ran a serial analysis of the antenatal records of healthy and toxemic pregnant women. Their results are shown in Table 3 and Figure 1. Their data indicate that an abnormal weight gain in toxemia begins around the 10th week of gestation, at the same time as normal weight gain in healthy women. But the separation between line A and line B is not very large (2.5 kg) until about the 30th week of gestation. Also, pathological edema does not usually appear from this excessive water accumulation

TABLE 3

Average weight gain throughout pregnancy (13)

Week of pregnancy	10	15	20	25	30	35	40
Healthy women							
Mean weight gain (Kg)	0.85	2.07	3.87	6.26	7.04	10.62	11.90
Standard Error of mean	0.27	0.24	0.20	0.23	0.22	0.27	0.26
Women with toxemia							
Mean weight gain (Kg)	2.33	3.39	5.55	7.80	10.60	12.71	14.65
Standard error of mean	0.27	0.27	0.28	0.24	0.23	0.81	0.30

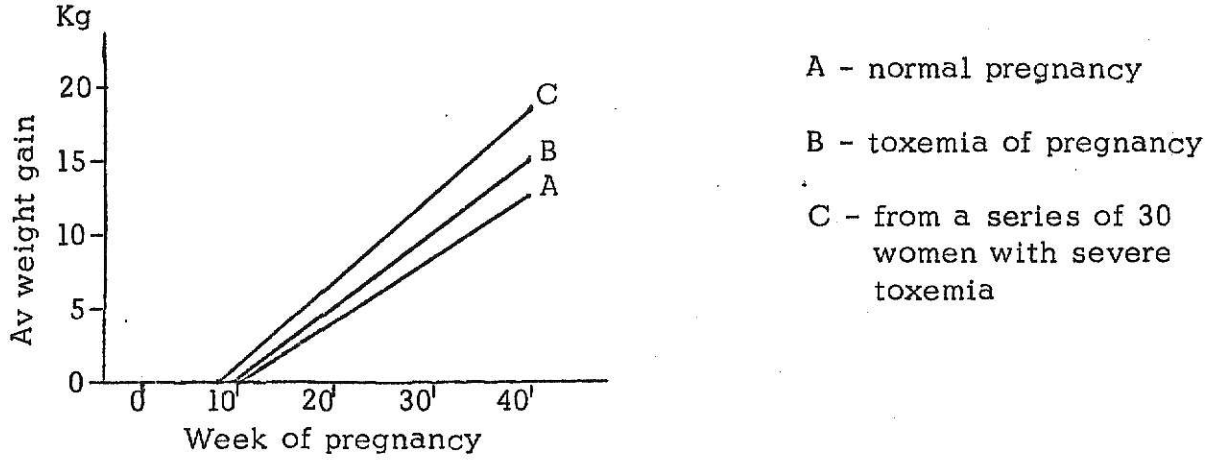

Fig. 1 - Regression lines of the average weight gain (13)

until around the last 10 weeks of pregnancy, when the amount of water retention becomes obviously different from normal pregnancy (12). The confounding factor before that time is that a degree of edema is normal and physiologic in pregnant women, who operate under the handicap of an upright position (8, 12). In summation, a woman presenting an abnormally high rate of weight gain during pregnancy should be considered suspect of developing TP, and should, therefore, be monitored often throughout her remaining prenatal care.

Ophthalmoscopic examination of patients with preeclampsia (mild or severe) generally reveals one or more of the following: papilledema, retinal edemia, retinal detachment, arteriolar spasm, arteriovenous hemorrhage (2). Repeated ophthalmoscopic examination is helpful in juding the success of treatment or extent of recovery (2, 15).

Symptoms of Severe Preeclampsia

Other than the major signs of mild preeclampsia (hypertension, proteinuria, edema), some common symptoms seen in severe preeclampsia include: headache, vertigo, malaise and nervous irritability (due in part to cerebral edema) (15); scintillating scotomas and visual impairment (due to arteriolar spasm and edema of the retina, retinal hemorrhage, or retinal detachment) (12); upper abdominal pain, anorexia, nausea, vomiting and liver tenderness (due to congestion, thrombosis of the periportal system and

small subcapsular hepatic hemorrhages) (15-18). The liver symptoms are rare but represent a very dangerous situation (16-18). If these symptoms are followed by signs of blood loss, shock and intra-abdominal hemorrhage, the rupture of a hemorrhagic liver is almost certain (16-19).

Symptoms and Signs of Eclampsia

The symptoms and signs of eclampsia, besides generalized tonic-clonic convulsions, may include: coma followed by amnesia and confusion; 3 to 5 plus proteinuria; marked hypertension preceding a convulsion and hypotension during coma or vascular collapse; stertorous breathing, rhonchi, frothing at the mouth; twitching of muscle groups (e. g. face, arms); nystagmus; and oliguria or anuria (15). In a study of fatal eclampsia (20) it was found that edema, headaches, tachycordia, convulsions, and coma were the most common (55% incidence) symptoms.

Jeffcoate, et al, (21) found that 32% of women who have eclampsia have their first fit after delivery (postpartum eclampsia). The convulsions were found to always commence within 14 hours of the completion of delivery and usually within 6 hours.

Laboratory Findings

A diagnosis of preeclampsia is made primarily on the basis of physical findings. Several laboratory tests are, however, helpful enough to be routinely ordered on patients found by presumptive diagnosis to have toxemia. These tests are helpful in revealing the severity of the disease.

Qualitative Urinalysis. Albuminuris is characteristic of preeclampsia even in its mild stages, but is only intermittently present (2). This probably reflects sporadic vasospasm in the kidneys or reduction in the glomerular filtration rate accompanied by an increased permeability of the glomerular capillary membranes (22). Such circumstances, of course, would permit leakage of protein. Quantitative estimations of albuminuris are of limited diagnostic value because the significance of any such estimation varies with the concentration of the urine sample. Albuminuris is the last of the three main signs of preeclampsia to appear and represents a serious development (23).

The absence, on microscopic examination, of blood in the urine differentiates acute glomerular nephritis from toxemia (25).

Blood Chemistry. The blood urea nitrogen (BUN) levels are within normal limits in mild preeclampsia. High levels suggest worsening or severe preeclampsia (15, 24). The BUN of a woman rises with increasing severity of her toxemia, the average concentration is 16.5 mg% in non-toxic pregnancy, 31.2 mg% in severe toxemia, and 21.3 and 24.8 mg% in mild and moderate TP (25).

Hyperuricemia is common in preeclampsia (8, 20, 24, 26). Serum uric acid levels of 5 mg% or more are significant in a differential diagnosis of TP since other causes of high uric acid levels, such as gout, can be easily ruled out. In one study (26) serum uric acid levels in eclamptic women were found to

average 8.6 mg%. A decrease in serum uric acid level is a good indication of recovery from TP.

Morrison (26) found that eclamptic women have elevated blood glucose levels that average 152 mg% compared to the control average of 103 mg% (26). Eclamptic women's blood had a lower pH with an average of 7.310 versus an average of 7.456 for normal pregnant women.

A low serum protein level is a sign of preeclampsia (27, 28). The absolute amount of the serum proteins decreases even before any clinical symptoms appear (27). In late TP, not only is the absolute amount of circulating proteins decreased, but even their concentration is significantly decreased (27). Electrophoretic studies have shown that this decrease in total proteins is mostly due to a significant reduction in the albumin fraction (29).

The significance of this hypoalbuminemia in TP is further emphasized by the fact that the decrease in protein concentration and concurrent dilution of plasma (drop in oncotic pressure) results in a decreased blood volume (35 to 50% reduced (30)). Thus, hypovolemia is present in TP.

Blood non-protein nitrogen levels have been reported to be increased significantly in TP (2), but Way (20) in a study of fatal eclampsia purports that the increase is minimal. His average

determination was only 37.2 mg% (normal range: 15 to 35 mg% (31)).

The heat stable fraction (shown to originate in the placenta exclusively (32, 33)) of serum alkaline phosphatase has been found to be outside the normal range in 14.6% of patients with mild preeclampsia and in 78% of those with severe preeclampsia (33). Most of these aberrant levels found in preeclampstics were above the normal range, although some were below. Curzen (33) considers this abnormal synthesis level of an important placental enzyme as evidence of tissue damage in the placenta, such as an infarction.

The blood levels of renin, a proteolytic enzyme secreted by the kidney which is responsible for activating anglotensinogen to angiotensin--a vasoconstrictor, in women with TP have been the realm of much controversy. Brown, et al (34) and Bonar, et al (35) reported that the concentration of plasma renin in patients with toxemia in the third trimester were on the average less than those found in normotensive controls, although there was marked overlap between the renin values of the two groups. It also has been established that the activity of this enzyme is lower in women with late toxemia of pregnancy (36-38). However, in a prospective study by Gordon, et al (37) it was shown that between the 13th and 27th week of gestation, the mean renin activity was higher in women who later developed TP than in women whose pregnancy was uneventful. A week of sodium restriction in both groups resulted in a further, and statistically significant, separation of the two group's plasma renin activity values.

Renin-substrate (angiotensin I) and angiotensin II serum concentrations have also been found significantly lower than controls in women with late toxemia (38).

The plasma concentration of aldosterone has been found to be lower (close to nonpregnant values) in women with TP than in matched controls (36, 39).

Cryofibrinogen (heparin-precipitable cold fibrinogen) is encountered in high amounts in patients suffering from preeclampsia (40).

Additional blood pictures that will be important later in this paper are the hypoplasminogenemia (41), thrombocytopenia (35, 36, 41), and the significant increases in serum fibrin/fibrinogen degradation products (21, 35, 36, 42) observed in women with preeclampsia.

Cerebrospinal Fluid. The cerebrospinal fluid (CSF) of preeclampstic patients was found on the average to have a higher than normal uric acid level (1.4 mg%) and a lower than normal pH (7.542) (26). The CSF of eclamptic patients was found on the average to have elevated levels of protein (78 mg%) white blood cells (16/mm3), red blood cells (17000/mm3) and uric acid (1.9 mg%), and an even lower average pH (7.410) than those with preeclampsia (26). An elevated CSF protein level is characteristic of the eclamptic patient, and the severity of the eclampsia appears to be related to the red blood cell content of the CSF (26).

INCIDENCE

Maternal Morbidity and Mortality

When death occurs from TP, it almost always happens in eclampsia (2,7). Very rarely, a woman with severe preeclampsia will succumb (2). Herbert, et al (7) found that about 4.7% of women with eclampsia died from it in 1968.

Over the past 35 years there has been a dramatic decrease in the incidence of TP (43) and in the number of deaths due to TP (3). In 1940 the maternal mortality rate in the U. S. due to TP was 52.2 per 100,000 live births (3). Marked decreases have since taken place in all states, but 8 of the 10 states that had the highest mortality rates from this cause in 1940 were still among the 10 states with the highest rates in 1965.

Race and Socioeconomic Status. The increased incidence of death due to TP in the low income states is observed in Table 4, (3, 19, 44). In areas of poverty many women do not have good prenatal care (3, 45, 46). Therefore, preeclampsia is not detected very early thus increasing the chance that the condition will progress to eclampsia and possibly death (3, 47).

It can also be readily seen that, as Ross (47) pointed out almost 30 years ago, TP is a grave obstetrical problem in the South, where poverty, especially extreme poverty and ignorance, is more prevalent than anywhere else in the U. S.

A further look into this inverse relationship between TP and income reveals that there is a higher mortality incidence due to TP

TABLE 4

Deaths from toxemias of pregnancy, by states ranked according to per capita income (3)

States in rank order (1963-65)	Number of live births (1961-65)	Number of deaths from TP (1961-65)	Rate per 100,000 live births	State rate/ U.S. rate X 100
United States	20,321,556	1,256	6.2	100
High income (17 states)	9,833,620	372	3.8	61
Dist/Columbia	98,134	5	5.1	82
Nevada	45,726	2	4.4	71
Connecticut	280,570	9	3.2	52
Delaware	56,864	2	3.5	56
California	1,872,062	57	3.0	48
New York	1,759,662	80	4.5	73
New Jersey	657,108	34	5.2	84
Illinois	1,123,758	50	4.4	71
Alaska	37,232	-	-	-
Massachusetts	545,516	18	3.3	53
Maryland	383,902	13	4.7	76
Michigan	897,444	36	4.0	65
Hawaii	87,076	2	2.3	37
Washington	300,756	7	2.3	37
Rhode Island	90,332	2	2.2	36
Ohio	1,065,434	28	2.6	42
Indiana	532,044	27	5.1	82
Middle income (17 states)	6,195,224	365	5.9	95
Oregon	176,014	3	1.7	27
Pennsylvania	1,111,644	52	4.7	76
Colorado	207,980	10	4.8	77
Wisconsin	456,082	10	2.2	35
Kansas	227,116	10	4.4	71
Missouri	451,746	27	6.0	97
Minnesota	398,728	12	3.0	48
Wyoming	38,004	1	2.6	42
Iowa	288,800	10	3.5	56
New Hampshire	68,742	7	10.2	165
Nebraska	159,692	7	4.4	71
Montana	78,856	1	1.3	21
Arizona	182,160	16	8.8	142
Florida	567,380	42	7.4	119
Utah	123,816	4	3.2	52
Virginia	476,494	42	8.8	142
Texas	1,181,990	111	9.4	152

TABLE 4 (Continued)

Deaths from toxemias of pregnancy, by states ranked according to per capita income

States in rank order (1963-65)	Number of live births (1961-65)	Number of deaths from TP (1961-65)	Rate per 100,000 live births	State rate/ U. S. rate X 100
Low income (17 states)	4,292,692	512	11.9	192
Idaho	75,718	5	6.6	106
Vermont	44,220	1	2.3	37
Oklahoma	242,872	11	4.5	73
Maine	109,464	3	2.7	44
New Mexico	138,092	11	8.0	129
North Dakota	75,242	1	1.3	21
Georgia	494,326	63	12.7	205
South Dakota	81,066	2	2.5	40
Louisiana	428,264	32	7.5	121
Kentucky	338,706	30	8.9	144
North Carolina	532,654	66	12.4	200
West Virginia	179,782	15	8.3	134
Tennessee	396,490	44	11.1	179
Alabama	382,278	63	16.5	266
Arkansas	202,462	19	9.4	152
South Carolina	286,174	60	21.0	339
Mississippi	284,882	86	30.2	487

among non-white than among white women. (Tables 5 and 6). This relationship, of course, is due to the lower economic status of the non-white families (Negro, Chicano, Indian) in the U. S.

Morbidity and mortality also are higher than average among rural white women (3, 47, 48). The results of such a low economic status are poor environmental factors, such as poor diets (5, 49-53), lack of prenatal care (3), and increased physican exertion (working mothers, standing for long periods of time, etc.).

TABLE 5

States with highest mortality rates from the toxemias of pregnancy among nonwhite women (3)

State	Rate per 100,000 live births
Idaho	58.1
Mississippi	52.4
South Carolina	42.8
Alabama	36.8
Nevada	36.1
Kentucky	34.4
North Carolina	31.6
Tennessee	30.7
Arizona	30.0
North Dakota	29.2
New Mexico	29.1
Virginia	24.8
South Dakota	23.3
Texas	22.9
Arkansas	22.1
Florida	20.5
Iowa	19.8

TABLE 6

Number of deliveries by Negro women in eight teaching hospitals, incidence of toxemia, and mean family income, 1959-1966 (3)

Hospital	Number of deliveries	Mothers with toxemia		Mean family income
		Number	%	
Medical College of Virginia Hospital, Richmond	1,396	140	10.0	$2,774
Charity Hospital, New Orleans	1,795	136	7.6	2,628
Gailor Hospital, Memphis	2,474	182	7.4	2,784
John Hopkins Hospital, Baltimore	1,839	119	6.5	4,301
Presbyterian Hospital, New York City	702	43	6.1	4,791

TABLE 6 (Continued)

Number of deliveries by Negro women in eight teaching hospitals, incidence of toxemia, and mean family income, 1959-1966 (3)

Hospital	Number of deliveries	Mothers with toxemia		Mean family income
		Number	%	
Pennsylvania Hospital Philadelphia	4,843	271	5.6	$3,303
Metropolitan Hospital, New York City	1,106	53	4.8	3,543.
Boston Lying-In Hospital, Boston	618	17	2.8	5,860

Concentrating on morbidity we find that the incidence of eclampsia has been reported to be from 0.1% to 0.2% (7, 43,44). The incidence of preeclampsia has been found to be between 3.4% (44) and 5.7% (54). But a recent study (43) which classified suspected preeclampsia together with definitely diagnosed mild preeclampsia came up with a much higher incidence (about 28%) (Table 7)

TABLE 7

Toxemia of pregnancy, by race (43)

Toxemia status	White		Negro	
	Number	%	Number	%
Normal pregnancy	7235	70.49	6681	61.01
No TP - Definite HCVD	134	1.31	357	3.26
Mild preeclampsia	2738	26.67	3413	31.16
Severe preeclampsia	155	1.50	486	4.43
Eclampsia	2	0.02	14	0.13
Total	10264	100.00	10951	100.00

The above table also reveals that the gap between whites and nonwhites is closing, probably due to the social changes in the last decade (civil rights, welfare, food stamps, education, etc.).

Age and Parity. The incidence of preeclampsia was found to be approximately threefold higher among primigravidas than among multigravidas (7, 44, 55). TP also was encountered more often in older (40's and beyond) and very young (teenage) primagravidae, with the very young primigravidae demonstrating the highest incidence of any group (2).

In one study (7) it was found that of those women with eclampsia, 49% were 19 years of age or less and 75% were under 25 years of age. Way and Durham (20) also found that the average age of the primiparous patient succumbing to fatal eclampsia was 19.7 years, with a range of women from 12 to 27 years of age.

The chances of a woman developing toxemia is increased many times in multiple pregnancies. The risk increases again when twinning occurs in primigravidas (1).

Predisposing Chronic Diseases. Two chronic diseases in particular seem to predispose a pregnant woman to toxemia--diabetes mellitus and chronic hypertensive cardiovascular disease (8, 16, 56, 57). It has also been discovered that the development of latent diabetes mellitus is 5 times the expected incidence in women who have had eclampsia as primiparas and 10 times that expected in those who have had eclampsia as multiparas (8).

Thus, even prediabetes may predispose women to toxemia in pregnancy.

Genetic. A familial tendency has been claimed by Adams (58) who made a comparison between sisters. She observed that 13% of the sisters of women who had preeclampsia developed preeclampsia in their first pregnancy. This seems insignificant when compared to the national average of 3.4 to 5.7% or higher; moreoever, most sisters live in the same socioeconomic strata which has a definite influence on the incidence of TP.

Another claim that was made for an inherited tendency was also unsubstantiated in a subsequent study. May (59) claimed that the maternal blood group A shows an increased risk of having TP. He found the relative risk (A:O) of TP in primigravidas in his study to be 2.7:2. His results were later contested by South and Noldrett (60), who found the incidence of TP to be 5.1% in primigravidas of blood group A and 5.5% in those of blood group O.

Recurrence. With respect to the incidence of recurrent TP, Gordon and Fell (54) analyzed 996 cases of toxemia from among 17,562 deliveries. Their data indicated that a woman who has preeclampsia in a given pregnancy has a 45% chance of having it again in her next pregnancy. If preeclampsia occurs in two consecutive pregnancies, the risk of another occurrence rises to 72%, while in patients who have had toxemia in 3 consecutive pregnancies,

recurrence in the next pregnancy is almost certain. If a woman with preeclampsia does not develop the syndrome in her next pregnancy, then the chance of her developing it again is only 6%, approximately the incidence of the nation at large.

Fetal Condition

Morbidity. It has been found that, on the average, both the fetus and the placenta of women with TP weigh less than the products of conception of a nontoxemic pregnancy at an equivalent week of gestation (44, 61) The womam with toxemia also tends to deliver earlier than does the woman without TP (44)

Mothers of male babies have TP significantly more often (Table 8) than do nontoxemic mothers (61) The ratio of males to females increases as the severity of the disease increases (Table 9); it is 1.71 in cases where the urinary output of protein was equal to or greater than 3 grams per day and 1.42 when the distolic blood pressure was greater than or equal to 110 mm Hg.

Upon delivery infants whose mothers had TP frequently exhibit signs of acute and/or chronic anoxia and may require immediate neonatal resuscitation (6). They are pale, often dehydrated, and have an increased tendency towards subsequent jaundice (6). They will probably show signs of undernutrition with decreased subcutaneous tissue (6) The incidence of fatal congenital malformations also seem to be higher in these infants (6).

TABLE 8

Ratio of males to females in newborn babies (61)

Group	Newborns (No.)		Ratio of males to females
	Males	Females	
Toxemia	588	473	1.24
Control	4196	4061	1.03

TABLE 9

Ratio of males to females in 1061 babies born to mothers with toxemia of pregnancy. The degree of the maternal disease was determined from the urinary protein output (UPO) or the diastolic blood pressure (DBP) (61)

Sex	Newborns (No.) to mothers with toxemias of					
	UPO (g/24 hour)			DBP (mm-Hg)		
	0.1	0.1-2.9	3.0	90	90-109	110
Males	332	203	53	41	277	273
Females	296	146	31	39	242	192
Ratio of males to females	1.12	1.39	1.71	1.05	1.14	1.42

Mortality. Fetal loss was found to be about 22% for all eclamptic women, but if the convulsions followed delivery the fetal risk was much less, about 5% (7).

The interrelationships between perinatal mortality, birth weight, and the time interval between the occurrence of convulsions and the termination of pregnancy can be seen in Table 10.

Of the listed fetal deaths, 22 were stillborn and 13 infants died neonataly. Two infants were undelivered at the time of maternal death, one estimated at 30 weeks and one at 32 weeks gestation. Twenty of the 37 infants lost were premature; 4 infants weighed less than 1,000 grams.

Babies from toxemic mothers face an increased risk of death before labor from intrapartum asphyxia, or in the first week of life from idiopathic respiratory distress, intraventricular hemorrhage, or massive pulmonary hemorrhage (6). In addition, it has been recognized that hypoglycemia may play an important role in the immediate postpartum period (6).

PATHOGENESIS

Burnett (3) stated that, with comparable degrees of albuminuria, elevation of blood pressure, and other signs of TP, one patient may have convulsions, while another will not. This can be explained by the concept that for a generalized motor discharge of the central nervous system, there exists a definite threshold as in any physiologic process. Most women who die from toxemia of pregnancy have progressed to eclampsia, but some have severe preeclampsia on excitus (20). This "individual-dependent" distinction between preeclampsia and eclampsia should be kept in mind, along with other such personal differences in

TABLE 10

Perinatal mortality in TP (7)

Time (convulsions to delivery)	Birth weight (grams)	Termination of pregnancy: Elective Infants at risk	Elective Perinatal loss	Spontaneous Infants at risk	Spontaneous Perinatal loss	Total Infants at risk	Total Perinatal loss
Less than 72 hours	2,500			29	6 (20.6%)		
	2,500			36	8 (22.2%)		
	Unknown	4	2 (50.0%)	1	0		
						70	16 (22.8%)
Greater than 72 hours	2,500	10	4 (40.0%)	20	10 (50.0%)		
	2,500	12	1 (8.3%)	19	2 (10.5%)		
	Unknown					61	17 (28.0%)
Post partum	2,500			4	0		
	2,500	3	0	29	2 (6.8%)		
	Unknown			2	0		
						28	2 (5.2%
Undelivered at time of maternal death						2	2
Total		29	7 (24.0%)	140	28 (20.0%)	171	37 (21.6%)

the reactions of given patients to particular conditions, when reviewing the pathogenesis of TP.

In the following section, the important anatomical lesions found in TP are presented. These are followed by an attempted correlation of current theories in an effort to gain insight into the pathophysiology and immediate causes of this disease.

Necropsy and Biopsy Findings

Liver. The traditional picture of the liver at autopsy is one of diffuse, irregular, patchy hemorrhagic lesions seen usually in the right lobe (16-18, 62, 63). The process is of variable severity (62, 63).

Rarely, rupture of Glisson's capsule with hemoperitoneum may occur. This exceptional complication occurs almost always in multigravidas (3). Haller (17) reported such an occurrence in a woman who was gravida 6; Call (16) in one who was gravida 8; and Pavlic (18) in a woman gravida 8. Upon autopsy their livers were found to be greatly enlarged with one or many lacerations present in the capsule through which a subcapsular hematoma protruded (16-18). Transection revealed areas of congestion and hemorrhage (16-18).

In the toxemic liver, yellow-white areas representing foci

of ischemic infarction are often scattered throughout (3). Histologically there is a periportal hemorragic fibrinoid necrosis with thromboses of the small portal vessels (arterioles) (16-18, 62) in the periphery of the liver lobules. There is also widespread compression of the blood sinusoids. The necrotic and hemorrhagic lesions have been related to mortality in eclampsia since they are found in early all who die of TP, but in only about a quarter who recover from TP and die of other causes (62).

The observations of liver biopsies do not always concur with the above autopsy finds. In preeclampsia and eclampsia needle biopsy specimens usually show some anisocytosis and anisonucleosis (dissimilar sized cells and nuclei) superimposed on an otherwise normal appearing histological picture (52, 63, 64).

Maqueo et al (52) observed fatty metamorphosis in 15 out of 50 biopsies from patients with TP. In 21 of these cases they observed small areas of necrosis, usually in the peripheral part of a lobule. The cells in these areas were shrunken and markedly eosinophilic, and the nuclei were freuqnetly missing. In two eclamptic patients fibrinous thrombi were seen in the sinusoids.

The incidence of observed changes in liver tissue is much lower in biopsy than in autopsy materal, and in biopsies these changes are seen primarily in patients with eclampsia (63). Sampling may account for some of these findings since the amount of tissue obtained with a needle is relatively small.

In 1968 Altchek (62) with electron microscopy made a dramatic finding in the liver biopsies which had not been previously reported in toxemia. The liver cell mitochondria were found to be enlarged; some were enormously enlarged and irregular and had a bizarre multilobulate shape (Figures 2 and 3) The cristae were increased in number, had a disturbed orientation and configuration, and often formed whorling or parallel lamellae against the inner membrane wall. The interior, or matrix, of the mitochondria contained longitudinal bands of rods or filaments of dense, parallel paracrystalline inclusions whose presence was abnormal. The matrix also had areas of focal rarefaction and an increase of small dense deposit granules. The smooth endoplasmic reticulum of the cytoplasm appeared hypertrophied and had formed vesicles (Figures 2 and 3).

These changes observed in the mitochondria and smooth endoplasmic reticulum, although not previously described in TP, have been described in diseases due to a variety of hepatic-injurious agents including alcohol and protein-caloric malnutrition (62). The mitochondrial changes are considered evidence of cellular injury, and are associated with arrest of cellular respiration and adenosine triphosphate deficiency (65).

Kidney. Renal biopsy or autopsy, by light microscopy, of those with preeclampsia or eclampsia reveals a characteristic lesion--a thickening of the wall of the glomerulus with secondary narrowing of the glomerular capillaries (62, 63, 66). The details are revealed

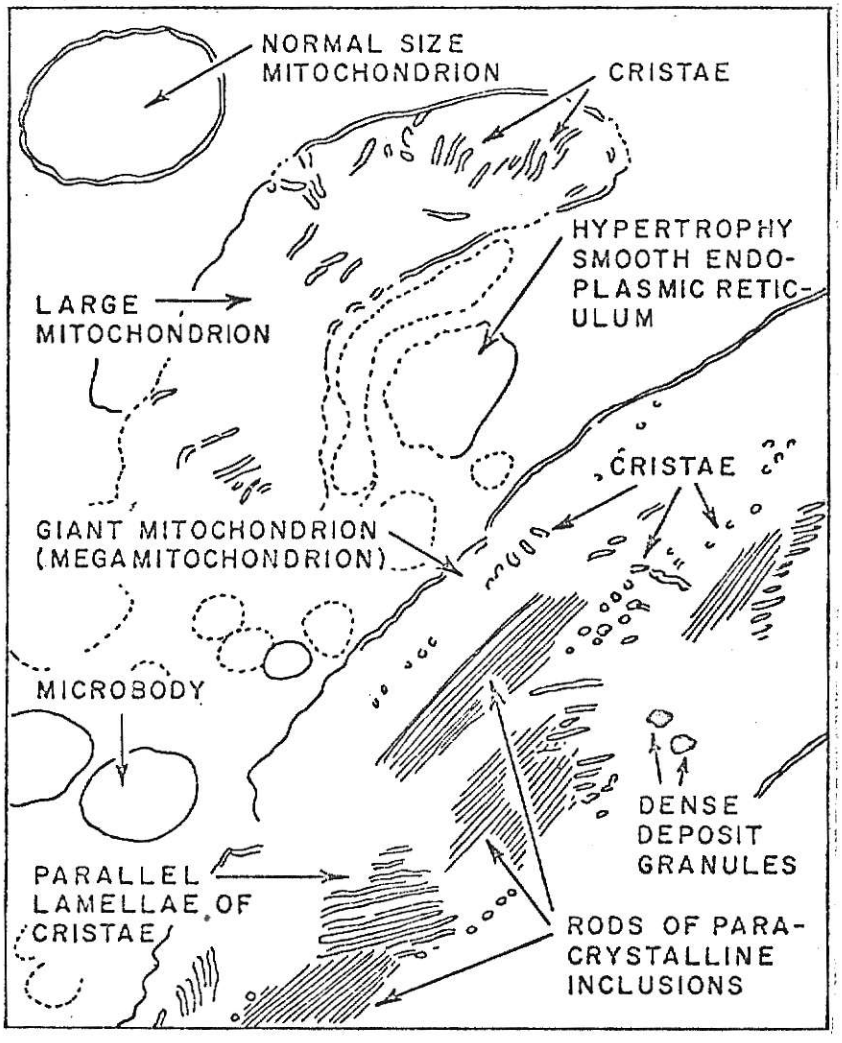

Figure 2. Diagrammatic schema of abnormal mitochondria in liver of women with TP. (62)

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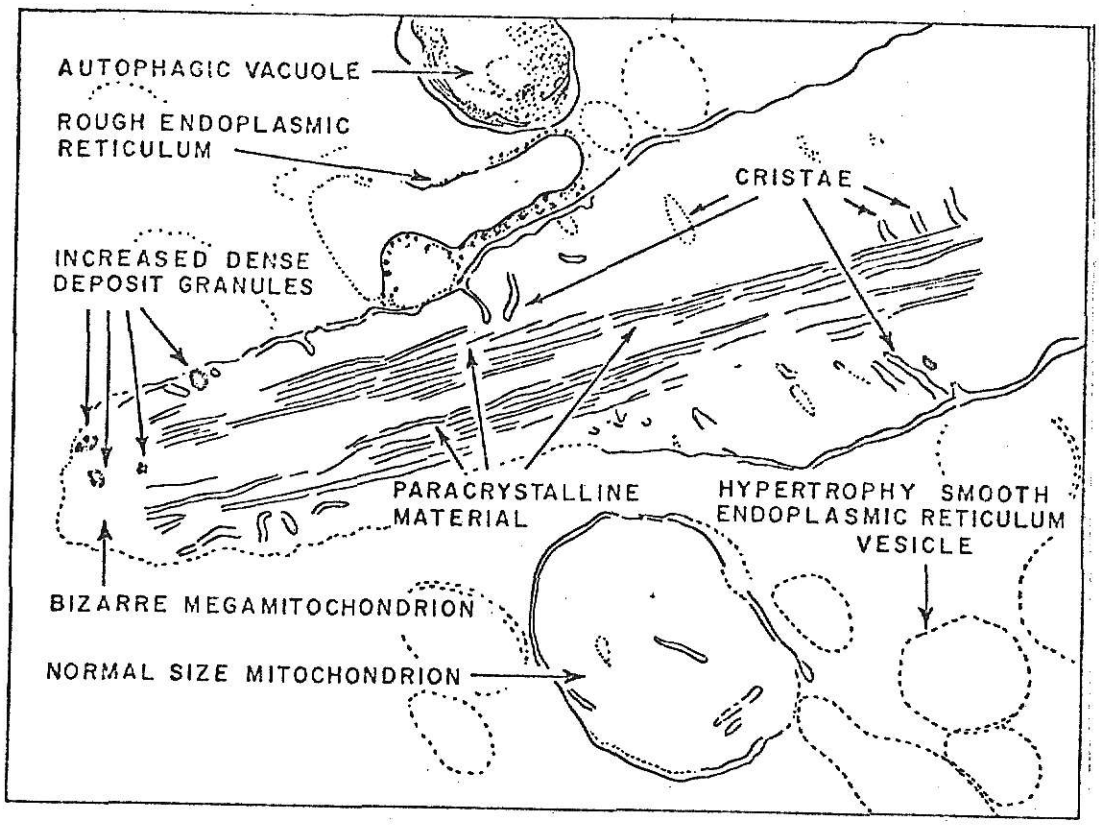

Figure 3. Diagrammatic schema of abnormal liver cell mitochondria and smooth endoplasmic reticulum (62)

only by the electron microscopy. There is a swelling of the endothelial cell cytoplasm of the capillary wall, an increase in the number of intercapillary cells and a deposit both within the swollen endothelial cytoplasm and on the inner surface of the basement membrane (62, 66). The deposit has two components--an amorphous mass and smaller densely staining granules (62). Part of the deposit presumably is made up of a fibrinogen-fibrin molecular series, since there is a positive fluorescent antibody stain (62). However, it does not give the typical electron microscope picture of fibrin (62). These typical glomerular lesions may appear with minimal if any clinical symptoms of TP and may persist during pregnancy even though the clinical signs are ameliorated by vigorous therapy (8).

A light microscope study by Altchek (62) of the kidney outside of the glomerulus proper revealed juxtaglomerular call typerplasia and an increase in their granularity, usually accompanied by macula densa enlargement; however, the mcaula densa cells are atrophic. Upon autopsy there is also frequently found a swelling of the glomerular artiolar wall with a thrombosis and necrosis of the glomerulus.

Placenta. The excessive incidence of infarcts in the placentas of women with TP (about 67%) has been noted by many (20, 63, 67-69) Microscopically, enlargement of the villi in the

infarcted areas with partial or complete thrombosis and blockage of the intervillous circulation is found (63, 67) These occlusions result in decidual necrosis and hemorrhage from necrotic vessels. The hematoma may develop enough to cause a progressive placental separation from the uterine wall which could lead to a functional myometrial disturbance with hypertonic uterine contractility (63). This is just a theory, the true pathogenesis of the increase uterine contractily and premature birth in TP is unknown (70) It has been recognized, though, for a long time, that patients with severe preeclampsia or eclampsia have an irritable uterus and for the most part are easily induced (65).

Adrenals. Way (20) found that 33% of his subjects who died of eclampsia showed lesions in their adrenal glands consisting of areas of necrosis and hemorrhage. Of these, 45% had practically no functional adrenal cortical tissue remaining. The other 55% showed involvement of approximately half of the cortical tissue. He found no cases with minimal lesions.

Haynes (2) also reported that necrosis of the suprarenal cortex is sometimes found on autopsy. The terminal appearance of a shock-like syndrone, known as toxemic collapse, was observed by Way (20) in those with adrenal damage.

Brain in Eclampsia. The brain characteristically shows

multiple petechial hemorrhages in the cortical tissue at scattered locations on autopsy (2, 5, 20). Way (20) observed necrosis in these same areas of the brain in 5 of 33 autopsies.

Other Organs. Occasionally, a toxemic patient is found at autopsy to have focal necrosis of the myocardium, with a heart-block (2, 20).

Way (20) found pneumonia of varying degrees in 50% of his subjects, usually marked by pulmonary edema which failed to respond to the usual therapy. Starkie et al (41) found abnormal lung scans in 6 out of 8 patients with TP, and support the concept of localized intravascular coagulation and suggest that the pulmonary vessels, like many other organ blood vessels, may become involved in that process.

Focal necrosis is also occasionally seen in the pancreas due to thrombosis (20).

Pathophysiology

The pathophysiology of TP is still poorly understood, but some prominent features of the total picture have been elucidated. These are hypoalbuminemia, disseminated intravascular coagulation, and uteroplacental ischemia. A summary of the physiological alterations in TP are shown in Table 11. It is obvious that the

precarious physiologic balances between those factors contributing to the retention and loss of water and sodium, to vascular pressor and depressor mechanisms, and to coagulation and fibrinolysis have broken down.

Hypoalbuminemia, Edema and Sodium. In TP the value of whole blood and the absolute amount of serum proteins decrease not only in the developed clinical picture of the illness, but, also even before any symptoms appear (27, 28). In potential patients, the volume of the whole blood was found to be lower by about 495 ml and the absolute amount of serum proteins about 23.6 gm lower than in normal pregnancy (26). In severe preeclampsia the amount of circulating protein is even smaller than in the nonpregnant state (25, 27, 73).

This decrease in protein concentration, which is largely due to a decreased level of albumin (19, 29, 71), causes an initial dilution of the plasma and a, therefore, decreased onocotic pressure leading to a net outflux of fluid from the blood vessels (19, 30, 74). This net outflux of fluid pulls sodium with it to keep the osmolarity the same (74). This shift in fluid, of course, leads to sodium retention, edema and hypovolemia (74, 75) (Fig. 4) Sodium retention is not, therefore, the cause of edema in preeclampsia (74, 76). Also, the low levels of aldosterone found in TP are against

TABLE 11

Physiologic alterations in TP (Derived from 8, 21, 26, 37, 40, 41, 62, 70-72)

Change	
Lowered total serum protein	TP
Lowered serum albumin	TP
Elevated plasma cryofibrinogen	Early preeclampsia
Elevated cryofibrinogen fraction	TP
Elevated plasma fibrinogen	Early preeclampsia
Elevated fibrinogen turnover	TP
Markedly shortened partial thromboplastin time	Early TP
Shorter prothrombin time	Early TP
Prolonged partial thromboplastin time	Late TP
Slightly prolonged thrombin time	Late TP
Elevated serum fibrinogen/ fibrin degradation products	TP
Slow intravascular coagulation	TP
Lowered plasma plasminogen	TP
Thrombocytopenia	Severe TP
Decreased uteroplacental circulation (50%)	TP
Decreased concentration of placental monoamine oxidose	TP
Elevated plasma renin activity	Very early preclampsia
Lowered plasma renin activity	Late TP
Lowered plasma angiotensinogen	TP
Unidentified pressor agent (Placentin)	TP
Elevated placental pressor amines	TP
Increased vascular sensitivity to angiotensin II, vasopressin & cathecholamines	TP
Peripheral arteriolar spasm	TP
Hypertension	TP
Pathological edema	TP
Lowered plasma volume	TP
Lowered renal plasma flow	TP
Lowered glomerular filtration rate	TP
Elevated blood urea nitrogen	TP
Elevated serum uric	TP
Slightly lowered serum pH	Severe TP
Elevated CSF uric acid	Severe TP
Slightly lowered CSF pH	Severe TP
Elevated protein, glucose, RBC & WBC in CSF	Eclampsia
Lowered plasma aldosterone	Severe TP
Elevated serum glucose	Severe TP
Elevated serum glumatic oxalacetic transaminase	Severe TP
Elevated serum glutamic pyruvic transaminase	Severe TP
Elevated lactic dehydrogenase	Severe TP
Elevated serum pyruvic acid	Severe TP

aldosterone and, therefore, sodium resorption being necessary for maintaining this edema (39).

Slow Disseminated Intravascular Coagulation. The only reasonable explanation for the presence of fibrin (or a material closely related to fibrin) in the reticuloendothelial cells and the fibrin thrombi in various organs found on biopsy or autopsy of women with severe TP is a slow disseminated intravascular coagulation (20, 21, 40, 41, 77-79).

In an experiment by Coopland (40), rabbits were perfused with varying amounts of thromboplastin, producing intravascular coagulation and a glomerulor lesion whose ultrastructure was indistinguishable on electron miscroscopic examination from that seen in preeclampsia. The plasma clotting factor levels observed in TP (Table 11) support this theory. Cryofibrinogen, the cold precipitable fraction of fibrinogen is found in increased amounts throughout TP and the total fibrinogen is elevated in the early stages of TP (40).

Increased fibrinogen turnover (36), increased plasma fibrinogen/fibrin degradation products (FDP) (77, 79, 80), decreased blood plasminogen (41), decreased fibrinolytic activity (20, 77), shorter prothrombin times (76), and thrombocytopenia (20, 77) are seen in advanced TP and represent further proof that intravascular coagulation is present. The slightly longer thrombin time is probably

due to antithrombin effects of FDP compleases, which are found in increased amounts in severe TP (78, 79). In late TP the plasma fibrinogen level drops (40) because of the increased fibrinogen turnover (36). Also, the partial thromboplastin time is markedly shortened in early TP and abnormally prolonged in late TP (40).

All of these facts lead to the conclusion that early in the disease process, before any sumptoms are apparent, an abnormal slow intravascular coagulative process is initiated, possibly by the larger amount of circulating cryofibrinogen synthesized by a liver which has been shown at this stage of toxemia to have a subcellular lesion. This abnormal coagulative process (Fig. 5) proceeds for some time and begins to lower the blood levels of the clotting and fibrinolytic factors(synthesis cannot keep up with demand). Meanwhile, the level of cryofibrin, as both small aggregates and larger thrombi, and its degradation products are increasing in the blood (40). In an attempt to counteract the high plasma levels of this abnormal fibrin-like material, which has recently been shown to elicit a fibrin antibody response (81, 82), the reticuloendothelial cells (of the liver, kidney, and placenta in particular) phagocytize the aggregates of cryofibrin (62, 66). This material for some unknown reason is not broken down readily and collects in these specialized endothelial cells and causes them to slowly swell in size (called

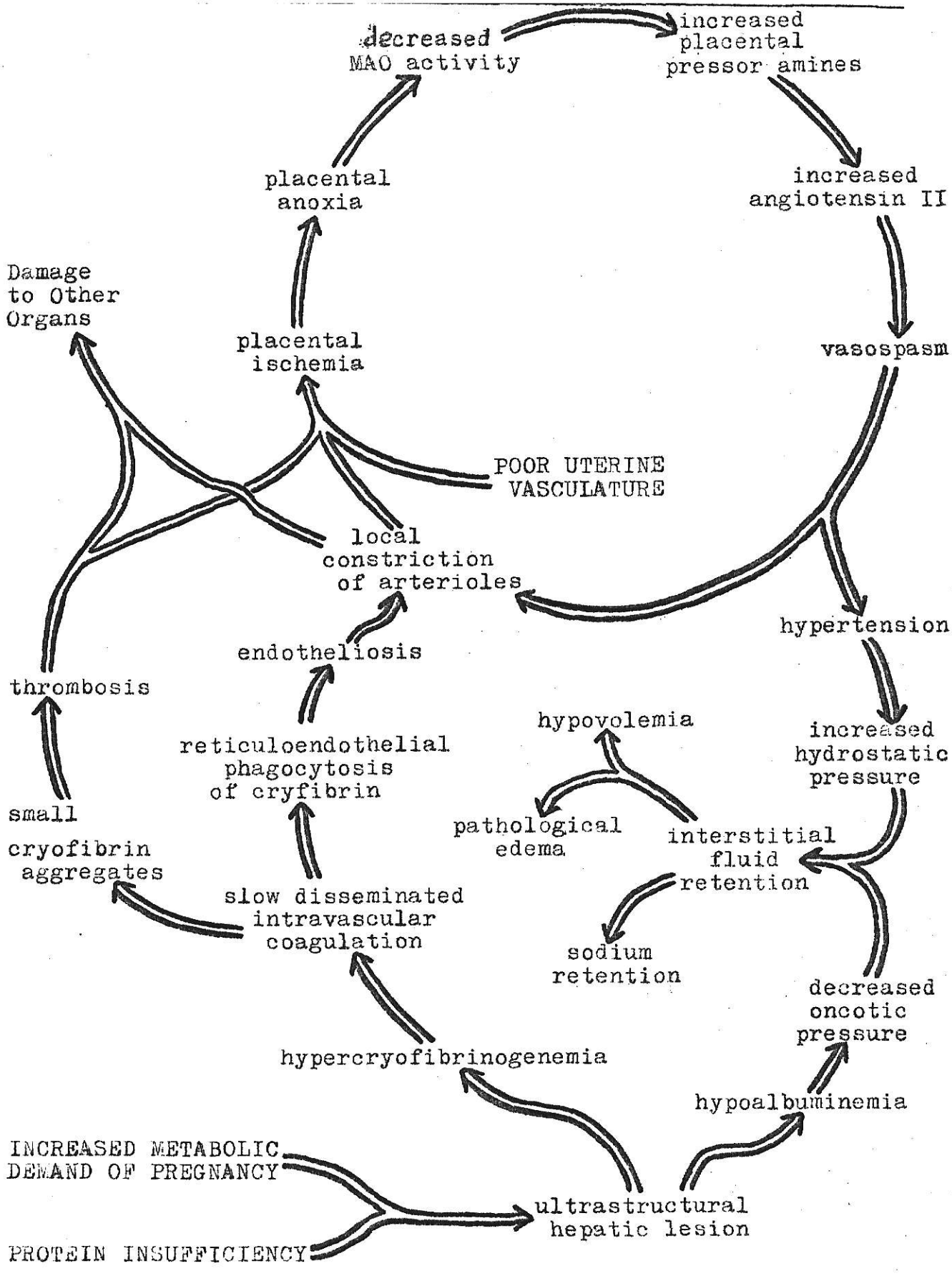

Figure 4, Pathophysiology of TP

NORMAL COAGULATION:

Prothrombin

Thromboplastin

Fibrinogen $\xrightarrow{\text{Thrombin}}$ Fibrin Monomers $\xrightarrow{\text{polymerization}}$ Fibrin clot

ABNORMAL COAGULATION OF TP:

Cryofibrinogen $\xrightarrow[\text{reaction}]{\text{slow spontaneous}}$ Cryofibrin Monomers $\xrightarrow{\text{polymerization}}$ Cryofibrin Clot

Figure 5 Slow disseminated intravascular coagulation in toxemia of pregnancy.

endotheliosis) (36, 81). These swollen endothelial cells, which lie on the inner surface of the arteriolar walls, cause the lumen of the arterioles to decrease in diameter (62). This, of course, increases the incidence of infarctions in these areas (arterioles with reticuloendothelial tissue) especially since there are increasing amounts of cryofibrin thrombi flowing through these narrowed vessels. A ficious circle can thus be started (Fig. 4)

These arteriolar occlusions and the decreased plasma flow (ischemia) in the periportal areas of the liver, glomeruli of the kidney, villi of the placents, and the cortex of the adrenals can readily lead to focal necrosis and the release of thromboplastin into the circulation to further enhance the coagulation process.

Poor Uterine Vasculature, Anoxia and Hypertension. Utero-placental circulation is decreased by about 50% in late TP (Table 11) (71, 72) by this process of coagulation, endotheliosis, occlusion and ischemis, and enhanced by an already borderline blood supply due to poor uterine vasculature (5, 83). Preeclampsia is more common in first pregnancies, twin, and multiple pregnancies,--all situations in which the growth of the uteroplacental unit is likely to outstrip the development of an adequate blood supply (36, 84). For the developing fetus and its placenta, the nutritional value of its mother (placental perfusion) increases with parity, since the uterus adapts by an increase and vasculature (85). Also, TP is relieved to some extent by bed rest and abdominal decompression, which enhance the blood supply

to the uterus (5, 36, 82). Arteriography also shows that a very poor uterine blood supply is visualized in patients with preeclampsia (36). The already inadequate (or barely adequate) uterine blood supply of these women can be made insufficient by endotheliosis and infarctions.

A decrease in the placental levels of monoamine oxidase was found concomitant with this uteroplacental ischemia (20, 67, 72). Monoamine oxidase (MAO) is the enzyme involved in the deactivation of catecholamines (67, 72). The reduced blood flow decreases the oxygen tension within the intervillous spaces and decreases the efficiency of MAO to deal with placental pressor amines, which have been found to be in higher concentrations in toxemic placentas (72).

It has been demonstrated that there are two pressor substances in eclamptics: a heat-stable substance from the decidua and amniotic fluid (termed hysterotonin) and a heat-labile substance (placentin) which activates the angiotensin system (Fig. 6) (86).

Goretzlehner and Riethling (86) with a method for angiotensin II assay isolated a vasoconstrictive substance from the venous blood, urine, amniotic fluid, decidua, and placenta of patients with TP. No such vasoconstrictive activity was observed in normal pregnant women. Such a result would explain the decreased plasma angiotensinogen seen in late TP (Table 11).

NORMAL PRESSOR MECHANISM:

Angiotensinogen —Renin→ Angiotensin I —ubiquitous plasma factor→ Angiotensin II

ABNORMAL PRESSOR MECHANISM OF TP:

Angiotensinogen —Placentin→ Angiotensin I —ubiquitous plasma factor→ Angiotensin II

Figure 6 Action of placentin: One of the placental pressor amines

Another physiologic change seen in women with TP also is very important--increased vascular reactivity (20, 87-90). For some unknown reason, possibly the aforementioned arteriolar endotheliosis, women with TP have a markedly increased sensitivity to angiotensin II, catecholamines, vasopressin and to cold stimulation (88). Thus, not only do women with TP have higher blood levels of pressor substances, but also a more reactive vascular system--making them hypertensive (Fig. 4).

Impaired placental function, shown by poor fetal growth, reduced excretion of estrogens, and declining plasma levels of placental lactogen, is characteristic of late TP and is an important harbinger of intrauterine death (Fig. 7)

Renal Ischemia, Oliguria and Proteinuria. A theory that renal ischemia caused the hypertension of TP was popular until it was found that the plasma renin activity is decreased in late TP

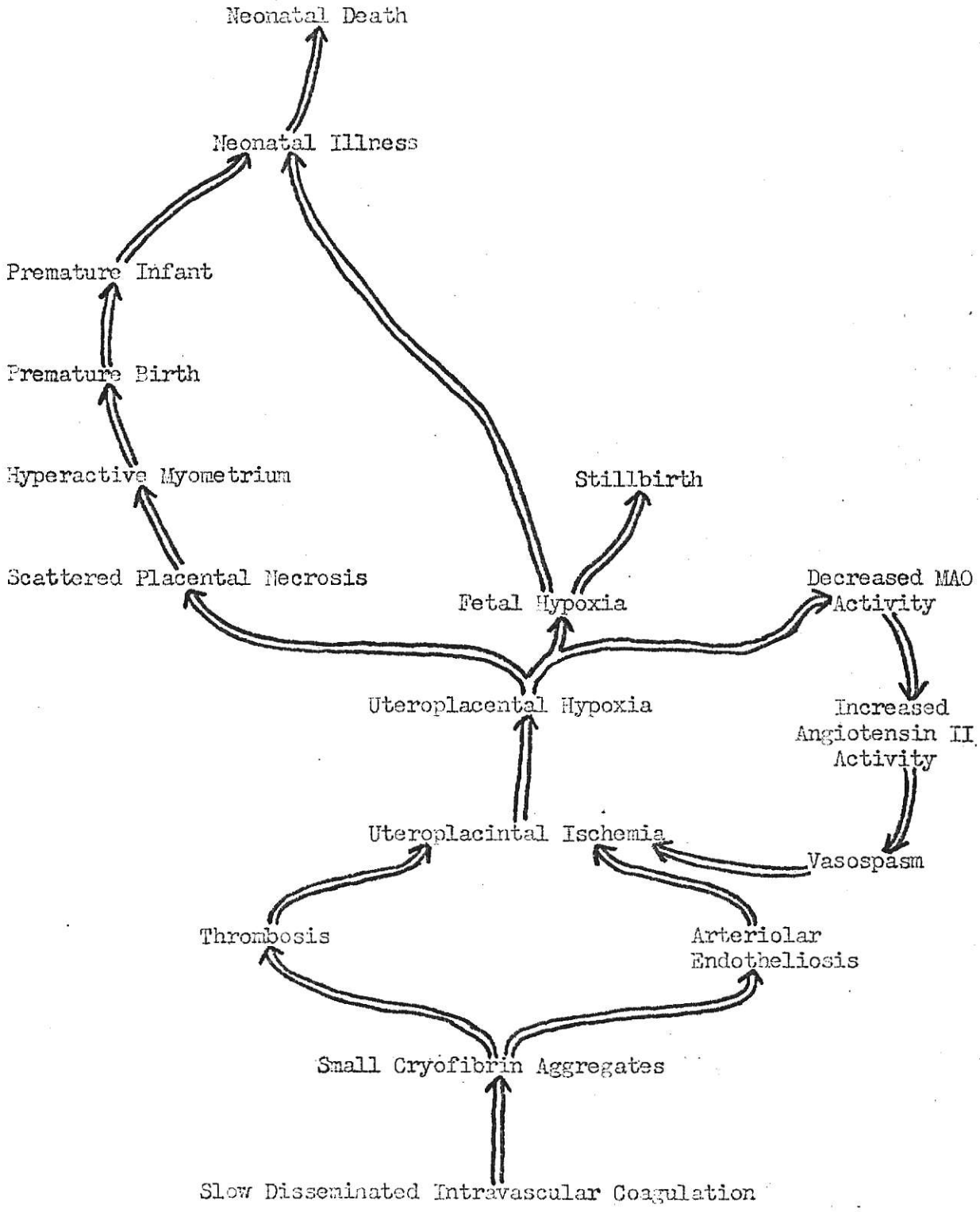

Figure 7 Pathophysiology of placental and fetal damage in TP

(34, 37, 38, 70, 77, 88) to near nonpregnant levels. Gordon (37) found that plasma renin activity is increased in women during the latter part of the second and early part of the third trimester who later develop toxemia, but at that time they were not hypertensive.

Although the kidneys are not the cause of hypertension, they are definitely a victim of it by way of the endotheliosis and the so-called uterorenal reflex (Fig. 8) (91). When an animal placenta is made ischemic (by distension of the uterus or by placing teflon bands about uterine arteries), the renal arteries are found to constrict with a decrease in the renal plasma flow, glomerular filtration rate (Table 11) and renal cortical necrosis and proteinuria result (20, 36, 89, 92). The cortical necrosis is presumed to lead to a degeneration of the filtering membrane thereby allowing the dumping of the large protein molecules (albumins, etc.) into the urine (2). The decreased glomerular filtration rate accounts for the oliguria, hyperuricemia, and elevated BUN seen in many toxemic patients (2, 5).

Hepatic Lesion and Etiology. From what is presently known about the pathology and pathophysiology of TP it would seem that TP is a disease that starts out with the subcellular hepatic lesion which leads to the initial hypoalbuminemia and hypercryofibrinogenemia (albumin and fibrinogen are synthesized by the liver) followed by the

decreased onocotic pressure, slow disseminated intravascular coagulation, and vasoconstriction. All of the other organ lesions are seen only in fully developed TP and can be attributed to intravascular coagulation (2). But megamitochondria with paracrystalline inclusions and vesicularized smooth endoplasmic reticulum are observed in hepatocytes during early, mild TP before any other lesions are apparent (62). Also, many of the liver function tests are abnormal in mild preeclampsia (Table 11). The serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are often elevated (2, 62). The serum lactic dehydrogenase (78) and pyruvic acid levels (93) also are elevated in many toxemic women, which may be related to the impaired liver mitochondria (Kreb's cycle shut down and liver cells can only use anaerobic pathway, leading to a backlog of pyruvic acid and a need for more lactic dehydrogenase to shunt excess pyruvic acid to lactate). Also, the standard bromsulphthalein (BSP) clearance test is sometimes altered (52).

These changes observed in the liver mitochondria and smooth endoplasmic reticulum seen during TP also have been described in alcoholic hepatitis (62) and experimental protein-calorie malnutrition (65). They are thought to be a basic response to injury and are associated with arrest of cellular respiration and adenosine triphosphate deficiency (62).

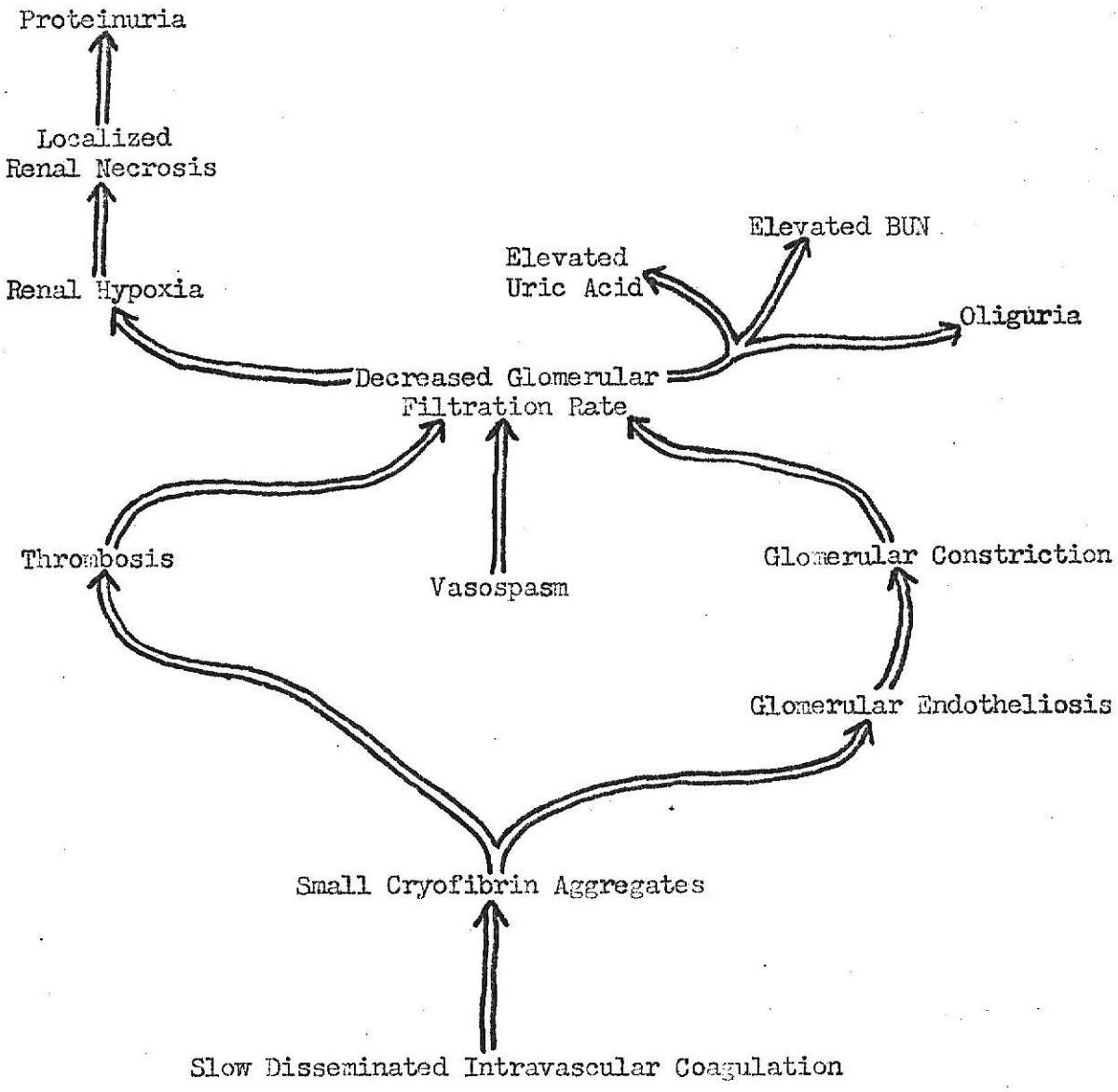

Figure 8 Pathophysiology of renal damage in TP.

The next question is that of etiology--what causes this primary subcellular hepatic lesion? The exact answer to this question is unresolved but clinical studies have indicated malnutrition as the ultimate cause with poor uterine vasculature as a prominent compounding factor.

In particular, malnutrition would affect the liver first because, unlike other organs (kidneys, placenta, etc.) hepatic blood flow is unchanged in pregnancy despite the increased cardiac output and blood volume, and therefore has a smaller percent of the total blood flow (62). This implies that the liver cells have to work more efficiently to carry the increased metabolic demands of pregnancy (62). Thus, the liver can readily become malnourished in pregnancy if the diet which may have been borderline-sufficient in the non-pregnant state, remains poor (and the body stores are low) during this period of increased metabolic demand (1).

RELATIONSHIP OF MALNUTRITION TO ETIOLOGY

Toxemia of pregnancy is thought to be caused, at least in part, by malnutrition (5, 19, 28, 29, 48, 51, 52, 94-98). No adequate alternative explanation has been advanced (5, 96). Almost any homeostatic mechanism can be altered by diet and the outcome of pregnancy is governed by, and almost an expression of, nutrition (5). The increased physiological nutritional requirements during pregnancy

enhance the liklihood of nutritional deficiencies occurring during this period (98). Metabolic adjustments during this period may so alter the metabolism in some patients that a conditioned deficiency state may develop in spite of what would otherwise be considered an adequate dietary intake (98). The expectation of alterations in nutrient requirements is reflected in estimates of nutrient allowances for pregnant women such as the Recommended Dietary Allowances (99).

The fact that some mothers escape toxemia, even though some of their blood nutrient levels are very low, does not eliminate malnutrition as a factor in TP (51). While most clinicians long have been convinced of the association between dietary factors and TP by prima facie evidence, objective proof, supported by data from a suitably controlled investigation, is still scant (51).

A basic handicap is the lack of broad nutritional studies before, throughout and after pregnancy. Many pregnant women, particularly those in the low-income groups who are most susceptible to TP,are not seen by a physician until the third trimester of pregnancy and, thus, a considerable period of pregnancy cannot be covered in a dietary study (3). Methods for detecting the effects of diet are not yet sufficiently precise to detect subtle changes that may, in fact, occur at the cellular and subcellular levels (3).

The only logical conclusion from the evidence presented thus far is that TP is causally related to poor uterine vasculature and poor

nutrition (5). The following sections are concerned with the malnutrition associated with TP. They include a discussion of the general dietary studies and an examination of the nutrients implicated.

General Dietary Trends

The Vanderbilt Cooperative Study of Maternal and Infant Nutrition (98) in 1949 showed that the average nutrient intake of women who developed TP and were under doctor's care, tended to be lower than that of the total study group throughout the prenatal period, and was significantly lower in the first and third trimesters.

Intakes of protein, calories, calcium, iron, thiamine, riboflavin, niacin, vitamin A and vitamin C were evaluated. Average recorded intakes of protein, iron, riboflavin and niacin of women with TP were significantly lower than those of the control group during the first trimester. The average caloric intake was 230 kcal lower than that of the total group. Nutrient intake of women with TP improved during the second trimester and only niacin was significantly lower than the average of the total group, with protein still low but not significantly so. In the third trimester, there was again a general decline in nutrient intake of the women with TP but it was only in calories and niacin. The urinary excretion of N-methylnicotinamide tended to be low throughout the prenatal and peurperal period, but was significantly so only in the latter.

The incidence of obesity in women with TP was significantly higher than that of the total study group (35% compared to 18%). The obese patients had received physician's instructions early in their pregnancy to restrict their nutrient intake. This was done, oddly enough, with the idea that limitation of weight gain by caloric restriction protects against TP (which in this case, as in many before it, obviously failed).

This idea, which made its way into medical textbooks for a time, goes back to an observed reduction in mortality from eclampsia in England and Wales during the Second World War, a period of privation and rationing of food (5). These women suffered no little strain, but the rationing system benefited (not deprived) expectant and nursing mothers and for the first time women of the poorer socioeconomic groups were fed as well as others (5). They were allowed an extra pint of milk per day and by 1943 an extra half-ration of meat and larger allowances of eggs. Vitamin supplements containing vitamins A, C and D were also given free to these women. But because they gained less weight on the average, it was concluded without further study that a restricted diet was protective (3, 5).

Burke et al (94) at the Boston Lying-in Hospital did a nutrition study with 216 middle-class white women. A dietary history, 24-hour recall and 3-day diet record were recorded for each woman. The amounts eaten daily of such important foods as milk, meat, eggs,

whole grain products, vegetables and fruits were carefully studied. Each woman's diet was classified by the mean of percentages of the dietary standards eaten for each nutrient. The dietary standards used in this study are listed in Table 12.

TABLE 12

Nutritional standards for pregnancy (derived from 94)

Nutrient	Amount
Calories	2600 kcal
Protein	85 g
Thiamin	2.0 mg
Riboflavin	2.5 mg
Miacin	18 mg
Vitamin C	100 mg
Vitamin D	400 I.U.
Vitamin A	8000 I.U.
Calcium	1.5 g
Phosphorus	2.0 g
Iron	20 mg

An "excellent" prenatal diet according to this study was one that had 100% of the recommendations in Table 12. A "good" diet was one that averaged 80% of these standards, a "fair" diet averaging 60%, a "poor" diet averaging 50%, and a "very poor" diet having an average less than 50% of the recommended intake.

In this study those women with poor to very poor prenatal diets had a 44% incidence of preeclampsia. There was no incidence of preeclampsia in any pregnancy where the diet rated good or excellent, and only an 8% (near national average) incidence in those

with fair diets. This, of course, revealed a very close relationship between the quality of the prenatal diet and the incidence of TP.

Mack et al (51) in a clinical study of pregnancy complications and nutritional status also found strong circumstantial evidence that malnutrition plays an important part in susceptibility to preeclampsia and eclampsia. Also, their data support the views of others (5, 48, 53) regarding the distinctly inferior nutritional status of underprivileged subjects, particularly blacks. They found a downward trend in median serum protein concentrations throughout gestation in women with TP. More white toxemic subjects had low levels of vitamin A in their serum than did women with uncomplicated gestations. For Negro women, this was notable only during the postpartum period. A similar situation was not found for blood levels of serum carotenoids.

Maqueo et al (52) also found a direct relationship between dietary insufficiency and TP (Table 13). They discovered, in addition, that the degree of malnutrition correlated strongly with the severity of the toxemia. Nutritional status was evaluated from the point of view of total caloric intake and amount of animal protein consumed. Nutrition was considered to be normal when animal protein intake was "adequate" (a quantity was never mentioned) and total caloric intake exceeded 2,300 calories per day.

Eighteen of the 50 women with TP were moderately deficient (total caloric intake 1200-2000 calories per day, protein intake subnormal). Three women had a severe deficiency in animal protein

intake and a caloric consumption below 1200 calories per day; these 3 women all developed eclampsia. The correlation between protein-calorie status and severity of toxemia was highly significant ($p < .001$). A possible correlation between the frequency of abnormal SGPT and the severity of the toxemia also was demonstrated (47). This, of course, supports the contention that the added burdens of the last trimester of pregnancy coupled with a poor diet, which might well have been marginally sufficient in the nonpregnant state, could decompensate the most metabolically active organ of the body--the liver.

TABLE 13

Clinical and laboratory findings in 50 patients with toxemia (52)

Observation	No. of patients		
	Mild Toxemia	Severe Toxemia	Eclampsia
Nutrition			
Normal	7	22	0
Moderately poor	1	12	5
Very poor	0	0	3
Clinical hepatic insufficiency	0	0	1
Abnormal cholesterol esters	0	2	2
Abnormal SGPT	1	13	5
Abnormal SGOT	4	20	6
Abnormal liver cytology	5	25	8
Areas of necrosis	0	7	5
Fatty metamorphosis	2	9	3
Total	8	34	8

Chaudhari (50) who conducted a study on 1,210 pregnancy cases found that the incidence of TP was significantly more in patients with a nutritional deficiency (25%) than in healthy subjects (7%). His serum protein analysis showed that in toxemic cases there was significant lowering of total serum protein, serum albumin, and albumin-globulin ratio as compared with those of the controls.

In summation, these broad nutritional studies have demonstrated a direct relationship between a generally poor diet and TP, and have pointed out insufficient protein as the most important causal factor.

Protein Insufficiency

Serum Proteins. In a Guatemala study (100) a comparison was made between two socioeconomic groups of the alterations in serum proteins during pregnancy. Previous dietary surveys had indicated a moderate total protein intake (68 g/day) but a low intake of animal protein (21 g/day) in the women of the low income group.

One alteration that they observed during pregnancy (most frequently in the last trimester of pregnancy) was the appearance of the "pregnancy zone" in the starch gel electrophoresis of many serum samples. Chi square analysis revealed a very significant increase in the intensity and frequency of its appearance in the low socioeconomic group. Also, this zone increased with the stage of gestation and the number of previous pregnancies.

The gamma globulin level was increased among the poorer subjects, with an additional difference sometimes noted in the individual bands within the gamma globulin zone in electrophoresis. These bands may be related to antibody production. In a study of children recovering from kwashiorkor the appearance and disappearance of similar bands in serial samples were noted (100).

Also, albumin levels and the albumin-globulin ratio were found to be lower (p 0.01) in the lower socioeconomic group (100). This agrees with studies (29, 101) which have shown a marked reduction of the fractional and absolute synthesis rates of albumin within a two week period after dietary protein restriction.

The importance of the albumin lowering effect by protein insufficiency on the course of TP was recently demonstrated by Cloeren et al (71). The administration of the plasma expander low-salt-content human albumin led to an improvement in the condition of hypovolemia as seen by increases in central venous pressures. Better renal function with increased urine secretion and an increase in uteroplacental blood volumes also were found.

Another possibly pertinent bit of data is the striking similarity in cord plasma aminograms (increased glycine/valine ratio) reported in newborn babies of mothers with toxemia and retarded fetal growth and in infants born of mothers with protein deficiency (102).

Liver Injury. A surprisingly close parallel can be drawn between the ultrastructure of a toxemic liver biopsy and that of a woman with protein-caloric malnutrition (and with that seen in experimental protein malnutrition). Although in mild cases of both diseases, liver function tests are normal and light microscopy shows only mild and non-specific alterations, recent electron microscope studies revealed organelle pathology of hepatocytes in all the patients with protein-calorie malnutritions. The endoplasmic reticulum was vesicularized or fragmented, mitochondria were of bizarre shape and many of large size (megamitochondrion), and some contained filamentous inclusion bodies just as in toxemia. And as in TP, these ultra-structural abnormalities are reversed to normal soon after recovery from protein-calorie malnutrition (65).

High Protein Diet and Recovery. As long ago as 1937 Dodge and Frost (29) demonstrated that in cases of mild toxemia a high protein diet (1.5 gm/kg of body weight) caused an alleviation of objective and subjective symptoms and signs of toxemia within a week or two and was well tolerated by the patient. They also showed that the serum albumin increased to normal values within this period.

About this same time Strauss (103, 104) studied the effect of very high protein diets (260 gm of protein daily, in the form of milk, lean meats and egg whites) on TP. His patients lost weight (edema), their blood pressure fell, the subjective symptoms abated and in many cases the albuminuria was decreased within two weeks after commencing the therapeutic diet.

In a four-year series, Harden et al (105) found that none of their preeclamptic patients when given a good protein diet (75-80 grams per day) developed eclampsia, while the frequency of eclampsia cases in the locality remained the same. Dodge and Frost (29) found that with a good protein diet (75-80 grams per day and high in animal protein such as eggs, milk, beef, etc.) their preeclamptic patients' symptoms abated and their serum albumin levels and colloid osmotic pressure rose. Also, none of their preeclamptic patients advanced to eclampsia in the four year clinical study, though previously there had been several cases in their clinic each year.

More recently, Brewer (30) using 2200 kcal and 120 grams of protein per day, arrived at the same conclusion. McGucken (28) also found that on encouraging a high protein diet, the condition stops progressing within two weeks. Primrose (106), Kramer (97) Cross and Walsh (95), Theobald (5), and Ross (47, 48) have found that a high protein prenatal diet (80-100 g) will protect against TP one hundred per cent of the time.

In pregnancy there is an increased need for first class proteins (100, 105, 107-112) and if this need is not met TP can result (13, 19, 28, 29, 49, 74, 110-112). The common factor among women with this disease is that they are all short of protein through excess demand (by the fetus and additional maternal tissue) and

insufficient intake (due to economics, education, poor diet or prolonged morning sickness) (28). Also, preeclampsia mainly occurs in the last trimester of pregnancy, when fetal protein needs are greatest.

Intake of B Vitamins

As was mentioned earlier in the general dietary studies, deficient B vitamin intakes are rather common among women with TP. Up to this date a direct or causal relationship between a deficiency of folic acid, thiamin or pyridoxine and TP has not been supported. It seems instead that the intake of these B vitamins parallels the intake of protein foods. Foods high in protein (especially animal protein) are good sources of the B vitamins. It is because of this and other aspects of a poor prenatal diet that very low amounts of niacin, pyridoxine, thiamin, and folic acid are often found on biochemical analysis in some women with TP. More studies are needed, though, within this area to further clarify the importance of the B vitamin levels in toxemia of pregnancy.

Folic Acid. Stone et al (referred to in 96) found that 22 of 36 patients with TP also showed folic acid deficiencies. Kitay (96) in a recent paper purported that the folic acid deficiency seen in some women with TP is not a cause of the disease, but, rather, just a sign of inadequate nutrition during pregnancy.

Thiamin. Chaudhuri (50, 113) claimed an etiologic relationship between TP and thiamin. The basis for his claim was a study of 5 patients with severe preeclampsia who had elevated serum pyruvic acid levels. They were given 10 mg thiamin injections intramuscularly daily for 7 days. His findings were reported as "a quicker improvement of the toxemic features" and a lowering of the pyruvic acid levels. This was all that was said about the results.

Pyridoxine. Wachstein and Graffeo (114, 115) in 1956 claimed a significant relationship between pyridoxine and TP. They found an increased urinary excretion of xanthurenic acid following a tryptophan load test in women with TP. In their study, 410 of 820 pregnant women were given 10 mg of pyridoxine hydrochloride daily as a supplement to an "apparently sufficient diet" throughout pregnancy. They found a decreased excretion of xanthurenic acid and a slight depression of preeclampsia in the treated group. The incidence of preeclampsia was found to be 4.4% in the control and 1.7% in the treated group. The dietary intake of pyridoxine was not monitored.

Klieger et al (116) also discovered an excessive urinary excretion of xanthurenic acid after a tryptophan load test. They, too, found that the administration of pyridoxine supplements abolished this xanthurenuria. But, they found that the administration of

pyridoxine to the patient with TP was of no significant demonstrable therapeutic value.

The findings of Hillman et al (117) support this lack of a causal relationship. They also found no clinical influence of the pyridoxine supplement on the frequency or progress of TP or any other complications unique to pregnancy.

Sodium Intake

The belief that sodium is associated with the etiology of TP is engrained in the minds of many physicians because of the prominent edema often seen. Salt retention is a result of TP, not the cause (118-120). The hypoalbuminemia causes a decreased colloid osmotic pressure, thereby leading to an outflux of fluid from the cascular system (30, 19, 119). As this fluid leaves it drags sodium along with it and collects in the interstitial spaces causing edema (30, 12, 115).

Proof of this has been found in studies using high salt versus lot salt diets (119). Patients with preeclampsia were given either a high salt or a low salt diet in a double-blind study. The average quantity of sodium was 6 to 7 grams in the high salt diets, and 0.5 to 1.0 grams in the low salt diet. The patients were carefully checked to ensure that sodium in other forms, for example, bicarbonate, was withheld. No diuretics were given to any of the women. Every day each patient's weight, fluid intake and output, blood pressure, and

blood and urinary sodium levels were recorded. Also, each patient was examined daily by a physician, including an ophthalmoscopic examination of the retinal arterioles. No differences were noted between the two diets. The time necessary for recovery to normotensive levels, disappearance of retinal arteriolar spasm, proteinuria, and the changes in patient's body weights were similar.

Robinson (referred to in 119) in 1958 reported that she started giving salt to pregnant women in order to lessen leg cramps. After giving salt to over one thousand pregnant women she ascertained that there was no increase in the incidence of toxemia.

Treatment

The first goal of treatment is to stop the disease from progressing further--to stabilize the patient's condition. The second goal of treatment is to reverse the disease process and return the patient to a normal, healthy condition. As with many other diseases, the attainment of this second goal in toxemic women takes a much longer period of time than the first. A reversal of TP can be attained only by an alleviation of the cause. Whereas, stabilization of the condition can be achieved by altering the patient's physiology in order to break the vicious circle in the patho-physiology of TP (Figure 6).

The stabilization of a toxemic woman is done by hospitalization and the use of drugs (121-123). The reversal of TP is

achieved through the use of infusions of human albumin and a high protein diet.

Medical

Bed Rest. Hospitalization and strict bed rest are basic essentials of management in TP (119, 121, 124, 125). Diagnosis of TP should be followed by prompt admission and close observation (49, 126). Bed rest allows for a better perfusion of the uterus by relieving the pressure, which was exerted while standing, on the arteries supplying it (121). This will supposedly lessen the utero-placental ischemia (Figure 6). It also has been found that postural effects upon renal function are accentuated in TP (129). Renal function is best while in the lateral recumbent position and decreases in supine and standing positions (124).

Sedation. Some physicians advocate the use of sedatives to help the patient tolerate bed rest and to provide some anti-convulsive activity (127).

Anti-convulsant Drugs. The convulsions and cerebral irritability of eclampsia can be controlled by the use of central nervous system depressant, such as magnesium sulfate (128, 129)

Anti-hypertensive Drugs. The successful management of severe toxemia of pregnancy requires control of the raised blood pressure as well as maintenance of adequate placental perfusion and renal function (130). Blood pressure should be controlled

in those patients with severe hypertension by the use of an adrenergic blocking agent which will interrupt sympathetic vasoconstrictor impulses (123, 127, 128, 130). By preventing severe vasoconstriction, the vicious circle of Figure 6 can be broken, and renal and placental perfusion can be improved.

Hydration. Atkins (121) and De Alvarez (131) suggested that hydration (an intake of three quarts of water per day) used as an adjunct in the treatment of TP, expands the effective blood volume and lowers the mortality rate from this disease.

Serum Albumin Transfusion. As was visualized in Figure 6, the hypoalbuminemia of TP leads to edema and hypovolemia. The administration of human serum albumin is indicated to restore the colloid osmotic pressure of the serum towards normal and to correct the hypovolemia that endangers the life of a woman with severe toxemia (19). A dramatic response to intravenous human serum albumin with a decrease in edema, diuresis, hemodilution and recovery from shock was reported by Brewer (19, 118).

Heparin. The only rational place for heparin therapy in TP would be during incipient preeclampsia before there is any significant deposition of fibrin (124). Heparin cannot remove or dispel the fibrin aggregates already deposited in the placenta in severe preeclampsia. When more serial investigations of the intravascular coagulation are carried out, it may become possible to adopt this treatment in early preeclampsia (122).

Diuretic Drugs. Even though many studies (118, 132-135) have shown that the use of diuretic drugs in the treatment of TP is useless and sometimes harmful, many medical textbooks (15, 24) still recommend their use. Flowers et al (133) also have found that there is no significant difference in the incidence of TP between patients who used a diuretic during their pregnancy and those who were given a placebo. The idea of using diuretics arose from the earlier contention that sodium retention was the cause of the edema seen in TP. Any such therapy which results in a further reduction of the plasma volume by renal excretion of water and sodium is hazardous to these patients because it can lead to hypovolemic shock, marked reduction in renal function associated with a decrease in renal blood flow, and a decrease in placental perfusion (118, 121).

A study by Share et al (132) which reinforces the observations of Palomaki and Lindheimer (135), showed that sufficient sodium depletion caused by dietary salt restriction and diuretic therapy caused a serious decrease in renal function and in increase in plasma renin activity.

Dietary

Dietary treatment is important in reversing the disease process of TP (19, 28, 29, 30, 103-105). Medical means are used to relieve any acute distress and to stabilize the patient's condition, but in the long run the use of a good therapeutic diet will reverse the disease.

Salt to taste. As was just discussed in the previous section, a low salt diet is useless as a therapy for TP. It no longer has any experimental or theoretical support (39, 75, 79, 118, 121). Such a diet, in fact, limits a patient's intake of such important foods as meat and milk, (49). A woman with TP should be allowed to use as much salt as she needs to make her meals palatable (49, 119). Some physicians, in fact, have declared that a high salt intake actually helps to improve the toxemic condition (121).

High Protein Diet. The reasons for the use of a high protein diet should be evident from the previous discussion on the relationship of protein insufficiency to etiology. A high protein diet has been shown to prevent (19, 49, 95, 96, 106, 136, 137) and to reverse (19, 28-30, 103-105) toxemia of pregnancy. Intakes of 100 grams per day (106), 120 grams per day (49), 80 grams per day (29, 105) and 85 grams per day (94) have proven effective in preventing TP. The biological value of this protein is, of course, most important especially in pregnancy--a period of unequaled anabolism. An adequate complement of amino acids is needed by the liver to function properly in the synthesis of fibrinogen and albumin.

Such a protective prenatal diet (80-120 grams of protein) can be readily conveyed to outpatients in terms of the basic four food troups (Table 14) with a special emphasis on high-quality protein foods such as eggs, lean meats, fish, and milk (55, 95, 138). Brewer

(49) showed clinical evidence of success in such an approach. He found in a study of over 1000 pregnant women that those women who received such dietary instructions showed a virtual absence of TP compared to controls not receiving such advice.

TABLE 14

Basic daily prenatal diet (Derived from 135)

Group	Foods	No. of servings
MILK	All milks, cheeses	4 or more
MEAT	Lean meats, fish, poultry, lentils, dried beans & peas, eggs, nuts	3 or more
FRUIT & VEGETABLE	Rich in vitamin C - citrus fruits & juices, broccoli, brussel sprouts, greens, peppers	1 or more
	Rich in vitamin A - dark green & yellow vegetables	1 or more
	Other fruits & vegetables	2 or more
CEREAL	Whole grain or enriched breads & cereals	5 or more

The therapeutic high protein diet, used in the treatment of TP, should contain 120-180 grams of high quality protein and should be monitored more closely than the basic four food group instructions will allow. This diet is being used, not to prevent, but to quickly alleviate a protein deficiency. Such a diet must be under the supervision

of a hospital dietician, who can work closely with the patient on a frequent basis to make sure that the prescribed quantity and quality of protein is being eaten.

Feeding such a large amount of protein improves the toxemic condition primarily by replacing the mobilized protein in the tissues which donated it earlier under the stress of the increasing demands of late pregnancy and a deficient dietary intake. It seems to be well established that the body does not possess protein stores containing specific "inert fractions" of body protein with the primary function of being available for such emergencies (1). Part of the normal maternal tissue protein can be mobilized to support the growth of the fetus, and liver protein seems to be particularly available as an amino acid source. In dietary protein deficiency the liver can lose 20 to 40 per cent of its total protein content, the remainder resists further mobilization (1).

The main objective of the therapeutic diet, therefore, is to replace these depleted tissue proteins as quickly as possible. Harden (105) used an 80 gram high-quality protein diet and got results within three weeks. Brewer (30), with a diet of 120 grams of protein, and Dodge (29), with approximately 100 grams per day, reported an alleviation of TP within two weeks. Strauss (103, 104) with his 260 gram protein diet also found a reversion of TP after 10

to 14 days. Thus, an optimum therapeutic protein intake seems to be somewhere between 100 and 200 grams, with no obvious advantage yet proved for a higher, less palatable, intake of protein.

The high protein diet (Table 15), as outlined in the Kansas Diet Manual (139) can be readily used for this purpose. The point system used in this diet (Table 16) permits maximum flexibility for individual food choices. Table 17 lists foods that contain protein of high biological value.

The amount of protein prescribed for a particular toxemic patient's diet should be somewhere in the range of 120 to 180 grams per day. It can be derived by essentially "titrating" the patient's diet to see what the maximum desirable intake of protein can be without a decrease in total caloric intake due to loss of appetite for the prescribed high amount of protein-rich foods. The caloric intake, of course, must be held high enough with carbohydrate and fat to spare the protein from being used for energy.

The caloric intake needed by such obstetric patients can be estimated by using height-weight tables (like that found in the Recommended Dietary Allowances (140) and additing 300 kilocalories (99) for the extra needs of pregnancy. For most young adult pregnant women the recommended caloric intake would fall in the range of 2200 to 2600 kilocalories per day.

TABLE 15

Suggested meal plan and sample menu for high protein diet (139)

Suggested Meal Plan	Sample Menu		PRO POINTS
BREAKFAST	BREAKFAST		
Fruit or Juice (Citrus)	Orange Juice	1 serving	0
Cereal	Cornflakes	1 serving	0
Egg	Cooked Egg	1	1
Bread	Toast	1 slice	0
Milk	Milk	1 cup	1
Beverage	Coffee or Tea		0
	Margarine or Butter,		0
	Cream, Sugar, Jelly		0
MID-MORNING	MID-MORNING		
Milk	Milk	1 cup	1
LUNCH OR SUPPER	LUNCH OR SUPPER		
Meat or Substitute	Chicken and	3 ounces	3
Potato or Substitute	Noodles	1 serving	0
Vegetable	Spinach	1 serving	0
Vegetable	Lettuce with	1 serving	0
	French Dressing		0
Bread	Bread	1 slice	0
Fruit	Apple Brown Betty	1 serving	0
Milk	Milk	1 cup	1
Beverage	Coffee or Tea		0
	Margarine or Butter,		0
	Cream, Sugar		0
MID-AFTERNOON	MID-AFTERNOON		
Milk	Cheese	1 ounce	1
Bread	Crackers	1 serving	0
DINNER	DINNER		
Meat or Substitute	Roast Beef	3 ounces	3
Potato or Substitute	Baked Potato	1	0
Vegetable	Green Beans	1 serving	0
Vegetable	Lettuce, Tomato	1 serving	0
	with Mayonnaise		0
Bread	Bread	1 slice	0
Dessert	Ice Cream	1 cup	1
	Cookie	1	0
Milk	Milk	1 cup	1
Beverage	Coffee or Tea		0
	Margarine or Butter, Cream Sugar		0
			0
			13

Quantities may be increased if desired.
Meal plans should meet the needs of the individual.

TABLE 16

Conversion of grams of protein to protein points (139)

Grams of protein in diet order	Protein points in diet in one day*
100	11
110	12
120	14
140	15
150	16
165	17

* Based on foods containing protein of high biological value only. A diet order of 100-165 grams of protein will include 80-120 grams of high biological value protein and approximately 20-45 grams of low biological protein from fruits, vegetables and cereals.

TABLE 17
Foods with high biological value protein (139)

FOOD	AMOUNT	PROTEIN POINTS	PROTEIN GRAMS
MILK AND MILK PRODUCTS			
Cheese:			
Blue or Roquefort	1 ounce	1	6
Cheddar	1 ounce	1	7
Cottage, Creamed	1/4 cup	1	7
Process, American	1 ounce	1	7
Cream:			
Half 'n Half	1 cup	1	7
Sour, Commercial	1 cup	1	8
Whipping	1 cup	1	6
Ice Cream	1 cup	1	6
Iced Milk	1 cup	1	6
Milk:			
Buttermilk	1 cup	1	9
Chocolate Flavored Drink	1 cup	1	8
Evaporated Skim	1/2 cup	1	9
Evaporated Whole	1/2 cup	1	8
Homogenized Whole	1 cup	1	9
Dry Skim Milk Powder	1/3 cup	1	8
Skim Fortified	1 cup	1	10
2% Skim	1 cup	1	10
Yoghurt, Low Fat:			
Fruit Flavored, Skim Milk	1 cup	1	11
Plain, Skim Milk	1 cup	1	8
MEAT AND SUBSTITUTES			
Bacon	3 slices	1	7
Bologna and Other Cold Cuts	2 ounces	1	6
Egg	1 large	1	7
Fish:			
Clams	2-4 (1 ounce)	1	7
Cod, Haddock, Hailbut, etc.	1 ounce	1	8
Crabmeat	1/4 cup	1	9
Lobster	1/4 cup	1	8
Oysters	4-6 medium	1	8
Salmon	1 ounce	1	6
Sardines	3 medium	1	7
Scallops	1 ounce	1	7
Shrimp	5 small	1	10
Tuna	1 ounce	1	9
Meat:			
Beef, Lamb, Liver, Pork Sweetbreads, Veal	1 ounce	1	7
Peanuts	2 tablespoons	1	9
Peanut Butter	2 tablespoons	1	7
Poultry	1 ounce	1	7
Sausage, Link	2 links	1	5

McGucken (28) found that the use of such a high protein diet arrests the condition after two weeks. After two more weeks, the recognized non-dietary treatment can be cautiously but successfully withdrawn.

SUMMARY

Toxemia of pregnancy, a disease most common among indigent women, especially the primigravidas, is divided into three stages--mild preeclampsia, severe preeclampsia, and eclampsia. Mild preeclampsia is diagnosed whenever a pregnant woman in the third trimester of pregnancy presents at least 2 of the following 3 cardinal signs: hypertension, pathological edema, and proteinuria. Severe preeclampsia is indicated when symptoms such as visual or cerebral disturbances appear or when the degree of proteinuria, hypertension or oliguria worsens in a woman with previous mild preeclampsia. Eclampsia is noted whenever a patient with antecedent preeclampsia develops convulsions.

This disease is thought by many researchers to be caused by a protein deficiency and to be most evident in women with a poor uterine vasculature.

Insufficient dietary intake of protein under the physiological stress of pregnancy leads to a depletion of protein from the liver tissue cells which presents itself on biopsy under the electron

microscope as a distinct subcellular lesion. This hepatic lesion somehow leads to a derangement in the synthesis of fibrinogen and albumin. Less albumin is made by the liver, leading to hypoalbuminemia, a lowered colloid osmotic pressure, hypovolemia and edema.

A fraction of the total fibrinogen in many people is found to be cryofibrinogen--a cold precipitable fibrinogen which appears to coagulate on its own in vitro. In toxemia of pregnancy the synthesis of this fraction increases, but the total amount of fibrinogen does not increase. This derangement leads to hypercryofibrinogenemia, slow disseminated intravascular coagulation, endotheliosis of the reticuloendothelial lining of the arterioles in the liver, kidney and placenta, a narrowing of these arteriolar lumens, and finally with a high enough hypertension--thromboses, ischemia, anoxia, and localized necrotic lesions particularly in the placenta, liver, and kidney.

If a woman has a very poor uterine vasculature, the lesions in the placenta can cause sufficient anoxia to lower the activity of the placental monoamine oxidase, giving rise to increased pressor amine activity, vasoconstriction and hypertension.

This disease can be prevented by a good prenatal diet with sufficient good quality proten (80-120 grams) and can be reversed by a

therapeutic high protein diet (120-180 grams), bed rest, and hypotensive drugs.

ACKNOWLEDGEMENTS

The author wishes to thank Dr. Beth Fryer, Major Professor, for her assistance in the preparation of this report and for her valuable guidance during the past year. Appreciation should also be extended to Dr. L. M. Wakefield, Head of the Department of Foods and Nutrition, Dr. H. T. Gier, Professor of Biology, and Ms. B. Finkelstein, Professor of Foods and Nutrition, for reviewing the manuscript and serving as members of the committee.

LITERATURE CITED

1. Goodhart, R. S. & Shils, M. E. (1973) In: Nutrition in pregnancy, Modern Nutrition In Health and Disease, Lea and Febiger, Philadelphia.

2. Haynes, D. W. (1969) In: Toxemia of pregnancy, Medical Complications During Pregnancy. McGraw Hill Co., New York.

3. National Academy of Sciences (1968) Relation of nutrition to the toxemias of pregnancy. In: Maternal Nutrition and the Course of Pregnancy, National Academy of Science, Washington, D. C.

4. Editorial (1971) Intensive care in obstetrics. Lancet 2, 912-3.

5. Theobald, G. W. (1969) The pregnancy toxemias seen in perspective. J. Reprod. Med. 2,302-315 and 3,75-91.

6. Holman, G. H. & Lipsitz, P. J. (1966) Effect of toxic pregnancy on the fetus and neonate. Clin. Obstet. Gynec. 9,922-927.

7. Harbert, G. M., Claiborne, H. A., McGaughey, H. S., Wilson, L. A. & Thornton, W. N. (1968) Convulsive toxemia. A report of 168 cases managed conservatively. Amer. J. Obstet. Gynec. 100,336-42.

8. Sims, E. A. (1970) Pre-eclampsia and related complications of pregnancy. Amer. J. Obstet. Gynec. 107,154-81.

9. Beaton, G. H. (1966) Some physiological adjustments relating to nutrition in pregnancy. Can. Med. Assoc. J. 95,622-629.

10. McCartney, C. P. (1966) Toxemia of pregnancy--classification. Clin. Obstet. Gynec. 9,864-870.

11. McElin, T. W., Faber, J. E. & Randall, L. M. (1951) True toxemia of pregnancy occurring before the third trimester. Report of three cases and review of the literature. Amer. J. Obstet. Gynec. 61,379-384.

12. Hytten, F. E. (1966) Body water in pre-eclampsia. J. Obstet. Gynaec. Brit. Comm. 73,714-6.

13. Vedra', B. & Paulikova, E. (1969) The onset of abnormal weight gain in toxaemia of pregnancy. J. Obstet. Gynaec. Brit. Comm. 76,873-876.

14. Fish, J. S., Bartholomew, R. A., Colvin, E. D., Grimes, W. H., Lester, W. M., & Galloway, W. H. (1959) The relationship of pregnancy weight gain to toxemia. Amer. J. Obstet. Gynec. 78,743-754.

15. Krupp, M. A. & Chattan, M. J. (1974) In: Gynecology and obstetrics Current Medical Diagnosis and Treatment. Large Medical Publications, Los Altos, Cal., 444-446.

16. Call, M. & Lorentzen, D. (1965) Rupture of the liver associated with toxemia. Obstet. Gynec. 25, 466-469.

17. Haller, A. P., Abels, D. W. & Straus, R. (1951) Spontaneous rupture of the liver in a patient with nonconvulsive eclampsia. Amer. J. Obstet. Gynec. 62, 1170-1172.

18. Pavlic, R. S. & Townsend, D. E. (1962) Spontaneous rupture of the liver in pregnancy. Amer. J. Obstet. Gynec. 83, 1373-1376.

19. Brewer, T. H. (1966) Metabolic Toxemia of Late Pregnancy. A Disease of Malnutrition. Charles C. Thomas, Springfield, III.

20. Way, G. T. & Durham, N. C. (1947) Fatal eclampsia, a clinical and anatomic correlative study. Amer. J. Obstet. Gynec. 54, 928-947.

21. Jeffcoate, T. M. & Scott, J. S. (1969) Some observations on the placental factor in pregnancy toxemia. Amer. J. Obstet. Gynec. 77, 475-488.

22. Studd, J. W. & Blainey, J. D. (1970) Pathogenesis of pre-eclampsia. Br. Med. J. 1, 568.

23. Black, W. P. Luke, R. G., Briggs, J. D., & Kennedy, A. D. (1967) Post-partum isotope renogram studies in hypertensive toxaemia of pregnancy. Amer. J. Obstet. Gynaec. 97, 970-975.

24. Merck Manual. (1972) Preeclampsia and Eclampsia -- The Toxemias of Pregnancy. Merck, Sharp and Dohme Research Laboratories, Division of Merk and Co., Inc., Rahway, N. J.

25. Kilpatrick, S. J. & McKay, E. (1965) Umbilical cord urea in toxaemia of pregnancy. J. Obstet. Gynaec. Birt. Cwlth. 72, 402-407.

26. Morrison, J. C. Whybrew, D. W. & Wiser, W. L. (1972) Laboratory characteristics in toxemia. Obstet. Gynecol. 39, 866-872.

27. Blekta, M., Hlavaty, V., Trnkova, M. Bendl, J., Bendova, L. & Chytil, M. (1970) Volume of whole blood and absolute amount of serum proteins in the early stage of late toxemia of pregnancy. Amer. J. Obstet. Gynec. 106, 10-13.

28. McGucken, J. B. (1973) Preeclampsia and plasma proteins. Med. J. Aust. 1, 1254.

29. Dodge, E. F. & Frost, T. A. (1938) Relation between blood plasma proteins and toxemias of pregnancy. J. Amer. Med. Ass. 111, 1898-1902.

30. Brewer, T. H. (1962) Role of malnutrition, hepatic dysfunction, and gastrointestinal bacteria in the pathogenesis of acute toxemia of pregnancy. Amer. J. Obstet. & Gynec. 84, 1953-1956.

31. Krupp, M. A., Sweet, N. J., Jawetz, E., Biglieri, E. G., & Roe, R. L. (1973) Physician's Handbook, Large Medical Publications, Los Altos, Cal.

32. Curzen, P. & Morris, I. (1965) Serum alkaline phosphatase in the hypertensive disorders of pregnancy. J. Obstet. Gynaec. Brit. Cwlth. 72, 397-401.

33. Curzen, P. & Morris, I. (1966) Serum heat-stable alkaline phosphatase in the hypertensive disorders of pregnancy. J. Obstet. Gynaec. Brit. Cwlth. 73, 640-646.

34. Brown, J. J., Davies, D. L., Doak, P. B., Lever, A. F., Robertson, J. I. & Trust, P. (1966) Plasma renin concentration in the hypertensive diseases of pregnancy. J. Obstet. Gynaec.

35. Bonar, J., Brown, J. J., Davies, D. L., Langford, H. G., Lever, A. F. & Robertson, J. J. (1966) Plasma renin concentration in American Negro women with hypertensive disease of pregnancy. J. Obstet. Gynaec. Brit. Cwlth. 73, 418-420.

36. Editorial (1974) Pre-eclampsia and the kidney. Br. Med. J. 1, 468-469.

37. Gordon, R. D., Parsons, S. & Symonds, E. M. (1969) A prospective study of plasma-renin activity in normal and toxaemic pregnancy. Lancet 1, 347-349.

38. Progress in preeclampsia. Lancet 1, 745 (1973)

39. Ehrlich, E. M. & Linheimer, M. D. (1972) Sodium metabolism, aldosterone and the hyper-tensive disorders of pregnancy. J. Reprod. Med. 8, 106-109.

40. Coopland, A. T. (1969) Blood clotting abnormalities in relation to pre-eclampsia: A Review. Canad. Med. Assoc. J. 100, 121-124.

41. Starkie, C. M., Harding, L. K., Fletcher, D. J. & Stuart, J., (1971) Intravascular coagulation and abnormal lung scans in preeclampsia and eclampsia. Lancet 2,889-891.

42. Preston, F. E., Malia, R. G., Tipton, R. H., & Smith, A. J. (1972) Intravascular coagulation and pre-eclamptic toxaemia. Lancet 1,34-35.

43. Niswander, K. R. and Gordon, M. (editors) (1972) The Women and Their Pregnancies. W. B. Saunders Co., Philadelphia.

44. Hendricks, C. H. & Brenner, W. E. (1970) Toxemia of pregnancy: Relationship between fetal weight, fetal survival, and the maternal state. Amer. J. Obstet. Gynec. 109,225-233.

45. Baird, E. (1973) Eclampsia and social change in the tropics. Br. Med. J. 2,716-717.

46. Thomson, A. M. (1958) Diet in pregnancy: dietary survey technique and the nutritive value of diets taken by primigravidae. Brit. J. Nutr. 12;446-461.

47. Ross, R. A. (1947) Late toxemias of pregnancy: The number one obstetrical problem of the South. Amer. J. Obstet. Gynec. 54,723-730.

48. Ross, R. A. (1971) Nutrition in maternal and perinatal morbidity and mortality in a rural state: 1930-1950. J. Reprod. Med. 7,245-250.

49. Brewer, T. H. (1966) Good prenatal nutrition prevents toxemia of late pregnancy. Postgrad. Med. 39,A-119-124,

50. Chaudhuri, S. K. (1971) Role of nutrition in the etiology of toxemia of pregnancy. Amer. J. Obstet. Gynec. 110,46-48.

51. Mack, H. C., Kelley, H. J. & Macy, I. G. (1956) Complications of pregnancy and nutritional status. I. Toxemias of pregnancy. Amer. J. Obstet. Gynec. 71,577-595.

52. Maqueo, M., Ayala, L. C. & Cervantes, L. (1964) Nutritional status and liver function in toxemia of pregnancy. Obstet. Gynec. 23,222-226.

53. Zuspan, F. P., & Goodrich, S. M. (1965) Metabolic studies in eclampsia. I. Nitrogen, potassium, and sodium alterations. Amer. J. Obstet. Gynec. 93,357.

54. Gordon, D. W. S. & Fell, M. R. (1958) Recurrent pregnancy

toxemia, J. Obstet. Gynaec. Brit. Emp. 65,727.

55. Annitto, J. E, Chesley, L. C. & Cosgrove, R. A. (1969) Nutrition and pre-eclampsia, Obstet. Gynec. 33,449.

56. Lindheimer, M. D. & Katz, A. K. (1971) Controlling the kidney in pregnancy. N. Eng. J. Med. 284,107.

57. Lindheimer, M. D. & Katz, A. I. (1973) Pregnancy and the kidney. J. Reprod. Med. 11,14-17.

58. Adams, E. M. & Finlayson, A. (1961) Familial aspects of pre-eclampsia and hypertension in pregnancy. Lancet 7210,1375-1378.

59. May, D. (1973) Maternal blood group A and pre-eclampsia. Br. Med. J. 4,738.

60. South, J. & Naldrett (1974) Maternal blood group A and pre-eclampsia. Br. Med. J. 1,641.

61. Toivanen, T. & Hirvonen, T. (1970) Sex ratio of newborns: Preponderance of males in toxemia of pregnancy. Science 170, 187-188.

62. Altchek, A. (1968) Liver-kidney interrelation in pregnancy and toxemia. Clin. Obstet. Gynec. 11,487-505.

63. Assali, N. S. & Brinkman, C. R. (1972) Pathophysiology of Gestation. Volume I, Academic Press, New York.

64. Anita, F. P., Bharadwaf, T. P., Watsa; M. C. & Master, J. (1958)
Lancet 2,776-780.

65. Tandon, B. N., Ramanujan, R. A., Tandon, H. E., Puri, B. K. & Gandhi, P. C. (1974) Liver injury in protein-caloric malnutrition: An electron microscopic study. Am. J. Clin. Nutr. 27,550-557.

66. Leon Sotomayor, L., Roberts, D. & Hampton, J. R. (1970) The nephrotic syndrome of preeclampsia. Southern. Med. J. 63, 360-364.

67. Davies, J. (1960) Survey of Research in Gestation and the Developmental Sciences. The Williams and Williams Co., Baltimore. pp. 176-181.

68. Wardle, E. N. (1969) Aetiology of preeclampsia. Brit. Med. J. 3, 472.

69. Wardle, E. N. (1972) Intravascular coagulation and pre-eclamptic toxaemia. Lancet 1,262-263.

70. Talledo, O. W. (1968) Renin-angiotensin system in normal and toxemic pregnancies. IV. Inactivation of angiotensin in toxemia pregnancy. Amer. J. Obstet. Gynec. 101,254-256.

71. Cloeren, S. E. (1972) Effect of plasma expanders in toxemia of pregnancy. N. Engl. J. Med. 287,1356-1357.

72. Demaria, F. J. & See, H. Y. (1966) Role of the placenta in preeclampsia. Amer. J. Obstet. Gynec. 94,471-476.

73. Zitsmiller, J. L., Lang, T. E., Yellenosky, P.F. & Lucas, W. E. (1974) Hematologic assays in pre-eclampsia. Amer.J. Obstet. Gynec. 118, 362-367.

74. Brewer, T. (1972) Metabolic toxemia, the mysterious affliction. J. Appl. Nutr. 24,56-63.

75. Chesley, L. C. (1966) Sodium retention and preeclampsia. Amer. J. Obstet. Gynec. 95,127-132.

76. MacGillivany, I. & Buchanan, T. J. (1958) Total exhangeable sodium and potassium in non-pregnant women and in normal and pre-eclamptic pregnancy. Lancet 2(7056), 1090-1093.

77. Bonnar, J. (1971) Coagulation and fibrinolytic systems in pre-eclampsia and eclampsia. Br. Med. J. 2,12-6.

78. Vardi, J. & Fields, G. A. (1974) Microangiopathic hemolytic anemia in severe pre-eclampsia. Amer. J. Obstet. Gynaec. 119, 617-622.

79. Wood, S. M., Burnett, C., Picken, A. M., Farrell, G. W. & Wolf, P. (1974) Assessment of coagulation and fibrinolysis. in preeclampsia. Br. Med. J. 2, 145-148.

80. Wardle, E. N. & Menon, I. S. (1969) Fibrinolysis in pre-eclamptic toxaemia of pregnancy. Br. Med. J. 2, 625-627.

81. Petrucco, O. M., Thomson, N. M., Lawrence, J. R. & Weldon, M. W. (1974) Immunofluorescent studies in renal biopsies in preeclampsia. Br. Med. J. 1,473-480.

82. Vardi, J. & Halbrecht, I. (1974) Toxemia of pregnancy. 1. Antigens associated with toxemia of pregnancy in placental connective tissue. Amer. J. Obstet. Gynec. 118, 552-557.

83. Blecher, J. A. & Heyns, O. S. (1967) Abdominal decompression in the treatment of the toxaemias of pregnancy. Lancet 2, 621-624.

84. Page, E. W. (1948) Placental dysfunction in eclamptogenic toxemias. In: The Normal and Pathological Physiology of Pregnancy (Committee on Human Reproduction of the NRC) pp. 13-21, Williams & Wilkins Co., Baltimore.

85. Giroud, A. (1966) The Nutrition of the Embryo, Charles C. Thomas, Springfield, Ill.

86. Goretzlehner, G. & Reithling, K. (1968) The presence of a vasoconstrictive substance in toxemia. Amer. J. Obstet. Gynec. 101, 397-400.

87. DelGreco, F. & Krumlousky, F. A. (1972) The renal pressor system in human pregnancy. J. Reprod. Med. 8, 98-101.

88. Simon, N. M. & Krumlovsky, F. A. (1972) The pathophysiology of hypertension in pregnancy. J. Reprod. Med. 8, 102-104.

89. Chesley, L. C. (1966) Vascular reactivity in normal and toxemic pregnancy. Clin. Obstet. Gynec. 9, 871-881.

90. Smith, R. W. (1970) Cardiovascular alterations in toxemia Amer. J. Obstet. Gynec. 107, 979-983.

91. Muresan, S. & Zehan, M. (1968) Effects of uterine overdistension on renal plasma flow, glomerulor filtration rate, and filtration fraction. Experimental research in dogs. Amer. J. Obstet. Gynec. 100, 230-239.

92. Sophian, J. (1969) Aetiology of pre-eclampsia. Brit. Med. J. 3, 241.

93. Chaudhuri, S. K. (1970) Relationship of protein-caloric malnutrition with toxemia of pregnancy. Amer. J. Obstet. Gynec. 107, 33-37.

94. Burke, B. S., Beal, V. A. Kirkwood, S. B. & Stuart, H. C. (1943), Nutrition studies during pregnancy. Am. J. Obstetc. Gynec. 46, 38-52.

95. Cross, A. T. & Walsh, H. E. (1971) Prenatal diet counseling. J. Reprod. Med. 7, 265-268.

96. Kitay, D. Z. (1971) Dysfunctional antepartum nutrition. J. Reprod. Med. 7, 251-256.

97. Kramer, M. E. (1973) Role of nutrition in preeclampsia. N. Engl. J. Med. 289, 45.

98. McGanity, W. J. (1954) The vanderbilt cooperative study of maternal & infant nutrition VI, Relationship of obstetric performance to nutrition. Amer. J. Obstet. Gynec. 67, 501-527.

99. Food & Nutrition Board, National Research Council (1973) Recommended Dietary Allowances, National Academy of Science, Washington, D. C. 9th Rev. Ed.

100. Beaton, G. H. Pild, G. A. & Flores, M. (1964). Alterations in serum proteins during pregnancy and lactation in urban and rural populations in Guatemala. Amer. J. Clin. Nutr. 14, 269-279.

101. Kelman, L.,Saunders, S. J., Frith, L., Wicht, S. & Corrigal, A. (1922) Effects of dietary protein restriction on albumin synthesis, albumin catabolism, and the plasma aminogram. Amer. J. Clin. Nutr. 25, 1174-1177.

102. Crosignani, P. G. (1974) Correlation of human chorionic gonadotropin and human chorionic somatotropin with fetal nutrition. In: Lactogenic Hormones, Fetal Nutrition, and Lactation (Josimovich, J. B., ed.), pp. 212-215, John Wiley & Sons, New York

103. Strauss, M. B. (1935) Observations on the eitology of the toxemias of pregnancy. Amer. J. Med. Sci. 190, 811-819.

104. Strauss, M. B. (1936) Observations on the etiology of the toxemias of pregnancy. Amer. J. Med. Sci. 193, 437.

105. Harden, B. (1937) The clinical management of preeclamsia and eclampsia. Peen. Med. J. 40, 835-837.

106. Primrose, T. P. & Higgins, A. (1971) A study in human antepartum nutrition. J. Reprod. Med. 7, 257-264.

107. Zuspan, F. P. (1966) Treatment of severe preeclampsia and eclampsia. Clin. Obstet. Gynec. 9, 954, 972.

108. Robinson, C. H. (1972) In: Nutrition During Pregnancy and Lactation, Normal and Therapeutic Nutrition. The Macmillan Co., New York.

109. Williams, S. R. (1973) In: Nutrition and Pregnancy, Nutrition and Diet Therapy. The C. V. Mosby Co., St. Louis.

110. Martinez, T. K. (1973) Nutrition in etiology of toxemia of pregnancy. Amer. J. Obstet. Gynec. 116,294-295.

111. Tompkins, W. T. & Wiehl, D. G. (1951) Nutritional deficiencies as a causal factor in toxemia and premature labor. Amer. J. Obstet. Gynec. 62,898-919.

112. Tompkins, W. T. & Wiehl, D. G. (1951) Nutritional deficiencies as a causal factor in toxemia and premature labor. Amer. J. Obstet. Gynec. 62,898-918.

113. Chaudhuri, S. K., Halder, K., Chowdhury, S. R. & Bagchi, N. (1969) Relationship between toxaemia of pregnancy and thiamin deficiency. J. Obstet. Gynaec. Br. Cwlth. 76,123-126.

114. Wachstein, M. (1956) Evidence for abnormal vitamin B_6 metabolism in pregnancy and various disease states. Amer. J. Clin. Nutr. 4,369-385.

115. Wachstein, M. & Graffeo, L. S. (1956) Influence of vitamin B_6 on the incidence of preeclampsia. Obstet. Gynec. 8,177-180.

116. Klieger, J. A., Evrard, J. R. & Pierce, R. (1966) Abnormal pyridoxine metabolism in toxemia of pregnancy. Amer. J. Obstet. Gynec. 94,316-321.

117. Hillman, R. W., Caboud, P. G., Nilsson, D. E., Arpin, P. D. & Tufano, R. J. (1963) Pyridoxine supplementation during pregnancy. Clinical and laboratory observations. Amer. J. Clin. Nutr. 12,427-430.

118. Brewer, T. H. (1962) Limitations of diuretic therapy in management of severe toxemia. Amer. J. Obstet. Gynec. 83,1352-1359.

119. Mengert, W. F., & Tocchi, D. A. (1961) Pregnancy toxemia and sodium chloride. Amer. J. Obstet. Gynec. 81,601-605.

120. Pike, R. & Gursky, D. S. (1970) Further evidence of deleterious effects produced by sodium restriction during pregnancy. Amer. J. Clin. Nutr. 23,883-886.

121. Atkins, S. M. Jr.(1972) Salt, water and rest as a preventative for toxemia of pregnancy. A commentary and review. J. Reprod.

Med. 9,223-228.

122. MacGillivary, I. (1972) Treatment of severe toxaemia of pregnancy. Lancet 1,198-199.

123. McEwan, H. P. (1972) Treatment of severe toxaemia of pregnancy. Lancet 1,374.

124. Redd, J., Mosey, L. M. & Langford, H. G. (1968) Effect of posture upon sodium excretion in pre-eclampsia. Amer. J. Ostet. Gynec. 100,343,347.

125. American Committee on Maternal Welfare, (1931) The management of preeclamptic toxemia and eclampsia. J. Amer. Med. Assoc. 104,1703-1705.

126. Mengert, W. F. & Tweedie, J. A. (1964) Acute vasospastic toxemia· Therapeutic nihilism. Obstet. Gynec. 24,662-666.

127. Baskett, T. F. & Bradford, C. R. (1973) Active management of severe preeclampsia. Can. Med. Assoc. J. 109,1209-1211.

128. Rogers, S. F., Flowers, C. E., & Alexander, J. A. (1969) Aggressive toxemia management. Obstet. Gynec. 33,724-728.

129. Pritchard, J. A. (1972) Treatment of toxemia of pregnancy. N. Engl. J. Med. 287,48.

130. Pohl, J. E., Thurston, H., Davis, D., & Morgan, M. Y. (1972) Successful use of oral diazoxide in the treatment of severe toxaemia of pregnancy. Br. Med. J. 2,568,570.

131. De Alvarez, R. R. (1940) The use of a neutral diet and hydration in the treatment of toxemias of pregnancy. Am. J. Gynec. 39, 478-480.

132. Share, L., Claybaugh, T. R., Hatch, F. E., Johnson, T. G., Lee, S. M., Muirhead, E. E., & Shaw, P. (1972) Effects of change in posture and of sodium depletion on plasma levels of of vasopressin and renin in normal human subjects. J. Clin Endocrinol. Metab. 35,171-174.

133. Flowers, C. E., Grizzle, J. E., Easterling, W. E. & Bonner, O. E. (1962) Chlorothiazide as a prophylaxis against toxemia of pregnancy. Amer. J. Obstet. Gynec. 84, 919-929.

134. Guthrie, H. A. (1971) In: Nutrition in pregnancy and lactation. Introductory Nutrition. The C. V. Mosby Co., St. Louis.

135. Palomaki, J. F. & Lindheimer, M. D. (1970) Sodium depletion stimulating deterioration in a toxemic pregnancy. New Eng. J. Med. 28 88-90.

136. Bourguin, A. & Bennum, R. (1957) The preconception diet of women who have had unsuccessful pregnancies. Amer. J. Clin. Nutr. 5, 62-69.

137. Speert, H., Graff, S. & Graff, A. M. (1951) Nutrition and premature labor. Amer. J. Obstet. Gynec. 62, 1009-1019.

138. Flowers, C. E. (1971) Editorial: Nutrition in pregnancy. J. Reprod. Med. 7, 200-219.

139. Kansas Diet Manual (1972) Diet for Pregnancy. Kansas Dietetic Association, Inc., Topeka.

140. Food & Nutrition Board, National ResearchCouncil (1968) Recommended Dietary Allowances, National Acad emy of Science, Washington, D. C.

TOXEMIA OF PREGNANCY: A DISEASE OF PROTEIN INSUFFICIENCY AND POOR UTERINE VASCULATURE

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AN ABSTRACT OF A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods and Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1975

A review of the literature was made on toxemia of pregnancy, a disease most common among primigravid women of the lower socio-economic strata. Other predisposing factors include antecedent essential hypertension, diabetes mellitus, and multiple births. Mild preclampsia, the first stage of the disease, is diagnosed whenever a woman in the third trimester of pregnancy demonstrates at least two of the succeeding three cardinal signs: hypertension, patholigic edema, and proteinuria. The preclampsia is classified as severe whenever visual or cerebral disturbances occur or whenever the proteinuria, hypertension or oliguria worsen beyond certain degrees. Exlampsia is defined as the stage of the disease wherein the patient with antecedent preeclampsia, mild or severe, develops convulsions with or without coma.

Many researchers have presented evidence that toxemia is caused by a protein deficiency during gestation, and there are proposed theories of pathophysiology that give credence and a logical succession to these findings.

The mainstream of ideas and findings seem to favor the following theory of pathogenesis. The insuffieient dietary intake of protein under the physiological stress of pregnancy leads to a depletion of protein from the liver tissue cells which presents itself on biopsy under the electron microscope as a distinct subcellular lesion. This hepatic lesion somehow leads to a derangement in the synthesis of fibrinogen and albumin. Less albumin is made by the liver, leading to hypoalbuminemia, a lowered colloid osmotic pressure, hypovolema and edema.

A fraction of the total fibrinogen in many people is found to be cryofibrinogen--a cold precipitable fibrinogen which appears to coagulate on its own in vitro. In toxemia of pregnancy the synthesis of this

fraction increases, but the total amount of fibrinogen does not increase. This derangement leads to hypercryofibrinogenemia, slow disseminated intravascular coagulation, endotheliosis of the reticuloendothelial lining of the arterioles in the liver, kidney and placenta, a narrowing of these arteriolar lumens, and finally with severe enough hypertension--thromboses, ischemia, anoxia, and localized nectrotic lesions particularly in the placenta, liver, and kidney.

When the above is combined with poor uterine vasculature, the lesions in the placenta can cause sufficient anoxia to lower the activity of placental monoamine oxidase, giving rise to increased pressor amine activity, vasoconstriction and hypertension.

Also lending support to these ideas are the findings of many physicians that toxemia of pregnancy can be prevented by a good prenatal diet containing 80 or more grams of protein, and can be reversed by a high protein diet (120-180 grams) along with sufficient medical measures to stablize a severely toxemic woman.