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Evaluation of five diagnostic tests for the toxemias of pregnancy

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AN EVALUATION OF FIVE DIAGNOSTIC TESTS FOR THE TOXEMIAS OF PREGNANCY

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INTRODUCTION

Although the toxemias of pregnancy have probably existed since the days of primitive man, there are no references to any conditions resembling them until the times of the ancient Chinese, Egyptian, and Greecian empires. In the treatises of Hippocrates and Galen there are numerous, rather confused references to the diseases recognized today as the toxemias of pregnancy. Throughout the eighteenth and nineteenth centuries the clinical entity of eclampsia was recognized and theories as to its pathogenesis were expounded. Still, little progress in the treatment of the toxemias was made until the present century. Despite all the advances made in defining, differentiating, managing, and treating the toxemias, little has been accomplished in regard to finding good differential, diagnostic tests for them.

Primarily in the last two decades medical science has strived to find a specific chemical or biologic fraction or reaction, the presence, absence, or concentration of which would identify the toxemias of pregnancy. In order to be ideal, such a test would probably have to possess several characteristics: it would have to be specific for that syndrome; it should warn the obstetrician of an impending toxemia; it should distinguish pre-eclampsia from essential hypertension; it should be of prognostic value; and the method of analysis should be relatively easy and accurate. In general, attempts in this direction have been along chemical, biologic, hormonal, or enzymatic lines.

It is the attempt of this paper to discuss five of the more recent and promising tests - the pituitrin test, cold pressor test, tetraethylammonium chloride test(TEAC floor), sodium amytal test and beta-glucuronidase test - and to present my findings utilizing these tests on a group of patients and compare these findings with those of other experimenters and researchers in the field.

HISTORY

PITUITRIN TEST

Oliver and Schafer in 1895 were the first researchers to note that an intravenous injection of a pituitary extract caused a rise in blood pressure. Howell in 1898 confirmed this and also proved that it was the posterior pituitary alone that was responsible for the blood pressure rise. He found that no pressor response was obtained using the anterior pituitary extracts. The pressor-oxytocic-diuretic properties of the posterior lobe of the pituitary were discussed by Abel, Roulier, and Geiling in 1923, and the question of whether only one hormone or three or four separate hormones were responsible was proposed. Stehle in 1927, although agreeing that parenteral or intranasal administration of extracts of the posterior lobe and the pars media produced a decrease in the volume of urine and increased the concentration of urinary chloride, stated that only a slight, if any, rise in blood pressure was produced.

Using green-fed rabbits, Bugbee and Simond(1928) found that the pressor principle of the posterior lobe had a diuretic and a subsequent anti-diuretic effect, but the oxytocic principle had little, if any, such effect. Isolation and separation of the two elements of the posterior lobe, pitressin and pitocin, were accomplished by Kamm, Aldrich, et al.(1928) who stated that pitressin contained the pressor and anti-diuretic components and that pitocin contained the oxytocic principle. Ward, Lyons, and Bemis in 1928 found that in normal patients pitressin and pituitrin produced systolic blood pressure increases of 17 and 10 mm. Hg re-

spectively, which lasted fifteen mimutes, while pitocin caused a rise of only five mm. Hg, returning to normal in five minutes. They thought that the use of pitocin would be most desirable in obstetric cases with high blood pressure such as in toxemia and eclampsia.

It was von Fekete in 1930 who noted that pregnancy serum could so modify the chemical structure of the posterior hypophysis lobe that it would no longer stimulate contractions of the gravid uterus. The effect of the serum was found to be greatest in the last two months of pregnancy. It was also found that the gravid uterus would no longer respond to the posterior pituitary hormone which had been acted upon by the pregnancy serum. Von Fekete repeated his findings in 1932 and elaborated upon them by stating that the blood during pregnancy contains neither "hypophysin" nor "uterinum" because of a substance in the serum which destroys "hypophysin" (pituitrin). He further declared that the substance is especially abundant toward the end of pregnancy and must be regarded as one of the important factors which insure the gravid uterus against hormonal stimulation to contraction.

Anselmino, Hoffman, and Kennedy in 1932 claimed that there was a relation between hyperfunction of the posterior lobe of the pituitary and eclampsia and "nephropathy" of pregnancy. They claimed to have found excessive amounts of anti-diuretic and pressor principles in patients with eclampsia and "toxic albuminuria of pregnancy," and they stated that these principles were identical

in action to the hormones of the posterior pituitary. Hofbauer (1933) and de Wesselow and Griffiths(1936) agreed with the findings of Anselmino, but Byrom and Wilson(1934), Theobold(1934), Levitt(1936), and Melville(1937) could find no correlation between hyperfunction of the posterior pituitary gland and the toxemias of pregnancy.

Gullard and Macrae(1933) disputed the results of von Fekete by stating that the enzyme in pregnancy serum that destroys pitocin (i.e., "pitocinase") is not identical with any impure enzymes, but it is simply a contaminant. He went further by stating that these impurities are crystalline chymotrypsin and concentrates of yeast aminopolypeptidase, "angiotonase" (extracts of red blood cells or kidney), tyrosinase, papain, and the dipeptidases and the aminopeptidases of the intestine.

On the other hand, Robson in 1933 confirmed von Fekete's findings by stating that during the twelfth to the twenty-fourth week of pregnancy, the human uterus is more sensitive to pituitary oxytocic substances. Using pitocin, pituitrin, and pitressin, he found that only an oxytocic effect was manifested, and no pressor or anti-diuretic effects could be significantly determined. Moffat in the same year administered one c.c. of obstetric pituitrin to a number of patients and found no constant change in blood pressure. Generally, the trend of the blood pressure was down rather than up with the downward trend more marked in the systolic than in the diastolic readings.

Heller and Urban in 1935 found that normal, defibrinated blood or serum was able to slowly inactivate large doses of pituitrin in vitro. Injecting one-half to two minims of pituitrin intramuscularly into ten normal pregnant and non-pregnant women and into twenty-one toxemic patients, Dieckmann and Michel in 1935 concluded that there was a decrease in the volume of urine, an increase in the urine chloride concentration, and an average rise in systolic pressure of fifteen mm. Hg in normal pregnant, non-pregnant, parturient, and puerperal women. In pre-eclamptics, however, there was a decrease in urine volume, an increase in urine chloride concentration, and an average rise in systolic blood pressure of forty-nine mm. Hg as well as a marked increase in diastolic pressure. Independently, Schockaert and Lambillon in 1935 also found that pregnancy serum was "antagonistic" to vasopressor activity of posterior pituitary extracts and that normal pregnant women were relatively insensitive to the blood pressure raising properties of this hormone.

Dieckmann and Michel, utilizing parenteral extracts of the posterior lobe of the pituitary gland, in 1937 obtained the following results: (a) decrease in urine volume, increased urine chlorides, and an average rise in systolic pressure of eleven mm. Hg in normal pregnant, parturient, and puerperal women (Similar results were obtained in the vascular-renal (hypertensive and nephritic) group); (b) markedly decreased urine

volume, increased urine chloride concentration, and an average systolic rise of fifty-one mm. Hg as well as marked diastolic rises in the group of pre-eclamptic patients. The dangers of using pituitrin as an oxytocic were cited, but its value as a test for pre-eclampsia was emphasized.

DeValera and Kellar(1938) using 0.66 c.c. of purified pressor principle of the posterior pituitary intravenously obtained the following results: pre-eclamptics, 52 ± 15.7 mm. Hg rise systolically and 35 ± 8.42 mm. Hg rise diastolically; hypertensive toxemias, 31 ± 12.8 mm. Hg systolically and 25 ± 10.1 mm. Hg rise diastolically; normal puerperals, 43 ± 11.1 mm. Hg systolic rise and 36 ± 11.7 mm. Hg diastolic rise; and normal non-pregnant females, 23 ± 10.68 mm. Hg systolic rise and 22 ± 9.12 mm. Hg diastolic rise. Although they stated that pre-eclamptics gave marked responses as did normal, non-pregnant women, they did not feel that their results were sufficiently consistent to justify the use of this test as a diagnostic test for pre-eclamptic toxemias.

Werle, et al. in 1941 studied the inactivating power of pregnancy blood on pitocin and pitressin. They demonstrated an enzyme in the second month of pregnancy and stated that the amount remains at a fairly constant level from the third to the eighth month, is highest at the time of delivery, and can no longer be demonstrated one month afterward. They detected no such activity in non-pregnant women nor in fetal cord blood, but they

found traces in all urine specimens and in colostrum.

Dieckmann(1941) studied the effect of pituitrin on pregnant women by the following test: Water was given to the patients by mouth in amounts varying from 150 to 250 c.c. per hour. Urine specimens were collected every hour until a satisfactory volume of urine had been obtained. Then, one-half to one minim of pituitrin was injected subcutaneously into pregnant patients and intravenously into those in the puerperium. Blood pressure readings were taken before the injection until they were constant and then every two minutes for a period of ten minutes following the injection. An increase of twenty-five mm. Hg or more in systolic pressure was considered an abnormal response. Normal pregnant patients had a mean rise of eleven mm. Hg, hypertensive toxemias displayed similar responses, and pre-eclamptics had a mean rise of fifty-one mm. Hg in systolic pressure as well as a marked diastolic response.

In 1946 E. W. Page found that in the blood of pregnant females there is an enzyme which destroys the oxytocic properties of pitocin and called it pitocinase. He further stated that from the fourth to the thirty-eighth week of pregnancy there is a thousand-fold increase in plasma pitocinase activity and that this activity is maintained during labor. Following delivery, the enzyme decreased logarithmically at the rate of approximately twenty-five per cent until it disappeared around four weeks postpartum. In sixteen cases of pre-eclampsia, seven had high values, six had

low values, and three were in the normal range. In seven cases of eclampsia, three had high values, three had low values, and one was in the normal range.

Woodbury, Ahlquist, et al.(1946) further substantiated that human blood from about the fifth month of pregnancy to at least seven days postpartum can rapidly inactivate pitocin and pitressin. Blood from males, non-pregnant females, and females in early pregnancy were not found to inactivate these substances as rapidly. They also found that toxemic patients could inactivate pitocin and pitressin as rapidly as normal patients, and thus they concluded that the hypersensitivity of pre-eclamptics and eclamptics to vasopressin and oxytocin was not associated with a diminished ability of the blood to inactivate these substances. They thought that the difference probably lay in increased sensitivity of the effector cells in the toxemic patients. They also found that sixty-five per cent of all pre-eclamptics and eclamptics they tested were hypersensitive to the action of pituitrin, pitressin, and pitocin. Dieckmann in 1950 also found that the blood of normal pregnant females was able to inactivate the anti-diuretic effect of commercial pitressin in the latter half of pregnancy.

As it has been shown above, much work has been done in determining the role of the posterior pituitary gland in relation to the toxemias of pregnancy. Since it has also been noted by some that pre-eclamptic blood cannot deactivate or decrease the effect of posterior pituitary hormones as can normal pregnant

blood, several tests have been devised using these hormones to determine the presence or impending threat of toxemias - primarily pre-eclampsia. The pituitrin test is one of the apparently successful of these tests.

COLD PRESSOR TEST

Hines and Brown in 1933 were the first investigators to devise the cold pressor test. There method was as follows: The patient rests for fifteen minutes, or until the blood pressure has approximated the basal level (this requires up to forty-five minutes in some cases). With a sphygmomanometer cuff placed on one arm, the hand of the other arm is placed in water having a temperature of four to five degrees centigrade. The blood pressure is taken at the end of thirty seconds and again at the end of sixty seconds. The hand is then removed, and readings are taken every two minutes until the blood pressure has returned to normal. The basis on which the test was devised is that the blood pressure response to cold is on a purely neurogenic basis because the speed of the reaction is too rapid to allow intervention by known hormonal or chemical factors. They substantiated this theory by demonstrating that a tourniquet producing stasis of blood flow in the immersed arm failed to inhibit the reaction. They considered their test ninety-eight per cent accurate in diagnosing essential hypertension, and they emphasized its prognostic value in determining what individuals would be more likely to develop hypertension later on in life and stressed its possible usefulness in determining the

efficiency of therapeutic measures to control vasomotor irritability.

Again in 1935 and 1939, Hines and Brown reiterated their successful findings. They also established an increase of twenty mm. Hg in systolic pressure and/or an increase of fifteen mm. Hg in diastolic pressure as the upper limits of normal, and they considered anyone above that level as a hyperreactor with a great potentiality for developing essential hypertension. Further, if the maximum response is above the limits mentioned and the reading is higher than 140 mm. Hg systolically and ninety mm. Hg diastolically, the individual is even more likely to develop hypertension. So effective did they feel the test to be that they called it a blood pressure "fingerprint."

Randall, Murray, and Mussey in 1935 found that all pre-eclamptics tested had a hypertensive reaction to the cold pressor test, and no patient of theirs who had a persistent normal response subsequently developed toxemia. Of those who appeared normal but had hyperreactive responses, thirty-three per cent subsequently developed toxemia. However, in spite of their findings, they felt that they could draw no definite conclusions.

Dieckmann and Michel in the same year obtained no uniform results in pre-eclamptic or eclamptic patients; however, they did obtain hyperreactive responses in those patients with nephritic toxemia. A mean antepartum rise of 51.88 mm. Hg in systolic pressure and 37.5 mm. Hg in diastolic pressure was obtained in this

group. They also noted that normal non-pregnant women with a family history of hypertension showed more marked responses than those without a hypertensive background. Because of the small number used in their test group, they could draw no conclusions, but they did state that the test had possibilities of being used as an aid in the diagnosis and prognosis of vascular disturbances during pregnancy.

Pickering and Kissin(1936) disagreed completely with the findings of Hines and Brown. They could not confirm that a relatively large rise of blood pressure in response to a cold stimulus is peculiar to potential or developed cases of essential hypertension or chronic nephritis.

In 1937 Briggs and Oerting found a direct correlation between results in the cold pressor test and family histories of essential hypertension in pregnant patients. There were no hyperreactors in the group having no history of hypertension in either parent, but two in this group developed toxemia. Of the thirteen hyperreactors with a history of hypertension in one parent, only three had an abnormally increased blood pressure at term with only one of these developing toxemia. In the group having a history of hypertension in both parents, all were hyperreactors, and nine of the ten in the group showed definite alterations from normal at the end of gestation with six developing hypertensive toxemia. They stated, however, that no conclusions could be drawn from their work, but they suggested that toxemia occurring on a hypertensive

background may possibly be predetermined by means of the cold pressor test.

Dieckmann, Michel, and Woodruff(1938) utilizing a group of 152 patients set a response of twenty-nine mm. Hg in systolic pressure as the upper limit of normal. They concluded that an abnormal reaction to the cold pressor test in a pregnant woman seems to indicate that she may develop a toxemia in which hypertension is the predominant finding. They also suggested that this test be used as a method of differentiating pre-eclampsia from hypertensive toxemia because they found that pre-eclamptics had abnormal pituitrin tests and normal cold pressor tests while hypertensive toxemia patients had a normal pituitrin test and an abnormal cold pressor test.

Reid and Teel(1939) and Chesley and Chesley(1939) disagreed with the previous work on the cold pressor test, since they found the results to be inconstant. They found no essential difference in the incidence of toxemia between the normal and the hyperreactor groups. It was further stated that the test was of no value in the differential diagnosis of the pregnancy toxemias. Also, they brought out the great variation in results obtained in the same patient at different times. Chesley, Markowitz, and Wetchler in the same year, however, noticed that there was an albuminuria in hyperreactive patients following the test, whereas there was no albuminuria detected in normal reacting patients. They concluded that the proteinuria in the susceptible patients began

with the release of the vascular spasm following the cold pressor test.

Horton and Roth(1939) explained the difference between the cold pressor test and the cold "hypersensitivity" test and explained the importance of each. In the cold hypersensitivity test the hand is placed in water at a temperature of ten degrees centigrade, whereas the temperature for water used in the cold pressor test is four to five degrees centigrade. They stated that the response in the cold pressor test was due to the painful stimulus and was usually immediate, but in the cold hypersensitivity test the response was not due to pain and did not come on until three or four minutes after the hand was removed from the water. Furthermore, a decrease in blood pressure is usually found with the cold hypersensitivity test, but increase in blood pressure is usually the rule with the cold pressor test. In one patient, however, they obtained an increase in blood pressure up to 215/105 mm. Hg using the hypersensitivity test, and two years later she developed hypertension.

Browne(1940) testing fifty-two normal primiparas stated that it was not the rise in blood pressure produced by the cold pressor test but rather the peak blood pressure obtained that was important. Twenty-three of the fifty-two patients had a peak systolic pressure of 130 mm. Hg or over, and of these twelve or fifty-two per cent developed pre-eclamptic toxemia. Nine of these twelve had pressures of 140 mm. Hg or over, and of these six or sixty-seven per cent developed pre-eclamptic toxemia. Five of these

nine patients had peaks over 150 mm. Hg, and four of these or eighty per cent developed pre-eclamptic toxemia. However, twenty-nine patients had peak blood pressures of 130/70 mm. Hg or under, but eleven of these or thirty-eight per cent developed toxemia. He concluded that the higher the peak obtained, the greater the chances of that patient developing pre-eclamptic toxemia, and he felt that the difference between the high range and the basal level of blood pressure did not appear to be of value.

TETRAETHYLAMMONIUM CHLORIDE TEST (TEAC FLOOR)

Acheson and Moe(1945) first demonstrated in animals that tetraethylammonium chloride produces a transient blockade of the autonomic nervous system at the ganglionic level and that the resulting fall in blood pressure is due primarily to a decrease in peripheral resistance (arteriolar tonus). They confirmed that the fall in blood pressure was not dependent on the heart, vascular smooth muscle, or the medullary vasomotor center. They concluded, after extensive tests, that the tetraethylammonium ion produced a block of preganglionic impulses at the sympathetic ganglion and that there was no effect on the postganglionic fibers because the pressor action of epinephrine was not affected by the administration of tetraethylammonium chloride.

Later, in 1946, Moe, Rennick, Hoobler, Neligh, and Lyons found that the TEAC depressor response in normotensives is minimal, but in hypertensives the response is roughly proportional to the initial diastolic pressure. Lyons, Campbell, Moe, et al.

in 1947 obtained the same results in man as Acheson and Moe did in animals in 1945. They found that the average fall in blood pressure produced by TEAC in 143 patients with essential hypertension was 23.5 mm. Hg in systolic pressure and 19.3 mm. Hg in diastolic pressure although twenty-six of the hypertensives failed to have a fall in blood pressure with the first dose (the test dose). In cases of nephritis or of essential hypertension with impaired kidney function responses were similar to those obtained with patients having only essential hypertension. Patients with malignant hypertension had depressor responses with some being so profound as to bring on circulatory collapse. They concluded that TEAC in doses of two hundred to five hundred mg. intravenously or up to twenty mg. per kilogram intramuscularly produced changes which were best described by autonomic ganglia blockade, and they stated that there are possibilities that TEAC would be useful diagnostically and therapeutically.

Brust, Assali, and Ferris(1948) devised the standard TEAC test and published their experiences with the test in normal pregnant and in toxemic patients. They injected four c.c. (400 mg.) of TEAC intravenously and then recorded the blood pressure at half minute intervals for six minutes and then at one minute intervals for ten to thirty minutes afterward. They used the "TEAC floor," which is the lowest point to which the blood pressure descends in the first five minutes after injection, as the basis for their work. They found that the mean floor in

normal non-pregnant females was 137/67 mm. Hg, and the mean difference between the basal readings and the floors were ten mm. Hg in systolic pressure and five mm. Hg in diastolic pressure. In normal pregnant patients at term, the mean antepartum floor was 68/49 mm. Hg with mean differences between floor and basal levels of fifty-seven mm. Hg systolically and 16 mm. Hg diastolically. Postpartum levels were within normal range. Antepartum findings in pre-eclamptic patients were a mean floor of 131/94 mm. Hg and mean differences of twenty-eight mm. Hg in systolic pressure and thirteen mm. Hg in diastolic pressure. postpartum levels here also fell into the normal range. The findings in eclampsia were similar to those in pre-eclampsia except that the floor was higher (135/103 mm. Hg), and the postpartum levels were in the normal range. In cases of essential hypertension with superimposed toxemia, the floor was 145/95 mm. Hg with mean differences of forty mm. Hg systolically and thirty-five mm. Hg diastolically, but postpartum findings were again within normal limits. They concluded that in normal term pregnancy the TEAC floor is strikingly low and rises to normal levels after delivery; however, in toxemia the TEAC floor is higher than normal and consistantly returns to normal levels after recovery. Since TEAC blocks autonomic ganglia thus eliminating neurogenic tone, they suggested that the hypertension of toxemia of pregnancy is supported by an excessive degree of humoral tone. They further stated that clinical assay with TEAC may be helpful as an aid in

the diagnosis of toxemia and in the evaluation of change in severity during the course.

Ferris, Reiser, Stead, and Brust showed in 1948 that TEAC produces a complete sympathetic blockade when it is given in acute intravenous doses of 400 mg. They came to that conclusion when they found that the TEAC floor parallels but is lower than the blood pressure floor induced by a high spinal anesthetic to the third thoracic level and that the TEAC floor is not lowered further by doubling the dose in the same individuals. They also found that the administration of TEAC completely abolishes the cold pressor response - a response which is mediated through the sympathetic nervous system.

In 1948 Levinson, Reiser, and Ferris found that although there is considerable daily fluctuation in both the magnitude of depressor response and the blood pressure floor, there is no evidence of development of increasing tolerance to the depressor effect of TEAC on repeated administrations. Their findings suggested that fluctuating humoral and neurogenic mechanisms interact as factors in clinical hypertension.

Lyons, Hoobler, Ngligh, and Moe(1948) suggested that a 500 mg. dose of TEAC be used to secure complete autonomic ganglia blockade and that any doses under 500 mg. were inadequate for man. They further stated that the extent of decrease of blood pressure produced by TEAC is dependent on the initial elevation of pressure and thus that the greater the increase of blood pressure over normal initially, the greater the drop in blood pressure with TEAC.

There is also a greater decrease in systolic pressure with TEAC than there is in diastolic pressure; twenty-four per cent of the hypertensives had less than a ten per cent decrease in diastolic pressure. They also brought out that structural changes in vessels as well as apprehensiveness on the part of the patient cause variability in results.

Stead, Reiser, Rapoport, and Ferris(1948) stated that the blood pressure at any time (random or casual blood pressure) reflects the total effect of the humoral and neurogenic factors operating plus whatever intrinsic tone the vascular bed may possess. The fall in blood pressure produced by TEAC autonomic blockade (TEAC response) represents the neurogenic compnnent of the random pressure. The pressure following the drug (TEAC floor) reflects the part played by the non-neurogenic factors, i.e., all the humoral agents plus the intrinsic tone in a given blood pressure.

Assali, Brust, Garber, and Ferris(1950) stated that there was a drop of fifty to sixty mm. Hg in diastolic pressure in normal pregnant females who were given TEAC in doses of 400 mg. intravenously, but there was a persistence of diastolic hypertension in toxemic patients. However, they found that there was an opposing action between TEAC and veratrum viride. Administering the veratrum in doses of 0.2 c.c. (three minims) intravenously, they found that it produced no significant effect in normal pregnant females, but it caused a significant mean decrease of both

systolic and diastolic blood pressure in toxemic patients (from mean of 171/110 mm. Hg to a mean of 100/60 mm. Hg). They, therefore, suggested the use of both TEAC and veratrum viride in a clinical test for the toxemias of pregnancy since TEAC produces little or no depressor response while the depressor response with veratrum is accentuated in the toxemias.

Assali and Prystowsky(1950) stated that the autonomic blockade produced by either the administration of TEAC or high spinal anesthesia resulted in a negligible drop in blood pressure in the toxemias of pregnancy.

SODIUM AMYTAL TEST

Sodium amytal is isoamylethyl barbituric acid sodium (Amobarbital Sodium, Lilly), which is classified as a moderate duration barbiturate which may be administered orally or intravenously. In general, the sedative and hypnotic doses of the barbiturates used clinically cause no significant change in circulation, and Tatum (1939) stated that experimental work shows that barbiturates produce no importantalterations on cardiac action. However, Krantz and Carr(1949) state that there is a vagus-inhibiting effect which may slightly quicken the heart rate. Tatum(1939) further found that large doses of the barbiturates given orally or by rapid intravenous injection cause a fall in blood pressure due to vasodilatation although there is generally a rather prompt return to normal when the drug is metabolized or eliminated.

The first mention of the sodium amytal test is found in

Dieckmann's book on the toxemias of pregnancy (1941). He stated that he and Odell used doses of 0.2 Gm. of sodium amytal every thirty minutes until the patient was asleep or until 0.6 Gm. had been given. The blood pressure was recorded at fifteen minute intervals until the patient was asleep. In using this test it was found that the systolic and diastolic pressures of the mild pre-eclamptic patients usually decreased to the normal level, whereas the patient with early hypertensive disease had a decrease in blood pressure to a lesser degree. The blood pressures of patients with severe pre-eclampsia or with a long history of essential hypertension showed no decrease. At the time of publication of the book they were using sodium amytal to determine if there were any constant difference between the response in pre-eclampsia and that in hypertensive disease, but no conclusions were made.

The only other mention of the use of the sodium amytal test in reference to the toxemias of pregnancy was in a paper by Odell, et al.(1951). A slightly different procedure than that of Dieckmann was used. In their test 0.03 Gm. of sodium amytal were administered orally every half hour for three doses or until the patient fell asleep. The blood pressure was taken every fifteen minutes, and the sleeping blood pressure was considered basal. The difference between the basal and the control systolic pressures was then recorded. The writers of the paper did not feel, however, that this test was either of specific or prognostic value in the toxemias of pregnancy.

BETA-GLUCURONIDASE TEST

In 1946. Talalay, Fishman, and Huggins developed a procedure for determining the activity of mono-beta-glucuronidase in blood and tissues. Phenolphthalein mono-beta-glucuronide is prepared biosynthetically from the urine of rabbits to whom the water soluble derivative of 500 mg. of sodium phenolphthalein has been administered subcutaneously. Tissues or blood which is to be assayed is added to the substrate, and the substrate is rapidly hydrolyzed by the mono-beta-glucuronidase in the material being assayed. The free phenolphthalein which is liberated may be readily determined photocolorimetrically in alkaline solution.

McDonald and Odell in 1947 found that the beta-glucuronidase activity in pre-eclamptics was markedly increased, but there was no significant increase in hypertensive toxemia patients or in eclamptics. They used 17.5 micrograms of beta-glucuronidase as the upper limit of normal. In normal pregnant females they found that there was a downward curve of activity from the sixth to the twelfth week which paralleled the fall in serum gonadotropins at that time. From the twelfth week on there was a steady rise in glucuronidase activity (from eight to 17.5 micrograms with a mean of 13.5 micrograms) paralleling the rise in serum estrogens, but by the fifth to the seventh postpartum day there was a drop in values to less than 9.4 micrograms per milliliter which was in the normal, non-pregnant range. Ten of the twelve pre-eclamptics had values over 20 micrograms per milliliter; the other two had values of fifteen and nineteen micrograms respectively.

Odell and McDonald in 1948 further stated that they felt the serum beta-glucuronidase levels would differentiate most cases of pre-eclampsia and hypertensive toxemias of pregnancy, but the serum concentration does not reflect the severity of the situation. They also stated that the serum concentration of beta-glucuronidase apparently reaches a maximum just before or early in the course of pre-eclampsia and then falls during the duration of the syndrome. They did not find the levels during convulsive toxemia to be diagnostic, but they did suggest that glucuronidase levels may warn the obstetrician of impending pre-eclampsia.

Later in 1948 Fishman, Springer, and Brunetti improved the glucuronidase assay methods for studying human blood beta-glucuronidase. They developed a more accurate substrate (mono-beta-glucuronide), and it may now be obtained commercially using their revised method of preparation. Finding that the leukocytes of the blood (mainly the polymorphonuclear leukocytes and the lymphocytes) contain the greatest glucuronidase activity in relation to any other of the blood components, for assay they used the buffy coat which forms between the serum and the packed red blood cells after centrifugation. This buffy coat is laked with ten c.c. of distilled water after alternate freezing (in carbon dioxide snow - acetone mixture) and thawing at room temperature to facilitate lysis. The laked cells are added to 0.1 c.c. of substrate, and a colorimeter with a 540 millimicron filter is used to deter-

mine the amount of phenolphthalein liberated in the alkaline solution. The activity of the blood cells is determined as follows: micrograms of phenolphthalein liberated in the digest X $\frac{1}{\text{hours of incubation}}$ X $\frac{\text{vol. of laked blood cells}}{\text{vol. of substrate (0.1 c.c.)}}$ X $\frac{100}{\text{vol. of original specimen}}$ = gamma units of glucuronidase per 100 c.c. of whole blood.

They felt that the role of glucuronidase in the body is associated with the metabolic conjugation processes. They consider it to be an enzyme since it is secreted by glandular epithelium (it may be found in saliva, tears, gastric juice, spinal fluid, and urine).

METHODS

PITUITRIN TEST

The method used for the pituitrin test is essentially that used by Moffat(1933) and Dieckmann and Michel(1935,1937). The patient was allowed to secure as near a basal blood pressure as possible by resting for fifteen minutes to a half hour and then taking three blood pressure readings at fifteen minute intervals. The lowest pressure obtained was used as the basal level. Pituitrin in the dosage of 0.2 mg. (0.2 c.c.) was then injected intramuscularly, and the blood pressure readings were then taken every minute until the pressure returned to basal levels. The difference between the basal level and the greatest reading obtained in both systolic and diastolic pressures was computed and recorded.

COLD PRESSOR TEST

The cold pressor test used is that of Hines and Brown(1933, 1939) who first developed it. The subject is allowed to rest in the supine position in a quiet room for fifteen minutes, or until the blood pressure has approximated the basal level. This requires up to sixty minutes in some cases, particularly with those who will be hyperreactors. With the subject still supine, a sphygmomanometer cuff is placed on one arm, and the hand of the opposite arm is immersed in ice water (four degrees centigrade) to a point just above the wrist. Blood pressure readings are then taken at intervals of thirty and then sixty seconds. The hand is

then removed, and readings are taken every two minutes until the blood pressure returns to the previous basal level.

The temperature should not vary more than one degree from the four degrees set forth in the test. No vasodilators or sedatives should be administered within a time prior to the test wherein they might exert some effect on the patient tested. The entire test should be performed with the patient in the supine position; she should not be sitting or standing.

The difference between the basal and maximum response levels is determined for both systolic and diastolic pressures and the results recorded.

TETRAETHYLAMMONIUM CHLORIDE TEST (TEAC FLOOR)

The standard TEAC test was devised by Brust, Assali, and Ferris(1948), and their method was the one used in this series. 400 mg. (4 c.c.) of tetraethylammonium chloride is slowly injected intravenously into the antecubital vein of the subject. The subject's blood pressure is then recorded at half minute intervals for six minutes and then at one minute intervals for ten to thirty minutes afterward, or until the blood pressure returns to the basal level. The basal level is originally determined in the same manner and under the same conditions as in the cold pressor test.

The lowest point to which the blood pressure descends during the first five minutes after injection is the TEAC floor. The difference between basal and TEAC floor levels in systolic and diastolic pressures is determined.

SODIUM AMYTAL TEST

The test used here is essentially the same as that used by Dieckmann(1941). The patient is allowed to attain a blood pressure as close to the basal level as possible by the same means used to attain it in the preceding tests. The subject is then given 0.2 Gm. of sodium amytal by mouth, and the dosage is repeated at thirty minute intervals until the patient is asleep or until 0.6 Gm. has been given. Blood pressure is recorded at fifteen minute intervals until the patient falls asleep or until the blood pressure returns to the basal level. Differences between the basal levels and the lowest systolic and diastolic pressures obtained are determined.

BETA-GLUCURONIDASE TEST

The beta-glucuronidase test used is that described by Fishman, Springer, and Brunetti(1948). A quantity of blood was obtained from the antecubital vein of the patient. This was then centrifuged and the buffy coat pipetted off after the serum was drawn off. The buffy coat was then laked and lysed, and it was then added to the substrate of phenolphthalein mono-beta-glucuronide, which was obtained comercially. After incubation, the free phenolphthalein which was liberated by hydrolysis was determined photocolorimetrically using a 540 millimicron filter. The pH of the solution is made uniform between 10.2 and 10.4 prior to the colorimetric determination. Using the equation previously cited, one determines the number of

gamma units of glucuronidase per one hundred c.c. of whole blood.

CLASSIFICATION OF THE TOXEMIAS OF PREGNANCY

Since the etiology of the toxemias of pregnancy is relatively unknown, there has been considerable difficulty in arriving at a suitable classification, and various classifications have been proposed. Because of lack of uniformity in nomenclature, the Ammerican Committee on Maternal Health in 1937 (De Lee and Greenhill, 1947) appointed a committee to work out a suitable classification. Their classification was :

1. Hypertensive disease
2. Renal disease
3. Pre-eclampsia, severe; pre-eclampsia, mild
4. Eclampsia
5. Vomiting of pregnancy
6. Acute yellow atrophy of the liver
7. Unclassified

The majority of the original committee of five and two additional members appointed in 1939 favored the following amplification and modification of the 1937 classification (American Committee on Maternal Welfare, 1940):

Group A. Diseases not peculiar to pregnancy:
- I. Hypertensive disease (hypertensive cardiovascular disease)
  - (a) Benign (essential hypertension)
    1. Mild
    2. Severe
  - (b) Malignant
- II. Renal disease
  - (a) Nephrosclerosis or chronic vascular nephritis
  - (b) Glomerulonephritis
    1. Acute
    2. Chronic
  - (c) Nephrosis
    1. Acute
    2. Chronic
  - (d) Other forms of severe renal disease (chronic pyelonephritis, etc.)

Group B. Disease dependent on or peculiar to pregnancy:
- I. Pre-eclampsia
  - (a) Mild
  - (b) Severe (pre-convulsive)
- II. Eclampsia
  - (a) Convulsive
  - (b) Non-convulsive (coma with findings at autopsy typical of eclampsia)

Group C. Vomiting of pregnancy

Group D. Unclassified toxemias

Dieckmann(1941) stated that he felt Group C, Vomiting of pregnancy, should be omitted because it is not his belief that it belongs to the toxemias. He also felt that Group D, Unclassified toxemias, should be omitted because it is his contention that every case of toxemia should be classified, even if the diagnosis has to be changed at a later date. His classification is as follows:

A. Eclampsia. -- The clinical diagnosis of eclampsia is based on the occurrence of convulsion and/or coma in a pregnant, parturient, or puerperal woman (twenty-four hours after delivery), if associated with edema, hypertension, or proteinuria.

B. Pre-eclampsia. -- The appearance and/or disappearance by the fourth postpartum month of one or more (or all) of the following in a normal pregnant woman is indicative of pre-eclampsia:
   - (a) A systolic blood pressure of 140 mm. Hg or more for two days or longer
   - (b) An edema of at least the ankles and legs which has no obvious etiology
   - (c) A proteinuria which is present for two days or more (a clean specimen with no urinary tract infection)
   - (d) Occasionally cerebral, visual, gastrointestinal, and renal symptoms

C. Essential hypertension. -- A systolic blood pressure of 140 mm. Hg or more which is present for two days or longer, which is either present before pregnancy or appears during pregnancy, and persists longer than the fourth postpartum month or recurrs in a subsequent pregnancy, is indicative of essential hypertension.

D. Vascular-renal disease. -- This disease is characterized by the presence of any two or more of the following signs:
   (a) Hypertension
   (b) Edema
   (c) Proteinuria
which are present before conception or develop during pregnancy and persist longer than the fourth postpartum month.

Titus in 1944 proposed a new classification of the toxemias of pregnancy using the 1939 Committee on Maternal Welfare chart, but arranging the toxemias in relation to the pregnancy (the pregnancy was the common denominator). It is as follows:

Group A. Toxemia types most common in early pregnancy (nausea and vomiting).
   1. With demonstrable, pre-exisiting, predisposing causes (including dietetic, or endocrine, or cardiovascular disturbances, alone or in combination)
   2. Without demonstrable pre-existing, predisposing causes

Group B. Toxemia types occurring without predilection to any time during pregnancy (acute yellow atrophy of the liver, acute nephritis or renal disease, acute hypertensive cardiovascular disease, and certain unclassified types).
   1. With demonstrable pre-exisiting, predisposing causes (including dietetic or endocrine disturbances, or general physical defects), alone or in combination
   2. Without demonstrable pre-existing, predisposing causes

Group C. Toxemia types most common late in pregnancy (pre-eclampsia and eclampsia).
   1. With demonstrable pre-existing, predisposing causes (including dietetic, or endocrine disturbances, or general physical defects, alone or in combinations)
   2. Without demonstrable pre-existing, predisposing causes

Savel in 1947 suggested abandoning the use of "mild" and "severe" in the classification of pre-eclampsia. He stated that one must

adhere to the objective findings and thus come to the conclusion that a woman either has or does not have pre-eclampsia. He also stated that vomiting of pregnancy may or may not be a toxemia.

In this paper the author uses Dieckmann's classification because he believes that it is by far the most logical classification at the present time and is sufficiently objective to make the classification of toxemias a rather simple matter rather than the confusing and sometimes laborius task that it has been when utilizing other methods.

RESULTS

In these series of tests a total of twenty-six patients were studied. These twenty-six were divided into the following groups: pre-eclamptics - eleven, hypertensive toxemias - eight, and normal pregnant females - seven. However, due to such conditions as the rapidity of labor or the physical condition of the patient in some instances, there are some instances where it was not possible to run a complete series of tests on a patient. The results, therefore, are as complete as possible considering the unexpected circumstances which may have arisen in any particular case. Both antepartum and postpartum results will be discussed.

PITUITRIN TEST

It may be seen from Table I that the pre-eclamptic group tested had a mean increase in systolic pressure of 36 $\pm$ 4.3 mm. Hg and in diastolic pressure of 24 $\pm$ 3.9 mm. Hg. Arbitrarily setting up a standard of 1 to 20 mm. Hg increase in systolic pressure and an increase of 1 to 15 mm. Hg in diastolic pressure as normal responses, it was found that all systolic responses were hyperreactive, but one of the eight tested or 12.5% had a normal diastolic response. The above are antepartum responses. From Table IV we note that the mean systolic and diastolic responses are 21 $\pm$ 7.2 and 15 $\pm$ 3.9 mm. Hg respectively. Two of the five tested or 40% had nprmal responses systolically, while three of the five or 60% had normal diastolic responses.

In the hypertensive group Table II shows antepartum mean

responses of 10 ± 2.9 mm. Hg increase in systolic pressure and 12 ± 2.6 increase in diastolic pressure. None of the seven patients tested fell into the hyperreactive systolic group, but one or 14.3% had a hyperreactive diastolic response. Postpartum findings as shown in Table V show mean responses of 16 ± 6.1 mm. Hg systolically and 6 ± 3.5 mm. Hg diastolically. Two of the six or 33.3% had hyperreactive systolic responses, and only one of the six or 16.6% had a hyperreactive diastolic response.

In the normal group (see Table III) there was only one hyperreactive response and that was in the diastolic group. This constituted a 16.6% finding of hyperreactive findings diastolically in the total group of six tested. Mean antepartum values were 8 ± 2.5 mm. Hg systolically and 11 ± 2.7 mm. Hg diastolically. Only three patients were given a postpartum pituitrin test, and of these one of the three or 33.3% had hyperreactive systolic responses and two of the three or 66.7% had hyperreactive diastolic responses.

COLD PRESSOR TEST

Utilizing the recommendation of Hines and Brown (1939) that 20 mm. Hg systolic pressure and 15 mm. Hg diastolic pressure were the upper limits of normal responses to the cold pressor test, it was found that only three of the seven patients or 43% in the preeclamptic antepartum group had a hyperreactive systolic response with only one of the seven or 14.3% having a hyperreactive diastolic response. Mean antepartum values were 18 ± 3.8 mm. Hg response systolically and 13 ± 3.8 mm. Hg diastolically. In the

postpartum group only one of six or 16.7% had a hyperreactive systolic response, and the same number and percentage had a hyperreactive diastolic response (See Table IV).

Hypertensive antepartum responses had mean values of 34 ± 8.7 mm. Hg systolically and 20 ± 4.6 mm. Hg diastolically. Three of the eight tested fell into the normal group (37.5%) of systolic responses, and five of the eight or 67.5% had normal diastolic responses. In the postpartum the mean responses were 23 ± 7.4 mm. Hg in systolic pressure and 18 ± 6.6 mm. Hg in diastolic pressure. Three of the six or 50% had responses within the normal range systolically, and the same number and percentage had normal range responses diastolically. (Table II,V)

In the normal pregnant group there were no hyperreactive responses in either systolic or diastolic pressure in both the antepartum and postpartum periods. Mean antepartum responses were 7 ± 2.1 mm. Hg in systolic pressure and 5 ± 1.7 mm. Hg in diastolic pressure. There were not enough patients tested in the postpartum to obtain any mean results. (Table III)

TETRAETHYLAMMONIUM CHLORIDE TEST (TEAC FLOOR)

The pre-eclamptic group in the antepartum showed a great amount of variance in responses to this test with mean values of 24 ± 6.5 mm. Hg decrease in systolic pressure and 6 ± 3.8 mm. Hg decrease in diastolic pressure. The variance of antepartum responses were from 6 to 56 mm. Hg in systolic decreases in pressure and from an increase of 8 mm. Hg to a decrease of 24 mm. Hg diastolically. No definite limits of normal responses have been set

forth by investigators using the test, but they have stated responses were greater in the normal pregnant group near term than in any other of the groups with the hypertensive responses being next greatest and pre-eclamptic responses the least of the three groups in the antepartum. All three groups have insignificant responses comparable to that found in normal non-pregnant females when the test is run in the postpartum. Postpartum pre-eclamptic means were 11. $\pm$ 2.7 mm. Hg systolically and 10 $\pm$ 2.6 mm. Hg diastolically with responses varying from 2 to 22 mm. Hg in systolic decrease and 0 to 20 mm. Hg in diastolic decrease. (See Tables I and IV for antepartum and postpartum results respectively.)

In the antepartum, hypertensive responses varied from 0 to 30 mm. Hg systolically and from an increase of 6 mm. Hg to a decrease of 25 mm. Hg in diastolic response in the group of eight tested (See Table II). Mean values were 14 $\pm$ 4.1 mm. Hg systolically and 6 $\pm$ 3.5 mm. Hg diastolically. Postpartum responses varied from an increase of 10 to a decrease of 22 mm. Hg systolically and from an increase of 2 to a decrease of 14 mm. Hg diastolically. Mean values were 12 $\pm$ 3.4 mm. Hg in systolic pressure and 8 $\pm$ 2 mm. Hg in diastolic pressure (See Table V).

Six normal pregnant women were tested with the TEA^{C} test. In the antepartum their responses varied from an increase of 4 to a decrease of 38 mm. Hg systolically and from 0 to 38 mm. Hg decreases in diastolic pressure. Mean values were 20 $\pm$ 5.7

mm. Hg and 12 ± 5.5 mm. Hg in systolic and diastolic pressures respectively. (See Table III) There were not a sufficient number of postpartum results to ascertain means.

SODIUM AMYTAL TEST

Even less is known about expected responses when using the sodium amytal test than when using the TEAC test. However, mild, early pre-eclamptics have been found to have decreases in systolic and diastolic pressure to normal limits with hypertensives showing lesser decreases. Severe eclamptics have shown no decreases. In this series of six pre-eclamptics tested in the antepartum there were vraiances in responses from an increase of 4 to a decrease of 26 mm. Hg systolically and decreases from 2 to 16 mm. Hg diastolically. The mean systolic response was 15 ± 4.7 mm. Hg, and the mean diastolic response was 9 ± 2.2 mm. Hg. (See Table III) Since only one postpartum result was obtained, there was insufficient data to determine means.

Among the seven hypertensives tested with this test there was a variance of response ranging from a decrease of 4 to 60 mm. Hg systolically and from 0 to 40 mm. Hg diastolically in the antepartum. 22 ± 7.2 mm. Hg and 12 ± 5.2 mm. Hg were the mean systolic and diastolic responses respectively. (Table II) Insufficient postpartum tests were run to tabulate means and variances.

Only four antepartum normal results were obtained. These ranged from an increase of 8 to a decrease of 10 mm. Hg systolically and from an increase of 4 to a decrease of 14 mm. Hg diastolic-

ally. Mean values were 3 ± 4.2 mm. Hg systolically and 6 ± 4.1 mm. Hg diastolically. (Table III) Only one normal postpartum woman was tested; thus, information was inadequate for comparison.

BETA-GLUCURONIDASE TEST

The antepartum results in the nine pre-eclamptics tested varied from 460 to 2000 gamma units of glucuronidase activity. If 500 gamma units is taken as the upper limit of normal, then only one patient or 11% fell into the normal range with the remaining eight or 89% falling into the abnormal response group. (See Table I) In the postpartum activity ranged from 312 to 969 gamma units with 50% falling into the normal range. Means were 1301 ± 173 gamma units in the antepartum and 550 ± 151 in the postpartum. (See Table IV)

Of the five hypertensives tested in the antepartum the mean activity of glucuronidase was 1930 ± 560 gamma units with responses varying from 1833 to 3400 gamma units. Thus, all were in the abnormal response group (Table II). Only two postpartum results were obtained, one being within normal limits and the other in the abnormal range.

All four normal pregnant females tested in the antepartum had hyperactive responses varying from 1333 to 2600 gamma units. The mean value was 1941 ± 293 (Table III). No postpartum results were obtained.

TABLE I

PRE-ECLAMPTIC

ANTEPARTUM RESPONSES

Name	Number	Pit		Cold		TEAC		Amytal		Gluc
		S	D	S	D	S	D	S	D	
D.O.	106016	48	20	7	7	10	+8	22	6	1500
I.W.	104732	32	10	12	8	16	9	16	14	2000
L.C.	104088	26	20	6	5	16	+8	22	16	1042
J.G.	104203	70	38	30	14	50	14	+4	2	460
Z.H.	106904	38	26	40	34	8	10			1513
L.K.	105036	24	22	4	6	22	10	6	2	1332
E.A.	105580	30	16	26	14	16	0	26	10	1400
L.S.	107741	37	43			56	24	8	6	
M.P.	104014									562
B.W.	103721									1900

ANTEPARTUM RANGES AND MEANS

Test	Systolic		Diastolic	
	Range	Mean	Range	Mean
Pituitrin	24 to 70	36 ± 4.3	10 to 43	24 ± 3.9
Cold pressor	4 to 40	18 ± 3.8	5 to 34	13 ± 3.8
TEAC	8 to 56	24 ± 6.5	+8 to 24	6 ± 3.8
Na Amytal	+4 to 26	15 ± 4.7	2 to 16	9 ± 2.2
Glucuronidase	Range: 460 to 2000;		Mean: 1301 ± 173	

TABLE II

HYPERTENSIVE

ANTEPARTUM RESPONSES

Name	Number	Pit S	Pit D	Cold S	Cold D	TEAC S	TEAC D	Amytal S	Amytal D	Gluc
G.T.	107151	20	24	46	25	10	0	36	20	833
D.B.	107233	20	15	70	40	30	25	60	5	
V.W.	104562	2	6	9	6	2	∔6	8	4	3400
P.S.	104220	12	14	22	9	11	4			1350
L.P.	104651	2	3	10	14	9	9	10	6	3135
B.S.	107382	16	14	48	40	18	0			
N.G.	106375	0	10	8	14	30	14	4	0	
M.A.	105643			58	8	0	0	30	40	933

ANTEPARTUM RANGES AND MEANS

Test	Systolic Range	Systolic Mean	Diastolic Range	Diastolic Mean
Pituitrin	0 to 20	10 ± 2.9	3 to 24	12 ± 2.6
Cold pressor	9 to 70	34 ± 8.7	6 to 40	20 ± 4.6
TEAC	0 to 30	14 ± 4.1	∔6 to 25	6 ± 3.5
Na Amytal	4 to 60	22 ± 7.2	0 to 40	12 ± 5.2
Glucuronidase	Range: 833 to 3400;		Mean: 1930 ± 560	

TABLE III

NORMAL

ANTEPARTUM RESPONSES

Name	Number	Pit S	Pit D	Cold S	Cold D	TEAC S	TEAC D	Amytal S	Amytal D	Gluc
A.H.	104681	15	16	6	5	36	38	9	4	1333
G.A.	106725	8	10	2	10	8	14	10	14	
E.W.	104965	16	18	8	0	22	4			
G.B.	104316	6	4	16	10	22	8	2	0	
J.W.	104694	2	2	6	2	38	10	6	4	1600
M.W.	106794	2	14	2	4	+4	0			2600
N.B.	105645									2230

ANTEPARTUM RANGES AND MEANS

Test	Systolic Range	Systolic Mean	Diastolic Range	Diastolic Mean
Pituitrin	2 to 16	8 ± 2.5	2 to 18	11 ± 2.7
Cold pressor	2 to 16	7 ± 2.1	0 to 10	5 ± 1.7
TEAC	+4 to 38	20 ± 5.7	0 to 38	12 ± 5.5
Na Amytal	+8 to 10	3 ± 4.2	+4 to 14	6 ± 4.1
Glucuronidase	Range: 1333 to 2600;		Mean: 1941 ± 293	

TABLE IV

PRE-ECLAMPTIC

POSTPARTUM RESPONSES

Name	Number	Pit		Cold		TEAC		Amytal		Gluc
		S	D	S	D	S	D	S	D	
D.E.	106016	34	25	0	0	8	6			
I.W.	104732	2	6	12	8	10	7			570
L.C.	104088	10	4	4	6	22	20			337
J.G.	104203	33	14	12	10	20	16	8	4	312
G.D.	105543	44	24	24	28	10	14			
B.W.	103721			4	8	8	10			960
M.P.	104014					2	0			

POSTPARTUM RANGES AND MEANS

Test	Systolic		Diastolic	
	Range	Mean	Range	Mean
Pituitrin	2 to 44	21 ± 7.2	4 to 25	15 ± 3.9
Cold pressor	0 to 24	9 ± 3.5	0 to 28	10 ± 3.9
TEAC	2 to 22	11 ± 2.7	0 to 20	10 ± 2.6
Na Amytal	--	--	--	--
Glucuronidase	Range: 312 to 960;		Mean: 550 ± 151	

TABLE V

HYPERTENSIVE

POSTPARTUM RESPONSES

Name	Number	Pit		Cold		TEAC		Amytal		Gluc
		S	D	S	D	S	D	S	D	
G.T.	107151	40	0	35	5	22	10			
D.B.	107233	0	0	25	35	20	10			
V.W.	104562	18	2	2	3	±10	±2	2	±2	
P.S.	104220	14	22	12	6	2	8	10	10	312
L.P.	104651	1	3	11	18	20	14			740
B.S.	107382	24	10	51	40	0	0			

POSTPARTUM RANGES AND MEANS

Test	Systolic		Diastolic	
	Range	Mean	Range	Mean
Pituitrin	0 to 40	16 ± 6.1	0 to 22	6 ± 3.5
Cold pressor	2 to 51	23 ± 7.4	3 to 40	18 ± 6.6
TEAC	±10 to 22	12 ± 3.4	±2 to 14	8 ± 2
Na Amytal	--	--	--	--
Glucuronidase	--			

COMPARISON OF THE FIVE TESTS STUDIED

ANTEPARTUM RESULTS

In Graph I significant difference is noted between the pre-eclamptic group and the hypertensive and normal groups in regard totthe pituitrin test. All pre-eclamptics had hyperreactive systolic responses and all but one had hyperreactive diastolic responses. Responses in both the hypertensive and normal groups were significantly less, and only a few fell into the hyperreactive ranges. It appears that the systolic response is a better criteria than the diastolic response when utilizing this test.

With the cold pressor test (Graph II) greatest responses were noted in the hypertensive group, although several hyperreactive responses were seen in the pre-eclamptic group. No hyperreaction was noted in the normal group. It must be noted that three of the eight hypertensives had normal systolic responses. Again, systolic responses seem to display a better basis for hyperreactive ranges in the test.

Graph III showing results with the tetraethylammonium chloride test indicates that more profound decrease in blood pressure were produced in the pre-eclamptic group with the next greatest responses occurring in the normal group. The least amount of response was seen in the hypertensive toxemia group. Considerable variability in responses are seen, however, in all three groups, each group shwoing at least one patient with either a systolic or diastolic increase in pressure instead of the expected decrease. Here, too,

systolic pressures appear to be most indicative of the patients' responses to the test.

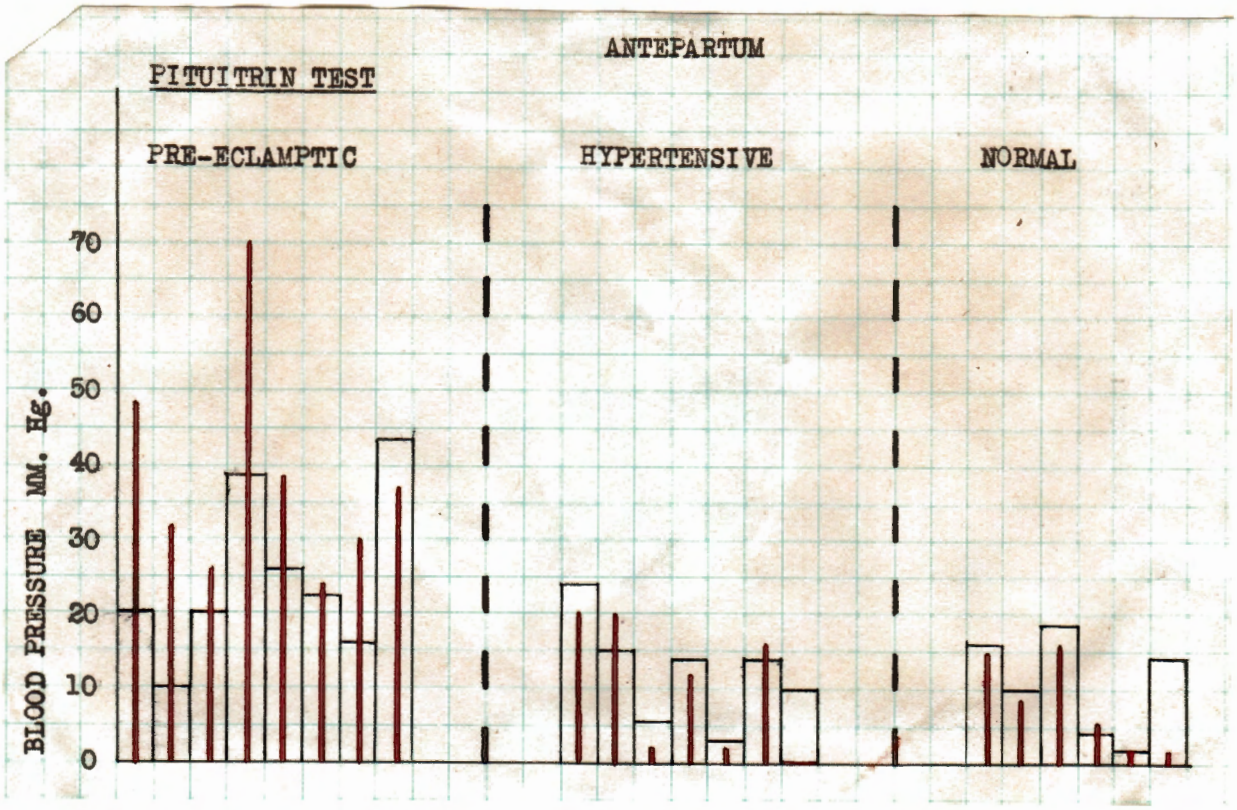
In the sodium amytal test (Graph IV) most profound blood pressure decreases were noted in the hypertensive group. Pre-eclamptics showed the next greatest responses, and normals showed little response in blood pressure drop to the drug. Only one increase in blodd pressure was noted, and that was in the pre-eclamptic group. Systolic and diastolic responses paralleled each other, but systolic responses were greater. Considerable variance was noted within both the pre-eclamptic and hypertensive groups, but little variance was seen in the normal group.

Except for two rather marked increases in activity in the hypertensive group, all groups displayed rather similar amounts of beta-glucuronidase activity were seen in all three groups tested (See Graph V). There are apparently no significant alterations from the normal.

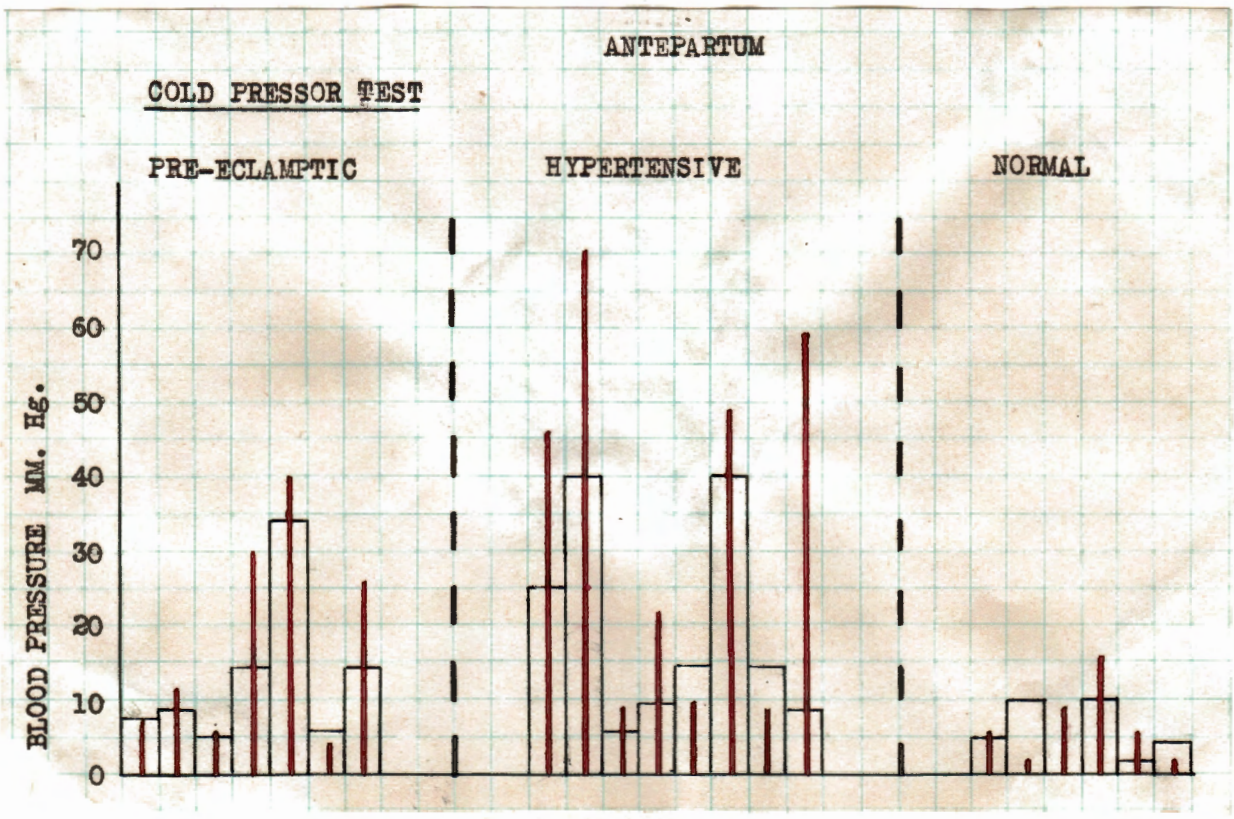
POSTPARTUM RESULTS

In the postpartum series, there was little variation between responses in the three groups in all five tests except the cold pressor test. Here, the hypertensive group showed somewhat marked responses than the pre-eclamptic or normal groups. In the four blood pressure response tests, the systolic responses were considered to be most indicative of the patients' reactions to the tests. (See Graphs VI, VII, VIII, IX, and X)

GRAPH I

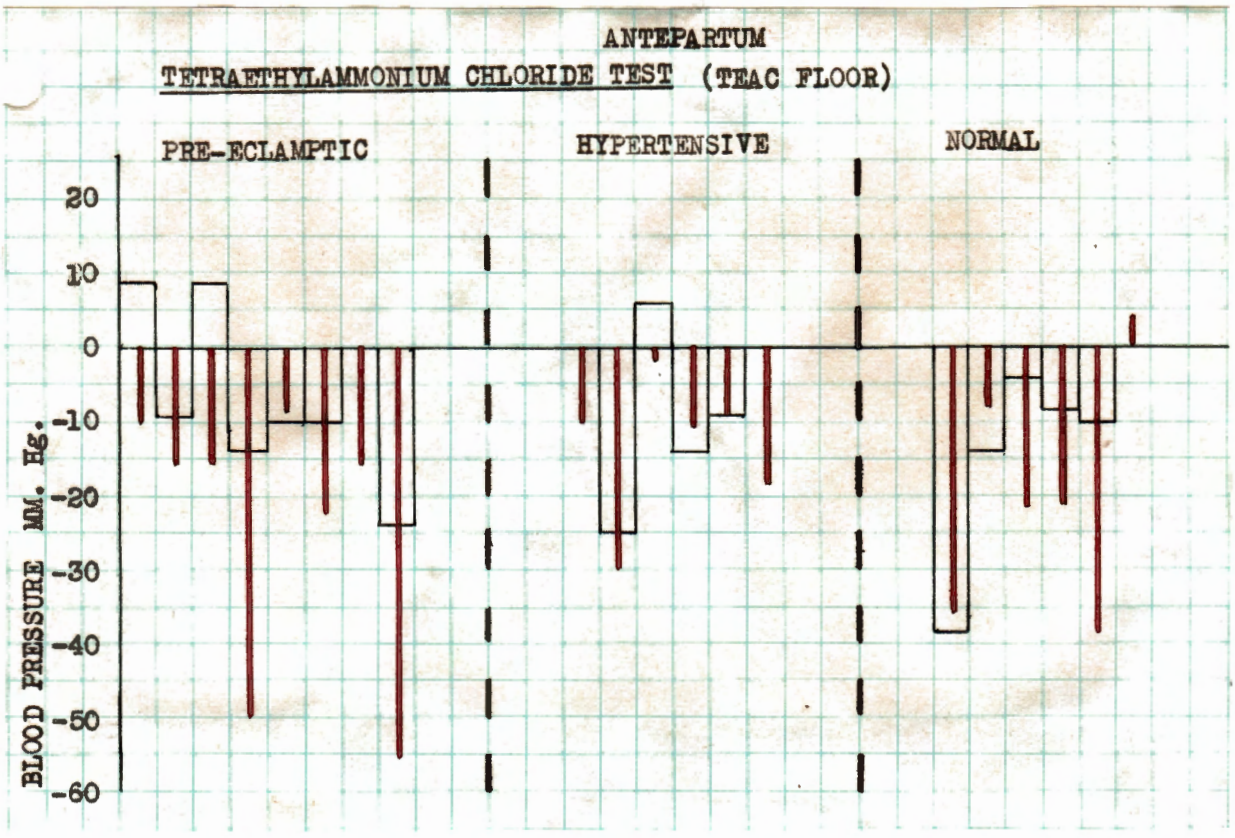


GRAPH II

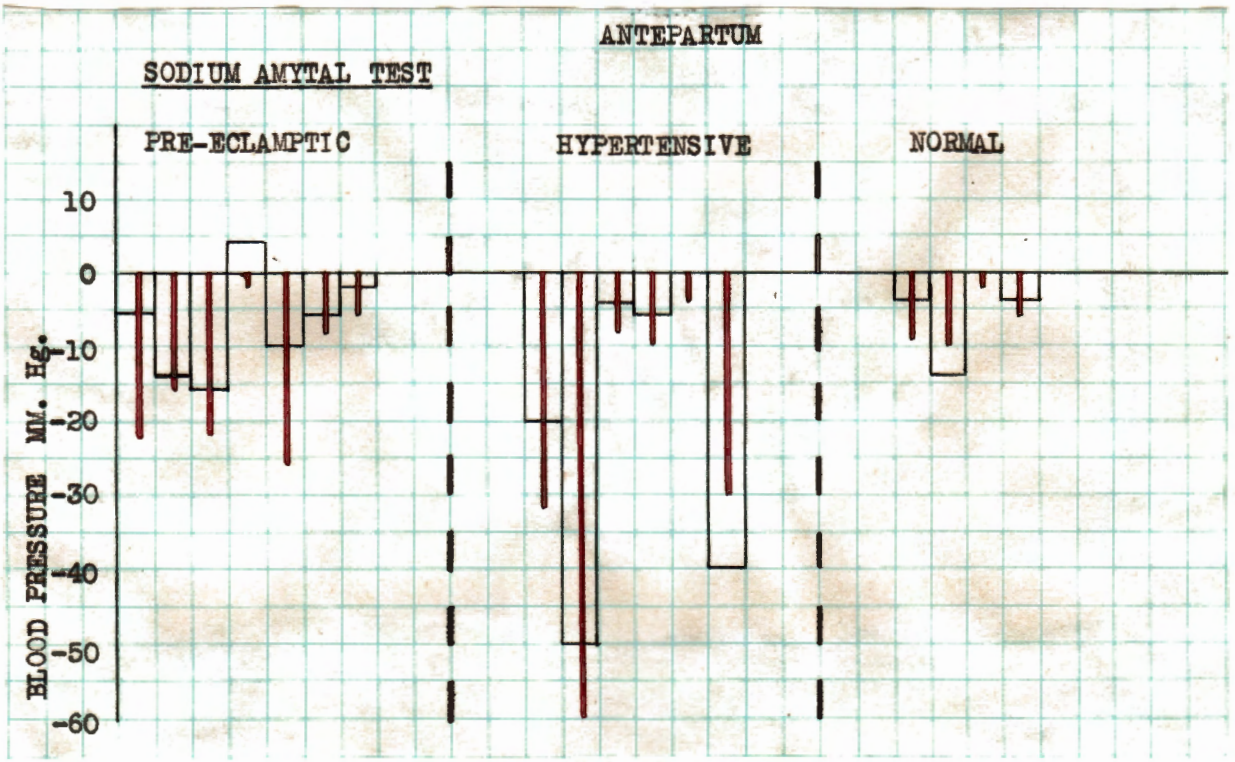


Systolic pressure - straight line
Diastolic pressure - bar

GRAPH III

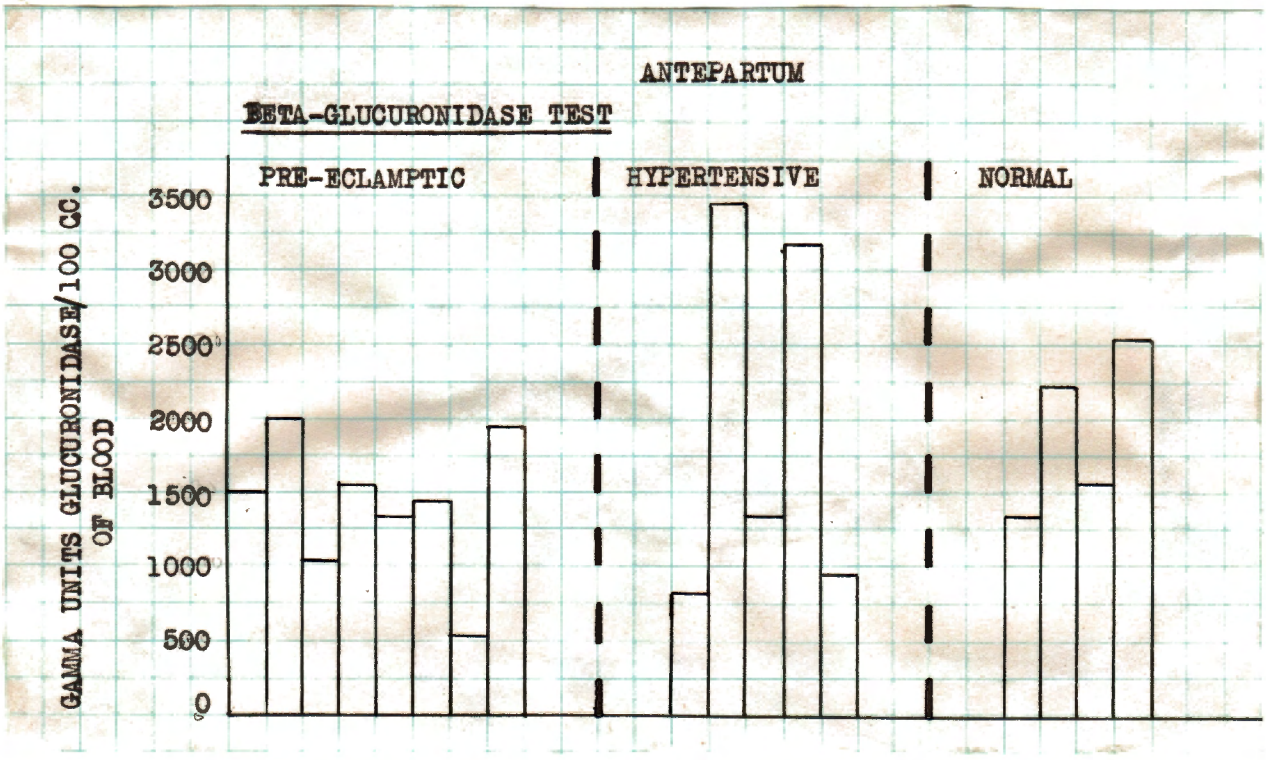


GRAPH IV

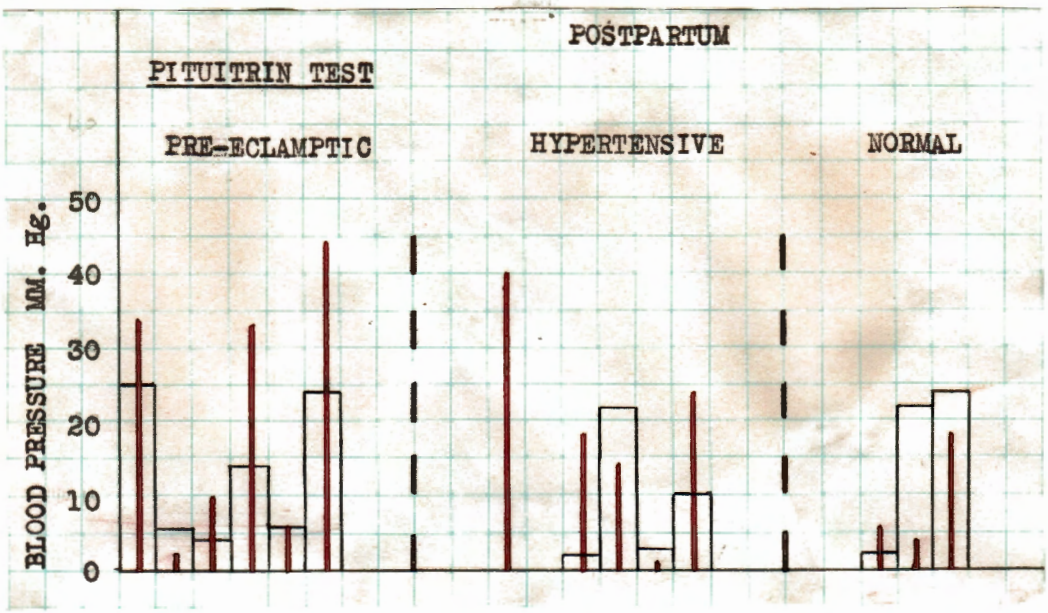


Systolic pressure - straight line
Diastolic pressure - bar

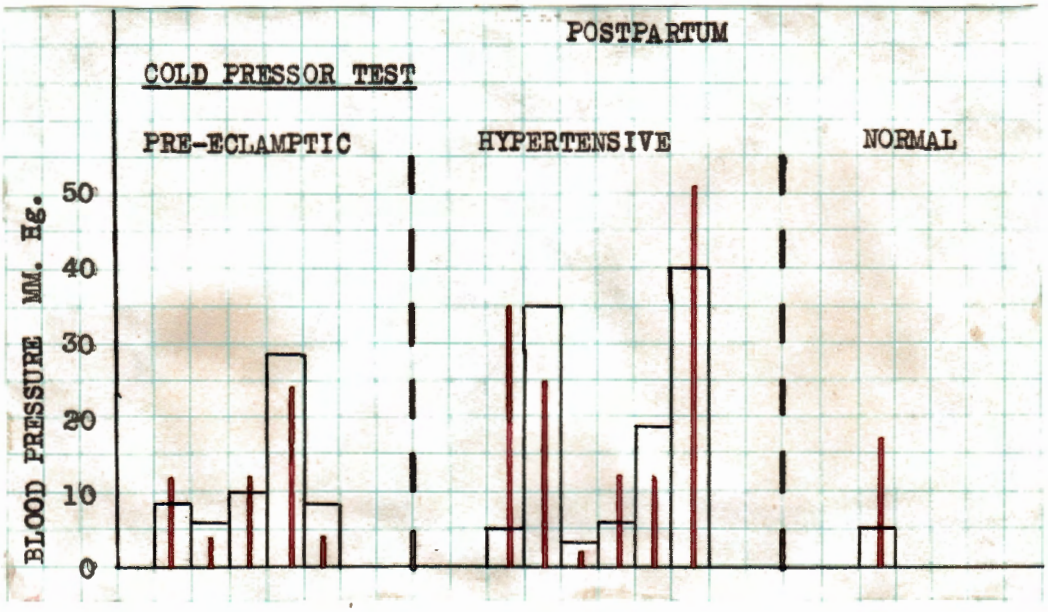
GRAPH V


ANTEPARTUM
BETA-GLUCURONIDASE TEST
PRE-ECLAMPTIC
HYPERTENSIVE
NORMAL
GAMMA UNITS GLUCURONIDASE/100 CC. OF BLOOD
3500
3000
2500
2000
1500
1000
500
0

GRAPH VI

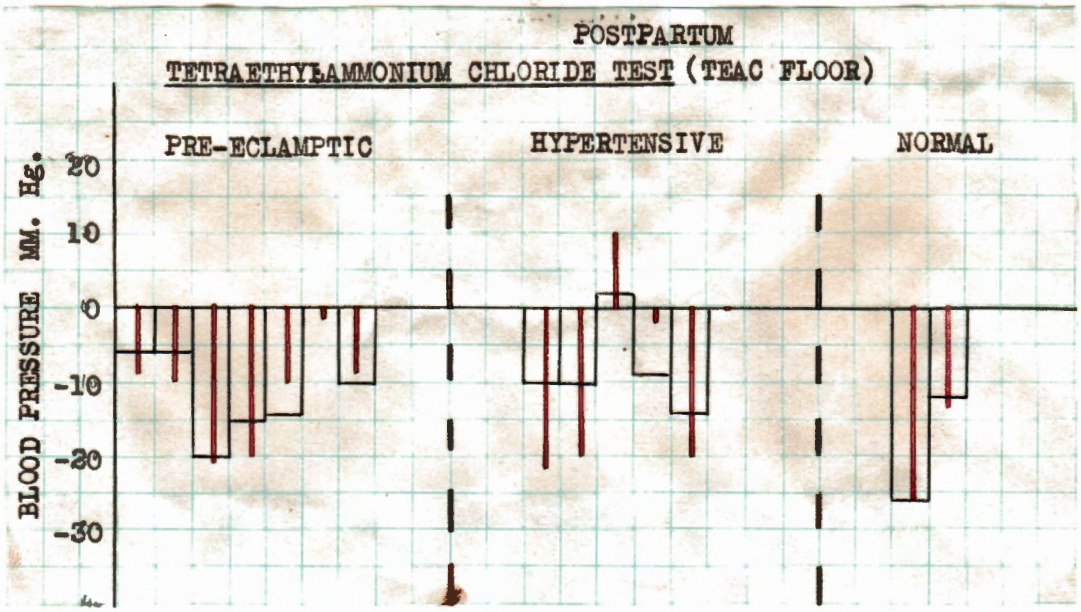


GRAPH VII

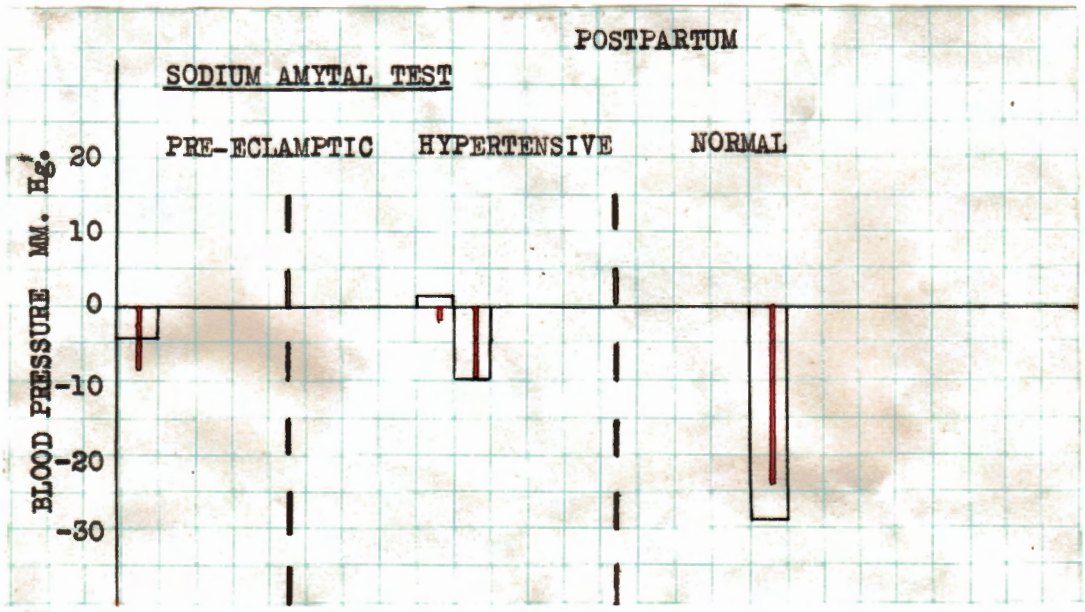


Systolic pressure - straight line
Diastolic pressure - bar

GRAPH VIII

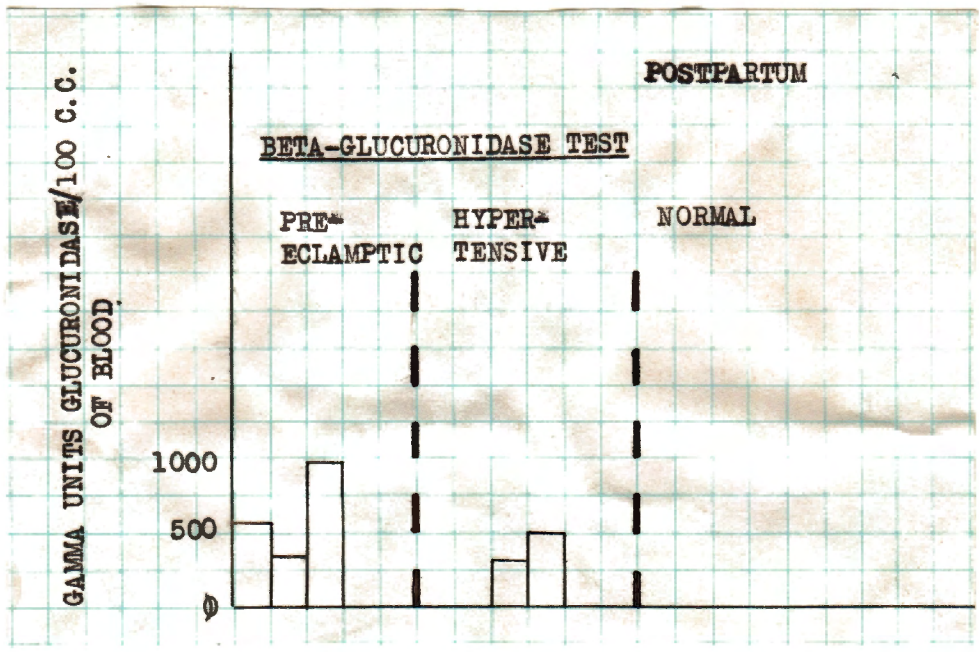


GRAPH IX



Systolic pressure - straight line
Diastolic pressure - bar

GRAPH X


POSTPARTUM
BETA-GLUCURONIDASE TEST
PRE-
ECLAMPTIC
HYPER-
TENSIVE
NORMAL
GAMMA UNITS GLUCURONIDASE/100 C.C.
OF BLOOD
1000
500
0

ADDITIONAL CLINICAL AND LABORATORY FINDINGS

PRE-ECLAMPTICS

The average age of pre-eclamptics used in these series of tests was 23.3 years. Six of the eleven were primigravida, and none of the eleven had had a previous toxemia. Every onset of symptoms occurred after the twenty-eighth week of pregnancy; the average week of onset of symptoms, however, was 35.1 weeks. All blood pressures were greater than 140 mm. Hg systolically and 90 mm. Hg diastolically; all patients had proteinuria, and eight of the eleven had edema. Six of the eleven had cerebral, visual, gastrointestinal, or renal symptoms. Two of the eleven did not deliver viable fetuses. The only abnormal eye findings were spasm of the retinal vessels in five of the ten patients checked. There were no arteriosclerotic findings or hemorrhages. Considering the normal blood uric acid level to be 2 to 4 mg.%, only one of six patients checked had an abnormal value; this was 4.6 mg.%. Of the nine urea clearance tests performed, all were found to have normal values. Four urine chloride determinations were done. Considering a value of 10 to 15 Gm. of chlorides (as NaCl) in twenty-four hours to be normal, all four patients tested had considerable decreases in their urine chlorides varying from 3.8 to 5.4 Gm. in twenty-four hours. Table VI lists all findings.

HYPERTENSIVES

The average age of the hypertensive toxemia patients tested was 29.3 years. No primigravidas were found in this group, and

five of the eight in the group had had previous toxemias. The average onset of symptoms was 31.8 weeks. Blood pressures were all above 140 mm. Hg systolically and 90 mm. Hg diastolically. All patients had proteinuria, but only three had edema of the ankles and legs and only two had visual, cerebral, gastro-intestinal or other symptoms. Two of the patients did not deliver viable babies. Abnormal opthamologic findings were seen in six of the eight patients - four showed spasm of the arterioles and four showed arteriosclerotic changes in the vessels either alone or in combination. Blood uric acid values were above normal in three of the seven patients tested; abnormal values were 4.6, 4.9, and 5.7 mg.%. Urine chloride values were markedly decreased in all five patients tested here, and only one of seven patients had an abnormally decreased urea clearance test.

NORMALS

The average age of the normal pregnant group was 20.5 years. Three of the seven patients were primagravidas, and none had a history of previous toxemia. All blood pressures were around 110 mm. Hg systolically and 80 mm. Hg diastolically. One patient had a trace of proteinuria, and two had edema - one and two plus respectively. All delivered viable infants, and blood uric acid levels and all urea clearance tests done were normal.

TABLE VI

PRE-ECLAMPTICS

ADDITIONAL CLINICAL AND LABORATORY FINDINGS

Name	Number	Age	Para-grav	Prev Tox	Wks onset	Blood pressure	Protein-uria	Edema	Symptoms	Preg Terminate	Weeks	IN LABOR Alive	IN LABOR Weight	PP Wt loss	PP Hemory Spasm	PP Hemor. After.	Blood Uric Ac.	Urine Chloride	Urea Clearance
D.O.	106016	18	0/1	0	37	155/100	2.75	0	0	Spn	38	+	7' 9"	23	+/0	0/0	2.95	5.4	63-94% 88-78%
I.W.	104732	19	0/1	0	32	160/100	3.9	++	+	C S	32	+	3' 0"	25	+/0	0/0			NPN 61
L.C.	104088	28	2/3	0	28	170/105	5.6	++	+	Spn	30	-	2' 5"	20	+/0	0/0			107%
J.G.	104203	18	0/1	0	32	160/100	4.8	+++	+	Ind	33	+	3' 5"	19	+/0	0/0	3.3		101%
Z.H.	106904	35	4/5	0	30	140/90	1.7	++	+	C S	34	-	7" 1"	21	0/0	0/0	2.15	4.43	
L.K.	105036	21	0/1	0	38	140/90	0.15	0	0	Spn	40	+	7' 4"	19	0/0	0/0	1.40	3.8	93-107% 207-72%
E.A.	105580	36	0/1	0	37	170/100	tr	+	0	Spn	39	+	5' 2"	9½	+/0	0/0	3.10	4.0	116-110%
I.S.	107741	17	0/1	0	36	160/110	2.7	++	+	Spn	38	+	8' 0"		0/0	0/0	4.6		86%
G.D.	105543	27	3/4	0	40	160/110	tr	0	0	Spn	40	+	7' 9"						95%
M.P.	104014	19	1/2	0	40	160/90	++	+	0	Spn	40	+			0	0			161%
B.W.	103721	18	0/1	0	36	160/100	6.4	+++	+	Spn	36	+	5' 7"		0	0			72%

TABLE VII

HYPERTENSIVES

ADDITIONAL CLINICAL AND LABORATORY FINDINGS

Name	Number	Age	P/G	Prv Tox	Wks onset	Blood press.	Proteinuria	Edema	Sympt	Preg termin	Weeks	Alive	Wt.	PP wt loss	E Spsm	Y Art	E Hem	Blood Uric A.	Urine Cl⁻	Urea Clear.
G.T.	107151	26	3/4	0	36	150/110	0.5	0	0	Ind	39	+	7' 9"	25	0	0	0	5.7	2.24	54% 92%
D.B.	107233	31	3/5	0	27	155/100	0.3	0	0	Ind	39	+	8' 15"	25	0	0	0	2.75		89% 73%
V.W.	104562	22	1/3	0	22	170/110	0.2	0	0	Spn	40	+	9' 6"	32	0	0	0	4.6	5.1	153% 92%
P.S.	104220	17	1/2	+	30	165/110	3.0	0	+	C S	31	-	3' 5"	23	±	±	0			74%
L.P.	104651	28	5/6	+	39	145/90	0.9	++	0	Spn	39	+	6' 12"		±	0	0	2.9		146%
B.S.	107382	31	2/3	+	36	160/110	0.7	tr	+	C S	36	+	6' 2"	10	±	0	0	4.9	1.45	
N.G.	106375	43	5/6	+	32	155/95	tr	+++	0	Spn	40	-	9' 8"		0	±	0	2.4	6.5	160%
M.A.	105643	36	3/7	+	32	160/95	0.3	0	0	Spn	32	+	3' 8"		0	?	0	2.15	2.0	151%

TABLE VIII

NORMALS

ADDITIONAL CLINICAL AND LABORATORY FINDINGS

Name	Number	Age	Para-Grav	Prev Tox	Weeks onset	Blood pressure	Proteinuria	Edema	Symptoms	Preg terminate	Weeks	IN FANT Alive	Wt	PP wt loss	E Hemory Arter E Spasm	Blood Uric Acid	Urine Chloride	Urea Clearance
A.H.	104681	22	2/3	0	38	110/80	0	0	0	Spn	38	+	8' 13"	20	0 0 0 0 0 0	3.7		115%
G.A.	106725	22	0/1	0	38	110/80	0	0	0	Spn	40	+	7' 5"					
A.W.	104965	20	2/3	0	40	110/80	0	++	0	Spn	40	+	6' 3"			2.15		148% 115%
G.B.	104316	24	1/2	0	38	110/80	0	0	0	Spn	38	+	7' 1"		0 0 0			
J.W.	104694	17	1/2	0	40	110/80	0	0	0	Spn	40	+	8' 3"		0 0 0	2.31		161%
M.W.	106794	20	0/1	0	40	110/80	0	+	0	Ind	40	+ +	5' 1" 5' 4"	27	0 0 0 0 0 0			
N.B.	105645	18	0/1	0	40	110/80	tr	0	0	Spn	40	+	7' 2"					

SUMMARY

Medical science for centuries has strived to understand more fully the toxemias of pregnancy. Yet, the etiology is still unknown, classifications are numerous and confusing, and attempts to determine their presence pre-clinically have been fraught with failure. Five tests which have been devised to attempt to determine the impending development of toxemias, to differentiate the toxemias, and to judge the severity of the process and prognosticate its eventual outcome have been analyzed with reference to the findings of others and the findings of my own working with a group of obstetric patients. These tests are the pituitrin test, the cold pressor test, the tetraethylammonium chloride test, the sodium amytal test, and the beta-glucuronidase test.

Only two of the tests analyzed seem to offer any possibility of usefulness in detecting impending toxemia and differentiating them. These are the pituitrin test and the cold pressor test. The pituitrin test appears to be quite specific for the determination of pre-eclampsia, and the cold pressor tests appears fairly accurate in determining essential hypertension in pregnancy (hypertensive toxemia). None of the other tests give sufficiently accurate or constant results to warrant their use.

In none of the tests was it found that the amount of response was correlated to the severity of the condition; nor,

was it felt that they could successfully prognose the outcome of the toxemias tested.

In all of the tests, except the beta-glucuronidase test, where blood pressure response is the basis, there is great possibility of variance in responses due to differences in the accuracy of the sphygmomanometers used and variability of the blood pressure of the patient herself due to such factors as apprehensiveness, relationship to meals, and position of the patient while blood pressure readings are taken. It may be considered, however, that these alterations may be relative to the real basal pressure in many cases, but in some cases the probable accuracy and reliability of the test may be completely thrown off by these factors mentioned.

Therefore, it appears that there is a great need for a test or tests that are based on more objective methods and produce more reliable results, but until such a test or tests are developed, it would appear that the pituitrin test and the cold pressor test may be of value in determining the impending presence of the toxemias and differentiating the pre-eclamptic toxemias from the essential hypertensions of pregnancy.

CONCLUSIONS

1. Five tests for the toxemias of pregnancy are discussed. These are the pituitrin test, cold pressor test, tetraethylammonium chloride test, sodium amytal test, and beta-glucuronidase test.

2. The history of the development of these tests and the methods for performing them are presented.

3. The tetraethylammonium chloride test, sodium amytal test, and beta-glucuronidase test appear to be of no value in diagnosing or differentiating the toxemias of pregnancy or in following their courses or prognosticating their outcome.

4. The pituitrin test appears to be quite accurate in determining the presence of pre-eclampsia both pre-clinically and clinically.

5. The cold pressor test appears fairly accurate in determining the presence of essential hypertension of pregnancy (hypertensive toxemia) pre-clinically and clinically.

6. There is still a great need for a more objective and more reliable test or tests to aid in diagnosing, differentiating, following the clinical course, and prognosing the outcome of the toxemias of pregnancy - pre-eclampsia and essential hypertension of pregnancy (hypertensive toxemia) in particular.

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