

LIVER FUNCTION TESTS IN THE TOXEMIAS OF PREGNANCY*

BY EDWARD LACY KING, A. B., M.D., F.A.C.S., NEW ORLEANS, LA.

(Assistant Professor of Obstetrics at Tulane University)

MANY tests have been devised for the study of the various functions of the liver, but of the many articles in the literature dealing with this subject during the past few years, only a few treat specifically of the application of these tests to the study of the toxemias of pregnancy. It will be well, therefore, to consider the work which has been done by others along this line before passing to a consideration of my results in a series of tests performed upon 24 patients suffering from these disorders of pregnancy.

One of the first investigators to employ functional liver tests in these toxemias was Walthard,¹ who published the results of his investigations in 1922. After careful and elaborate studies of the blood sugar, the storage capacity of the liver for glucose administered by vein or by mouth, the bilirubin content of the urine, and the rest nitrogen of the blood, he concludes that there is a hyperglycemia and an impairment of the storage ability of the liver in normal pregnant

*Read, by invitation, before the American Gynecological Society, May 20-22, Stockbridge, Mass.

The work herein reported was aided by a grant from the David Trautman Schwartz Research Fund of Tulane University.

women during labor, and that there is also an increase in the urobilin content of the urine. These findings, he believes, cannot be explained on the basis of excessive muscular effort during parturition, as severe exertion on the part of normal pregnant women did not produce similar results. Analogous findings, however, have been noted in diabetic women after severe exertion, and from this Walthard concludes that there is normally some impairment of liver function during labor (the so-called *Geburtsleber*), which tends to clear up rapidly during the puerperium. In eclampsia Walthard found marked disturbance of liver function, as evidenced by a considerable elevation of the blood sugar, a marked depression of the storage capacity for glucose, and an increase of the rest nitrogen of the blood. The urobilin content of the urine showed no characteristic change.

Williams,¹⁴ in 1922, reported the results obtained by employing the phenoltetrachlorphthalein test of Rosenthal in twenty pregnant women. One was in the sixth month, two were tested the first day postpartum, while the others were from seven to nine months pregnant. Fifteen of these patients were healthy, two were nephritic, while three were toxic patients with albuminuria who were evidently not nephritic. The dye was given intravenously, and the time of its first maximum appearance in the bile obtained through the duodenal tube was noted. In the normal cases this point was reached in from 16 to 24 minutes, with an average of 20 minutes. In the pathologic cases this period of time was variable, being 19 minutes in a nephritic patient with convulsions, while in the others the time was 20, 22, 25, and 28 minutes, respectively. In view of these variable results in patients in whom liver damage might reasonably be expected, the author concluded that further studies would be necessary in order to ascertain if the method has any value in such cases. It is interesting to note that in the nephritic case with convulsions, the appearance time was within the normal limits. This corresponds with case 10 of my eclamptic series (see table); this patient was really suffering from a very severe nephritic toxemia, and there was no retention of the bromsulphalein. I might also note that the duodenal tube method was soon superseded by a colorimetric method (devised by Rosenthal) of estimating the percentage of retention of the dye in the blood stream, and this latter method was employed by the authors mentioned below.

Smith² of the Boston Lying-In Hospital, employing the phenoltetrachlorphthalein test of Rosenthal, studied 20 clinically normal pregnant women and 44 pregnant women suffering from varying degrees of toxemia. In the former group he found occasional slight degrees of retention; in the latter group the test gave normal readings in 24 cases, while retention was noted in 20 instances. Of the 24 patients who reacted negatively to the test, 2 developed convulsions, one of whom died; autopsy revealed very slight liver damage. Of the 20 patients who showed retention of the dye, 5 had convulsions, while 6 of the 20 died from toxemia, operative shock, or infection (one case). Smith concludes that definitely abnormal dye retention suggests that the toxemia is severe, but that the percentage of retention does not in all cases parallel the degree of liver damage. As the severely toxic conditions will be readily recognized by clinical observation alone, it is possible that the chief value of this test in pregnancy will be as an aid in the classification of the milder toxemias.

Naujoks³ employed this test in 20 patients suffering from the various toxemias of pregnancy, and reaches practically the same conclusions as Smith. He believes also that the test should be especially valuable in deciding for or against therapeutic abortion in cases of hyperemesis gravidarum.

Krebs and Dieckmann⁴ used the Rosenthal test in a study of 37 patients with symptoms or physical signs indicative of varying degrees of the toxemia of pregnancy. They report no cases of eclampsia. Some of the patients gave normal readings and a few showed marked retention, but in the majority of instances the test indicated only moderate impairment of liver function, and the findings in the main appeared to agree fairly well with the clinical pictures presented. In two groups, however, one composed of patients with high blood pressure and no symptoms of toxemia, the other composed of patients with toxic symptoms but normal blood pressures, the test indicated dysfunction of the liver in most instances. The authors are of the opinion that such findings indicate a developing toxemia. In 6 patients who showed retention of the dye before delivery, the test 10 to 12 days postpartum was uniformly negative, while in 12 normal pregnant women it was uniformly negative. The authors feel that the test offers considerable promise in the study and management of the toxemias of pregnancy.

Rosenfield and Schneiders,⁵ working with the same dye, found normal excretion in 6 cases of uncomplicated pregnancy. In 7 cases of hyperemesis gravidarum the test corresponded with the clinical picture, and in some instances disclosed impairment of liver function before it was manifested clinically. In 9 patients suffering from hypertension, retention in varying degrees was noted. The test returned to normal in every instance in which clinical improvement was noted. The authors feel that the test is of definite value as an index to treatment, particularly when therapeutic abortion or the induction of labor is under consideration.

Couinaud and Clogne,⁶ employing the digestive hemoelasis test of Widal and the study of the excretion of glycuronic acid in the urine following the ingestion of camphor, advocate the determination of liver function by this method. Additional studies were made by them on the toxicity of the urine and on the intermittent renal elimination observed in cases of hepatic insufficiency.

Tallerman,⁷ in studying the effect of the ingestion of levulose on the blood sugar, found no evidence of liver dysfunction in normal pregnancy. In three cases of the toxemia of late pregnancy studied by this method there was but one positive reading; this patient had a severe eclamptic attack.

Hyn and Messtorff,⁸ working with the hemoelastasis test of Widal, found it to be positive in one-third of a series of healthy women in the last month of pregnancy. Didier and Phillips⁹ obtained positive readings in 35 per cent of 26 apparently healthy pregnant women, and Kobarth¹⁰ obtained a similar result in 56.2 per cent of 32 similar cases. Couinaud and Clogne also obtained positive reactions in the majority of healthy pregnant women upon whom they performed this test.

Of particular interest is the work of Berkeley, Dodds and Walker,¹¹ who studied the question of liver function tests in the toxemias of pregnancy as a guide to the induction of labor. They employed the Fouchet test for bile pigment in the blood, Ehrlich's test for urobilinogen in the urine, Schlessinger's test for urobilinuria, and Lowenhart's method of estimating the blood lipase. Control tests were made on known healthy students, as well as on patients definitely affected with various disorders of the liver. In 10 cases of albuminuria in pregnancy without toxic symptoms all tests were negative, and in no instance did a demonstrable toxemia develop. In 17 pregnant women with albuminuria and symptoms of toxemia the tests were likewise negative; the patients were allowed to proceed to term without induction of labor, and in no instance did eclampsia develop. Seven patients with albuminuria and definitely toxic symptoms reacted positively to all tests, and of these seven, four developed eclampsia before pregnancy could be terminated. I might add here that I have employed these tests (with the exception of the blood lipase estimation) in several cases of toxemia of late pregnancy, as will be detailed later, and I have failed to duplicate the results of these authors. One hesitates to differ with Comyns

TABLE I
LIVER FUNCTION TESTS—ECLAMPSIA

AGE	PARITY	MAXIMUM BLOOD PRESSURE	N. P. N.	CREATININE	URIC ACID	P. S. P.	VAN DEN BERGH	BROMSULPH.	EHRlich	FOUCHET	SCHLES-SINGER	REMARKS
24	1	180	34	1.4	3	33%	Neg.	40%. Trace 2 days P.P.	—	—	—	Severe case. Child dead in utero on admission
19	1	160	37	2	5	—	Neg.	Trace	Neg.	Neg.	Neg.	Mild, postpartum type, 4 convulsions. Child stillborn prior to admission
34	1	210	Max. 75	Max. 3.53	Max. 8	—	—	5% 3 days P.P.	—	—	—	Very toxic, probably nephritic, 2 convulsions. Child stillborn. 2¾ lbs.
17	1	160	30	1.5	5.3	—	Neg.	Neg.	—	—	—	Mild, postpartum type. Developed puerperal psychosis. Child born before admission.
20	1	200	Max. 75	Max. 3.11	Max. 11.4	—	—	35%. 10% 8 days P.P.	—	—	—	Extremely toxic, hyperpyrexia, anuria. Child dead in utero on admission. 15 convulsions, coma
16	1	150	30	1.2	4.5	40%	—	Neg.	Neg.	Neg.	Neg.	Mild case, 8 convulsions, child lived
19	1	165	30	1.2	5	40%	—	7.5%	Neg.	Neg.	Neg.	Mild case, 10 convulsions, child lived
21	1	155	38	2.1	5	40%	—	5. %	Neg.	Neg.	Neg.	Mild case, 3 convulsions, child lived
17	1	160	39	3	2.5	35%	—	25 %	Neg.	Neg.	Neg.	Mild case, 9 convulsions, child lived
23	1	168	Max. 264	Max. 6	Max. 8	0%	Neg.	Neg.				Probably nephritic, 16 convulsions, died of bronchopneumonia

TABLE II
LIVER FUNCTION TESTS—TOXEMIA WITHOUT CONVULSIONS

AGE	PARITY	MAXIMUM BLOOD PRESSURE	N. P. N.	CREATININE	URIC ACID	P. S. P.	VAN DEN BERGH	BROMSULPH.	EHRlich	FOUCHET	SCHLES-SINGER	REMARKS
35	7	190	30	.8	5	—	Neg.	25%, later 0%	—	—	—	Bag induction. Child lived. 5 lbs. 3 oz.
39	7	165	30	1.5	4	50%	Neg.	Neg.	Neg.	Pos.	Neg.	Labor induced by Watson's method. Full term, child lived
28	3	200	37	2	5	37%	—	Neg.	Neg.	Neg.	—	Premature separation of placenta, death of child in first stage of labor
34	3	142	26	1.1	3	60%	—	Neg.	Neg.	Neg.	Neg.	Mild case; improving. Not yet delivered
30	7	240	35	2	4	30%	Neg.	40% before delivery; 20% 2 days P.P. Trace 10 days P.P.	—	—	—	Bag induction. Stillborn twins, first anencephalic; second hydrocephalic with spina bifida
20	1	175	37.5	1.2	4	48%	Neg.	Neg. twice before delivery	—	—	—	Bag induction. Child lived
26	3	190	57	2	6.1	20% twice	Direct delayed Indirect 4 units	Neg. error?	—	—	—	Chronic nephritis and myocarditis. Induction by catheter and pituitrin. Child died 1 hr. after birth
34	6	200	30	1.2	2.5	40%	—	Neg.	Neg.	Neg.	—	Full term, induction of labor. Child lived
23	6	190	37	2	4	35%	—	15%	Neg.	Pos.	Neg.	Induction of labor. Twins; first child macerated, second lived
40	7	170	92.1	2.6	7.24	5%	—	—	Neg.	Neg.	—	Chronic nephritis. Premature separation of placenta. Child dead in utero on admission.

Berkeley, and it may be that further work will supply an explanation for my negative findings, but at present I can only record my results.

In this investigation I have employed the bromsulphalein test of Rosenthal and White,¹² the Van den Bergh and Fouchet tests on the blood serum, and the Ehrlich and Schlessinger tests on the urine. The Van den Bergh tests were performed by Dr. T. A. Tumbleson of the Department of Medicine of Tulane University, to whom my thanks are due for his cooperation. The study includes eleven cases of toxemia without convulsions, ten of eclampsia, and three of severe vomiting of pregnancy. A detailed consideration of the results may be of interest.

Bromsulphalein (phenoltetrabromphthalein sodium sulphionate) was introduced in 1925 by Rosenthal and White,¹² who claim that this dye has none of the disadvantages of phenoltetrachlorphthalein, which was previously popularized by the work of Rosenthal, who simplified and perfected the technic of its employment. Instead of the three readings necessary with phenoltetrachlorphthalein, only one is required when the new dye is used. Five milligrams per kilogram of body weight are injected intravenously; a blood sample is withdrawn at the end of half an hour, and the dye content of the serum is estimated with the aid of a special colorimeter. In patients with no pathologic changes in the liver no dye should be found at the expiration of this interval of time; if retention of the dye is disclosed by the test, the authors claim that the percentage of the retention parallels the degree of liver injury.

I found that this test, when employed in cases of toxemia without convulsions, was negative in the milder types, as well as in those patients whose toxemia was nephritic rather than preeclamptic in origin. It was positive in 4 cases, and in another instance a possible error in technic may have affected the result, though the negative reading might have been expected, as the patient apparently belonged in the nephritic group. One patient gave a reading of 25 per cent the day following delivery (labor had been induced by a bag), but a week later the test was negative. The second patient who reacted positively was very ill, and most probably belonged in the preeclamptic group, as evidenced by a nonprotein nitrogen reading of 35.1 and a systolic blood pressure of 240. In this instance the first reading, the day before delivery, showed a 40 per cent retention of the dye; the second test the following day gave a reading of 20 per cent; eight days postpartum there was still a slight retention, and it was not until the seventeenth day that the test was negative. In both these patients the test indicated severe liver damage, especially in the second case, and the findings coincided with the clinical pictures. The two other patients who reacted positively gave readings of 15 per cent and 25 per cent, respectively. The first was not very toxic, but

the second had a systolic blood pressure of 190, and there was considerable albumin and acetone in the urine. The test was not repeated in either case.

In the ten cases of eclampsia the test was negative in only three instances. One of these patients was suffering from a toxemia of a very mild type; in another patient with postpartal eclampsia the results were vitiated by an error in technic. In the third case there is no doubt that we were dealing with chronic nephritis complicated by convulsions. The phenolsulphonaphthalein test was zero on two occasions, and the nonprotein nitrogen was 264 the day before death, which occurred six days after admission. This patient was the only one in the series who died, and the immediate cause of death was bronchopneumonia; the toxemia had been markedly improved.

The seven other cases gave readings varying from a trace to 25 per cent retention, and in every instance the percentage of retention agreed fairly well with the clinical findings and the laboratory data. In the three cases of hyperemesis gravidarum the bromsulphalein test gave positive results, varying from 10 to 25 per cent retention. Clinical improvement was apparently associated with lower readings, but definite conclusions cannot be drawn from so small a number of cases.

The Van den Bergh test¹³ is based upon Ehrlich's diazo reaction and is both qualitative and quantitative. It also distinguishes between bilirubinemia due to obstruction of the biliary passages and that caused by increased destruction of the red cells by hemolysis. The standard matches a dilution of 5 mg. bilirubin per liter of blood volume. This is the unit of comparison. Normally there is found 1 to 3 mg. of bilirubin to the liter of blood, so that the normal reading is 0.2 to 0.6 units. In this study this test was found to be uniformly negative in the nonconvulsive toxemias, and in eclampsia as well, even though in many instances the blood was withdrawn immediately after admission, in the intervals between convulsions. In one patient in the nonconvulsive type, it is true, the test showed a mild grade of bilirubinemia of the nonobstructive type (2 units), but this patient presented a complicated clinical picture of chronic nephritis and chronic myocarditis, with increased fragility of the red cells, the cause of which could not be determined. On the other hand, the Van den Bergh test was positive in all three cases of hyperemesis gravidarum, and the readings paralleled the clinical findings.

Fouchet has devised a test for bilirubin in the blood serum, which is much simpler than the Van den Bergh test, although not so delicate. It detects bilirubin in a dilution of 1 to 60,000. Three drops of the serum are mixed on a white porcelain surface with three drops of the reagent (20 c.c. of water, 2 c.c. of a 10 per cent solution of ferric chloride, 5 gm. trichloroacetic acid). A white coagulum is formed, which, if the reaction is positive, turns a greenish yellow, reaching

6. The dye tests, as well as the studies on the blood sugar and on the storage and mobilization of glucose and levulose, indicate that in the toxemias peculiar to pregnancy there is definite impairment of the liver function.

REFERENCES

- ¹Walshard: Arch. f. Gynäk., 1921-22, cxvi, 68-97; Zentralbl. f. Gynäk., August 12, 1922, xlvi, 1301-1303.
- ²Smith: AM. JOUR. OBST. AND GYNEC., September, 1924, viii, 298.
- ³Naujoks: Zentralbl. f. Gynäk., 1925, xlix, 2755.
- ⁴Krebs and Dieckmann: AM. JOUR. OBST. AND GYNEC., January, 1924, vii, 89.
- ⁵Rosenfield and Schneiders: Jour. Am. Med. Assn., March 17, 1923, lxxx, 743.
- ⁶Couinaud and Clogne: Gynec. et Obst., May, 1923, viii, 372-387.
- ⁷Tallermann: Quart. Jour. Med., October, 1923, xvii, 37.
- ⁸Hyn and Messtorf: Klin. Wchuschr., June 11, 1923, ii, 1114.
- ⁹Didier and Phillips: Presse Med., June 15, 1921, xxix, 473.
- ¹⁰Kobarth: Zentralbl. f. Gynäk., Nov. 25, 1922, xlvi, 1883.
- ¹¹Berkeley, Dodds, and Walker: Jour. Obst. and Gynec., British Empire, Spring, 1924, xxxi, 1.
- ¹²Rosenthal and White: Jour. Am. Med. Assn., April 11, 1925, lxxxiv, 1112.
- ¹³Van den Bergh: Presse Med., June 4, 1921, xlv, 441.
- ¹⁴Williams, P. F.: AM. JOUR. OBST. AND GYNEC., July, 1924, iv, 26-30.

MAISON BLANCHE BUILDING.