HEPATIC FUNCTION TESTS IN TOXAEMIAS OF PREGNANCY
THYMOL TURBIDITY TEST

BY

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The thymol turbidity test, first described by MacLagan (1944-1944a) is recognised as a test for damage to the hepatic parenchyma. According to the author himself, it "does not test any known function of the liver and should be regarded as an indication of disturbed liver metabolism rather than a function test". Recent study by Franklin, Popper, Steigmann and Kozoll (1948) indicates the presence of a relationship between histological liver damage and the results of the thymol turbidity test. The test itself is allied to the colloidal gold reaction (MacLagan, 1944a) and the cephalin-cholesterol flocculation test (Saifer, 1948).

Method.

For the purposes of the present investigation MacLagan's original method was employed, in which the serum turbidity produced by a thymol buffer is compared with standard turbidity comparators and the results expressed in units. As far as can be ascertained no systematic investigations have been carried out on thymol turbidity in either normal pregnancy or toxaemia. The results are presented below.

1. Normal Pregnancy.

Seventy-two cases of normal pregnancy at different periods of gestation attending the antenatal clinic were selected for this study. The thymol turbidity test was uniformly negative (less than 4 units) in all cases. The density of the turbidity, however, appears to increase as pregnancy advances to term. Values were uniformly low in early pregnancy. Upto the middle of gestation the maxium turbidity was 1.3 units (one case). At term, however, values up to 2.1 units were observed. The average turbidity for the whole series was 1.22 units $\pm$ 0.39, and that at term was 1.54 $\pm$ 0.28. The difference between these two values is not of much statistical significance.

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TABLE I.

Thymol Turbidity Test at Different Periods of Gestation in Normal Pregnancy

Duration of pregnancy (months)	No. of cases	Thymol turbidity (Units)	Average	Standard Deviation
3	6	1.0; 0.8; 0.6; 0.75; 1.1; 0.8.	0.82	0.17
4	8	1.1; 1.0; 0.9; 0.8; 0.75; 0.7; 0.65; 0.80.	0.82	0.15
5	7	1.3; 1.1; 0.6; 1.0; 1.0; 0.7; 0.6.	0.86	0.25
6	7	1.0; 1.0; 1.1; 0.8; 0.9; 0.7; 0.7.	0.88	0.13
7	8	0.9; 1.3; 1.4; 1.0; 1.8; 1.0; 1.2; 1.2.	1.12	0.21
8	12	1.0; 1.3; 1.2; 1.0; 0.9; 1.0; 1.3; 1.2; 1.0; 1.0; 1.3; 1.4.	1.14	0.15
9	12	1.2; 1.6; 1.4; 1.7; 1.8; 1.5; 1.6; 1.7; 1.9; 1.8; 1.8; 1.9.	1.66	0.19
10	12	1.4; 1.8; 2.0; 1.8; 1.9; 1.8; 2.1; 2.0; 1.7; 1.6; 1.9; 1.8.	1.81	0.17
Average	72	0.6—2.1	1.22	0.52
Average last 3 months	36	0.9—2.1	1.54	0.38

2. Pre-eclamptic.

The thymol turbidity test was, on an average, negative in pre-eclamptic patients. The turbidity was only 2.07 units ± 0.63, i.e. just over 50 per cent of the maximum allowed for normal individuals. Nevertheless, compared with normal pregnancy the increase in turbidity in toxaemias is 26.4 per cent. Individual values were scattered between wide limits (0.3 to 4.5). The thymol turbidity in 50 cases of mild pre-eclampsia varied from 0.3 to 2.5 units with an average of 1.19 ± 0.36. This is actually a little less than the average for the last trimester of normal pregnancy. Cases of severe pre-eclampsia had a slightly higher thymol turbidity. The average was 2.95 ± 0.536 units; and the range was from 1.0 to 4.5 units. A positive result was obtained in only 2 cases (4 per cent). The frequency distribution is shown in Table II.

TABLE II.

Frequency Distribution of Thymol Turbidity in Pre-Eclampsia

Frequency units	Normal	Mild pre-eclampsia	Severe pre-eclampsia	Total
0 — 1.0	6	26	2	28
1.1 — 2.0	29	21	11	33
2.1 — 3.0	1	3	19	22
3.1 — 4.0	..	..	13	13
4.1 — 5.0	..	..	2	2
Average	1.54	1.19	2.95	2.07
P. E.	0.38	0.55	0.80	0.95

Although the figures do not exceed the maximum limit of normal in 98 per cent of all cases of toxaemia, the distribution frequency clearly demonstrates that there is an increasing number of higher values when toxaemia becomes severe. However, in the two patients where the test was positive the turbidity was only slightly more than the normal maximum (4.2 and 4.5 units respectively). One of them was jaundiced at the time the test was done.

It is interesting to note, however, that during the three weeks following her admission into hospital the toxaemia deteriorated although the jaundice showed some apparent improvement. Because of the bad state of her toxaemia, labour was induced and at this time the serum turbidity increased to 5.1 units. In the other patient the toxaemia improved during the treatment and the turbidity decreased to 3.5 units. It is interesting to note that on the fifth day after confinement the thymol turbidity in both cases was found to be 0.2 units.

Clinical Course of Toxaemia.

The clinical course of toxaemia appeared to affect the values in a manner similar to that observed with other hepatic function tests. Abnormal values were observed in a small number of cases only when the disease had attained marked severity. The results are presented in Table III.

TABLE III

Thymol Turbidity in Pre-eclampsia; Relation between Thymol Turbidity and the Clinical Course of Toxaemia.

Weeks	IMPROVED			DETERIORATED		
	Average	Standard deviation	Minimum Maximum	Average	Standard deviation	Maximum Minimum
1	1.89	1.05	0.3 — 4.2	2.33	1.06	0.7 — 4.5
2	1.73	1.00	0.3 — 4.3	2.49	1.18	0.8 — 4.9
3	1.64	0.99	0.3 — 4.0	2.49	1.37	0.8 — 5.1
4	1.45	0.87	0.3 — 3.0	3.75	0.88	3 — 4.7

One patient in each group had a value of more than 4 units at the time of admission. The position remained unaltered during the second week. But when improvement occurred, during the third and fourth weeks abnormal values were no longer observed. The case where the thymol turbidity was 4.3 units during the second week was a case of toxaemia with jaundice. The jaundice persisted during this investigation. When her condition showed almost complete return to normal the thymol turbidity was 2.6 units.

As the toxaemia deteriorated the incidence of abnormal values increased in each successive week. During the four weeks of study the percentage of cases with abnormal thymol turbidity was 1.96, 10.6, 31.2, and 68.5 per cent respectively. A better understanding of the behaviour of thymol turbidity is possible where this is studied in relation to the duration of toxaemia from the time of its onset. The results obtained from such an analysis are submitted in Table IV.

TABLE IV

Thymol Turbidity in Relation to the Duration of Toxaemia.

Duration of toxaemia, weeks	1	2	3	4	5
Min.-Max.	0.7 - 3.6	0.8 - 4.0	1.0 - 4.9	1.0 - 4.8	2.1 - 5.1
Average ..	1.99	2.29	2.65	2.80	3.94
Standard deviation	0.90	0.92	0.99	1.19	0.81

These figures demonstrate that, upto the second week of toxaemia, values higher than maximum normal did not occur. Subsequently, the number of abnormal values increased progressively as the toxaemia persisted or became worse. The incidence of abnormal values in the third, fourth and fifth weeks of toxaemia was 10.5, 48.6 and 79.0 per cent respectively. This is the cause of the progressive increase of the average values in each group. A study of the range of disturbance and of the standard deviation shows the gradual shift of the values to the right throughout this period, the lower values being gradually elevated, while the maximum moves only slightly. Grossly abnormal values from a quantitative point of view were not observed in pre-eclampsia. The change appears to be more of a qualitative nature and is revealed only when the cases are followed during successive weeks of toxaemia.

Blood Pressure and Thymol Turbidity.

When the systolic blood pressure reaches the hypertensive level the thymol turbidity also shows some increase. The average values, however, seldom exceed the limit of normality. Individual abnormal values appear to be scattered in each blood-pressure group above 170 mm. Hg. Below this level, however, the maximum values were below the maximum normal standard although considerably higher than the maximum observed in normal pregnancy. No definite correlation could be found between the levels of systolic blood pressure in pre-eclampsia and thymol turbidity. For this reason the details of the values are not presented.

A study of the diastolic pressure seems to show a slightly closer relationship with thymol turbidity.

TABLE V

Thymol Turbidity in Pre-eclampsia, in Relation to Diastolic Blood Pressure.

B. P. mm. Hg.	Average	Standard deviation	Minimum Maximum	B. P. mm. Hg.	Average	Standard deviation	Minimum Maximum
Less than 90	1.79	0.85	0.5 - 2.3	106 to 110	2.54	1.06	1.5 - 4.7
91 to 95	2.37	0.64	1.5 - 3.4	111 to 115	3.85	0.27	3.5 - 4.3
96 to 100	2.15	0.81	1.0 - 4.2	116 to 120	3.99	0.90	1.51- 5.1
101 to 105	2.70	0.51	2.6 - 3.5				

As in the case of systolic blood pressure, the average shows some fluctuation at the lower ranges of diastolic hypertension, but these variations are small and reveal a general tendency to an increase. At higher levels of diastolic pressure (110 mm. Hg. or more) these variations almost disappear. The first abnormal value in this series (4.2 units) was noticed in a patient with a diastolic pressure of 100 mm. Hg. A consistent increase in thymol turbidity was observed when the diastolic blood pressure exceeded 110 at each stage above this level the incidence of abnormal values increased (14.6, 48.6 and 86.1 per cent respectively) steadily. However, the statistical significance of these values is variable.

sions. One of these patients presented a particularly interesting feature. She was admitted with a history of one convulsion and in a semicomatose state with a blood pressure of 180/110 mm. Hg., and 13 parts (Esbach) albumin in the urine. At this stage the serum thymol turbidity was 3.7 units. She remained in a semi-comatose state for 3 days when the test was repeated and the thymol turbidity was found to be raised to 9.7 units. This case had a fatal outcome.

The lowest thymol turbidity in the series of eclampsias was 1.8 units in a patient whose blood was examined after 3 convulsions. This patient was comatose for less than an hour and made a spontaneous recovery. It may be of interest to mention that she was

TABLE VI

Thymol Turbidity in Eclampsia.

	Pre-convul-stage	Convulsive stage		Post-Convulsive Stage					
		1	2	1	2	5	12	22	days
Min	2.4	1.8	5.7	3.0	2.6	1.3	1.1	1.0	
—	—	—	—	—	—	—	—	—	
Max.	4.4	7.5	9.7	5.0	4.8	3.6	3.0	2.0	
Average	2.8	4.35	7.26	4.17	3.33	2.40	2.10	1.47	
Standard Deviation	0.61	1.01	1.41	1.07	0.83	0.94	0.88	0.39	

.3 *Eclampsia.*

The average thymol turbidity in eclampsia was 4.35 units ± 0.92. Individual values were found between 1.8 and 7.5 units. Thirty-nine per cent (7 out of 18 cases) of patients in this series had less than the maximum normal value in spite of convul-

a subject of essential hypertension before pregnancy occurred. Two other patients, one with 3 and another with 4 convulsions, showed only 2.8 and 2.7 units of serum thymol turbidity. In general, the number of convulsions, *per se*, do not seem to have a consistent effect on the level of thymol tur-

bidity. Of the three patients who were under investigation before the onset of eclampsia, one showed no change in thymol turbidity (2.8 units) after the occurrence of eclamptic convulsions. Another patient showed an actual decrease (from 3.6 to 3.3 units). In only one case was there an increase of thymol turbidity from 2.4 to 4.4 then to 5.7 units. Nevertheless, when the series is taken as a whole, it is found that repeated convulsions tend to raise the thymol turbidity to abnormal levels. In 3 patients who had a fatal outcome the thymol turbidity values were 10.1 to 10.5 and 9.7 units 7 to 21 hours before death.

However, the changes in the liver function, which are responsible for high thymol turbidity values in eclampsia, appear to be of short duration, for the values were found to return to normal in most of the cases within 48 hours after the cessation of convulsions. The results of the follow-up study presented in Table VI demonstrate the changes caused by eclampsia.

The persistence of the convulsive stage seems to affect the thymol turbidity more than the mere onset of the eclamptic convulsions. In 9 patients in the series the convulsive stage was prolonged for more than 24 hours, and in each patient the value obtained was higher than normal. In spite of this, 24 hours after the cessation of convulsions, in one-third of the patients in this series normal values were obtained. After a further 24 hours, only 16.6 per cent of the values were above 4 units. By the latter part of the first week the values returned to normal in all cases.

Discussion.

The results of thymol turbidity in normal pregnancy are uniformly negative. MacLagan (1944a) studied the results of this test in 12 cases of normal pregnancy and arrived at the same conclusion. The mechanism of a positive thymol turbidity reaction is not yet clearly understood, but from comparative studies (MacLagan, 1944a; Kobat, Hauger, Moore and Ladow, 1943; Salfer, 1948) with colloidal gold and cephalin-cholesterol flocculation tests, it appears that the turbidity depends mainly upon gamma globulin. Gray and Barron (1943) and several other investigators have pointed out that infective hepatitis and cirrhosis, conditions which cause organic and functional damage of the liver, are associated with an increase in plasma globulin, and it is usually these cases which give the most strongly positive results. From this point of view, normal pregnancy does not appear to be associated with a gross metabolic change. There is one obvious difficulty in interpreting the results of this test as an evidence of hepatic dysfunction. There is no absolute proof that the protein responsible is actually produced by the liver; a possible origin in the reticulo-endothelial system must be considered, and it appears that diseases of the reticulo-endothelial system, e.g. glandular fever and lymphogranuloma, also give a positive result to this test. The significance of this lies in the fact that there is some evidence of abnormal formation of globulin in pregnancy toxaemias (personal observation). Nevertheless, the incidence of positive results in pre-eclampsia is

low. In 304 estimations only 17 positive results were obtained (5.6 per cent). However, from these frankly abnormal values obtained at the time of admission, the follow-up study in pre-eclampsia reveals that with the progress of the disease the density of the thymol turbidity tends to increase. These facts suggest that the process of toxaemia imposes a continuous strain on the liver and probably reduces its reserve capacity. Abnormally high values are obtained only when this reserve is exhausted. It is possible that this is dependent upon the degree of vascular spasm (indicated by the level of diastolic blood pressure) which accompanies toxaemia.

The incidence of positive results in eclampsia (on admission) was much higher than that in pre-eclampsia (39.0 per cent). If, however, all the values obtained during the stages of convulsions and coma are considered the incidence of positive results increases to 71.5 per cent. The nature of the change in thymol turbidity revealed by the follow-up study in both the fatal and surviving cases suggest that eclampsia is usually attended by marked disturbance of liver function. The results seem in conformity with those already described.

Conclusions.

The results of the thymol turbidity test in normal pregnancy are uniformly negative. In toxaemia of pregnancy turbidity is found to increase when compared with that in normal gestation. But abnormal values are obtained in cases of toxaemia only when the disease is of long duration and of marked severity. The incidence of positive results is higher in eclampsia than in pre-eclampsia. The results obtained from this test indicate that there is no gross hepatic damage except in a few cases of severe pre-eclampsia and eclampsia, but they also indicate that there is a progressive decrease in the functional reserve of that organ when the disease persists or increases in severity.

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