GALACTOSE TOLERANCE IN NORMAL AND TOXAEMIC PREGNANCY

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Galactose tolerance test for determining the functional efficiency of the liver has been performed in several different ways. They can be briefly summarised as follows:—

1. Oral galactose, followed by blood-sugar determination (Beaumont and Dodds, 1931).

2. Oral galactose, followed by estimation of urinary sugar (Shay, Schloss and Rodis, 1931).

3. Forced galactosuria after graded test meals of galactose (Rowe, McManus and Rielly, 1935).

4. Oral galactose, followed by determination of blood-galactose (Althausen and Wever, 1937; MacLagan, 1940).

5. Intravenous galactose, followed by estimation of blood-galactose (King, 1940).

Each method has its advantages, provided due consideration is given to conditions which modify or interfere with the results. For the purpose of the present investigation we employed the method described by MacLagan (1940), and expressed the results as a galactose index (G.I.). MacLagan suggested the use of this term as the sum of the four blood-galactose values obtained at ½, 1, 1½ and 2 hours. (mg. per 100 ml.) after the ingestion of 40 gms. of galactose dissolved in 250 ml. of water. The test was performed in each instance on an empty stomach and after a period of over-night fast. In a small number of cases forced galactosuria (Rowe et al, 1935) test was also employed.

Galactose Index

Normal Pregnancy. Galactose index was determined in 10 cases of normal pregnancy between 36 weeks of gestation and term. The average galactose index in this series was 81.86+13.20. The minimum value was 63.7, and the maximum 128.0. MacLagan (1940) gives 68 as the average value for normal persons. According to this standard 9 out of 10 cases of normal pregnancy had more than normal galactose index. In none of these patients, however, did it exceed the normal maximum. The values obtained in our cases of normal pregnancy are given below.

1. M.	1 Gravida	36 weeks	Galactose	Index	69.7
2. S.	1 „	38 „	„		85.5
3. McN.	2 „	37 „	„		63.7
4. H.	6 „	40 „	„		71.6
5. A.	1 „	39 „	„		128.0
6. McD.	4 „	40 „	„		76.4
7. G.	3 „	36 „	„		86.9
8. C.	1 „	39 „	„		80.5
9. McL.	2 „	38 „	„		85.4
10. P.	1 „	40 „	„		70.9

Pre-eclampsia. Galactose index was determined in 38 cases of pre-eclampsia. There was considerable variation of the values obtained in individual cases. The mild and severe toxaemias will therefore be considered separately.

Mild Pre-eclampsia. This series consists of 13 cases. The average galactose index was 105.66 ± 12.77. The minimum and maximum values were 69.1 and 136.9 respectively. In all cases the value exceeded the normal average (MacLagan, 1940), but in none was this more than the normal maximum. In 10 cases (77%) the galactose index was more than the average for normal pregnancy, but in only one patient it was more than the highest value found in normal gestation.

Severe Pre-eclampsia. Galactose index was determined in 25 cases of severe pre-eclampsia (Blood pressure more than 150/100 mm. Hg.). The minimum galactose index in this series was 100.6, and the maximum 214.6. The average value was 166.5 ± 19.76. In all cases of severe toxaemia the galactose index exceeded the average for normal pregnancy. In 11 cases (44%) it was higher than the maximum observed by MacLagan (1940) in normal persons, and in 16 cases (64%) it was above the maximum found by us in normal pregnancy.

The increase of galactose index which occurs in both mild and severe pre-eclampsia has been found to be statistically significant when compared with the values obtained in normal gestation. The difference in the galactose index between mild and severe toxaemia also shows statistical significance. In order to provide comparison, the frequency distribution of the data obtained in normal pregnancy and pre-eclampsia are shown in Table 1.

TABLE I

Frequency Distribution of Galatose Index in Normal and Toxaemic Pregnancy.

Frequency Galactose Index	Norm. Preg.	Mild Pre-ec.	Severe Pre-ec.
61-80	5 (50%)	3 (23.1%)	0
81-100	4 (40%)	5 (38.5%)	0
101-120	0	4 (30.7%)	2 (8%)
121-140	1 (10%)	1 (7.7%)	2 (8%)
141-160	0	0	6 (24%)
161-180	0	0	5 (20%)
181-200	0	0	7 (28%)
201-220	0	0	3 (12%)

The figures indicate a gradual change in the galactose index from normal pregnancy to severe toxaemia. The distribution of values in the latter condition is in striking contrast to that of either of the other two groups of cases. The shift of the

values to the right is evident even in mild pre-eclampsia, although this is hardly note-worthy, compared with the results obtained in severe pre-eclampsia.

Galactose Index and the Clinical Course of Toxaemia. Of the 38 cases of pre-eclampsia studied in this series, 11 were cured and in 27 patients the toxaemia either persisted or became worse. The results of a weekly follow-up in these two groups of cases are shown in Table 2.

TABLE II

Galactose Index in Relation to the Clinical Course of Toxaemia (38 cases of Pre-eclampsia)

	Improved (11 cases)			Deteriorated (27 cases)		
Weeks:	I	II	III	I	II	III
Minimum	71.8	72.1	80.7	69.1	89.4	91.6
Maximum	190.7	148.6	121.0	214.6	248.7	238.0
Average	132.2	115.2	105.8	145.4	167.5	188.1
Stand. Dev.	19.9	16.3	16.8	20.5	17.9	19.6

The average values for the galactose index follow the clinical course of the disease. During the course of the study clinical improvement was accompanied by a 20 per cent decrease in the galactose index, while deterioration of the toxaemia was associated with an increase in the value which was 11 per cent more than that obtained at the time of admission. This change in the galactose index in both series of cases appears to be statistically significant. Individual values in each group, and at each period of investigation, however, showed considerable variation. The rate of improvement or deterioration of the galactose index also was not uniform.

Galactose Index and Blood Pressure. The most important manifestation of toxaemia of pregnancy is hypertension. So, galactose index obtained from 113 tests performed on 38 cases of pre-eclampsia were studied in relation to the level of blood pressure at the time of the experiments. The results are shown in Table 3.

TABLE III

Galactose Index in Pre-eclampsia in Relation to Different Levels of Systolic and Diastolic Blood Pressure.

Syst. B.P. mm. Hg.	Galactose Index	Syst. B.P. mm. Hg.	Galactose Index	Dia. B.P. mm. Hg.	Galactose Index
150 or less	111.9 ± 10.7	181—185	201.8 ± 12.7	90 or less	108.1 ± 11.7
151—155	133.1 ± 16.1	186—190	222.8 ± 14.7	91—95	117.0 ± 7.6
156—160	144.6 ± 11.6	191—195	178.0	96—100	121.8 ± 15.5
161—165	188.6 ± 9.7	196—200	185.1 ± 10.8	101—105	163.5 ± 12.6
166—170	186.2 ± 17.5			106—110	178.8 ± 7.0
171—175	190.2 ± 11.4			111—115	200.1 ± 6.5
176—180	193.9 ± 10.3			116-120	220.7 ± 5.9

It is evident that in toxaemia of pregnancy the galactose index varies in a direct manner with the blood pressure. The changes in relation to the systolic blood pressure, however, are neither consistent nor uniformly significant at all stages. Increase of the diastolic pressure causes a progressive rise in the value of the galactose index. Nevertheless, it is only slight and below the normal maximum (160-MacLagan, 1940) until the pressure exceeds 100 mm. Hg. Above this level the increase in galactose index is steady and marked, and definitely beyond the range of normal values.

Eclampsia. For obvious reasons the galactose tolerance test employed by us in pre-eclampsia was not suitable for eclamptic patients during the stage of active convulsions and coma. The test was performed on 7 cases of eclampsia as soon as sufficient consciousness was regained. The average galactose index in these cases was 200 $\pm$ 14.67, with a range of values between 166.9 and 224.3. Thus, apart from the fact that in all cases of eclampsia the galactose index was abnormal, it is evident that the extent of the increase in value (25% above normal maximum) is much higher than that observed in even severe pre-eclampsia. In only one patient in our series the galactose index in the pre-eclamptic state was known. This was 158.6 and 160.4 eight and three days respectively, before the onset of eclampsia. The patient had one convulsion, and nine hours later the galactose index was found to be 183.6. This is 14.5 per cent above the highest value obtained during the pre-eclamptic state. In all patients in this series the test was repeated on the tenth day of convalescence. The galactose index at this stage was 74.8 $\pm$ 15.27, maximum 104.6, and minimum 50.7. These figures scarcely vary from the normal values given by MacLagan (1940).

Forced Galactosuria

After a period of overnight fast, each patient was given a graded test meal (Rowe et al, 1935) of galactose dissolved in 150 to 250 ml. of water. Just before the test the bladder was emptied, and then urine was collected at hourly intervals for 5 hours after the administration of galactose. Each sample of urine was tested qualitatively for galactose, and a positive result was recorded only when a definite reducing reaction was obtained. For every test adequate controls with urine (obtained before the test), yeast (used for fermentation), standard galactose solution, and a mixture of galactose and yeast were put up.

The dose of galactose employed was from 15 to 40 gms., increasing by 5 gms. at each stage. Thirty cases of normal pregnancy between 36 weeks and term were tested in order to obtain normal values. Fifty cases of pre-eclampsia of varying severity and 10 cases of eclampsia were used for this experimental study with a view to determine the incidence of forced galactosuria in pregnancy toxaemia. The results obtained are shown in Table 4.

TABLE IV

Galactose Tolerance in Normal Pregnancy and Pregnancy Toxaemias. The Incidence of Galactosuria after Graded test Meals of Galactose.

Galactose Test-meal Gms.	Norm. Preg. 30 cases.		Pre-eclamp. 50 cases		Eclampsia 10 cases	
	No. of cases (Galactosuria)					
	+	—	+	—	+	—
15	0	30	3	47	6	4
20	0	30	14	36	10	0
25	4	26	31	10	—	—
30	9	21	50	0	—	—
35	21	9	50	0	—	—
40	30	0	—	—	—	—

It will be evident that, while 20 gms. of galactose failed to give rise to galactosuria in any case of normal pregnancy, 40 gms. produced a positive result in all of them.

The limit of tolerance in normal pregnancy appears to be 30 gms. of galactose, for above this level 70 per cent of the patients had galactosuria. This indicates that pregnancy reduces the tolerance for galactose in an otherwise normal person.

The reduced tolerance is even more marked in pre-eclampsia. Twenty-eight per cent of the pre-eclamptics had an overflow in the urine after an ingestion of 20 gms. of galactose. With 30 gms. galactosuria occurred in all cases of pre-eclampsia. The limit of tolerance in pre-eclampsia is about 10 gms. less than that in normal pregnancy. It is of interest to note that 14 out of 19 cases of pre-eclampsia where the tolerance was more than 20 gms. were suffering from a mild toxaemia. Eclampsia causes a further decrease in the tolerance for galactose. The limit appears to be less than 15 gms., which caused galactosuria in more than half the total number of cases in this series.

Discussion.

The results of galactose tolerance test in normal pregnancy reveal only a slight decrease in the tolerance for this sugar. The galactose index in normal pregnancy does not appear to be grossly different from the values obtained by MacLagan (1940) in normal "controls". The average value in normal pregnancy is slightly higher than that in non-pregnant persons (MacLagan, 1940), but the statistical significance of this difference is slight. The results of forced galactosuria are more striking. Dietel (1936) observed that 14 per cent of normal pregnant women developed galactosuria after the ingestion of 20 gms. of galactose. Rowe, McManus and Plummer (1936) found that the limit of galactose tolerance at term

was between 20 and 30 gms. The results of the present investigation are in close agreement with this finding. This reduced galactose tolerance in normal pregnancy does not appear to be due to a disturbance of the hepatic function. Alkaline phosphatase, and prothrombin content of the plasma and the results of the thymol turbidity test (Mukherjee, 1950) during pregnancy confirms this assumption. It seems more probable that the diminished tolerance to galactose is merely an expression of the altered carbohydrate metabolism which is present during gestation.

In toxaemias of pregnancy a different state of affairs exists. The results of both galactose index and forced galactosuria suggest that the capacity of the body to utilise galactose for the synthesis of glycogen suffers markedly. In non-nephritic toxæmia of pregnancy Rowe and co-workers (1936) observed that the limit of tolerance was between 25 and 30 gms. in 87 per cent of cases. In the present series, 25 gms. of galactose failed to produce galactosuria in only 38 per cent of cases. The results of galactose index also demonstrate a greatly reduced tolerance for galactose in severe pre-eclampsia and eclampsia. The behaviour of the galactose index in relation to the clinical course of toxaemia also point out that abnormal values are directly related to the severity of the condition.

The decreased tolerance for galactose in toxaemia of pregnancy may be a manifestation of the abnormal carbohydrate metabolism which characterises this disorder. Evidences are accumulating to indicate the presence of an over-activity of the anterior lobe of the pituitary body in some cases of pregnancy toxaemia. In this connection, it is interesting to find that Rowe (1935) observed a decreased tolerance for galactose in hyperfunctional states associated with the anterior lobe of the pituitary. However, the study of galactose index in relation to blood pressure point out that an increase of vascular spasm (indicated by diastolic hypertension) in toxaemias of pregnancy is associated with high levels of galactose index. In this respect the results of the galactose tolerance test are in agreement with those of the other hepatic function tests already described (Mukherjee, 1950). King (1940) observed that the tolerance for galactose decreased in experimental hepatic poisoning. In 10 cases of toxic jaundice MacLagan (1940) found the galactose index to vary from 197 to 584. The values obtained by us are not so high, but MacLagan's figures refer to conditions which are known to produce damage to the hepatic parenchyma. Nevertheless, the galactose index is beyond doubt abnormal in both severe pre-eclampsia and eclampsia. The relation which exists between the diastolic blood pressure and the galactose index suggests that disturbance of the hepatic function may be one of the factors responsible for the high values observed in these cases. In the present state of our knowledge it is difficult to decide to what extent this abnormal galactose tolerance is due to a generally disordered state of carbohydrate metabolism apart from hepatic inefficiency which is believed to exist in toxaemias of pregnancy.

Summary.

1. The results of MacLagan's galactose tolerance test done on 10 cases of normal pregnancy, 38 cases of pre-eclampsia, and 7 cases of eclampsia show that toxaemias of pregnancy give an abnormal galactose index. Forced galactosuria test, in order to determine the limit of galactose tolerance, was employed in 30 cases of normal pregnancy, 50 cases of pre-eclampsia, and 10 cases of eclampsia. The results indicate that toxaemias of pregnancy cause a marked reduction in the tolerance for galactose.

2. The abnormal galactose tolerance follows the clinical course of toxaemia, and bears some relation to the level of the diastolic blood pressure.

3. The findings suggest that pregnancy toxaemias are probably associated with some degree of hepatic dysfunction. However, in evaluating the results of galactose tolerance tests in toxaemias of pregnancy the state of disturbed carbohydrate metabolism, which exists in this condition, should also be taken into account.

References.

1. Althausen, T. L. and Wever, G. K.: J. Clin. Invest.; 16,257, 1937.
2. Beaumont, G. E. and Dodds, E. C.: Recent Advances in Medicine; Churchill; London; 1931.
3. Dietel, H.: Arch. & Gynak.; 161, 242, 1936.
4. King, E. J.: Lancet; 2, 541, 1940.
5. MacLagan, N.F.: Quart. J. Med.; 9 (N.S.), 151, 1940.
6. Mukherjee, C. L.: In Press; 1950.
7. Rowe, A. W.: Amer. J. M.Sc.; 190, 686, 1935.
8. Rowe, A. W., McManus, M.A. and Rielly, G. A.: Amer. J. Obst. and Gyn.; 30, 841, 1935.
9. Rowe, A. W., McManus, M.A. and Plummer, A. J.: Amer. J. Obst. and Gyn.; 31, 856, 1936.
10. Shay, H., Schloss, E. M. and Rodis, I.: Arch. Inst. Med.; 47, 650, 1931.