A STUDY OF LIVER FUNCTION IN NORMAL PREGNANCY.*

BY

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On account of the importance which has been given to the liver in eclampsia and other toxemias of pregnancy, an investigation of the liver function in the various toxemias was undertaken; but before the work had gone far there was evidence of disturbed liver function in a surprisingly large number of, apparently, normal women, who presented a distinct problem with which this study will deal.

The Choice of a Functional Test.—One faces some difficulty in selecting a functional test from the many which have been advocated, because they all have their drawbacks and none of them are absolutely specific. The urobilinogen and urobilin test was selected because it is as nearly specific as any, and on account of its simplicity of application, it may be used in any clinical laboratory; it does not require the elaborate estimations of the physiological chemist and is, probably, as accurate as any of the more difficult methods. It consists of finding urobilinogen or urobilin in the urine. None of the other functional tests can be said to so certainly deal with functions which are specific to the liver as the urobilinogen test. The muscles play a large rôle in carbohydrate metabolism, and Van Slyke says the kidney possibly participates in the conversion of amino acids into urea. "The results of the tests seem to be inconsistent with the possible exception of the urobilinogen test which is positive in even mild diseases of the liver. It is the most positive of all tests for liver injury; the great difficulty with it, however, is in determining the amount of the injury by any satisfactory quantitative method."

Technical difficulties interfere with most of the tests; giving large amounts of carbohydrates leads to nausea, vomiting and diarrhea; considerable chemical training and equipment are necessary in determining nitrogenous metabolism while large quantities of blood are needed for the fibrinogen studies.

As far as is known the paradimethylaminobenzaldehyde test is specific, because to no other than liver cells has been ascribed the ability to convert urobilinogen into ordinary bile pigment, and Falk and Saxe concluded that urobilin is found in the urine when there is very slight injury to the liver. v. Jaksch, as long ago as 1892,

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averred that urobilinogen in the urine was an indication of liver disease. Urobilinogen does not occur in the urine in health except in very small quantities which are not found by the usual methods. Since Jaffe in 1868 described urobilin in the urine much discussion has taken place both as to its origin and its clinical significance. The most generally accepted view of the formation of urobilinogen and urobilin is that of Friedrich v. Müller which is supported by the known facts of hemoglobin metabolism. Addis in the Archives of Internal Medicine, March 15, 1915, gives us the most recent thought on this subject in his article on "Hemoglobin Metabolism." "Hemoglobin is produced and decomposed in the liver. Hemoglobin is liberated from the old red blood corpuscles into the blood plasma, is taken up by the Kuppfer cells from which droplets of hemoglobin have been seen to pass to liver cells. This liberation of hemoglobin from corpuscles is the first step in the process of hemoglobin pigment decomposition. Hemoglobin pigment is set free and converted into bilirubin in the liver.

"The bilirubin then passes into the intestines where it is converted by bacterial decomposition into urobilinogen, part of which may become urobilin, which is simply an oxidation product of urobilinogen; the two, from a physiological standpoint, may be considered as one. It is then absorbed and goes to the liver through the portal circulation and in the liver is again transformed into bilirubin, if the liver functionates normally. In inefficiency of the liver they pass into the general circulation and are found in the urine. Urobilin or urobilinogen does not occur in the urine in more than normal amount in complete obstruction of the common duct in stone and cancer. Müller gave bile by the stomach tube in a case of complete obstruction and immediately the urobilin action was positive. Also urobilinogen or urobilin are rarely found in the urine of the newborn before bacteria appear in the intestines. In marked diarrhea, when the bile is swept from the intestines too rapidly to permit the influence of the bacteria, urobilin is absent.

In Ecks artificial fistula and patent ductus venosus, in both of which the blood of the intestines goes directly into the general circulation, urobilinuria or urobilinogenuria occurs, because the liver has no opportunity to reconvert it. According to Wilbur and Addis, "Urobilinuria or urobilinogenuria is indicative of the fact that bile is reaching the intestine, and large amounts of urobilin or urobilinogen in the urine means there is either abnormal destruction of red blood cells or an insufficiency of the liver." Therefore, if we can exclude conditions in which there is increased blood destruction we, in all probability, have an inefficiency of the liver. This can usually

be done, clinically, with a fair degree of accuracy and, positively, by examining the duodenal contents. A large amount of urobilin or urobilinogen in the stools indicates increased blood destruction. For example: In decompensation with congestion of the liver the urobilin and the urobilinogen in the urine is increased more than in the duodenum, and just the opposite occurs in hemolysis.

Hegern says urobilin or urobilinogen in the urine always means liver inefficiency either: (1) *Absolute* which is due to pathological changes in the liver or (2) *Relative*, due to extraordinary quantities of blood pigment being brought to the liver as occurs in blood dyscrasias associated with marked destruction of red blood cells, thus exaggerating the normal function.

While not every case of urobilinuria, not due to blood destruction, can be attributed to disturbance of the liver function, yet that is usually the case.

According to v. Müller "Urobilinogenuria and Urobilinuria necessarily depend on pathological changes in the liver or increased blood destruction." Addis says "On the whole clinical evidence is strong that urobilinogenuria or urobilinuria is associated with liver disturbance if marked increase in hemoglobin disintegration can be excluded. When urobilinogen or urobilin appears in the urine, the whole liver is affected but, not as a rule, sufficient to disorganize any of its other functions to a recognizable extent." Various authors have found urobilinogen in diseases which interfere with the function of the liver. Münzer found it in atrophic cirrhosis and Fischler stated that a diagnosis of alcoholic cirrhosis was incorrect, unless urobilinogen was found in the urine; Münzer, Bloch and Fischer found it in acute catarrhal jaundice prior to the appearance of icterus. It is also found in acute diseases associated with liver involvement, *e.g.*, typhoid and pneumonia, and Bauer says it occurs in almost all liver diseases.

Technic.—It is not difficult to detect urobilinogen and urobilin qualitatively. The test for urobilinogen is made by adding four or five drops of Ehrlich's solution[1] to 5 c.c. of urine and leaving it in a dark place for at least fifteen minutes when, if positive, a distinct pink or deep red color will appear. To make sure that the red color is due to urobilinogen shake with chloroform; if urobilinogen is present the chloroform will become red. Indol and skatol are broken up by heat and give the same reaction as urobilinogen, so one must not use

[1] Ehrlich's Solution

Paradimethylamidobenzaldehyde	2 gm.
Hydrochloric acid (con.)	15 c.c.
Distilled water	15 c.c.

heat. To test for urobilin add 10 c.c. of Schlesinger's solution[1] to the same amount of urine and filter. If urobilin is present a green fluorescence will be seen which is best brought out by throwing condensed light through the fluid by a lense or flask of water. A successful method of absolute quantitative determination of these exceedingly labile substances has not yet been found. Connor and Roper, in 1908, made approximate measurements of the amount of urobilin in the urine by noting the number of dilutions required to obliterate the urobilin band in the spectroscope. This method, however, left the urobilinogen undetermined, because of the impossibility of converting all of it into urobilin without loss.

Wilbur and Addis conceived the idea of estimating the two together by the spectroscope method which, though not giving an exact quantitative determination, yields an approximate result of great clinical value. After adding Ehrlich's solution urobilinogen and urobilin each show an absorption band in the spectroscope; one between *D* and *E* and the other between *B* and *F*. They describe their method as follows: "The only way the quantity of urobilinogen can be determined, except gravimetrically, is by the spectroscope through the absorption bands of the pigment produced by its reaction with Ehrlich's solution. To 10 c.c. of urine is added an equal amount of Schlesinger's solution and filtered. This will contain all the urobilin and urobilinogen of the urine except a negligible amount absorbed in the precipitate.

To 10 c.c. of the filtrate is added 1 c.c of Ehrlich's solution, this gives enough acid to bring out the urobilin band more clearly and, at the same time, brings out the urobilinogen band so that the dilution values of both urobilin and urobilinogen can be estimated in the same filtrate. After adding Ehrlich's solution it is allowed to stand for fifteen minutes to allow the urobilinogen reaction to take place. The filtrate is then diluted with distilled water till the two absorption bands disappear, which will be at different dilutions. The time of disappearance of each is noted. The dilution required gives the value for 5 c.c. of urine; 10 c.c. having been taken only half of which was urine. If the dilution figure is multiplied by the number of 5 c.c. quantitatives in the twenty-four-hour urine, the number of dilutions which would have been necessary if all of the urobilin and urobilinogen of the twenty-four-hour specimen had been concentrated into 5 c.c.

I present herewith a table in which the essential features only of each case showing a positive reaction are given.

[1] Schlesinger's solution is a supersaturated solution of zinc acetate in absolute alcohol.

Case No.	Age	Para	Months gestation	Urobilinogen urobilin	Complications	Remarks
P3	32	IV	8	+	Patient listless.....	Ablatio placentæ. death.
6955	20	I	9	+ Trace	Systolic murmur over whole heart area, not transmitted, albuminuria, pus.	Delivered 7–20–15.
P4	28	II	8½	+		
6437	23	.....	9	+ Trace	.....	Delivered 4–15–15.
P5	....	.....	.....	+	.....	Not delivered.
6444	36	.....	9	+	Dental caries.....	Delivered 4–16–15.
6596	22	I	9	+	Hemoglobin 56 per cent., Wassermann +.	Delivered 5–16–15, R. B. C. 4,500,000.
6482	22	I	9	+	Mitral regurg., kidney of pregnancy, hemoglobin 76 per cent.	Compensation Wassermann+.
6571	24	I	.....	++		
6580	38	.....	.....	++		
6404	29	.....	9	+ Trace	Mitral regurg., aortic regurg., hypert., dil'n dental caries.	Delivered 4–19–15.
6540	20	I	9	+ Trace	Poorly nourished, chron. urticaria, hemoglobin 58 per cent., albumin trace, pus.	R. B. C. 700,000 Wassermann.
6923	32	IV	9	+	Dental caries mitral regurg. obesity, hemoglobin 80 per cent.	Delivered 7–15–15, Wassermann,— R. B. C. 4,000,000.
6285	....	.....	9	+	Dental caries.....	Wassermann— delivered 3–17–15.
6458	31	.....	.....	+	Mitral regurg.....	Compensation.
6318	18	I	.....	+ Trace	Hemoglobin 68 per cent...	Wassermann—.
6341	18	I	9	++	Dental caries.....	Wassermann— delivered 4–4–15.
6387	26	.....	9	+	Dental caries.....	B. P. 122, Wassermann—.
6414	31	.....	9	+	Hydramnios.....	Precipitate labor Wassermann+ 4–20–15.
6531	22	I	9	++	Albumin ft. trace.....	Wassermann—.
6267	26	.....	.....	+	Pyorrhea mitral regurg., pulse irreg., heart hypert. and dilated, hemoglobin 68 per cent.	Delivered 3–20–15, well compensated, Wassermann—.

Case No.	Age	Para	Months gestation	Urobilinogen urobilin	Complications	Remarks
6936	27	I	.....	+	Albuminuria, few hyaline and gran. casts.	Delivered 7–16–15.
6590	25	V	9	+	Pyelitis, hemoglobin, 69 per cent.	Delivered 7–31–15.
6570	21	III	9	++5–11–15, 0, 5–17–15	Hydramnios, pyorrhea, Wassermann+.	Delivered 5–23–15.
P6	32	II	8½	+		
6316	20	.....	.....	+	Dental caries, edema cervix, hemoglobin 50 per cent.	Wassermann.–
6276	34	.....	.....	+	Hydramnios, glycosuria, mitral regurg.	Wassermann,– compensation.
6979	41	X	9	+	Hemoglobin 60 per cent...	Delivered, 7–25–15, Wassermann.–
P7	30	II	8	+		
6992	28	IV	9	+	Hemoglobin 65 per cent., alb. v. ft. trace.	Delivered 7–27–15, Wassermann.
7077	25	I	8½	+	.....	Wassermann.–
6801	35	III	9	+	Ichthyosis.	Delivered 6–21–15, Wassermann.–
6845	36	VII	9	+	Mitral regurg., aortic regurg., obesity.	Delivered 6–29–15.
P8	26	I	8	+		
6855	30	III	9	++	.....	Wassermann, – delivered 7–1–15.
6688	34	IV	9	+	Hemoglobin 81 per cent., albumin trace.	Delivered 5–31–15.
P1	30	II	8	++	.....	Delivered 4–13–15.
6818	19	I	9	+	Mitral regurg., hemoglobin 72, albumin trace, 1 cast.	Compensation good, Wassermann,– del. 7–14–15.
6335	22	I	9	++	Hemoglobin 65, dental caries, gingivitis.	Delivered 3–29–15.
6446	17	I	9	++	Heart, all sounds accentuated, gonorrhea, hemoglobin 65 per cent.	Delivered 4–16–15, complete compensation.
6881	19	I	.....	.....	No history, patient in hospital but one day, albumin faint trace.	Did not return for delivery.

Case No.	Age	Para	Months gestation	Urobilinogen urobilin	Complications	Remarks
6550	23	I	8½	++5–7–15, 0–5–19–15	Colloid goiter, mitral regurg., hemoglobin 56.	B. P. 108–71, compensation, Wassermann.–
6515	29	II	6	+	Pulmon. tuberc., no T. B. found, hemoglobin 68 per cent., albumin ft. trace.	B. P. 138–68, W. B. C. 7200 not delivered in hospital.
6289	22	I	9	+	Dental caries, pyorrhea, mitral regurg., hemoglobin 62 per cent., albumin ft. trace, some pus in urine.	Compensation, slight dilatation Wassermann.–
P2	32	II	8½	+	Normal.....	
6332	34	.....	9	+	.....	Not delivered in hospital.
6382	23	.....	.....	+	Hemoglobin 68.....	Delivered 4–15–15.
P15	....	I	.....	+	Not examined.....	Left hospital.
6626	18	I	9	+	Dental caries, pyorrhea, colloid goiter, albumin ft. trace.	Hemoglobin 86 per cent., R. B. C. 4,300,000, not delivered in hospital.
6896	28	IV	9	++	Hemoglobin 77 per cent., albumin ft. trace.	Wassermann, – del. 7–16–15, sapremia.
6441	31	.....	9	+	Pyorrhea, hemoglobin 70 per cent.	Delivered 7–1–15, R. B. C. 4,100,000.
6891	22	II	9	+	Dental caries, alb. v. ft. trace.	Delivered 7–15–15, Wassermann.–
6972	21	I	9	+	Hemoglobin 58 per cent.	Delivered 7–23–15, sapremia, Wassermann.–
7120	18	I	9	+	Hemoglobin 74 per cent...	.....
7095	26	III	9	++	Alb. trace.....	Wassermann.–
7134	27	I	9	++	Mitral regurg.....	Compensation.
P9	40	III	7	+	None.....	
P10	32	II	6	+	None.....	
P11	28	V	6	+	Contracted pelvis.....	Never had living child.
P12	34	I	7	+	Hydramnios.....	Premature delivery.
P13	32	II	4	+	Headaches.....	B. P. 120.
P14	25	I	6	+	None.....	

SUMMARY.

Nonpregnant cases examined	71
Cases showing positive reaction	00
Per cent. positive reaction	00
Pregnant cases examined	200
Cases showing positive reaction	62
Per cent. positive reaction	31
Cases which might account for the reaction by other conditions than pregnancy	12
Net reactions probably due to pregnancy	50
Per cent. net reactions	25

This study is based upon the examination of the urine of 271 cases; 200 of which were women apparently normally pregnant and seventy-one were healthy nonpregnant women. It is hardly necessary to try to prove that urobilinogen or urobilin are not present in the urine of healthy individuals. This has been established by many observers after the examination of hundreds of cases and, it is accepted as a fact, that these substances do not occur in the urine in amounts which give a reaction with the ordinary methods, such as the one employed here. Nevertheless, the urine of seventy-one healthy women was examined and in no case was urobilinogen or urobilin found.

In the 200 cases of so-called normal pregnancy sixty-two gave the reaction for urobilinogen or urobilin. This gives us the surprising proportion of 31 per cent. Now, if we accept the statements of those who have studied these substances in other fields, that urobilinogen or urobilin in the urine means either increased blood destruction or inefficiency of the liver, we must come to the conclusion that, in the absence of blood dyscrasia, there must be interference with the function of the liver during pregnancy, and, on account of it, unless the woman has some disease which causes functional disturbance of the organ, such as congestion of the liver in cardiac decompensation.

In none of the cases was there evidence of blood dyscrasia, although some of the patients were quite anemic; however, simple anemia is not accompanied by urobilinuria, as is the case in the pernicious variety. There being no great destruction of blood we have only to deal with disturbed function of the liver; and if the patient has no complicating disease which alters the function of the liver we will be justified in coming to the conclusion that the inefficiency is due to the pregnancy itself.

In analyzing the cases, shown in the accompanying table, we find no complications which are known to be accompanied by reduced liver function except, possibly, eleven cases of valvular heart lesions

and one of infection of the urinary tract with high fever. In cardiac disease urobilinuria is not present unless there be decompensation. In none of these cases was there marked clinical evidence of decompensation; however, it is not always possible to know exactly when decompensation begins, so there might be beginning failure of the heart to do its whole work and a resulting congestion of the liver with altered function. There were two cases with slight dilatation as well as hypertrophy in which there would be even more likelihood of heart weakness.

On account of the possibility, if not probability, of these eleven cases of heart lesion being attended by a congested liver and resultant decreased function, perhaps we should exclude them as well as the one case of infection with high fever.

This would leave *fifty* cases in which the interference with the functions of the liver could be accounted for only by the pregnancy itself. This still leaves us 25 per cent. of disturbed liver function during pregnancy attributable to no other cause than the pregnant condition. Just why pregnancy should cause interference with the function of the liver, future investigation must tell us; however, it may not be out of place to suggest the possibilities: The first one that comes to mind is the congestion of the liver possibly caused by the enlarging uterus. This is favored by the fact that the urobilinuria occurs more often in the latter months of pregnancy, increasing in frequency as the end of term approaches. The earliest I have observed was in the fourth month, in which, of course, the size of the uterus was not responsible. If the liver is congested late in pregnancy, this theory is strongly supported by the well-established fact that the congestion of the liver and urobilinuria in cardiac decompensation increase or decrease, synchronously, as the compensation grows or fails. If on the other hand, the liver is always congested in late pregnancy, why do we not always find urobilinuria. We are yet in the realm of theory. The effect of toxins on the liver suggests the possibility of toxemia as a cause of the altered function.

While this series of 200 cases is small, they are enough to prove that urobilinogen and urobilin are found in the urine of pregnant women in a large percentage of cases and their presence is due, in all probability, to disturbed liver function. It also suggests that there may be a "liver of pregnancy" as well as a "kidney of pregnancy." In nine of the cases the quantity of urobilin and urobilinogen was estimated according to the Wilbur and Addis method of dilution to the point of disappearance of the absorption bands, of each substance, in the spectroscope.

Case No.	Amount of dilution	Number of dilutions	Dilution, value per liter
6531	60 c.c.	12	2400
6341	90 c.c.	18	3600
6458	60 c.c.	12	2400
6540	50 c.c.	10	2000
6444	85 c.c.	17	3400
P 5	25 c.c.	5	1000
6437	140 c.c.	28	5600
6446	30 c.c.	6	1200
P 1	50 c.c.	10	2000

CONCLUSIONS.

1. Urobilinogen and urobilin do not appear in the urine of healthy individuals except in quantities too small to detect by ordinary methods.

2. Urobilinogen or urobilin in the urine usually mean increased blood destruction or inefficiency of the liver, although there may be other causes.

3. Urobilinogenuria and urobilinuria occur in a large percentage of pregnant women; 31 per cent. in this series.

4. Excluding cases which might be due to other causes than pregnancy there are 25 per cent. distinctly attributable to pregnancy, suggesting the possibility of a "liver of pregnancy."

5. This is, probably, due to deficient liver function.

6. The causes are unknown, but it is probably due to congestion of the liver or toxemia.

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