until gastrostomy was performed the patient lost 85 pounds (38.6 kg.); following insertion of the tube, however, he regained 25 pounds (11.3 kg.). In spite of the pronounced dysphagia, fluids would occasionally pass from the esophagus into the stomach.

Roentgenoscopic and esophagoscopic examination revealed cardiospasm (Fig. 1). Dilatation of the cardia and closure of the gastric stoma relieved the patient of his symptoms.

Case 2. A man, forty years of age, was examined August 8, 1933. In December, 1932, he had been ill with influenza for about three weeks. About the time he was able to be up he was injured in an automobile accident and suffered considerable trauma over the abdomen, associated with the vomiting of blood. A week later he vomited a large amount of blood. This was repeated three days later, and then, for two or three weeks, he noted tarry stools. By the first of April, 1933, he was able to be out of bed, but soon after this he noted a burning pain in the epigastrium associated with hiccoughs and obstruction to solid food in the lower portion of the esophagus. The pain soon disappeared but the dysphagia became more pronounced.

Examination revealed a benign stricture in the lower portion of the esophagus (Fig. 2). Dilatations were carried out and, at the end of the last treatment in December, 1935, the patient was eating normally and his general condition was excellent.

Case 3. A woman, sixty-six years of age, was well until June, 1921, when she suffered a severe injury in a railroad wreck. Several ribs were fractured, and there was considerable abdominal pain associated with the passage of blood by bowel. Following this accident the patient continued to have attacks of epigastric pain which was projected substernally to the neck and lower jaw. Two months later occasional obstruction to food at the cardia was noted.

The dysphagia very gradually became worse and at the time of her *first examination* at this Clinic, in October, 1931, a diagnosis was made of cardiospasm (Fig. 3). Dilatation of the cardia was followed by almost complete relief from dysphagia, but the attacks of pain, although not so severe or so frequent, continued until the time of the patient's last examination in April, 1936.

Case 4. A man, twenty-nine years of age, who had previously been in excellent health, was in an automobile accident April 4, 1936. He was struck in the chest by the steering wheel. Immediately following this he suffered severe substernal pain which was increased on respiration; there were cough and expectoration of bloody sputum, and the temperature rose to 102 to 104° F. Five days after the accident the patient began to have difficulty in swallowing, and any attempt at ingestion of fluids was followed by severe attacks of coughing. A Rehfuss tube had been introduced for feeding.

The patient was brought to this Clinic for *examination* two weeks after the accident and his condition on admission was quite critical. He was coughing up large amounts of foul, purulent sputum and had a continuous fever, with rapid respiration and an increased pulse rate. *Roentgenographic examination* of the thorax revealed the tube in the stomach; there was a large angulated section of the tube that apparently had passed through the esophageal wall (Fig. 4). From this finding it was concluded that perforation of the esophagus had occurred and that the tube was protruding into the mediastinum. Sudden terminal hemorrhage occurred two days after admission.

Postmortem examination revealed a longitudinal rupture, 1½ inches (3.7 cm.) long on the anterior wall of the esophagus and the posterior wall of the trachea (Figs. 5 and 6). This rupture communicated with the mediastinum and gangrenous mediastinitis was present. There was very little evidence of external injury.

A Study of the Hippuric Acid Excretion as a Test of Hepatic Function*

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THE measurement of hepatic function is especially difficult because of the tremendous reserve capacity of the liver and because of the multiplicity and interrelation of its functions. When the change is within the limit of the physiological reserve of this organ, the determination of the amount of hepatic damage cannot be measured with any degree of accuracy by the majority of the clinical tests now in general use. Tests measuring carbohydrate metabolism or excretory function may be entirely normal even when the physiological detoxification mechanism may be markedly impaired. It is in only the most severe and advanced instances of hepatic damage that we are likely to find all functions of the liver impaired to an equal degree. The detoxification mechanism of the liver is one of the more important functions of this organ, as failure of this mechanism may produce metabolic dysfunction in other organs of the body.

In 1933, Quick (1), who studied the detoxication of noxious substances by conjugation with glycine, presented a method for testing the detoxifying function of the liver. Following the work of Bryan (2), Quick devised a clinical test in which sodium benzoate was administered orally and the amount of hippuric acid excreted in the urine during a four-hour period determined. After the work of Bunge and Schmeideberg (3), and until recently, the site of the conjugation of sodium benzoate and glycine was believed to be in the kidney. These investigators used dogs in their experiments but Quick (4) repeated their work using

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TABLE I

This group is composed of individuals showing no clinical evidence of liver damage (that is, no jaundice and no enlargement of the liver). In each case the Wassermann was negative

Case No.	Sex and Age	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
1	M. 35	—	104	3.08	Ext.	Normal
2	M. 25	—	94	2.97	Ext.	Normal
3	M. 20	—	136	3.52	Ext.	Normal
4	M. 32	—	89	3.33	Ext.	Normal
5	M. 19	—	159	3.69	Ext.	Normal
6	M. 40	30	—	3.00	Ext.	Only diagnosis hysteria.
7	F. 50	—	90	2.93	Ext.	Laparatomy for cholelithiasis; no stones; normal gall bladder.
8	F. 30	34	—	3.00	Ppt.	Lymphosarcoma (proved by biopsy).
9	F. 23	30	—	3.20	Ppt.	Gonorrheal arthritis of right knee.

rabbits. He believed that in man, as in the rabbit, the site of the conjugation, as well as the site of the synthesis, of glycine is in the liver.

Bryan was the first investigator to report the use of sodium benzoate as a liver function test but he was primarily interested in its use as a kidney function test. Quick (1, 5) reported two series of cases of various types of liver disease which were studied by means of the hippuric acid test. Vaccaro (6) reported a series of 44 cases and Snell and Plunkett (7) reported a series of 38 cases. The results published in all of these reports indicate that this test furnishes an accurate and reliable method of testing the detoxifying function of the liver. Although Quick described

TABLE II

All of these cases were diagnosed clinically as Alcoholic Cirrhosis. There was definite enlargement of the liver with ascites in every case. All showed negative Wassermanns.

Case No.	Sex and Age	Jaundice*	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment*
10	F. 45	None	39.5	—	0.983	Ppt.	Large amount of fluid in abdomen.
		None	—	—	1.18	Ppt.	4 months later; no fluid present.
11	M. 35	10†	—	72	1.90	Ppt.	Taken at time of admission.
		None	—	—	2.70	Ppt.	4 months later—at end of period of hospitalization; markedly improved clinically.
		None	—	—	2.02	Ext.	Readmitted to hospital 16 months later; condition the same clinically as on first admission.
12	M. 53	52†	35	—	1.19	Ppt.	Advanced case of cirrhosis.
		—	—	149	1.01	Ext.	One week later; died several weeks after this test of sudden hemorrhage.
13	M. 49	None	27	—	1.28	Ext.	Very large liver with ascites.
14	M. 60	None	—	79	1.90	Ext.	Bromsulphalein test showed 30% retention in 30 minutes (A).
15	M. 72	34†	—	98	0.38	Ext.	Bromsulphalein test showed 80% retention; died following exploratory laparotomy (A).

*In this and the succeeding tables
† = icteric index.
‡ = serum bilirubin mg. per 100 c.c.
(A) = diagnosis confirmed by autopsy.

TABLE III

This group is composed of cases diagnosed as syphilis from history and positive serology. In each case the Wassermann was four plus at the time of examination

Case No.	Sex and Age	Jaundice	Hepatic* Enlargement	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
16	M. 56	117†	++	33	—	2.27	Ppt.	Not on treatment.
		40†	++	—	—	2.59	Ppt.	2 months later; clinically greatly improved; size of the liver apparently the same.
17	M. 50	4.2‡	None	30	—	3.07	Ppt.	Chancre 3 months before jaundice; received one injection of neoarsphenamine.
18		5.2‡	+	35	—	1.94	Ppt.	Had gumma of arm; several previous attacks of jaundice following neoarsphenamine.
19	M. 44	4†	++++	35	—	2.46	Ppt.	Hepatic enlargement with large amount of ascites.
20	F. 49	None	None	28.5	—	2.83	Ppt.	No evidence of hepatic damage.
21	M. 50	2.4‡	++	36	—	2.72	Ppt.	Ascites; had had no treatment.
22	M. 55	40†	++++	—	98	1.006	Ext.	Ascites; no treatment.
23	F. 32	None	++++	34	—	2.13	Ext.	Ascites; no treatment; marked hepatic enlargement.
24	F. 32	328†	None	—	100	1.18	Ext.	Jaundice during course of antiluetic treatment; chancre several years before.
25	F. 30	2.5‡	None	—	73.4	2.01	Ext.	Jaundice during course of antileutic treatment.
26	M. 37	None	?	—	99	3.40	Ext.	Tumor mass in upper right quadrant; refused surgery.
27	M. 51	2.35‡	++++	—	70	0.937	Ext.	Ascites and hepatic enlargement of long standing.
28	F. 31	None	None	—	65	2.90	Ext.	Neurosyphilis; jaundiced for one year.

*In this and in the succeeding tables + = slight, ++ = definite, +++ = marked, and ++++ = extreme hepatic enlargement.

two methods, all of the other investigators used only the simple clinical method in their series of cases.

Since the rate of excretion of hippuric acid depends on the kidney function as well as on the rate of synethesis of glycine and its conjugation, it is necessary to measure kidney function in these cases. Quick suggested the determination of non-protein nitrogen as a control for kidney function because hippuric acid behaves like other nitrogenous excretory products. In some cases in our series urea clearance was substituted for non-protein nitrogen determination since it was found that this test is a more delicate control for the hippuric acid excretion.

METHODS

5.9 gm. of sodium benzoate was given orally in a half glassful of water at 8 a.m. Breakfast was limited to coffee and plain toast. Quantitative urine specimens were collected at hourly intervals for 4 hours. At first four separate determinations were made, but later the specimens were pooled and a single determination was made.

These determinations were carried out exactly as outlined by Quick (1). Although the precipitation of hippuric acid by the addition of concentrated hydrochloric acid gave good results in most cases, the second method described by Quick, in which the hippuric acid is removed from the specimen by means of the continuous ether extraction method, offers some advantages which are of great practical value. These advantages are: (1) the presence of bilirubinuria does not interfere with the test; (2) the long, tedious concentration of specimens is eliminated; (3) small amounts of hippuric acid can be determined. In addition to the technical advantages of this method, a urea clearance test can be performed with the same specimens used for hippuric acid determination because after the volume has been determined only 10 c.c. of the total specimen is used for extraction, leaving the rest of the specimen for the urea clearance test. Van Slyke's (8) method was used for the urea clearance determinations.

RESULTS

Table 1. This group of 9 cases showed *no evidence of hepatic pathology.* The first 7 cases were studied by means of the extraction method and in the other 2 cases the precipitation method was used. All of these cases gave results within the limits of normal as established by Quick (1) and the other investigators (6, 7). The extraction method gave results similar to those obtained by the precipitation method.

Case 7 is of especial interest because this case presented all the symptoms of cholecystitis although surgical exploration of the abdomen revealed no evidence of pathology. However, the excretion of hippuric acid was within normal limits.

Table 2. This table includes a group of 6 cases of *definite cirrhosis* with hepatic enlargement and ascites. None of the cases in this group showed serologic evidence of syphilis.

Two determinations were made in Cases 10 and 12 at varying intervals. Case 11, who had alcoholic cirrhosis, was studied for a period of 3 years. The first

TABLE IV

Malignancies of the stomach or other organs with metastases to the liver, all cases showing enlargement of the liver of varying degrees. The Wassermann was negative in all cases except 37

Case No.	Sex and Age	Jaundice	Hepatic Enlargement	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
29	M. 48	3.9‡	++++	28.5	—	0.74	Ext.	Carcinoma of stomach (inoperable) with metastasis to the liver.
30	M. 45	20†	+++	32	—	1.23	Ppt.	Carcinoma of gall bladder with hepatic involvement (A).
31	M. 31	10.4‡	+	30	—	0.93	Ext.	Pancreatitis with obstruction of common bile duct; surgical exploration and cholecystogastrostomy.
		None	None	—	124	3.21	Ext.	20 months later; clinically well; gained weight; moving furniture.
32	F. 62	160†	++++	34	—	1.25	Ext.	Carcinoma of stomach with metastasis to the liver.
33	F. 61	222†	++++	31	—	0.73	Ext.	Carcinoma of stomach (A).
34	F. 65	None	++++	34.9	—	1.70	Ext.	Carcinoma of stomach (X-ray).
35	M. 67	None	++++	30	—	1.19	Ppt.	Carcinoma of stomach (X-ray).
		None	++++	—	—	2.30	Ppt.	2 weeks later; no change clinically.
36	M. 39	None	++	32	—	1.94	Ppt. Ext.	Primary adenocarcinoma of liver (A).
37	M. 39	12.8‡	+++	21.4	110	2.22		Carcinoma of rectum with widespread metastasis to the liver (A).

two determinations were made by the precipitation method and the last by the extraction method. The results obtained in this case corresponded in every way with the clinical course. The second determination was made at the end of several months' hospitalization and the final observation was made 16 months after his release from the hospital. Clinically, the patient had regressed to the same level as at the time of the first determination.

Case 15 was operated upon because it was thought there was common duct obstruction. However, postmortem examination showed that the only pathology present was a marked cirrhosis. With a normal urea clearance in this instance the low hippuric acid output must be attributed to the extensive liver damage. In this case, the precipitation and titration method would have been very inaccurate as due to the very low output the amount of precipitate would have been very small, and the marked bilirubinuria would have made titration impractical. Death in this instance was a typical "liver death" due to failure of liver function postoperatively.

Table 3. This is a *group of cases affected with syphilis* and varying degrees of hepatic involvement. Two determinations were made in Case 16. The second was made 2 months after the first and, although the jaundice had greatly decreased, there was only a negligible increase in the output of hippuric acid. This would indicate that the decrease in jaundice does not necessarily indicate a similar improvement in liver function. This finding has been noted by both Quick and Vaccaro.

It is interesting to compare the histories of Cases 17 and 18. In each instance the patient became jaundiced following a single injection of neoarsphenamine. In Case 17 the liver function was normal and the history revealed that the patient had acquired syphilis only a few months previously. However, Case 18 gave a history of having been jaundiced following previous treatment and his syphilis was of several years' duration. In the latter case there was a lowered liver function with definite widespread liver damage, but in Case 17 the jaundice was probably due to an acute arsenical hepatitis of very recent origin.

In this group the results vary from limits of normal to 0.9 gm., the total four-hour output indicating the great variation in amount of liver damage produced by hepatic syphilis.

Table 4. This group is composed of cases of *malignant tumors* with widespread hepatic involvement as evidenced by clinical studies. All of the 4 cases which came to autopsy showed extensive metastases. Case 31, who was deeply jaundiced and whose liver function was extremely low, was operated for carcinoma of the head of the pancreas. After a stormy convalescence following a cholecystogastrostomy the patient recovered and at the present time is engaged as a furniture mover. Twenty months after his release from the hospital the patient returned for another liver function test and the output of hippuric acid was found to be normal. This patient had a reduced liver function as the result of prolonged obstructive jaundice but when the obstruction was relieved the detoxification mechanism returned to normal.

The results in this group were, on an average, the lowest of any obtained in this series.

Table 5. In this group are 22 cases of *disease of the biliary tract,* all of which were operated upon. The test results varied widely. In cases with normal liver function the postoperative reaction was mild and recovery was uneventful. Two deaths occurred in cases with low liver function. In each instance the clinical syndrome could be described as typical hepatic failure terminating in "liver death." A third death occurred

TABLE V

This is a group of cases of extrahepatic biliary disease, all of which were operated. The diagnosis given is the final diagnosis. The Wassermann was negative in all cases but Case 42

Case No.	Sex and Age	Jaundice	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
38	F. 44	8.8†	30	—	2.32	Ppt.	Cholecystitis without stones; recovered.
39	M. 39	None	27.3	—	2.90	Ppt.	Cholecystitis without stones; cholecystectomy; recovered.
40	F. 42	None	30	—	1.76	Ppt.	Cholelithiasis; typical "liver death" following surgery.
41	F. 60	None	38	—	1.94	Ppt.	Cholelithiasis; this test taken preoperatively.
		None	—	—	1.78	Ppt.	3 months later, at end of stormy convalescence.
42	F. 45	None	30	—	2.08	Ppt.	Cholelithiasis; died following surgery; autopsy refused.
43	F. 54	49.4†	38	—	0.92	Ppt.	Cholelithiasis; test taken preoperatively.
		8†	—	—	2.74	Ppt.	2 months later; stormy recovery.
44	F. 35	None	30	—	2.27	Ppt.	Cholelithiasis; cholecystectomy; uneventful recovery; test taken preoperatively.
		None	—	—	2.52	Ppt.	1 month postoperative.
45	F. 45	None	30	—	3.20	Ppt.	Cholelithiasis; cholecystectomy; recovered.
46	F. 58	7.5†	35	—	3.07	Ext.	Cholecystitis without stones; cholecystectomy; uneventful recovery.
47	F. 50	35.0†	34	—	2.01	Ext.	Choledocholithiasis; cholecystectomy; obstruction of short duration.
48	F. 32	200† 9.4‡	32	—	0.901	Ext.	Cholelithiasis, with obstruction over a long period; direct van den Bergh; typical "liver death" following surgery.
49	F. 43	1.3‡	—	98	3.00	Ext.	Preoperative diagnosis cholelithiasis; postoperative diagnosis appendicitis.
50	F. 42	None	—	80	3.03	Ext.	Cholelithiasis; cholecystectomy; one large stone; uneventful recovery; mild postoperative symptoms.
51	F. 31	None	—	130	2.48	Ext.	Cholelithiasis; cholecystectomy; violent and prolonged postoperative course.
52	F. 25	3.1‡	40	73	1.28	Ext.	Choledocholithiasis; long period of obstruction; stormy recovery.
53	F. 40	2.0‡	—	82	3.20	Ext.	Cholelithiasis; uneventful recovery.
54	M. 48	None	—	77	3.11	Ext.	Cholecystitis without stones; uneventful recovery.
55	F. 40	5.5‡	—	65	2.5	Ext.	Cholelithiasis; cholecystectomy; moderate postoperative symptoms.
56	M. 28	4.1‡	—	87	3.23	Ext.	Cholelithiasis; cholecystectomy; liver showed marked changes; uneventful recovery.
57	M. 49	7.5‡	—	96.5	3.30	Ext.	Cholelithiasis; cholecystectomy; uneventful recovery.
58	M. 28	None	—	94	3.70	Ext.	Cholelithiasis; cholecystectomy; uneventful recovery.
59	F. 59	None	—	69	2.85	Ext.	Cholelithiasis; cholecystectomy; uneventful recovery.

in a case with only moderate liver damage but which was complicated by syphilis. Other cases operated upon when there was low liver function recovered, but in all of these cases the convalescence was exceedingly stormy and accompanied by hyperpyrexia with nausea and vomiting. The results indicate that the severity of this postoperative reaction increases as the output of hippuric acid decreases.

In Cases 41, 43 and 44 tests were made after the patients had completely recovered from surgery. In none of these cases had the hepatic function, which had been lowered preoperatively, returned to normal. The excretion of hippuric acid had decreased in one instance. These results would indicate that in cases of cholelithiasis and cholecystitis surgery offers a much greater risk when there is evidence of an impaired detoxicating mechanism as shown by the hippuric acid test. Furthermore, surgical removal of the gall bladder does not serve to restore pre-existing hepatic damage, although it may serve to eliminate a source of furthering this damage.

Table 6. This group consists of 4 cases of *catarrhal jaundice.* All of these patients recovered, and the diagnosis was made from clinical study. As the precipitation method is considered very inaccurate in these

TABLE VI

All of these cases were diagnosed clinically as catarrhal jaundice and made uneventful recoveries. There was no history of lues or antiluetic treatment and the Wassermann was negative in each case

Case No.	Sex and Age	Jaundice	Hepatic Enlargement	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
60	M. 60	4‡	None	—	124	3.38	Ext.	Normal liver; in relapse of pernicious anemia.
		20‡	None	—	—	1.68	Ext.	During acute catarrhal jaundice—3 months after first test.
61	M. 25	4‡	++	27	—	1.90	Ext.	Acute catarrhal jaundice; direct van den Bergh positive.
62	M. 25	75†	++	30	—	2.04	Ext.	Acute catarrhal jaundice; direct van den Bergh.
63	F. 40	103†	++++	28	—	0.764	Ext.	Acute catarrhal jaundice; severe hepatitis of unknown cause; two determinations run.
						0.988	Ext.	

severely jaundiced individuals all of these cases were studied with the extraction method.

Case 60 is particularly interesting because by chance this patient had had a hippuric acid test 3 months before the jaundice developed. At the time the first test was taken the liver function was normal but during the acute attack of typical catarrhal jaundice there was a marked reduction in excretion of hippuric acid.

Table 7. This is a small group of patients with *toxemia of pregnancy*, in all of which the hippuric acid output was reduced. The severity of clinical symptoms seemed to bear a definite relationship to the degree of liver damage as measured by this test. When the test was repeated during the post-partum period in Cases 66 and 67 each of these showed a marked increase in hippuric acid excretion. However, this problem is very complex and these results indicate only the need for further study of the hepatic detoxifying mechanism during pregnancy.

Table 8. This table includes a variety of *miscellaneous cases*, in each of which there was a decrease in urea clearance. Some of the patients showed clinical evidence of hepatic involvement plus renal damage, but others showed renal dysfunction only.

In Case 69 malignancy with metastasis to the liver was the preoperative diagnosis. Although nitrogen retention was not present the urea clearance was greatly reduced. The reduced hippuric acid output was probably due to poor renal function, as in surgery the liver appeared normal grossly and only a fibroid of the uterus was removed. Cases 72 and 76 showed no nitrogen retention and in Case 75 there was only slight retention, but the lowered urea clearance and the decreased hippuric acid output indicate the necessity for combining these two tests. Case 77 showed that nephritis alone without liver damage is capable of reducing the output of hippuric acid. Furthermore, there was no evidence of nitrogen retention, although the urea clearance was very low.

DISCUSSION

The fact that the urea clearance test can be combined with a liver function test so that both liver function and kidney function can be studied on the same urine specimens, increases the value of both tests to the clinician. The urea clearance is a better control for the hippuric acid test than is the simple measurement of nitrogen retention, because, as stated by Van Slyke, *et al* (9), "it is only when the renal function, as measured by the urea clearance, has fallen to less than 20% of normal that a great part of the blood urea

TABLE VII

This is a group of cases of toxemia of pregnancy. In Cases 66 and 67 tests were taken during both the prenatal and post-partum periods. In none of these cases was there jaundice, hepatic enlargement, or a positive Wassermann

Case No.	Sex and Age	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
64	F. 33	24	106	2.40	Ext.	Mild toxic symptoms.
65	F. 35	28	68	2.33	Ext.	Definite toxemia; albuminuria plus hypertension.
66	F. 22	—	83	1.39	Ext.	Definite toxemia.
		—	—	2.03	Ext.	Taken 10 days post-partum; no signs of toxemia present.
67	F. 30	28	63	1.68	Ext.	Toxemia of pregnancy.
		—	—	2.12	Ext.	Taken 15 days post-partum; no signs of toxemia present.
68	F. 31	30	86	1.58	Ext.	Toxemia of pregnancy; albuminuria, headache, hypertension and vertigo.

TABLE VIII

All cases in this group had definite nephritis. Although only urea clearance test is given some of these cases showed reduction in other kidney function tests. The Wassermann was negative in each case.

Case No.	Sex and Age	Jaundice	Hepatic Enlargement	Blood Urea Nitrogen mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
69	F. 45	None	None	8.0	42	1.44	Ext.	Ascites; exploratory laparotomy done and large uterine fibroid removed.
70	M. 60	5.5‡	++	—	41	2.01	Ext.	Pancreatitis; cholecystostomy autopsy diagnosis.
71	F. 60	30†	+++	—	41	1.17	Ext.	Jaundiced for some time; albuminuria and fixed specific gravity; refused surgery.
		4†	?	—	—	1.37	Ext.	Jaundice completely cleared; no evidence of hepatitis; 3 months after first test.
72	F. 64	100†	+++	7.8	50	0.841	Ext.	Hepatitis.
73	F. 32	3‡	None	84.8	38	0.826	Ext.	Marked nephritis; patient became jaundiced during antiluetic treatment.
		0.5‡	None	—	—	0.796	Ext.	No visible jaundice; patient greatly improved clinically.
74	F. 51	10†	++++	—	29	1.00	Ext.	Inoperable carcinoma of the stomach; died soon after exploratory laparotomy.
75	F. 62	None	None	25.6	39	1.86	Ext.	Pernicious anemia; no evidence of liver damage but patient had a definite nephritis.
76	F. 35	None	None	15.8	46	1.59	Ext.	Pernicious anemia; advanced nephritis.
77	F. 46	None	None	14.4	25	2.00	Ext.	No evidence of liver disturbance; marked nephritis.

concentrations become definitely elevated." (See Case 77).

This *combined liver and kidney function test* offers an added safeguard in the preoperative study of surgical cases, because postoperative complications which may result in the so-called "liver death" are most likely to occur in those cases in which the hepatic detoxifying mechanism or the renal function is impaired. The exact mechanism which brings about the syndrome terminating in "liver death" with its accompanying disturbances in metabolism is unknown. However, the fact remains that there is a combined failure of hepatic and renal functions in these cases. Helwig and Schutz (10) suggested that the pathogenesis of this syndrome depends primarily on some intracellular hepatic damage. They believe a toxin is the causative factor and that this toxin may be produced by a perversion of functions of the damaged liver cells or by a lack of the proper physiological detoxifying ability of the cells. This failure of hepatic detoxification would thus permit the accumulation of substances which are toxic to the kidney. The presence of a low four-hour output of hippuric acid with a normal urea clearance would indicate that the liver is unable to synthesize sufficient glycine during this period. However, when the urea clearance is less than 50% of normal the diminished output of hippuric acid may be due to kidney damage as well as to hepatic damage. When there is a low hippuric acid excretion or low urea clearance the case should be considered a poor surgical risk, especially when the surgery would involve the extrahepatic biliary system.

The tests described are of equal importance to the internist in his study of diseases of the liver. A knowledge of the degree of impairment of the detoxifying mechanism of the liver is essential whenever the use of hepatotoxic drugs is contemplated. As shown by Wile and Sams (11), the low incidence of jaundice in untreated syphilis (0.18%) as compared with that (1.37%) following arsphenamine treatment indicates the high degree of hepatotoxicity exerted by this drug. Posttherapeutic jaundice is most likely to occur in cases in which there is pre-existing damage of the detoxifying mechanism as indicated by the hippuric acid test. A low output of hippuric acid would therefore be a contraindication for the use of arsphenamine in the usual manner.

The hippuric acid test offers also a means of determining the progress of cirrhosis and of other diseases of the liver. This test is a more accurate method of determining the recovery from hepatic disease with jaundice than is the determination of the serum bilirubin. This variation between the rate of disappearance of jaundice and the recovery of the detoxifying ability, as previously reported by Quick, is borne out by studies made on the cases in this series.

The results reported in the present series of cases are similar to those obtained by the other investigators. However, the hourly determination of hippuric acid is not of great clinical value and for general use the single determination of the total four-hour output is sufficient.

SUMMARY AND CONCLUSIONS

1. The hippuric acid test was used in a series of 77 cases. The results indicate that there may be a marked reduction in the detoxifying ability of the liver before

any of the clinical signs of hepatic disease can be detected.

2. The simultaneous determination of the urea clearance increases the value of the hippuric acid test.

3. The ether extraction method with the formol titration is the most practical as well as the most accurate method of determining the hippuric acid in the urine.

4. The combined urea clearance and hippuric acid test is a reliable and valuable adjunct in the study of hepatic disease.

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The Relation of Gastric Acidity to the Erythrocyte Content of the Blood*

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IN 1931 it was shown by Apperly and Crabtree (4) that the concentration of hydrochloric acid in the human stomach after a test-meal was regulated by the CO_2 content of the plasma of the fasting subject. This was found to be true not only when the plasma CO_2 was artifically varied in the subject of experiment, but also when different normal individuals were compared. A recent survey of all available clinical data relating to conditions in which plasma CO_2 varied within and beyond the normal limits has entirely confirmed the above experimental results. (Apperly, 1936) (3). Among these is the group of anoxemic conditions, of which anemia has special interest.

It has long been felt that anemia tends to lower both gastric acidity and plasma CO_2. Our preliminary experiments, however, showed us that in anoxemia, gastric acidity was considerably lower than could be accounted for by the fall of plasma CO_2. It appeared that anoxemia was of itself able to lower gastric acidity, and even result in achlorhydria. This raised the question, viz. Is there an anemic achlorhydria in contrast to the achlorhydric anemia of Witts? These considerations led us to investigate gastric acidity over a wide range of red cell content of blood.

A. *Relation of gastric acidity to red cell content of blood in normal people.*

The first interesting fact that we noticed was the striking similarity between the graph representing the average gastric acidities for different age and sex groups (as determined by Vanzant, Alvarez, *et al* (11) from 3746 cases), (Fig. 1), and the graph showing the average hemoglobin content of the blood for similar age and sex groups (from Peters and Van Slyke) (10), (Fig. 2). When the figures from these two series of observations are plotted against each other a straight line relationship is revealed, (Fig. 3). There is, of course, a considerable individual scattering about these average curves. These charts suggest two things: (a) That variations in average gastric acidity for different age and sex groups are at least partly dependent on hemoglobin differences, or whatever causes the latter, and (b) That, assuming the straight line in Fig. 3 continues as such to the base line, gastric acidity disappears when the hemoglobin of the blood falls to an average of about two-thirds its normal value; that is, that anemia can bring about achlorhydria. These figures, however, show us the relationship of gastric acidity and hemoglobin only over the range found in normal people. What happens in anemia and polycythemia?

B. *Relation of acidity to red cell content in hemorrhagic anemia.*

For our study of gastric acidity in anemia we chose afebrile cases of recent and chronic hemorrhage, since it appeared to us that these were of the simplest type, uncomplicated by hypochromia, toxic or other factors of which the effects were unknown. In all cases red cell volume (hematocrit) and gastric acidity at one hour (gruel meal of 400 c.c. and Rehfuss tube) were determined in the resting and fasting patient on different occasions, e.g. on admission, during hospitalization and sometimes after discharge. As Fig. 4 shows, although the acidity is far from being the same in different individuals with the same erythrocyte volume, in all cases acidity rises with increase in red cell volume. In some cases achlorhydria accompanied the lower erythrocyte levels. (Three cases with gastric symptoms and high acidity referred to later are omitted from Fig. 4).

In all examinations the blood was drawn from the median-basilic vein under oil to prevent loss of CO_2 and therefore changes in pH and red cell volume. It was then defibrinated by the technique of Eisenmann

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