STUDIES IN LIVER FUNCTION

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BALTIMORE, MARYLAND

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Introduction. This investigation was undertaken to determine (1) to what extent and with what frequency demonstrable functional changes accompany anatomically diseased livers; (2) in what clinical types of liver diseases the functional changes are most marked; (3) whether or not dissociated functional changes occur; and (4) the value and limitations prognostically and diagnostically that attach to these various tests. The objects are two-fold: to ascertain the behavior of the liver in pathological conditions, and to see if the behavior allows of diagnostic and prognostic deductions.

The incompleteness of the information obtained with the usual clinical studies is apparent to every thoughtful clinician. The clinical picture and the anatomical changes do not furnish an accurate conception of the functional condition of the liver nor do they furnish reliable criteria concerning the outcome of these functional changes, nor is there a well-defined symptom complex which can be accepted as the picture of hepatic insufficiency such as exists in relation to certain other viscera, notably the kidney, heart, suprarenals and thyroid. The desire of broadening and deepening our acquaintance with the functional conditions in disease of the liver is apparent and is attested to by a large number of tests devised and introduced for this purpose.

The Function of the Liver in Health. The liver plays an important role in the general nutrition of the body. No anatomical or functional differentiation of liver cells exists, all being identical

as far as can be determined. Three functions of liver cells are definitely established: (1) The glycogenic function, relating to carbohydrate metabolism. This consists of (*a*) the conversion through enzymatic activity of monosaccharides (dextrose, levulose, and galactose) brought to the liver cells by the blood, into glycogen, a polysaccharide closely related to starch; (*b*) the temporary storage of glycogen as such, until (*c*) the reconversion of glycogen by liver enzymes into dextrose as need arises for sugar throughout the body. (2) The formation of urea in relation to nitrogenous metabolism through the activity of the liver cells. This consists in the conversion of certain nitrogenous bodies (NH_3, amino-acids, etc.) into urea, which in turn is carried to the kidneys, where it is excreted. (3) The formation of bile, which is in part an excretion carrying with it waste material and in part a secretion concerned in digestion, playing an important role, particularly in the absorption of fats.

Other functions are frequently ascribed to the liver. Their connection with it, however, is not so well established and they have not played so important a role in the studies of liver physiology. In this group must be considered the formation of fibrinogen and of antithrombin. Undoubtedly still other important functions exist of which at present little or nothing is known.

THE TESTS OF LIVER FUNCTION. Until recently tests of the functional capacity of liver in disease have been based exclusively on the well known physiological functions of the liver, and have attempted quantitatively or qualitatively to determine its capacity along such lines. In this connection carbohydrate studies first occupied the clinicians, physiologists, and pathologists. The French school led by Roger,[1] Achard and Castaigne, Baylac,[2] Bierens de Haan,[3] championed the sugars as tests of liver function, while the German school under the leadership of Quincke,[4] Frerichs, von Noorden,[5] Kraus and Ludwig,[6] Bloch[7] and Müller were unable

[1] Rev. de Méd., 1886, vi, 935.
[2] Compt. rend. Soc. de Biol., 1897, iv, 1065.
[3] Arch. f. Verdauungskrankh., 1898, iv, 4.
[4] Berl. klin. Woch., 1876, xiii, 529.
[5] Pathologie des Stoffwechsels, 1893, p. 274.
[6] Wien. klin. Woch., 1891, iv, 855.
[7] Ztschr. f. klin. Med., 1893, xxii, 524.

to demonstrate any marked or constant reduction in sugar tolerance in cases of liver disease.

In a series of papers in 1898-1900 Strauss[1] established the view that the discrepancies in the results of these various workers could be explained by differences in the particular carbohydrate employed, together with the differences in the amounts of sugar administered. He followed his criticism of these carbohydrate studies by the introduction of his levulose test, based on the work of Sachs,[2] which showed a constant decreased tolerance for levulose in liverless frogs. His test has come into rather widespread use. Strauss' results as well as those of Ferranini,[3] Landsberg,[4] Chajes,[5] v. Halasz,[6] Hohlweg,[7] v. Frey,[8] Churchman,[9] Falk and Saxl,[10] Bruining,[11] being tabulated in our recent paper. It appears that the test is far from satisfactory and that little reliance diagnostically or prognostically can be placed in its findings.

In 1906 Bauer[12] introduced galactose as a test of liver function laying particular emphasis on its value in cases of catarrhal jaundice. This has been confirmed by Bondi and König,[13] Reiss and Jehn,[14] and Hirose.[15] Falk and Saxl,[16] v. Frey, and Hirose have demonstrated that the findings of the test are very inconstant in diseases of the liver other than catarrhal jaundice.

Before the International Congress of Medicine in 1913, Strauss[17] reported a comparative study in which levulose and galactose were both employed—levulose 100 gm. and galactose 30 gm.—in which he showed that the levulose gave a positive finding more than twice as often as the galactose. He advises the above doses for a com-

[1] Berl. klin. Wchnschr., 1898, xxxv, 398; 1899, xxxvi, 159; Deutsch. med. Wchnschr., 1901, xxvii, 757.
[2] Ztschr. f. klin. Med., 1899, xxxviii, 87.
[3] Zentralblatt f. inn. Med., 1902, xxiii, 921.
[4] Deutsch. med. Wchnschr., 1903, xxix, 563.
[5] Ibid., 1904, xxx, 696.
[6] Wien. klin. Wchnschr., 1908, xxi, 44.
[7] Deutsch. Arch. f. klin. Med., 1909, xcvii, 443.
[8] Ztschr. f. klin. Med., 1911, lxxii, 383.
[9] Johns Hopkins Hosp. Bull., 1912, xxiii, 10.
[10] Ztschr. f. klin. Med., 1911, lxxiii, 325.
[11] Berl. klin. Wchnschr., 1902, xxxix, 587.
[12] Wien. med. Wchnschr., 1906, lvi 20–23.
[13] Ibid., 1910, lx, 2617.
[14] Deutsch. Arch. f. klin. Med., 1912, cviii, 187.
[15] Deutsch. med. Wchnschr., 1912, xxxviii, 2, 1414.
[16] Ztschr. f. klin. Med., 1911, lxxiii, 131 and 325.
[17] Proceed. Seventeenth Internat. Cong. Med., 1913, Sect. V, Part II, p. 395.

parative study. From his collective review of the literature it appears that in normal individuals 15 per cent. of positive findings, in congested livers 17 per cent., in cirrhosis 83 per cent., in icterus in early stages of lues 75 per cent., in obstructive jaundice 62.5 per cent., and in tumors 38 per cent. positives have been obtained with his levulose test.

Bloomfield and Hurwitz,[1] studying lactose tolerance in $CHCl_3$ and phosphorus dogs, feel that little value in relation to liver function can attach to studies of tolerance of any sugar.

Urea, Amino Acid, and NH_3 Nitrogen of Urine. In 1907 Glaessner[2] showed that in most instances of liver disease an unusually high excretion of NH_2N occurred and that the ratio of NH_2N to total non-proteid nitrogen was increased. Subsequent work by Falk and Hesky,[3] Falk and Saxl, and v. Frey indicates that a knowledge of the urinary N is important, and that liver insufficiency is characterized by a decreased percentage of urea N and increased percentage of NH_3N and NH_2N. Levene and Van Slyke[4] and Yoshida[5] each reported two cases of liver cirrhosis in which a normal NH_2N per cent. of the total nitrogen was found.

Urobilinogen. As early as 1892 the presence of urobilinogen in the urine was considered as indicative of disease of the liver by v. Jaksch.[6] Neubauer[7] demonstrated that Ehrlich's[8] p. dimethylamino-benzaldehyde test given by certain urines is really a test of urobilinogen. This is the test which has been generally employed. The work of Münzer,[9] Münzer and Bloch,[10] Fischler,[11] Bauer,[12] Falk and Saxl indicates that urobilinogen occurs in the urine in many forms of liver disease. The recent thorough and comprehensive study of the question of urobilinogen by Wilbur and Addis[13] shows conclusively that observations on a single or a twenty-four-

[1] Johns Hopkins Hospital Bull., 1913, xxiv, 375.
[2] Ztschr. f. exper. Path. u. Therap., 1907, iv, 336.
[3] Ztschr. f. klin. Med., 1910, lxxi, 261.
[4] Jour. Biol. Chem., 1912, xii, 301. [5] Biochem. Ztschr., 1909, xxiii, 239.
[6] Klinische Diagnostik, 1892, 3 Aufl., 348.
[7] Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol., München, 1903.
[8] Berl. med. Wchnschr., 1901, No. 15.
[9] Med. Klin. (Berl.), 1913, ix, 586.
[10] Arch. f. Verdauungskrankh., 1911, xvii, 260.
[11] München med. Wchnschr., 1908, lv, 1421.
[12] Zentralbl. f. inn. Med., 1905, xxvi, 833
[13] Arch. Inter. Med., 1913, xiii, 235.

hour specimen have no significance, since tremendous variations occur from day to day, and that only where repeated observations are made over a period of at least two weeks, and then only where control studies of the urobilin contents of the feces have been made to exclude blood destruction as a factor in the production of urobilinogen, can its findings be accepted. The discussion of Hildebrandt's urea paper before the International Congress by v. Noorden[1] and by Müller,[2] together with a consideration of the work of Wilbur and Addis, indicate clearly how futile are deductions based on urinalysis alone.

The basis for each of these tests is some well-recognized physiological function of the liver. Other tests have been recently employed empirically or because reasons have been recently adduced indicating their connection with liver function.

Fibrinogen. Following the observations of Doyon and Kareff[3] and Nolf[4] that the fibrinogen disappeared from the blood after liver extirpation, and of Doyon[5] and his school that decreased content occurred in chloroform poisoning, and of Corin and Ansiaux[6] and of Jacoby in phosphorus poisoning, Whipple[7] and his co-workers developed a quantitative method which they have applied in studies of the fibrinogen content of the blood in health and disease, in clinical and experimental conditions. Their findings in acute and chronic liver injury make it reasonably certain that the liver is very active in the formation of fibrinogen and is the most important factor in maintaining a constant fibrinogen balance. Therefore, a study of fibrinogen content of the blood has been undertaken in this investigation.

Lipase. In 1913, Whipple, Mason and Peightal[8] utilizing Loevenhart's technique, demonstrated that the lipolytic activity

[1] Proc. Seventeenth Internat. Congress of Medicine, Sect. VI, Part II, p. 55.
[2] Ibid.
[3] Compt. rend. Soc. de Biol., 1904, lvi, 612.
[4] Arch. intern. d. Physiol., 1905, iii, 1.
[5] Compt. rend. Soc. de biol., 1905, lviii, 30; Doyon, Morel, and Billet, Compt. rend. Soc. de biol., 1905, lviii, 108.
[6] Jahresb. u. d. Fortschr. d. Thier. Chemie, 1894, xxiv, 642.
[7] Whipple and Hurwitz, Jour. Exp. Med., 1911, xiii, 136; Whipple, Arch. Int. Med., 1912, ix, 365; Whipple, Mason, and Peightal, Johns Hopkins Hosp. Bull., 1913, xxiv, 207.
[8] Johns Hopkins Hosp. Bull., 1913, xxiv, 207; Whipple, Peightal, and Clark, Johns Hopkins Hosp. Bull., 1913, xxiv, 343; Whipple, Amer. Jour. Physiol., 1914, xxxiii, 50.

of the blood varied from normal in certain diseases of the liver. Severe experimental injury to the liver resulting from chloroform, phosphorus and hydrazine always produced increase in plasma lipase from two to eight times the normal. Clinically Whipple found an increased lipolytic activity in several cases of eclampsia, invariably so in those showing hemorrhagic portal vein necrosis, in pneumonia, peritonitis, leukemia and in the early stages and sometimes in the late stages of cirrhosis. The lipolytic activity of the blood in pernicious vomiting, uremia, jaundice, and obstructive jaundice, was normal. He therefore concludes that high lipase values will be found in practically all cases of eclampsia, liver injury with necrosis due to poisons, intoxications or infections, acute yellow atrophy, cholangeitis, and abscess of liver with considerable destruction of liver tissue.

PHENOLTETRACHLORPHTHALEIN. Simultaneously, clinical studies by Rowntree, Hurwitz and Bloomfield[1] and experimental studies by Whipple, Peightal and Clark were carried on to determine whether the excretion of this drug through the intestines in health and disease afforded information relative to liver functional capacity. Whipple's studies revealed the facts that in chloroform and phosphorus poisoning marked decrease in the phthalein output resulted, together with the appearance of the drug in the urine, and, further, that associated with the decrease in phthalein output decrease in fibrinogen and increase in blood lipase occurred. The clinical studies, 80 determinations on 67 patients, showed that a normal could be established and that many liver injuries, particularly of severe grades, were associated with a decided decrease in the phthalein putput.

FIBRINOLYTIC FERMENT. Dr. Goodpasture, of the pathological staff, was already interested in the presence of a fibrinolytic ferment in the blood in liver cirrhosis when this work was undertaken. Samples of blood from all our patients were submitted to him for study. Through his courtesty we present the results of his studies on this series of cases. The ferment is specific for fibrin, does not attack fibrinogen, and is destroyed by heating to 65° C. Details of his studies will appear shortly.

[1] Johns Hopkins Hosp. Bull., 1913, xxiv, 327.

REGIMEN. In order to obtain comparable results an attempt was made to have the patients under conditions as identical as possible. The patients were kept in bed and on the ward cardiac diet. That the diet was not the same is indicated by the difference in the amounts of urinary nitrogen excreted—some of the patients eating all the food given to them, while others apparently ate but little. Following the ingestion of the phthalein one or two compound cathartic pills were given, depending upon the ease with which the individual responded to purgation. No metabolic studies with determination of nitrogen balance were made.

METHODS. PHENOLTETRACHLORPHTHALEIN. This test was employed according to the technique described by Rowntree, Hurwitz, and Bloomfield. The methods for preparing the solution, administration, collection of materials for study and determining the amount of phthalein excreted are given in full in their publication.[1] The only point of variation has been in the employment of 0.8 per cent. NaCl instead of H_2O in diluting the dye prior to injection. In many instances 8 c.c. of the dye have been injected directly with the syringe, no dilution being made.

FIBRINOGEN. The heat coagulation method as described by Whipple[2] was used in these determinations. It is as follows: Clear plasma, obtained from the oxalated blood, was measured into a centrifuge tube and heated in a water bath at 58° to 60°, for twenty-five minutes. The precipitate was collected by centrifugalization, washed thoroughly with cold and hot water and alcohol, with repeated centrifuging, washed into a weighed Gooch crucible with alcohol, washed with alcohol and ether, and dried to constant weight at 110° to 115°. This method has been carefully studied by Whipple and has been shown to give constant results and has been controlled by the plasma-serum coagulum method. However, where the fibrinogen content is very low, the method may give slightly too low values.

Lipase. This determination can be made either on oxalated plasma or serum, there being little difference in the results, except that the serum lipase is slightly higher owing to the dilution of the

[1] Rowntree, Hurwitz and Bloomfield, Loc. cit.
[2] Amer. Jour. Physiol., 914, xxxiii, 501.

plasma by the oxalate. All our estimations have been made on plasma lipase with the exception of two or three cases, where serum was utilized. Loevenhart's[1] method of determining the lipolytic activity was utilized. The technique is as follows: Four tubes are prepared, each containing 1 c.c. of plasma and to each is added 4 c.c. of distilled water and 0.3 c.c. of toluol. To two of the tubes is added 0.26 c.c. of ethyl butyrate, the other two serving as controls. The tubes are stoppered and shaken and incubated at 38° for eighteen to twenty-four hours. They are now titrated to neutrality with $\frac{N}{10}$ acid and $\frac{N}{10}$ alkali using azolitmin as indicator. The controls show the titrable blood alkalinity to be about 0.1 c.c. $\frac{N}{10}$ acid. The ethyl butyrate tubes give the amount of acid production above the neutral point and the sum represents the total acid production or lipolytic activity.

The Total Non-protein Nitrogen, Urea Nitrogen, and Amino Acid Nitrogen of the Blood. Blood serum has been used in these analyses unless otherwise stated. Ten to 15 c.c. of serum were mixed with nine volumes of 95 per cent. ethyl alcohol,[2] allowed to stand twenty-four hours or longer, and filtered through a dry paper, 10 c.c. of this filtrate, corresponding to 1 c.c. of serum, were used for the estimation of the total non-protein nitrogen by the micro method of Folin and Denis.[3] However, instead of removing the ammonia from the digestion mixture with the use of the air current, it was distilled[4] from a small flask into 1 c.c. of $\frac{N}{10}$ hydrochloric acid, made up to 50 or 100 c.c. in a graduated flask, Nesslerized, and compared with a standard solution of pure ammonia sulphate containing 1 mg. nitrogen per 100 c.c. in the Rowntree and Geraghty's modification of Autenrieth-Königsberger colorimeter. The remainder of the alcoholic filtrate was evaporated to dryness, and used for an amino acid determination by Van Slyke's[5] nitrous

[1] Amer. Jour. Physiol., 1902, vi, 331.

[2] At first we used acetone, methyl alcohol and zinc chloride to precipitate the free proteins (Folin and Denis, Jour. Biol. Chem., 1912, xi, 527), but since zinc chloride apparently precipitates some amino acids (Van Slyke, Jour. Biol. Chem., 1913, xvi, 187), we changed to the simpler procedure of using only ethyl alcohol. A few comparative determinations with methyl alcohol and zinc chloride and ethyl alcohol alone gave practically the same value for the non-protein nitrogen.

[3] Jour. Biol. Chem., 1912, xi, 527.

[4] This modification willl be described shortly by Dr. B. B. Turner.

[5] Jour. Biol. Chem., 1912, xii, 399.

acid method. The correction for urea and amines other than α-amino acids was always determined and appropriate correction made. The urea was determined by Marshall's[1] method, utilizing soy bean urease for the hydrolysis of the urea.

The Total Nitrogen, Urea, Ammonia and Amino Acids in the Urine. All determinations were made on a complete twenty-four-hour specimen, which had been collected under toluene. The total nitrogen was estimated by the usual Kjeldahl-Gunning method, the urea by Marshall's[2] method, and the ammonia by Folin's[3] method. In the amino acid determination in urine the free amino nitrogen was determined. Any increase in the conjugated amino nitrogen should also be evident from this determination and disturbing effect of albumin is here obviated. Van Slyke's[4] method was utilized, of which the technique is as follows: 25 c.c. of the urine were treated with 10 c.c. of an extract of soy bean urease and 5 c.c. of water. This was digested at 38° until the decomposition of the urea was complete, and then made up to 50 c.c. with a 10 per cent. suspension of calcium hydrate. The mixture was filtered, and 20 c.c. of the filtrate evaporated to dryness in a Jena glass dish. The residue was moistened with acetic acid, diluted to 10 c.c. and 2 c.c. used for an estimation of the amino nitrogen in the micro-apparatus.[5] A blank with 25 c.c. of 1 per cent. urea solution instead of urine was always run as a control and appropriate correction made. The slight correction for other amines not α-amino acid was neglected as it is very small and constant[6] and would not at all influence the results. The figures obtained represent the free amino nitrogen in 2 c.c. of the original urine.

Galactose. Bauer's galactose test was performed as follows: 30 grams of galactose as advised by Strauss[7] are administered to the patient in the morning, and the urine collected for the next five to six hours. The presence or absence of galactose in the urine was determined by Fehling's test. No quantitative studies of the amount excreted were made.

[1] Jour. Biol. Chem., 1913, xv, 487.
[2] Ibid., xiv, 283; xv, 495.
[3] Zeitschr. f. Physiol. Chem., 1902, xxxvii, 161.
[4] Jour. Biol. Chem., 1913, xvi, 125.
[5] Van Syke, Ibid., 121.
[6] Ibid.
[7] Loc. cit.

Levulose. One hundred grams of levulose are administered in the morning, and the urine voided during the following five to six hours tested by Fehling's and Seliwanoff's tests for the presence or absence of levulose. Considerable difficulty was experienced with the performance of this test owing to nausea and vomiting following the consumption of such large amounts of sugar.

Normal Limits of Each Test. *Phenoltetrachlorphthalein* injected in twenty-four cases in which the livers were believed to be normal showed an excretion from 30 to 53 per cent. The average output in afebrile cases was 37.4 per cent., while that in the febrile class was 39 per cent. The lower limit of normal is, therefore, considered 30 per cent. for forty-eight hours. In health following the injection of 400 mg. of the substance, phthalein is practically never encountered in the urine. In cases of clinical or experimental liver lesions the excretion of the phthalein in the urine as well as bile is a common occurrence.[1]

Fibrinogen. Whipple[2] in a series of thirty observations of the fibrinogen content of normal dogs found variations from 200 to 867 mg. per 100 c.c. Individual fluctuation is very large even in a short space of time. However, in human cases no such wide variation was noted. In a series of approximately normal cases the fibrinogen varied between 385 to 618 mg. per 100 c.c. We have placed the lower limit of normal at 350 mg.

The normal *lipase* values for human plasma determined by the above method correspond to an acid production of 0.2 to 0.35 c.c. of $\frac{N}{10}$ acid. Owing to some difficulty in titrating the mixtures and frequent variation of 0.05 or even 0.1 c.c. in duplicate determinations, we feel that no significance is to be attached to values (chloroform or phosphorus poisoning) the lipolytic activity of the lower than 0.4 c.c. In experimental liver lesions in animals plasma is always increased, and frequently reaches values of 1 c.c., 2 c.c., or even greater.

The *total non-protein nitrogen, urea N,* and *amino acid N* of the blood or the relations existing between these constituents have never been utilized in connection with studies on liver function.

[1] Rowntree, Hurwitz, and Bloomfield, loc. cit.
[2] Amer. Jour. Physiol., 1914, xxxiii, p. 56.

The fibrinolytic ferment does not normally occur in human blood serum, and appearance must be taken as an indication of a pathological condition.

THE PHENOLTETRACHLORPHTHALEIN TEST. Previously the results of eighty applications of the test on sixty-seven patients were reported. The total number of patients studied to date is 113, 33 of whom had no clinical evidence of liver disease. The positive findings in health and in various types of liver disease, together with the appearance of the drug in the urine are shown in Table II.

TABLE II

	Examined.	Less than 30 per cent.	Urine examined.	Positive.
Cirrhosis	18	9	11	7
Congestion	32	11	10	6
Carcinoma of liver	6	6	3	2
Carcinoma	5	3	3	2
Luetic liver	5	2	2	1
Severe anemia	9	7	1	0
Miscellaneous	5	2	2	2
	80	40	32	20
Normals	33	2	22	3
Total	113	42	54	23

elimination of ammonia may, as shown by Munzer in the case of acute phosphorus poisoning, be dependent upon the formation of large quantities of acids, caused by abnormal metabolism, and these acids require a greater amount of ammonia for their neutralization. That an abnormal formation of acid occurs after cutting out the liver has been shown especially by Salaskin and Zaleski.[2]

Although amino acids have been known to occur in urine for a long time, it is only recently that suitable methods for their quantitative estimation have been devised. On account of the comparative newness of the subject, very little data regarding the amino acid content of the urine in health or disease is available. The two methods in general use are the "formol" titration method of Henriques and Sorensen and the nitrous acid method of Van Slyke.

[1] Skand. Arch. of Physiol., 1913, xxviii, 325.
[2] Zeit. f. Physiol. Chem., 1900, xxix, 517.

in which the presence or absence of this substance in the urine was determined, 21 showed its presence. Fibrinogen was determined in 40 instances, 8 of which were below 350 mg., and 12 below 400 mg., while 8 were above 800 mg., *e. g.*, 20 abnormal findings. The lipolytic activity of the blood was investigated in 39 cases, 5 of which showed an acid production of more than 0.4 c.c. and 3 above 0.5 c.c. The presence of fibrinolytic ferment was tested for in 40 instances, and found in 7, all of which were cirrhoses. The galactose test was applied in 29 and the levulose in 19 cases, the former showing only 4 and the latter 2 positive findings. The total non-protein nitrogen and urea N of the blood were determined in 37 cases. The urea N was less than 40 per cent. of the total in 9 instances. The amino N of the blood was determined in 35 cases, and amounted to more than 3 mg. per 100 c.c. in 25 instances and above 4 mg. in 13 instances. The total N, urea, and ammonia in the urine were determined in 41 cases. The total nitrogen of the urine was above 10 grams in 13 cases, and in these the urea N was below 80 per cent. in 7 instances and the ammonia N above 5 per cent. in 10 instances. Twenty-one cases showed a urinary nitrogen between 5 and 10 gm., and of these 4 cases showed a urea N below 70 per cent., and 11 an ammonia N above 8 per cent. The amino acid content of the urine was investigated in 22 cases, 12 of which showed values above 1.5 per cent. of the total nitrogen.

Liver Cirrhosis. The results in the fourteen cases of cirrhosis studied were as follows: Phthalein studied in feces in 14, positive in 6, in urine in 11, positive in 7; fibrinogen in 14, positive in 6; lipase in 14, positive in 2; fibrinolytic ferment in 14, positive in 7; galactose in 11, positive in 2; levulose in 10, positive in 2; urea N per cent. (blood) in 14, positive in 5; amino N (blood) in 14, positive in 10; urea percentage (urine) in 14, positive in 3; ammonia percentage (urine) in 14, positive in 10; amino N percentage (urine) in 7, positive in 5.

Myocardial Insufficiency. Twelve cases of myocardial insufficiency were studied. Phthalein studied in feces in 9 cases with 1 positive, lowest being 18 per cent., and in urine in 10 cases with 5 positive; fibrinogen in 11 with 1 positive; lipase in 11 cases and positive in 1; fibrinolytic ferment in 12, positive in none;

galactose in 7, positive in none; levulose in 3, positive in none; urea N per cent. (blood) in 12, positive in 1, in which 6 were over 50 per cent., and 3 over 60 per cent.; amino N (blood) in 9, positive in 7.

The functional injury in liver cirrhosis is relatively greater than in chronic passive congestion, for a consideration of all the tests in each condition indicates that in 10 of the 14 cases of cirrhosis there was definite functional injury, 3 with less marked injury and only one with a practically normal function throughout, while in chronic passive congestion only 4 showed definite decrease, while 7 showed a practically normal function.

Carcinoma of Liver. Little data outside of the phthalein has been collected. C. 28, who definitely had metastasis to the liver, showed a 23 per cent. output five months before death. H. 29, with gastric carcinoma and clinically thought to have metastasis to the liver, showed a 24 per cent. phthalein positive in urine and the urea only 21 per cent of the T. N. P. N. of blood. These cases are in keeping with the 3 cases of liver carcinoma reported last year in which the phthalein excretion was 8, 14 and 7 per cent. respectively. However, slight decrease in phthalein, *e. g.*, 20 to 25 per cent. does not indicate liver carcinoma, since such findings have been found in gastric carcinoma when no proof of liver metastasis was at hand, in which case it is merely the expression of the influence of anemia and cachexia on liver function.

Anemia. Experimentally and clinically a severe grade of anemia depresses the function of the liver as indicated by phthalein. That there is also a decrease in the fibrinogen has been shown by Whipple, but owing to the quantity of blood necessary for carrying out the test, it is not applicable in all cases of anemia. Changes in the urinary N partition may appear.

Luetic Hepatitis. Of the two cases studied one showed normal phthalein, a low lipase, urinary nitrogen partition changes and a positive galactose, while the other showed a low phthalein content in feces, positive in urine, an abnormally high fibrinogen, low urea per cent. of T. N. P. N. in blood, and urinary nitrogen partition changes.

TABLE III

Number.	Name.	Medical number.	Date.	Clinical diagnosis.	Size cm. below costal margin.	Phthalein per cent. in feces.	Phthalein in urine.	Fibrinogen mgm. per 100 c.c.	Lipase c.c. n/10 acid.	Blood nitrogen partition.				Urinary nitrogen partition.					Galactose.	Levulose.
										T. N. P. N. mgm. per 100 c.c.	Urea N mgm. per 100 c.c.	Urea N per cent. T. N. P. N.	Amino N mgm. per 100 c.c.	Urine c.c. in 24 hours	Total N gms.	Urea N per cent.	Ammonia N per cent.	Amino N per cent.		
1	G. C. T.	31474	Oct. 24, 1913	Atrophic cirrhosis	....	38	....	350 97 (death)	0.25	38	9	24	2.0	700 840	6.4 9.5	65 71	13.0 12.0			
2	J. M.	31703	Nov. 20, 1913	Hypertrophic cirrhosis; carcinoma of liver?	7.5	40	–	467	0.38	37	17	47	2.5	1300	8.5	76	8.9	...	–	–
3	W. K.	31746	Nov. 25, 1913	Atrophic cirrhosis	....	30	....	222	0.28	39	17	44	4.0	....	....	80 76	12.0 10.0	...	–	–
4	J. J.	(Univ. of Md.)	Feb. 10, 1914	Hypertrophic cirrhosis	....	48	....	390	0.20	29	14	47	4.4	350	4.3	59	21.0	3.9	–	–
5	A. G.	32152	Feb. 20, 1914	Hypertrophic cirrhosis; chronic nephritis	8.0	17	+	340	0.53	35	15	43	5.2	1010	5.9	85	3.4	1.7	–	–
6	W. A. S.	32265	Mar. 17, 1914	Cirrhosis; myocardial insufficiency	8.0	23	–	440	0.15	45	22	49	3.7	1800	8.9	81	2.5	1.2	–	+
7	W. F.	32252	Mar. 17, 1914	Cirrhosis; myocardial insufficiency	4.0	18	+	588	0.25	34	16	47	5.4	1430	9.5	88	5.0	1.6	–	–
8	A.	(Bay View)	Mar. 26, 1914	Cirrhosis;	....	25	+	1275	0.55	41	17	41	3.9	2220	13.2	86	7.5	2.4	–	–
9	E. G.	31757	Nov. 25, 1913 Apr. 11, 1914	Cirrhosis; myocardial insufficiency	... 2.0	34 30	– ...	820 450	0.36 0.28	40 28	12 14	30 50	4.9 3.0	1184 645	6.2 5.6	77 78	10.0 13.0	... ...	– –	– –
10	E. C.	32445	Apr. 21, 1914	Hypertrophic cirrhosis	....	38	++	330	0.30	35	11	31	3.8	1475	4.3	76	7.7	1.7		
11	H.	(Bay View)	Dec. 13, 1913	Atrophic cirrhosis	....	5	+++	120	0.19	29	9	31	2.9	770	4.6	60	15.0			
12	J. D.	32329	Apr. 21, 1914	Cirrhosis of liver? Arterio-sclerosis	Normal	30	–	480	0.14	53	24	47	5.5	1635	16.3	84	8.0	0.8	+	–
13	E. S.	31641	Jan. 6, 1914	Hypertrophic cirrhosis	5.0	44	+	700	0.21	31	9	29	3.8	872 1125	2.5 3.2	81 78	8.2 6.1	...	+	

14	S. H.	31763	Nov. 25, 1913	Hypertrophic cirrhosis; syphilis	8.0	28	+++	306	0.34	25	10	40	3.0	810 775	6.2 5.6	77 78	10.0 13.0	...	−	+
15	W. P.	31578	Nov. 7, 1913	Myocardial insufficiency; syphilis	4.0	37	....	....	0.31	32	18	56								
16	P. H.	31719	Nov. 21, 1913	Myocardial insufficiency	3.5	....	+	390	0.35	35	17	48	4.2	1425	6.3	79	8.0	...	−	−
17	T. P.	31612	Nov. 20, 1913	Myocardial insufficiency	7.0	34	−	630	0.30	35	16	45	...	1070	10.3	78	8.3	...	−	−
18	J. W.	32049	Feb. 20, 1914	Myocardial insufficiency; uremia; chronic nephritis	Normal	48	....	1640	0.42	120	74	62	7.6	2250	12.2	66	2.5	1.4	−	
19	A. V.	32333	Apr. 2, 1914	Myocardial insufficiency; chronic peritonitis	12.0	24	+	520	0.17	36	20	55	3.0	425	1.9	70	4.8	1.2	−	
20	A. McD	31998	Jan. 23, 1914	Myocardial insufficiency	4.0	18	+	530	0.25	33	20	61	6.3	1050	7.9	80	12.6	1.5		
21	M. W.	31988	Jan. 23, 1914	Myocardial insufficiency; diabetes	Normal	....	+	685	0.35	29	11	38	3.2	1570	12.2	79	5.0	1.6		
22	E. T.	31765	Jan. 14, 1914	Myocardial insufficiency	5.0	31	−	829	0.24	37	73	62	5.7	1385	12.2	80	6.9		−	
23	M. B.	31870	Jan. 6, 1914	Myocardial insufficiency	10.0	57	+	267	....	26	11	42	3.2	745	5.9	75	8.5	...	−	
24	C. H.	31904	Jan. 6, 1914	Myocardial insufficiency; uremia; chronic nephritis	Normal	30	−	630	0.28	60	36	60	3.0	310	3.2	78	5.9	1.6		
25	C.	(Bay View)	Jan. 13, 1913	Myocardial insufficiency	5.0	42	−	487	0.38	40	17	43	...	1230	8.9	72	9.3			
26	W.	31774	Dec. 2, 1913	Catarrhal jaundice; cholelithiasis	....	22	+	....	0.50	42	18	43	5.3	1190 1260	11.7 9.1	73 80	6.1 9.0	...	+	−
27	L.	3	Apr. 21, 1914	Myocardial insufficiency	8.0	....	−	360	0.24	39	17	43	3.7	1485	12.3	82	6.6	1.3	−	−
28	C.	(Bay View)	Dec. 13, 1913	Carcinoma with metastases to liver	....	23	−													
29	J. H.	31920	Jan. 6, 1914	Gastric carcinoma, metastases to liver?	....	24	+	536	0.28	34	21	61	3.4	780	7.9	84	7.0	...	−	
30	W. J.	32458	Apr. 21, 1914	Gastric carcinoma	Normal	30	+	....	....	...	..	..	...	620	7.8	76	7.8	1.5		
31	C. H.	31971	Jan. 24, 1914	Splenomyelogenous leukemia	Normal	38	+	....	....	...	..	..	...	1175	7.3	79	3.7	1.6	−	?

TABLE III—(Continued)

Number.	Name.	Medical number.	Date.	Clinical diagnosis.	Size cm. below costal margin.	Phthalein per cent. in feces.	Phthalein in urine.	Fibrinogen mgm. per 100 c.c.	Lipase c.c. n/10 acid.	Blood nitrogen partition.				Urinary nitrogen partition.					Galactose.	Levulose.
										T. N. P. N. mgm. per 100 c.c.	Urea N mgm. per 100 c.c.	Urea N per cent. T. N. P. N.	Amino N mgm. per 100 c.c.	Urine c.c. in 24 hours.	Total N. gms.	Urea N per cent.	Ammonia N per cent.	Amino N per cent.		
32	C. R.	31565	Oct. 25, 1913	Splenomyelogenous leukemia	Normal	43	....	510	0.19	..	..	..	..	700	9.2	83	4.9	1.0		
			Jan. 6, 1914			46	−	250	0.28	33	14	42	6.2	1390	12.1	82	4.4	0.8	−	−
33	C.	.....	Oct. 24, 1913	Uncinariasis with anemia	....	23	....	456	0.21	....	..	..	....	1240	10.5	78	8.4			
34	E. W.	31704	Jan. 14, 1914	Pernicious anemia	Normal	27	....	....	....	....	..	..	....	1480	6.3	64	14.0			
35	J. F.	32312	Mar. 26, 1914	Pernicious anemia	Normal	23	−	....	....	....	..	..	....	1530	8.7	76	13.1	1.0	−	−
36	M. H.	32436	Apr. 21, 1914	Syphilitic hepatitis	5.0	24	+	822	0.21	33	8	24	2.7	520	2.8	63	17.0	2.5	−	
37	H.	(Bay View)	Mar. 26, 1914	Syphilitic hepatitis	....	32	−	780	0.07	40	17	42	3.9	1790	4.3	69	8.4	7.5	+	
38	C. C.	31900	Jan. 6, 1914	Polyserositis; tuberculous syphilis	6.0	30	+	627	0.19	29	9	31	3.2	815	6.2	70	15.0	2.3	−	
39	J. D.	31742	Nov. 25, 1913	Polyserositis, tuberculous	6.0	31	+	887		....	..	..	....	880	8.9	76	10.0	....		
40	A. W.	32139	Feb. 20, 1914	Congenital hemolytic jaundice	6.0	31	....	672	0.36	30	11	36	2.7	830	6.5	77	8.0	....	−	−
								354	0.25	32	16	50	3.7	2230	15.6	79	5.4	1.6	−	−
41	J. T.	32443	Apr. 23, 1914	Acute lobar pneumonia; jaundice	Normal	24	+	716	0.20	41	22	53	2.5	2580	17.0	80	8.1	0.6		
42	R.	(Obstetric)	Feb. 20, 1914	Nephritis in pregnancy; eclampsia	.....	47	....	584	0.25	33	16	48	4.1	1610	8.5	80	5.0			
43	R. A.	32355	Apr. 18, 1914	Salvarsan poisoning	....	....	....	....	1.00	150	..	..	12.4							
44	M. S.	31496	Oct. 24, 1914	Pentosuria; peripheral neuritis	....	....	....	....	....	....	..	..	....	1050	11.9	76	5.7			
					....	39	....	....	0.29	....	..	..	....	850	13.0	79	5.0			
45	J. S.	(Surgical) 33712	Jan. 24, 1914	Gallstones; operation draining	Normal	4	++	830	0.27	33	15	45	2.8							

The following cases showed the presence of fibrinolytic ferment in the blood: Nos. 1, 3, 5, 7, 11, and 14.

POLYSEROSITIS. Two cases with much the same clinical condition and both with large livers showed practically identical findings, *e. g.*, normal phthalein in feces but positive in urine, fibrinogen and lipase normal, low urea per cent. of T. N. P. N. in blood, changes in urinary N partition but no decreased tolerance for sugar.

TABLE IV

	Total number of tests.	Total number of positive tests.	Cirrhosis of liver.		Myocardial insufficiency		Carcinoma.		Syphilitic hepatitis.		Pernicious anemia.		Polyserositis.		Miscellaneous.	
No. of cases tested.			14		12		3		2		2		2		10	
Name of test				+		+		+		+		+		+		+
Phthalein in feces	42	16	*14*	6	*9*	1	*3*	2	*2*	1	*2*	2	*2*	0	*9*	4
Phthalein in urine	34	21	*11*	7	*10*	5	*3*	2	*2*	1	*1*	0	*2*	2	*5*	4
Fibrinogen	36	8	*14*	6	*11*	1	*1*	0	*2*	0	—	—	*2*	0	*1*	1
Fibrinolytic ferment	40	7	*14*	7	*12*	0	*1*	0	*2*	0	—	—	*2*	0	*9*	0
Lipase	39	5	*14*	2	*11*	1	*1*	0	*2*	0	—	—	*2*	0	*9*	2
Galactose	29	4	*11*	2	*7*	0	*1*	0	*2*	1	*1*	0	*2*	0	*4*	2
Levulose	18	2	*10*	2	*3*	0	*0*	0	—	—	*1*	0	*1*	0	*3*	0
Blood—																
Urea N %	37	9	*14*	5	*12*	1	*1*	0	*2*	1	—	—	*2*	2	*6*	0
NH_2N	35	25	*14*	10	*9*	7	*1*	1	*2*	1	—	—	*2*	1	*6*	4
Urine—																
Urea N %	41	11	*14*	3	*11*	3	*2*	0	*2*	2	*2*	1	*2*	0	*8*	2
NH_2N %	41	28	*14*	10	*11*	7	*2*	0	*2*	2	*2*	2	*2*	2	*8*	5
NH_2N %	22	12	*7*	5	*6*	2	*1*	0	*1*	2	*1*	0	*1*	1	*5*	2

EXPLANATION: The figures in italics represent the number of times tests were made and the other figures indicate the number of positive results in the various types of diseases.

NECESSITY FOR COMBINED RENAL AND LIVER FUNCTIONAL STUDIES. In view of the facts that nitrogenous metabolism and the permeability of the kidney to sugars are markedly affected by renal diseases, a careful investigation of the functional capacity of the kidney should be made in all cases in which sugar tolerance, urea or blood nitrogen partition are entering into consideration, as in phosphorus and $CHCl_3$ poisoning in dogs or in myocardial insufficiency or anemia. Renal injury is suggested in cases 15, 33, and 43. The relative effect on liver and kidney function of general conditions such as anemia and myocardial insufficiency are worthy of investigation. A report of such a study will appear later in collaboration with Dr. R. R. Snowden.

Acidosis and Liver Function. It would have been advisable to have attempted to exclude increased ammonia excretion in the urine, by feeding alkalies (sodium bicarbonate, sodium citrate), since the NH_3 increase may be merely the expression of an acidosis.[1 2 3 4] This, unfortunately, has not been done but is contemplated in future studies.

Practicability of Tests. *The phthalein test* involves an intravenous injection and careful collection of stools for forty-eight hours. Not more than ten minutes are required for carrying out the determination of the phthalein after the feces are removed from the shaker. Three undesirable features are connected with its application: (1) The quality of red color obtained in certain instances (10 to 20 per cent. of the cases) is such that accurate quantitative estimation is difficult. Only in rare instances is this a serious difficulty leading to error of more than 5 per cent. (2) Thrombosis frequently follows at the point of injection, as evidenced by slight local pain or tenderness together with resistance offered to the palpating finger along the course of the vein. This occurred in eight instances in this series of cases, but in no case has it occasioned serious discomfort or resulted in actual harm to the patient. (3) With salt solution made with freshly distilled water chills following the injection are infrequent. When no dilution is employed chills are less frequent and not accompanied with increase in temperature.

Fibrinogen determination is inapplicable in the presence of severe anemia. It necessitates the withdrawal of 40 to 50 c.c. of blood. A high-speed centrifuge and considerable chemical equipment are requisites. The test is time-consuming.

Lipase determination is readily applied, requiring neither complicated apparatus nor expenditure of much time.

The determination of the total non-proteid nitrogen, urea N and amino acid N of the blood can not be carried out when severe anemia exists. Technically the determinations are easy but they are time-consuming.

[1] Camerer, Zeitschr. f. Biol., 1902, xliii, 13.
[2] Haskins, Jour. Biol. Chem., 1906-7, ii, 217.
[3] Janney, Zeitschr. f. Physiol. Chem., 1911-12, lxxvi, 99.
[4] Sellards, Johns Hopkins Hosp. Bull., 1912, xxiii, 289.

The nitrogen partition in the urine requires somewhat less time. Galactose can be administered without discomfort to the patient, but technical difficulties attend the use of levulose, at least 25 per cent. of the patients refusing to take the full amount or developing nausea or vomiting following its ingestion. Its findings are therefore vitiated.

The fibrinolytic ferment is readily determined if present.

Urobilinogen determinations in the urine are valueless unless made daily for a period of two weeks and unless associated with urobilin determinations in the feces.

Conclusions. 1. Outspoken changes in liver function can be demonstrated in most cases of advanced liver cirrhosis, in markedly congested livers associated with myocardial insufficiency, in carcinoma of liver, in luetic livers, and in conditions of cachexia with marked anemia.

2. Functional changes have been most marked in cirrhosis, in neoplasm of liver and in cachetic conditions with severe grades of anemia. The functional changes in chronic passive congestion have not been frequent or pronounced.

3. Harmony in the findings of the tests is present in some cases, *i. e.*, most of the tests indicating a decreased function or indicating a normal function, but in other instances the function in an individual case appears normal by some tests and diminished by others and absolutely no parallelism exists between the findings of the various tests in the latter instance, *i. e.*, with one test indicating decrease in function it is impossible to predict what the other tests will show.

4. From this small series of cases it is impossible to reach definite conclusions concerning the absolute and relative value and limitations of these various tests, but the following impressions are the outcome of our limited experience:

(*a*) Under clinical conditions a phthalein output under 30 per cent. or the appearance of phthalein in the urine is of unquestionable significance. When in accord, *i. e.*, both positive or both negative, the evidence is of more value than single or discordant findings. Positive value is not claimed for negative findings. A marked decrease in phthalein means a decided injury to liver

function. Autopsies in 11 cases have increased our belief in the value of this test.

(*b*) Low fibrinogen values are frequently but inconstantly encountered in cirrhosis which confirms the results reported by Whipple. Marked positive findings may carry prognostic significance, although they may not appear until shortly before death. Negative findings have no value.

(*c*) The determination of the lipolytic activity of the blood plasma furnishes very little or no information of prognostic or diagnostic significance in these types of clinical cases. Only in two or three instances have the clinical findings been comparable with our findings or those of Whipple in $CHCl_3$ or phosphorus poisoning. High values probably carry prognostic significance.

(*d*) Dr. Goodpasture's fibrinolytic ferment studies on this series of cases show that this ferment is present only in cirrhosis and hence when present of definite diagnostic importance.

(*e*) Bauer's galactose test is applicable without discomfort to the patient, but yields no information of consequence.

(*f*) Strauss's levulose test was attended with technical difficulties—nausea and vomiting frequently following its employment, and yielded information of no consequence in the limited number of cases in which it was successfully carried out.

(*g*) Blood N partition: Cumulative phenomena have not been encountered in this series except with coexistent renal disease.

The urea N percentage of total has been 40 per cent. or less in several instances, and especially low in cases of advanced cirrhosis.

The NH_2N has been high in a considerable proportion of the clinical cases. (In phosphorus poisoning the NH_2N increase was always present and was associated with increase in the urea N and total non-proteid nitrogen. In chloroform poisoning the absolute and relative values of the various forms of nitrogen did not vary from normal.)[1]

(*h*) Urinary Nitrogen partition: No instance of absolute normal urinary nitrogen partition has been encountered. However, the low level of protein metabolism so often present, together with

[1] Studies on Liver Function in Phosphorus and Chloroform Poisoning. To be published shortly.

the non-exclusion of acidosis, render the interpretation of the N distribution somewhat difficult. Practically all the cirrhosis cases showed definite N partition changes.

The NH_3N and NH_2N were definitely increased in most of the cases studied and particularly in cirrhosis.

Concerning the relative merits of these tests it appears that the phthalein, the fibrinogen, the blood and urine nitrogen partitions are of decided value in determining the presence and to a less degree the extent of functional involvement, while the demonstration of the presence of a fibrinolytic ferment is of decided diagnostic importance. The determination of sugar tolerance and of the lipolytic activity of the blood apparently afford information of much less value.

In this study marked variations from the normal have been indicated in many patients. Opportunity for studying only a limited number of types of liver injury has been afforded. The application of such studies to eclampsia, acute yellow atrophy, liver abscess, obstructive jaundice, etc., is most desirable, and also, to miscellaneous types of disease, in order to determine if the changes described above are specific to liver disease.

The information derived from these liver studies does not compare in diagnostic and prognostic importance with that from corresponding renal functional studies. This may depend upon several factors, the limited number of cases of severe liver injury under observation, the possible existence of a great "factor of safety" in the liver whereby in case of necessity function is carried on efficiently by a relatively small proportion of liver substance, the prognosis in many of these cases being controlled by factors other than decreased liver function, *e. g.*, myocardial insufficiency, carcinoma, lues, anemia, etc., and the lack at present of correlation of anatomical, clinical and functional findings occasioned by the newness of the subject. The results, however, encourage us in the belief that scientifically and also clinically this subject is worthy of extensive investigation.

APPENDIX[1]

No. 1, Med. No. 3147. G. C. T., aged forty-seven years, male, white, September 19, 1913.

Clinical Diagnosis. Cirrhosis of liver, pulmonary tuberculosis, tuberculosis of larnyx, ascites, bronchopneumonia. Pains in abdomen, swelling of abdomen and legs; duration four months. Markedly alcoholic. Hemoptysis and hemorrhoids. On admission weakness, emaciation, ascites, dilated veins on abdomen, liver dulness from sixth rib to 8 cm. below costal margin. Edema of extremities. Jaundice. Hemoglobin, 62 per cent. Wassermann negative. Repeated abdominal tappings. Injected October 23. Died November 19. *Autopsy:* No. 4024. (Dr. Whipple.) Anatomical diagnosis: Diffuse cirrhosis of liver (atrophic type); chronic pancreatitis; passive congestion of abdominal viscera; chronic fibroid apical tuberculosis; chronic laryngeal tuberculosis; general anasarca; emaciation; bronchopneumonia (organizing); congestion and edema of lungs; acute aortic endocarditis; acute splenic tumor; chronic gastritis; chronic ulcerative laryngitis (tuberculous). Microscope: A pretty diffuse type of cirrhosis. New formed connective tissue contains a good many new formed bile ducts, and mononuclear wandering cells. There is increase in connective tissue in many of the small lobules of hepatic parenchyma. The liver epithelium looks much damaged although some of the cells show a good deal of hypertrophy. Others show much pigmentation and various types of degeneration, even necrosis. Bile canaliculi in some liver cells are conspicuous. There is very little liver parenchyma which seems even approximately normal. Liver weighs 1480 gms. It presents the typical picture of Lænnec cirrhosis. The capsule is thickened and rather milky. The surface is coarsely granular, showing areas sticking above it. Collateral circulation in the suspensory ligament is very conspicuous. The gall-bladder is dilated, thin walled, but the bile passages are normal. On section parts of the organ show very extensive scarring, whereas other portions show a more diffuse and not so extensive involvement. There are nodules and lumps of liver parenchyma of all sizes between the scars. These nodules may be gray or pigmented yellowish-brown. There are bright red areas apparently associated with hemorrhage and perhaps necrosis in some of the liver cells. The architecture is greatly obliterated. The left lobe is thin, flattened and elongated, but in general presents the same changes found in the right lobe. The organ is very firm and hard. Mucosa of gall-bladder normal.

No. 2, Med. No. 31703. J. W. M., aged fifty-four years, male, white, November 20, 1913.

[1] We are indebted to Professor G. H. Whipple for the careful pathological study of sections from the cases coming to autopsy.

Clinical Diagnosis. Cirrhosis of liver. Carcinoma of liver (?). Alcoholic. Swelling of abdomen for six weeks, diarrhea for three weeks; loss of weight. No myocardial insufficiency. Ascites, liver dulness from fourth is to 7.5 cm. below costal margin; liver surface irregular and granular, suggesting neoplasm to some observers. Red blood cells, 2,780,000; white blood cells, 10,400; hemoglobin, 53 per cent. Tapping on two occasions, liver easily palpable, "finely nodular." Predominating opinion was that patient had cirrhosis, but the possibility of neoplasm was considered.

No. 3, Med. No. 31746. W. J. K., male, aged forty years, November 25, 1913.

Clinical Diagnosis. Cirrhosis of liver. Hydrothorax. Markedly alcoholic (bartender by occupation) for years. Bleeding hemorrhoids for seven years, swelling of ankles for one and a half years, later swelling of abdomen; hematemesis and bloody stools on two occasions. On admission: anemia, red cells, 2,920,000; hemoglobin, 55 per cent.; white blood cells, 2925; slight jaundice, ascites, enlarged superficial veins on abdomen; liver flatness from fourth rib to within 2 cm. of costal margin; moderate edema of ankles. After removal of 8 liters of fluid from the abdominal cavity liver dulness extended to costal margin, edge was not felt. Wassermann positive. Rapidly recurring ascites, necessitating tapping as often as once a week. Urine negative for albumin and casts except on day of admission. Death five months after tests were made. *Autopsy:* No. 4132, May 21. Atrophic cirrhosis of liver; portal stasis, ascites, dilated collateral circulation; organizing thrombosis of portal vein and its radicles; chronic interstitial hyperplasia of spleen; chronic interlobular pancreatitis; pancreatic necroses; hemorrhages into islands of Langerhans; chronic interstitial nephritis, jaundice, chronic fibrous pleuritis, bilateral atelectasis (lower lobes), chronic local peritonitis, perihepatitis and splenitis. Liver: Very small. Surface is nodular, weight 810 gms. Nodules of greenish yellow parenchyma measuring 4 to 5 mm. between which are dense connective-tissue bands. Branches of the portal vein show organized thrombi, some of which are completely occluding. Microscope: Cirrhosis is of annular type. Some of the scars are very dense and extensive. Proliferation of bile ducts not conspicuous. New formed connective tissue rich in wandering cells. Islands of liver tissue in places well preserved, showing hypertrophy of liver epithelium. In other places there are focal necroses and areas of fatty degeneration. Many of the liver cells contain yellow, granular pigment. The bile canaliculi are conspicuous, and distended with greenish, colloid material. Organizing thrombi present in portal vessels. One might estimate roughly that one-third to one-half of the remaining liver parenchyma shows definite degeneration, which should interfere with functional activity.

No. 5, Med. No. 32152. A. G., aged forty-five years, male, white, February 20, 1914.

Clinical Diagnosis. Cirrhosis of liver. Chronic nephritis. Psoriasis. Chronic bronchitis. Indefinite history of stomach trouble, loss of appetite and occasional attacks of belching, nausea and vomiting, extending over a period of twelve years. Previous admission to hospital, July, 1906, at which time a diagnosis of cirrhosis of the liver was made; liver extended 8 cm. below costal margin in right mammillary line. On present admission liver dulness extended three fingers' breadths below costal margin in mammillary line, slight dilatation of superficial veins on abdomen and psoriasis. Liver edge was firm, smooth, fairly sharp, surface smooth. Wassermann negative.

No. 6, Med. No. 32265. W. A. S., aged forty-six years, male, white, March 17, 1914.

Clinical Diagnosis. Cirrhosis of liver, myocardial insufficiency, aortic insufficiency (?), chronic nephritis (?). For about a year patient had dyspnea, orthopnea, tightness in the chest. Three months before admission the abdomen and legs began to swell. Blood-pressure has been elevated. On admission, pigmentation of exposed parts, icteric tint to scleræ, evidences of fluid in right pleural cavity, cardiac dulness 14.5 cm. to left and 5 cm. to right, snapping first sound at apex preceded by a short rumbling murmur, and followed by a soft blow, transmitted to posterior portion of axilla, ascites, enlarged liver, extending 10 cm. below tip of ensiform with rounded firm edge. Spleen not felt, edema of extremities present. Wassermann negative. Paracentesis March 27, 6500 c.c., dark, straw-colored fluid obtained, which showed some red cells in centrifuged specimens. After removal of the fluid the liver was felt plainly and a firm, hard rounded edge was made out about 8 cm. below costal margin in parasternal line and 12 cm. below the ensiform. On discharge, April 23, liver was thought by Dr. Thayer to be softer than on admission: the border was felt three fingers' breadths below the costal margin and 8 cm. below the xiphoid; surface was smooth. Urine showed albumin 2 to 5 gms. per liter and casts constantly. Blood-pressure 130 to 145.

No. 7, Med. No. 32252. W. F., aged fifty-one years, male, white, March 17, 1914.

Clinical Diagnosis. Tuberculosis (eye test). Pleurisy with effusion, thickened pleura. Myocardial insufficiency. Enlarged liver. Cirrhosis of liver (?). For five months shortness of breath on exertion and swelling of abdomen. Not markedly alcoholic. On admission slight yellowish tinge to scleræ, fluid in left pleural cavity, edema of both bases, cardiac dulness 12.5 cm. to left in fifth interspace, 5 cm. to right in fourth interspace, liver enlarged (three fingers' breadths below costal margin in right nipple line), moderate edema of the feet and ankles. Wassermann negative. Tuberculin test (Calmette) 1 per cent. positive. Under rest in bed all signs of myocardial insufficiency disappeared and patient was discharged. Liver at time of discharge seemed to be same size as on admission. Urine showed trace of albumin from time to time; no casts. Blood-pressure normal.

No. 9, Med. No. 31757. E. G., aged forty-three years, male, November 25, 1913.

Clinical Diagnosis. Chronic nephritis, myocardial insufficiency, dilated aortic arch, syphilis (Wassermann). Two previous admissions to hospital at which time same diagnosis was made. Trouble began in October, 1912, one year before admission, with dyspnea, orthopnea and edema of the face, ankles, and legs. Recovered after prolonged rest in the hospital on two separate occasions. Recurrence of symptoms two weeks before admission. On admission patient showed orthopnea, general anasarca, edema of both lungs, wide area of cardiac dulness (15 cm. to left and 5 cm. to right), ascites. After removal of 7.5 liters of fluid liver edge was palpable about 2 cm. below costal margin in the right mammillary line, not palpable in the median line. Liver border was firm. Wassermann positive. Urine showed albumin 1 to 2 gm. to liter and casts constantly; blood-pressure 160 to 210. Pulse persistently rapid. The interesting feature in this patient was the small size of liver in spite of the evidence of a marked chronic passive congestion.

No. 10, Med. No. 32445. Mrs. E. C. C., aged thirty-four years, female, white, April 21, 1914.

Clinical Diagnosis. Cirrhosis of liver. Patient accidentally noticed 15 months ago that she could feel her liver, and since that time the liver has gradually grown larger and firmer. She has always been constipated. Eleven months ago amebæ were said to have been found in the stools, which contained blood and mucus at the time. Emetine treatment cleared up the trouble. Hemorrhoids five weeks ago. On admission (Dr. Thayer) no jaundice, heart not remarkable, dilatation of veins over thorax and abdomen with current running upward. Border of liver was felt, edge sharp and firm on right, a little rounded on left, surface smooth and liver certainly harder than normal. Free fluid in abdominal cavity. Wassermann negative. Urine negative.

No. 12, Med. No. 32329. J. D., aged seventy-one years, male, white, April 21, 1914.

Clinical Diagnosis. Arteriosclerosis, myocardial insufficiency. Pulsus irregularis perpetuus. Chronic nephritis. Emphysema. Cirrhosis of liver. For six months before admission patient had swelling of legs, shortness of breath, and soreness in abdomen. Has been a heavy drinker for forty years. On admission he showed enlarged heart (12 cm. to left and 3 cm. to right by percussion), irregular pulse, liver dulness 3 cm. above costal margin, ascites and edema, with marked arteriosclerosis. Wassermann negative. Urine showed trace of albumin and a few casts. Blood-pressure, 200 on admission, fell to 130 to 140 after rest in bed. This case is evidently not one of outspoken cirrhosis of the liver as the diagnosis seems to rest on the presence of marked alcoholic history and a small liver although a moderate grade of myocardial insufficiency with chronic passive congestion was present.

No. 13, Med. No. 31641. E. S., aged fifty-four years, female, white, October 29, 1913.

Clinical Diagnosis. Cirrhosis of liver. Alcoholic, whisky every day for ten years. Swelling of legs and abdomen and tenderness at right costal margin, duration four weeks. No myocardial insufficiency; ascites, dilatation of superficial veins on abdomen. Wassermann negative. After tapping liver edge was palpable three fingers' breadths below costal margin, sharp, hard, and coarse nodules were palpable on the surface. Repeated tappings performed, hemorrhagic fluid being obtained on several occasions. Under potassium iodide patient improved; ascites finally disappeared and on last examination liver was palpable two fingers' breadths below costal margin, and no nodules were felt. Urine negative. Patient was injected December 7, while there were ascites.

No. 14, Med. No. 31763. S. H., aged fifty-one years, white, male, November 28, 1913.

Clinical Diagnosis. Cirrhosis of liver, syphilis (Wassermann). Pain in abdomen, weakness, loss of weight and swelling of abdomen; duration three months. Not alcoholic. On admission slight jaundice, general glandular enlargement, ascites. Urine showed a trace of albumin occasionally, no casts. After removal of 5.5 liters of fluid from abdominal cavity liver edge could not be definitely felt, but there was dulness several cm. below costal margin in mammillary line. Spleen was enlarged and firm. Wassermann positive. Red blood cells, 3,608,000; hemoglobin, 77 per cent.; white blood cells, 6680. The ascites recurred rapidly and patient had to be tapped repeatedly. At times there was a slight elevation of temperature but for the most part temperature remained normal. He did not improve under antiluetic treatment.

No. 15, Med. No. 31578. W. P., aged thirty-eight years, male, colored, November 7, 1913.

Clinical Diagnosis. Syphilis (Wassermann). Arteriosclerosis. Chronic nephritis. Mitral and myocardial insufficiency. For a year previous to admission patient had dyspnea following a "cold." For two weeks before admission abdomen began to swell. On admission patient showed signs of a marked myocardial insufficiency: dyspnea, orthopnea, edema of lungs with hydrothorax on the right side, enlarged heart (15 cm. to left and 5.5 cm. to right of mid line), systolic murmur at the apex, tachycardia, liver dulness 4 cm. below right costal margin, ascites, edema of genitalia and extremities, as well as walls of heart and abdomen. Blood-pressure 180 to 200. Urine showed albumin and casts constantly. Phenolsulphonephthalein output: First hour, 9 per cent.; second hour, 7 per cent.; total, two hours, 16 per cent. Wassermann positive. Despite rest in bed and use of heart stimulants, compensation was never restored and patient died February 4, 1914. *Autopsy:* 4064. Anatomical diagnosis: syphilitic aortitis involving the aortic valves and secondary chronic aortic

endocarditis; cardiac hypertrophy and dilatation (left); pulmonary thrombosis (right pulmonary artery) associated with fibrosis, induration and bronchiectasis of lower right lobe; chronic passive congestion of lungs; right-sided cardic hypertrophy and dilatation; chronic passive congestion of viscera; edema; ascites; pericardial effusion; chronic fibrous pleurisy (bilateral); chronic perihepatitis. Liver weighs 1150 gm., measures 24 x 15 x 6 cm. It shows a definite thickening of the capsule over the right lobe particularly in the region of the gall-bladder which, however, only extends through the capsule. Elsewhere the Glissonian capsule is delicate and translucent. On section the lobulation is distinct and somewhat irregular. In some zones the lobules are small and atrophic with depressed reddish black centres, while in other areas the lobules are larger and the liver tissue of a more homogeneous yellowish color with the centres less definitely congested. Liver shows a picture of long standing chronic passive congestion with lakes of blood in the region of the central vein and some slight increase in connective tissue in this area.

No. 16, Med. No. 31719. R. H., aged forty-one years, male, black, November 21, 1913.

Clinical Diagnosis. Syphilis (Wassermann), aortic insufficiency, myocardial insufficiency, dilated aortic arch, chronic nephritis, tabes dorsalis. Shortness of breath, cough, and swelling of legs for one week. On admission sluggish pupils, general anasarca, enlarged heart, edema of lungs, liver dulness 3.5 cm. below costal margin in mammillary line; ascites. Wassermann positive in blood and spinal fluid. Pleocytosis and increased globulin in cerebrospinal fluid. Under treatment signs of myocardial insufficiency disappeared, liver dulness was two fingers' breadths below costal margin on discharge.

No. 17, Med. No. 31612. T. P., aged forty-five years, male, November 20, 1913.

Clinical Diagnosis. Ateriosclerosis. Aortic insufficiency, myocardial insufficiency, dilated aortic arch, chronic nephritis; dyspnea and edema for eighteen months previous to this admission, which was the fifth. Markedly alcoholic. On admission he showed evidence of broken compensation, dyspnea, orthopnea, hydrothorax, wide area of cardiac dulness (17.5 cm. to left and 5.5 cm. to right), systolic murmur at apex, diastolic at the base, irregular pulse, ascites and edema. Liver was enlarged on admission, 13 cm. below costal margin in right mid line and 8 cm.below xiphoid. At time of injection cardiac dulness was 17 cm. to left and 6 cm. to right and liver dulness extended 7 cm. below the costal margin in the right mammillary line. The liver was still somewhat tender. Patient had evidently an extensive chronic passive congestion of the liver. Urine always showed albumin and casts and the blood-pressure was always elevated. Patient had two subsequent admissions and died in the hospital; no autopsy.

No. 18, Med. No. 32049. J. H. W., aged forty-five years, male, black, February 20, 1914.

Clinical Diagnosis. Syphilis (Wassermann), chronic nephritis, uremia, myocardial insufficiency, aortic insufficiency, dilated aortic arch, parotitis. For five days previous to admission patient had epigastric pain, shortness of breath, and swelling of abdomen. On admission he showed evidences of myocardial insufficiency, not marked, however, aortic insufficiency, enlarged heart, liver dulness one finger's breadth below costal margin, moderate edema of the extremities. Blood-pressure, 170 to 210. Urine showed constantly albumin and casts. Patient became very drowsy and developed a terminal parotitis. Died March 13. *Autopsy:* No. 4089. March 13, 1914. Subacute nephritis, hypertrophy of left ventricle; syphilitic aortitis; parotitis; pulmonary congestion; bronchopneumonia; cloudy swelling of viscera; rather old tuberculous lymphadenitis (bronchial lymph gland); lymphatic hyperplasia; mesenteric lymphadenitis. Microscope: Liver shows a moderate grade of cloudy swelling. Some of the liver cells contain an excess of granular golden yellow pigment. Others contain a few small fat droplets. Otherwise normal. Liver measures 27 x 19 x 8 cm.; weighs 1900 gm. The surface is smooth and glistening. The capsule is everywhere thin. On section the organ has a brown color. The lobulation is markedly prominent and regular. In localized areas there are scattered reddish dots suggesting dilated bloodvessels. The organ has a slightly boiled appearance.

No. 19, Med. No. 32333. A. V., aged thirty-one years, female, black, April 2, 1914.

Clinical Diagnosis. Syphilis (Wassermann). Mitral stenosis and insufficiency, tricuspid and myocardial insufficiency, chronic peritonitis, hydrothorax, dilated aortic arch. For four years has had shortness of breath, swelling of ankles, and swelling of abdomen. Two previous admissions to hospital, during each of which it was thought that she had cirrhosis of the liver in addition to the myocardial insufficiency; had many tappings, after which she felt fairly well until five months when symptoms recurred. On admission she showed signs of marked myocardial insufficiency; orthopnea, dyspnea, edema of the lungs, tachycardia, heart enlarged to the left, ascites, edema of the extremities. After tapping liver was palpable as a firm, irregular, nodular, tender, pulsating mass extending 12 cm. below costal margin in right mammillary line. Wassermann positive. Repeated tapping of peritoneal cavity necessary. Died April 15. *Autopsy:* No. 4108. April 16, mitral stenosis and insufficiency, chronic valvular endocarditis, pulmonary congestion; pulmonary and tricuspid insufficiency; cardiac hypertrophy and dilatation, especially of right side; chronic passive congestion of lungs and viscera, acute and chronic adhesive peritonitis, acute and chronic perihepatitis; atrophy and fibrosis of liver with areas of hypertrophy; chronic peri and interstitial splenitis;

acute and chronic endometritis; actute salpingitis; acute and chronic adhesive pleurisy (right), bilateral pleuritic effusion, atelectasis, mural thrombus, soldier's patches, subepicardial hemorrhages, pericardial effusion; tuberculous hilic lymph glands; acute and chronic lymphadenitis; syphilitic aortitis, edema of extremities; decubitus ulcer; hemorrhoids, pyorrhea alveolaris. Liver weighs 1800 gm. with the spleen attached, measures 26 x 15 x 7 cm. It is slightly larger than normal. The spleen is attached to the lower margin of the left lobe of the liver by rather dense adhesions and a portion of this lobe is pulled down forming a round bridge between the liver and the spleen. This pulled-out lobe is about 5 cm. from the edge of the liver. The diaphragm is firmly adherent to the spleen by the large, firm, cord-like adhesions which have a red, inflamed surface. In between these adhesions there is a serofibrinous exudate. The capsule of the spleen is markedly thickened. The liver surface is covered by dense adhesions binding it to the diaphragm and abdominal wall. The diaphragm is bound to the liver by cord-like adhesions about $\frac{1}{2}$ to 1 inch in length, and form numerous compartments between the liver and diaphragm. These compartments are filled with large amounts of serofibrinous exudate. There is an acute hemorrhagic appearance to the surface of the liver and about all these adhesions. On section the liver cuts with considerable resistance. The capsule is definitely thickened, measuring about 3 mm. and is of a grayish fibrous appearance. The surface of the liver presents a varied appearance. In general it has a greenish slightly bile-stained appearance. There are numerous areas of atrophy and scar formation. In other places there is a great increase of interstitial tissue with large liver lobules being scattered throughout. There is no evidence of marked contraction or cirrhosis, but the portal areas are distinctly contrasted with the markedly injected central area about which is evident atrophy of the liver substance. The picture is that of a chronic passive congestion with marked atrophy and area of hypertrophy, with great increase in interstitial connective tissue with small areas of scar formation. Microscope: Chronic passive congestion with extreme atrophy. In places liver cells show hypertrophy. There is an increase in connective tissue and in some areas there is a definite fibrosis with proliferating bile ducts. Nothing that could be called a true cirrhosis is found. Section has a thick fibrous capsule. Considerable pigmentation is present.

No. 20, Med. No. 31998. A. McD., aged fifty-nine years, male, black, January 23, 1914.

Clinical Diagnosis. Arteriosclerosis, myocardial insufficiency, pulsus irregularis perpetuus, bronchopneumonia. Several periods of shortness of breath and swelling of ankles. Duration of present attack ten days. On admission signs of marked myocardial insufficiency; dyspnea, orthopnea, edema of lungs, enlargement of heart, irregular pulse, enlarged liver (dulness extending from fifth interspace to three fingers' breadths below costal

margin), edema of genitalia and extremities. At time of test liver was firm and tender and edge extended four fingers' breadths below costal margin. Patient developed bronchopneumonia and died. No autopsy.

No. 21, Med. No. 31988. M. V. W., aged sixty-three years, female, black, January 23, 1914.

Clinical Diagnosis. Diabetes mellitus, arteriosclerosis, perforating ulcer. Polyphagia, polydipsia, polyuria, and ulcer on right foot; duration ten months. On admission nothing striking except arteriosclerosis and ulcer on plantar surface of right foot at base of great toe. Liver not enlarged, not felt. Urine showed 15 gm. glucose on admission, which disappeared on a carbohydrate-free diet. No acetone or diacetic acid at any time. Glucose reappeared on a full diet.

No. 22, Med. No. 31765. E. T., aged forty-five years, female, black, January 14, 1914.

Clinical Diagnosis. Arteriosclerosis, aortic, mitral and myocardial insufficiency, dilated aortic arch, chronic nephritis. Three previous admissions to hospital, the first in 1899 for acute rheumatic fever, the other two in 1911 and 1913 for symptoms similar to those of present admission. Dyspnea, swelling of legs and abdomen and nycturia, duration ten weeks. On admission signs of myocardial insufficiency, edema of lungs and extremities, ascites, enlarged heart (15 cm. to left and 4 cm. to right), liver edge felt three fingers' breadths below the costal margin, firm and rounded, tender. Albumin and casts constant in urine. Gradual improvement and decrease in size of liver under rest in bed and digitalis therapy.

No. 23, Med. No. 31870. M. B., aged sixteen years, female, white, January 6, 1914.

Clinical Diagnosis. Mitral stenosis and insufficiency, myocardial insufficiency, pulsus irregularis perpetuus. Frequent attacks of rheumatic fever, and attacks of palpitation of heart for eight years accompanied by swelling of feet. For two months gradually increasing swelling of abdomen and extremities with dyspnea and orthopnea. On admission signs of marked decompensation of heart, general anasarca, enlarged heart (17 cm. to left, 4.5 cm. to right), ascites sufficient to necessitate paracentesis. At time of injection liver flatness extended from sixth rib in mammillary line to below the level of the umbilicus. Compensation was never restored, and patient left hospital against advice of physicians. She was readmitted later because of return of symptoms.

No. 24, Med. No. 31904. C. B. H., aged sixty-two years, male, January 6, 1914.

Clinical Diagnosis. Arteriosclerosis, chronic nephritis, myocardial insufficiency, uremia. Dyspnea on exertion for nine months, weakness of legs and vague pains in abdomen. On admission Cheyne-Stokes respiration, cardiac dulness 15.5 cm. to left, marked atherosclerosis, liver not enlarged, hypertension (180 to 220), albumin and casts persistently present in urine,

Wassermann negative, phenolsulphonephthalein excretion, none at end of first hour, 15 per cent. at end of second hour. Patient was extremely restless and seemed on the verge of going into uremic convulsions, but under eliminative treatment he improved distinctly.

No. 29, Med. No. 31920. J. H., aged sixty-three years, male, white, January 6, 1914.

Clinical Diagnosis. Carcinoma of stomach, metastases. For four months pain in abdomen after eating or drinking, occasional vomiting and constipation, with loss of weight and strength. On admission patient showed emaciation, anemia, red blood cells, 3,520,000; hemoglobin, 46 per cent., and a mass in the epigastrium continuous with liver dulness. No jaundice, palpable liver, with nodular surface according to one observer. Occult blood in stools, no free hydrochloric acid in stomach juice. Wassermann negative, gastro-intestinal *x*-rays showed "gnawing out" of the shadow of the greater curvature, persisting in several plates and suspicious of carcinoma. Patient steadily lost weight and tumor in the epigastrium grew steadily larger. Death February 6; no autopsy. Prevailing opinion was carcinoma of stomach with metastases to liver.

No. 30, Med. No. 32458. W. N. J., aged forty-eight years, male, white, April 21, 1914.

Clinical Diagnosis. Carcinoma of stomach. For about twenty-four years patient has had abdominal pains before each meal, and five years ago an especially severe attack, since which time he has had weakness, loss of appetite, emaciation, pain in the epigastrium, occasional vomiting, chronic constipation, and edema of the ankles. On admission emaciation, anemia (red blood cells, 2,084,000; white blood cells, 8000; hemoglobin, 20 per cent.) and a palpable mass in the epigastrium, thought to be a carcinoma situated at the pylorus. Liver not thought to be enlarged. Gastric analysis showed sarcinæ, Oppler-Boas bacilli, white blood cells, subacidity, lactic acid, and occult blood. Bismuth *x*-rays showed pyloric obstruction and gastric retention.

No. 31, Med. No. 31971. C. H., aged thirty-nine years, white, male, January 24, 1914.

Clinical Diagnosis. Leukemia, splenomyelogenous. For three months patient had noticed slight fulness in left upper quadrant of abdomen, which has increased rapidly. On admission pallor, and enlarged spleen. Liver not palpable. Red blood cells, 4,448,000; white blood cells, 102,800; hemoglobin, 58 per cent. Differential count (Ehrlich), polymorphonuclear neutrophiles, 22.3 per cent.; polymorphonuclear eosinophiles, 4.7 per cent.; polymorphonuclear basophiles, 4.0 per cent.; small mononuclears, 3.3 per cent.; large mononuclears, 17.0 per cent.; transitionals, 10.3 per cent.; neutrophilic myelocytes, 27.3 per cent.; eosinophilic myelocytes, 5.7 per cent.; basophilic myelocytes, 3.7 per cent.; unclassified, 1.7 per cent.; normoblasts, 12 cells; megaloblasts, 17 cells. Wassermann negative.

Discharged April 6, 1914. White cells were reduced under benzol and *x*-ray therapy to 40,000 on discharge.

No. 32, Med. No. 31565. C. R., aged twenty-five years, male, white, October 10.

Clinical Diagnosis. Leukemia, splenomyelogenous. Enlarged spleen for two years, some pain in left side. Splenic dulness 25 x 35 cm. Liver dulness from fifth rib to one finger's breadth below costal margin; edge not felt. White blood cells, 229,000. Differential count: polymorphonuclear neutrophiles, 43.4 per cent.; polymorphonuclear eosinophiles, 3 per cent.; polymorphonuclear basophiles, 0.6 per cent.; small mononuclears, 0.6 per cent.; large mononuclears, 1.0 per cent.; transitionals, 0 per cent.; myelocytes: neutrophilic, 46.5 per cent.; eosinophilic, 1.1 per cent.; basophilic, 0.9 per cent.; unclassified, 1.6 per cent. Injected October 24, 1913, and January 6, 1914.

No. 34, Med. No. 31704. E. W., female, black, January 14, 1914.

Clinical Diagnosis. Pernicious anemia, gastric anacidity. For one year vague attacks of "indigestion," nausea and vomiting, and feeling of languor. On admission a slightly yellowish tinge to scleræ, marked pallor, moderate edema of the legs. Red blood cells, 1,198,000; white blood cells, 2960; hemoglobin, 24 per cent. Much anisocytosis and poikilocytosis. Monoblasts and megablasts seen. Gastric analysis showed absence of free hydrochloric acid.

No. 35, Med. No. 32312. J. E. F., aged forty years, male, white, March 26, 1914.

Clinical Diagnosis. Pernicious anemia, pyorrhea alveolaris. Periods of weakness, nervousness, "indigestion," and diarrhea for five years, increasing during the past year. On admission pallor, yellow skin, pyorrhea alveolaris, liver edge just palpable at costal margin, reflexes present. Red blood cells, 1,548,000; white blood cells, 6350; hemoglobin, 35 per cent. Marked poikilocytosis, anisocytosis, and variation in color of cells. One normoblast seen. Polychromatophilia. Gastric analysis showed absence of free HCl. Discharged after three weeks stay in hospital; no improvement in condition noted.

No. 36, Med. No. 32436. M. H., aged twenty-eight years, female, black, January 21, 1914.

Clinical Diagnosis. Syphilis (Wassermann). Syphilis of the liver. Ascites. Ventral hernia (incarcerated). Gradual swelling of abdomen eight months before admission; paracentesis six times in five weeks before admission; blood in stools on several occasions. On admission icteric tint to scleræ, glandular enlargement, ascites, hydrothorax, liver palpable three fingers' breadths below costal margin. Wassermann positive. Red blood cells, 4,640,000; hemoglobin, 60 per cent. Attempt made to aspirate pleural cavities; no fluid obtained. Calmette test positive, 5 per cent.; 6500 c.c. fluid removed at abdominal tapping. Subsequently patient

developed an incarcerated hernia and was operated upon by Dr. McClure. At operation liver was felt and found to be very hard and enlarged, to have a sharp edge and a slightly nodular surface.

No. 38, Med. No. 31900. C. C., aged twenty-seven years, male, white, January 6, 1914.

Clinical Diagnosis. Pleurisy with effusion, tuberculous peritonitis, pericarditis, adherent pericardium. Syphilis (Wassermann). Gradually increasing edema of ankles and swelling of legs for seven months, accompanied by some dyspnea, cough and abdominal pain. On admission patient showed marked orthopnea and dyspnea, jaundice (slight), tachycardia, marked ascites, edema of extremities, fever (105°), leukocytosis. After removal of 12.75 liters of fluid from the abdominal cavity the liver edge extended 6 cm. below the costal margin in right mammillary line and 8 cm. below the ensiform in median line. Surface was firm and slightly irregular. Tuberculin test (Calmette) positive. Wassermann positive. Ascites recurred necessitating repeated abdominal tappings. Later on fluid was removed from right pleural cavity. Patient maintained a remittent fever and died March 8. Urine negative. Clinically this patient was thought to have an advanced cirrhosis of the liver. At autopsy none was found. *Autopsy:* No. 4087. March 10. Anatomical diagnosis. Tuberculous peritonitis; adhesion of bowel to abdominal wall; paracentesis opening extending into it; ascites; adhesive pericarditis (tuberculous); cardiac hypertrophy and dilatation; collapse of both lungs; acute and chronic tuberculous lymphadenitis; tubercles of liver and spleen; chronic passive congestion of viscera; cloudy swelling of kidney, general anasarca, chronic pancreatitis (?). *Liver microscopically:* There are a few old scars made up of dense connective tissue which may be of syphilitic origin. No evidence of tuberculosis. The centres of lobules show a little atrophy of the liver cells with some fatty degeneration. There is a good deal of postmortem degeneration making it difficult to determine the condition of the liver cells. The main change can be explained by passive congestion of a moderate grade and there is no histological evidence of any other change which should interfere with the function. *Liver grossly:* Liver weighs 2300 gm. It is enlarged, measuring 28 x 19 x 9 cm. Its surface shows thick fibrinous exudate. This layer of exudate is hemorrhagic in appearance. When this is peeled off, the surface is left studded with small tubercles which are also reddish in color. There are also some dense fibrous adhesions between the under surface of the diaphragm and the liver. The cut surface is seen to be mottled dark grayish color with a rather prominent lobulation showing. However, on close inspection there is seen to be a definite congestion of the central areas with atrophy apparently and some hypertrophy of the liver substance about the portal areas. There are a few tubercles which can be made out definitely. In the left lobe of the liver there is a rather homogeneous boiled-like appearance,

as this portion of the liver has undergone rather rapid postmortem digestion. The demarcation line between this and the right lobe of the liver is quite distinct. Beside the congestion and definite tubercles being of apparent postmortem change there is nothing very remarkable about it. The atrophy and hypertrophy are secondary to the congestion. No definte cirrhosis.

No. 39, Med. No. 31742. J. W. D., aged forty-two years, male, November 25, 1913.

Clinical Diagnosis. Tuberculous pleurisy with effusion, peritonitis and pericarditis. Admitted complaining of dizziness, weakness and pains over heart, duration six weeks. On admission patient showed evidences of fluid in both pleural cavities and pericardial cavity, an enlarged liver, dulness extending from fifth rib to 6 cm. below the costal margin in the right mammillary line. Liver edge was palpable and there was shifting dulness in the flanks. Red blood cells, 4,152,000; hemoglobin, 61 per cent.; white blood cells, 5920. Patient maintained a remittent fever, temperature going as high as 103°, which gradually came to normal after rest in bed. Urine showed a trace of albumin from time to time; no casts.

No. 40, Med. No. 32139. A. L. W., aged forty years, male, white, February 20, 1914.

Clinical Diagnosis. Congenital hemolytic jaundice, ulcer of legs. Had malaria at twelve years, with jaundice and "ague cake" spleen; jaundice has persisted since. Since the age of sixteen he has had ulcers on the legs, which have healed and broken down again. He had three admissions to the hospital about thirteen years ago, at which time a diagnosis of splenic anemia was made. The eldest son (nine years old) of the patient has had jaundice for four years, no other symptoms. On admission jaundice of the skin and scleræ; palpable liver edge 6 cm. below the costal margin in the right mammillary line; enlarged spleen, and ulcers on the legs. Red blood cells, 3,504,000; white blood cells, 9250; hemoglobin, 70 per cent. Wassermann negative, after provocative salvarsan. Dr. George R. Minot stained the red blood cells vitally with brilliant crystal blue, and in 1500 cells counted found 5 per cent. reticulated and less than half of these showed large reticulæ. Calmette (5 per cent.) positive. Patient was seen by several observers, all of whom found enlarged liver and spleen as described above, in addition to the jaundice, and all of them thought that the case was one of congenital hemolytic jaundice. Studies of the blood, with regard to the presence of pigments, made by Dr. George R. Minot and Dr. C. G. Guthrie showed presence of bilirubin in the serum, but no definite evidence of urobilin in the serum. Urobilin and urobilinogen were present in the urine.

No. 41, Med. No. 32443. J. H. T., aged thirty-six years, male, black, April 23, 1914.

Clinical Diagnosis. Acute lobar pneumonia (right upper and lower). Syphilis (Wassermann). Four days before admission had malaise, weakness and giddiness, followed by chill, loss of appetite and cough with pain in the right chest, and difficulty in breathing. On admission signs of consolidation of right lower lobe, continued fever 104° to 106° and leukocytosis. Two days after admission he developed an intense jaundice, with bile in the urine. Liver dulness 2 cm. below costal margin. Stools not clay-colored. Course of disease uneventful except for occurrence of a delirium and rather slow resolution.

No. 43, Med. No. 32355. R. M. A., aged fifty years, male, white, April 18, 1914.

Clinical Diagnosis. Syphilis (Wassermann); tabes dorsalis; acute nephritis; chronic nephritis. Twenty-two years ago he had syphilis, treatment two years. Five years ago began to have lightning pains. Strabismus for one month. On admission inequality of pupils, internal strabismus of right eye due to paralysis of right internal rectus. Argyll-Robertson pupils on left, positive Romberg and slight ataxia on walking. K. K. absent. Blood-pressure, 184 to 120. Urine on admission showed a mere trace of albumin and no casts were found. Spinal puncture gave a clear fluid, 30 cells per cmm., slightly positive Noguchi, and a positive Wassermann. Wassermann in blood negative. Patient was given 0.3 gm. salvarsan intravenously and had no reaction afterward other than an increase in lightning pains. Five days later patient was given 0.5 gm. salvarsan intravenously, and about 30 minutes later had a chill and temperature rose to 106° (rectal), pulse became weak, and patient seemed dazed. Temperature remained high for two days; patient developed a blotchy, erythematous rash and urine contained a large amount of albumin and granular casts. Jaundice appeared, pulse failed, and patient died three days after the intravenous salvarsan. *Autopsy:* No. 4109. April 18. Tabes dorsalis (intravenous salvarsan); diffuse central necrosis of liver; jaundice; acute splenic tumor; acute glomerular nephritis; subserous hemorrhages; duodenal ulcer; chronic gastritis; arteriosclerosis; chronic orchitis. Liver weight 1500 gm. The surface is normal. On section the lobulation is distinct, the centres being of a brick red and the margin of a yellowish color. Microscope: shows central necroses associated with fatty degeneration affecting at least one-half of each liver lobule. The degenerated liver cells are partly dissolved and being removed by phagocytes, which are numerous in these areas. The remaining liver tissue shows a good deal of fatty degeneration but many normal liver cells. Great numbers of mitotic figures are found in the hepatic epithelium, indicating rapid regeneration following injury. The connective tissue is nowhere increased and the picture resembles that seen in chloroform poisoning. With a liver lesion of this extent the output in the dog would be decreased to less than one-half normal and might be much lower even.

No. 44, Med. No. 31496. M. S., aged forty-nine years, male, white, October 24, 1913.

Clinical Diagnosis. Peripheral neuritis, bronchial asthma, eosinophilia, pentosuria, pyorrhea alveolaris. Paroxysms of asthma for two years, loss of weight and increased frequency of micturition. Liver edge palpable 1 cm. below costal margin. Wassermann negative. White blood cells, 26,000. Eosinophiles, 83 per cent. Pentose in urine.

No. 45, Surg. No. 33712. J. S., aged forty-seven years, female, white.

Clinical Diagnosis. Gall-stone in common duct. For six years had recurrent attacks of abdominal pain, and for three months before admission she had continuous dull pain in right hypochondrium. Jaundiced for a week before admission to hospital. On admission patient had jaundice; slight prominence in right hypochondriac region; liver edge palpable 2 cm. below costal margin; spleen palpable; 13,000 leukocytes; bile in urine; acholic stools, and slight fever. At operation a stone was found in the common duct, adherent to the mucosa, and the common duct was widely dilated, about 3 cm. in diameter, and containing a great quantity of bile. The stone was removed, a small catheter placed in the common duct, with the end toward the liver, a drain was placed in the gall-bladder and the wound closed.