AN EXPERIMENTAL AND CLINICAL STUDY OF THE VALUE OF PHENOLTETRACHLORPHTHALEIN AS A TEST FOR HEPATIC FUNCTION.

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In this investigation an effort has been made to determine [327] whether the quantity of phenoltetrachlorphthalein excreted by the liver following its intravenous administration affords an index of the functional capacity of the liver. The specificity displayed by the liver in the excretion of this dye, which is analogous in every way to that exhibited by the kidney towards phenolsulphonephthalein, strongly suggests possibilities in this connection. Quantitative studies of the phthalein output in health and in liver diseases (clinical and experimental) have therefore been undertaken.

THE FUNCTION OF THE LIVER IN HEALTH.

The liver plays an important rôle 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

[327] 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 rôle, 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 rôle 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 Function of the Liver in Disease.

With the occurrence of disease in the liver, functional changes undoubtedly appear. Their character varies greatly with the nature of the underlying pathological processes at work. They can be associated with, or totally independent of, morphological changes, macroscopically or microscopically demonstrable. In most of the outspoken diseases of the liver, however, recognizable objective anatomical alterations occur,
[328] such as enlargement or contraction, changes in consistency, etc. They may or may not be associated with evidence of portal obstruction, ascites, the development of enlarged collateral circulatory channels or of biliary obstruction—jaundice, bile in the urine, acholic stools, etc.

Through routine clinical histories and examinations, with a study of the urine and fæces, the presence or absence of liver disease can be readily determined in most cases. Information concerning the severity of the disease and the extent of the involvement of liver function is, however, not so readily obtained. In certain liver affections symptoms either of an obstructive or toxic nature are ascribed to the liver changes. There is not, however, a well-defined symptom complex which can be accepted as the picture of hepatic insufficiency, such as exists, for instance, in relation to diseases

of other viscera—the kidney, heart, suprarenals and thyroid. [328] In other words, the clinical picture and anatomical changes, even when outspoken, 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.

In certain other diseases, concerning the etiology and physiological pathology of which no accurate knowledge exists, the liver is thought to be implicated. Information about hepatic function in these conditions is most desirable and necessary.

The unsatisfactory character of the information obtained through ordinary routine clinical studies is apparent to every thoughtful clinician. The desirability of broadening and deepening our acquaintance with the functional conditions present in disease is indicated by the existence of a large number of tests devised and introduced for this purpose.

The Ideal Functional Test

A perfect conception of the status of liver function in disease presupposes an accurate knowledge of all the physiological functions of the liver in health and in disease. Do dissociated injuries to one function or set of functions exist without interference with other functions? If so, reliable quantitative tests for each set of activities is demanded. Our knowledge of liver physiology, however, is inadequate and much information, fundamental in nature, is needed before such tests can be devised.

It is worth while to consider what would constitute an ideal single test of total liver function. Is such a test possible? What could be justly demanded of it?

1. The test should indicate within narrow limits a constant amount of work performed by all normal livers under normal conditions.

2. It should indicate constant variations in function where constant abnormal conditions of either an experimental or clinical nature exist.

3. It should indicate functional alterations independent of the histological appearance.

[328] 4. It should afford an indication of the absolute work accomplished as well as the relation of this to the normal standard under all conditions; that is, it should indicate correctly the degree of functional injury, thus carrying prognostic significance.

5. Where less than the minimal amount of liver capable of carrying on function is left free from disease or injury, corresponding lowering of function should be indicated.

6. Where all liver cells are diffusely involved, lowered function should be indicated, but where certain cells are injured while others take on, through compensatory activity, additional function, the total functional capacity alone should be indicated.

7. It should be applicable with as simple technic as possible, so as to be available for general use in all forms of liver injury.

8. It should be applicable without injury of any kind (local or general) to the patient and without placing the liver under any additional strain.

9. The method itself should be mathematically accurate.

10. Its results should be easy of interpretation.

11. Its results should not be subject to influence from involvement of any other organs or systems, except in so far as the liver function is secondarily affected; that is, the test should be specific for liver changes.

The Tests of Liver Function.

Numerous tests have been employed in the effort to determine the functional capacity of the liver in disease. They are mostly based upon the physiological functions of the liver and attempt quantitatively or qualitatively to determine its capacity along such lines.

The Carbohydrate Tests.

The discovery of the glycogenic function of the liver in 1857 by Claude Bernard immediately stimulated extensive work in carbohydrate metabolism by physiologists, pathologists and clinicians. During the course of a rather heated

controversy which waged in the German and French literature between 1875 and 1900 concerning the relationship of the liver to glycosuria after the administration of large amounts of carbohydrate, the idea of utilizing the sugars for testing hepatic function arose. The French school led by Roger,[1] Achard and Castaigne, Baylac[2] and Bierens de Haen[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 to demonstrate any marked or constant reduction in sugar tolerance in cases of liver disease. [328]

In a series of papers in 1898-1900 Strauss[8,9] 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 differences in the amounts of sugar administered. He demonstrated that 100 gm. of dextrose in 500 cc. water given on an empty stomach gave rise to glycosuria in but two out of 38 cases of liver disease, whereas a considerable proportion of all hepatopathies showed the presence of sugar in the urine following the administration of the same amount of cane sugar. He ascribed the difference to the presence of levulose in the cane sugar. He concluded that both cane sugar and dextrose were inapplicable, since there existed a mechanism other than that in the liver capable of metabolising them. He followed his criticism of this work by his levulose test, based on the work of Sachs,[10] which showed a constant decreased tolerance for levulose in liverless frogs. [329]

Strauss' Levulose Test.

One hundred grams of levulose are administered on an empty stomach, and the urine voided during the following four hours tested by Trommer's and Seliwanoff's tests, by fermentation and polarization. The normal individual should tolerate 100 gm. levulose without glycosuria. The test came rapidly into wide use, the results differing with various workers. A contrast between the findings in health and disease, together with the attitude of various workers concerning the value of the test, is seen in the following table.

Author.	Normal livers. Cases.	Positive.	Abn'rml livers. Cases.	Positive	Remarks.
Strauss[8 9]	58	6	25	23	Test is of value.
Ferranini[11]	..	..	16	15	Test preferable to glucose test, which showed only 10 positive.
Landsberg[12]	7	4	21	9	He thinks that normally tolerance varies so much that test is of no importance.
Chajes[13]	21	2	..	..	He thinks that positive findings are rare in normals.
v. Halasz[14]	20	1	23	8	The 8 positive findings were in cirrhosis; considers it of value.
Hohlweg[15]	..	..	30	9	Ten cases were chronic passive congestion.
v. Frey[16]	..	..	26	14	Considering only those positive with more than 0.1 gm. sugar in urine.
Churchman[17]	38	9	12	10	Considers test unsatisfactory since neither a positive nor negative finding is conclusive.
Falk & Saxl[18]	..	..	351	259	Collected from literature.
Bruining[19]	..	..	30	27	Considered the test of value.

In reading the reports of most of these workers, difficulty is experienced in arriving at a conclusion concerning the value of the test in individual cases, since detailed clinical data and autopsy findings are not given. It appears, however, that the test is far from satisfactory and that much reliance from either a diagnostic or prognostic standpoint cannot be placed in its findings.

BAUER'S GALACTOSE TEST.

In 1906 Bauer[20] introduced galactose as a liver test. He administered 40 gm. in 400 to 500 cc. of tea on an empty stomach and determined quantitatively the amount of sugar present in the urine voided in the next 4 to 5 hours. In severe catarrhal jaundice large amounts of galactose appeared in the urine, but as the condition improved the amount in the urine quickly diminished. The amount recovered was

greater in catarrhal jaundice than in jaundice due to other causes (gall stones, cancer). He considers it a test of liver function in catarrhal jaundice. Bondi and König,[21] Riess and Jehn,[22] and Hirose[23] confirmed this, believing it to be of importance in this connection. [329]

The work of Falk and Saxl,[24] v. Frey[10] and Hirose[23] shows that the results of the test are very inconstant in diseases of the liver other than catarrhal jaundice.

In general, the shortcomings and disadvantages of carbohydrate tests, as they have been utilized, might be summarized as follows: (1) The use of arbitrary amounts of sugar without consideration of the normal tolerance of the individual patient; (2) the difficulty of keeping the patient on a carbohydrate free or a carbohydrate constant diet at the time of the test; (3) the practical difficulties of administration (nausea, vomiting, diarrhœa); (4) the disregard of such complications as portal obstruction, autonomic nervous derangement and disturbances of internal secretions influencing carbohydrate metabolism.*

Urea, Amino Acid, and Ammonia Nitrogen.

Glaessner[25] showed in 1907 that in most instances of liver disease an unusually high excretion of amino acid N occurred and that the ratio of amino N to total N was also increased. Whereas normally he found the amino N constitutes only 0.2 to 0.4 per cent,† in pathological conditions of the liver it is decidedly higher, *e. g.*, secondary cancer of the liver 12.4

* Strauss (Deutsche med. Wchnschr., 1903, xxxix, 1780), presents further evidence to establish the value of the levulose test, and insists upon the adoption of a constant amount of galactose (30 gm.) in utilizing Bauer's test in order that the finding of the other tests may be compared.

† Henriques[26] using Sorensen's formol titration method, states that the amino acid N in man on an ordinary mixed diet constitutes 2 per cent of the total N. Levene and Van Slyke[27] place the normal amino acid content of urine as 1 per cent to 2.8 per cent of the total N.‡

‡ Kober (J. Am. Chem. Soc., 1913, xxxv, 1567), utilizing his new method for determining amino N places the amino N at 2.7 to 3.1 of the total N.

[329] to 16.2 per cent, catarrhal jaundice 4.5 per cent, chronic alcoholic and fatty liver 6.9 to 8.33 per cent, luetic hepatitis 4.1 per cent, cirrhosis 3 to 13.4 per cent and in phosphorus liver 6 per cent. Falk and Hesky [28] showed that the urine of pregnant women contained increased amino acid N in 75 per cent of pregnancies. This they attributed to liver injury associated with pregnancy.

Falk and Saxl [24] have attempted further to follow the peptid N as well, determining both the amino and peptid N after feeding various nitrogenous foodstuffs to patients with normal and diseased livers. On feeding glycocoll to patients, they learned that diseased livers could not convert this amino acid into urea, but that it was excreted in part unchanged in
[330] the urine. The peptid nitrogen they found increased when the amino N was high.

In a second communication these authors divided the liver cases into four groups, giving the results as indicated in the literature.

Group I.—Comprising tumors, sarcoma, carcinoma, leukæmia, amyloid disease, and chronic passive congestion. Normal amino and urea N values are encountered in sarcoma, leukæmia, amyloid disease, and chronic passive congestion (Stadelmann). In carcinoma the urea N may be reduced while the amino N per cent is high.

Group II.—Consisting of various intoxications, *e. g.*: chloroform, phosphorus and alcohol; and febrile conditions, such as typhoid, scarlet fever, and pneumonia. The febrile diseases are associated with only slight diminution of urea N, while in the other conditions—phosphorus poisoning, for instance, the decrease is somewhat greater, 74 to 86 per cent (Münzer), 55 to 85 per cent (Sjöqvist) of the total N instead of the normal 91 per cent.

Group III (Icterus).—In 27 cases of catarrhal jaundice and cholelithiasis there was no appreciable reduction of urea N which remained 80 to 87 per cent of the total N (von Noorden), 85 per cent (Mörner and Sjöqvist). The amino N is occasionally increased 8.1 per cent (Mörner and Sjöqvist), 4.9 to 9.5 per cent (von Noorden). The amino and peptid N is increased 4.5 per cent (Glaessner), 4.6 per cent (Falk and Saxl).

GROUP IV (CIRRHOSIS).—The urea N is slightly decreased. The amino N is invariably increased to more than 0.5 gm. according to v. Frey. This he considers of tremendous importance, since only rarely is so high an amino acid N output found in other diseases of the liver. The ammonia N is also constantly increased. [330]

There is found in severe liver involvement, therefore, increase in the amino acid, peptid and NH_3N at the expense of urea N.*

UROBILINOGEN.

As early as 1892 the presence of urobilinogen in the urine was considered as indicative of disease of the liver by v. Jaksch.[29] The test consists simply in the qualitative determination of the presence of urobilinogen in the urine. Since Neubauer's[30] demonstration that Ehrlich's[31] p. dimethyl-amino-benzaldehyde test given by the urine in certain diseases is really a test for urobilinogen, this test is utilized. A few crystals of p. dimethyl-amino-benzaldehyd are added to a few cubic centimeters of urine, the mixture is shaken, and made definitely acid with HCl or acetic acid, whereupon an intense red color develops if urobilinogen be present.

Urobilinogen does not occur in health, the cycle in relation to bile pigments being as follows: Bile pigments are converted in the intestine into urobilinogen, which is absorbed, carried to the liver, and re-converted into ordinary bile pigments. The diseased liver cells having lost, to a greater or less extent, the capacity for reconversion, the urobilinogen, after absorption, continues to circulate and eventually finds its way into the urine. Urobilinogenuria, therefore, indicates functional incapacity of liver cells.

Münzer[32] states that urobilinogen appears in the urine in atrophic cirrhosis; Münzer and Bloch,[33] and also Fischer,[34] find that it appears in acute catarrhal jaundice prior to the appearance of the icterus, and in acute diseases associated with liver involvement (typhoid and pneumonia with acute

* Excellent reviews of this whole subject are given by v. Frey[18] and by Falk and Saxl.[24]

[330] hepatic parenchymatous changes). According to Münzer, urobilinogenuria is not present in pseudo-cirrhosis (Pick's disease), or in chronic passive congestion of the liver, where true liver disease is absent. He, therefore, considers the test of importance in differentiating between atrophic cirrhosis, on the one hand, and chronic passive congestion or pseudo-cirrhosis, on the other. Bauer,[23] however, states that it occurs in almost all diseases of the liver.

It is purely a qualitative test for the existence of liver disease. It probably has the advantage of specificity, since to no other cells has been ascribed the ability to convert urobilinogen into the ordinary bile pigments. From their own work and from a study of the literature, Falk and Saxl [24] conclude that urobilin excretion occurs in very slight injury to the liver, in which it is impossible to detect decreased carbohydrate tolerance or the N partition changes characteristic of insufficiency.

Fibrinogen.

Doyon and Kareff,[36] and Nolf [37] and his school showed that the extirpation of the liver was followed by the rapid disappearance of fibrinogen from the blood. In the report of an occasional experiment on animals, Doyon and his co-workers,[38 39 40] showed that decreased fibrinogen content occurred after chloroform poisoning, and Corin and Ansiaux [41] and Jacoby that it occurred also after phosphorus poisoning.

According to Whipple and Hurwitz,[42] fibrinogen normally exists in plasma of dogs in amounts varying between 0.2 to 0.5 gm. per 100 cc. blood. With the occurrence of liver injury produced by chloroform poisoning it decreases, falling at the time of injury and returning to above normal during the repair which rapidly follows. It may be present in such small amounts that hæmorrhage or hæmorrhagic tendency results, the clots being too soft to check bleeding.

In cases of acute hepatic disease (chloroform poisoning) in dogs and human beings it may fall to 0.048 to 0.034 gm. per 100 cc. blood, in chronic liver cirrhosis (Whipple [42]) to 0.05 gm. or even lower. This decrease is not constant. A

high fibrinogen content may exist in the presence of definite liver disease. However, when the content is low it is of grave prognostic import. [330]

The test is made as follows: 25 or 50 cc. of clear plasma obtained by centrifugalizing the blood, which has been received into oxalate solution, is heated in a water bath at 59° C. for 20 to 30 minutes. Fibrinogen is thrown out as a white flocculent precipitate, is collected on a Gooch crucible, washed with H_2O, alcohol and ether, dried and weighed. [331]

Lipase.

The amount of lipase in the blood has been shown to be markedly increased in certain diseases of the liver (Whipple, Mason & Peightal).[44] They utilized Loevenhart's[45] method of determining lipase, which is done according to the following technic: Four tubes are prepared, each containing 1 cc. of plasma, or serum, diluted with 4 cc. of distilled H_2O and to this is added 0.3 cc. toluol to prevent bacterial infection. To two of the tubes is added 0.26 cc. of ethyl butyrate, the other two serving as controls. After shaking, the tubes are stoppered and placed in an incubator at 38° C. for 18 to 24 hours, then cooled in water and to each is added three drops of azolitmin as an indicator. They are then titrated in pairs to neutrality, the controls with 1/10 N acid, the other with 1/10 N alkali. The controls with this indicator show the blood alkalinity to be 0.1 cc. of N/10 acid, while the butyrate tubes show an acidity of 0.1 to 1.2 cc. of N/10 alkali. The lipolytic activity of normal blood or serum expressed in terms of N/10 HCl is, therefore, 0.2 to 0.3 cc.

Experimental injury to the liver resulting from chloroform, phosphorus, hydrazine, etc., always produces an increase in plasma lipase to from 2 to 8 times the normal. After chloroform anæsthesia of 1 to 2 hours' duration, in dogs the plasma lipase increases to 1 to 2 cc. N/10 acid. This increase occurs during the first few hours after anæsthesia, lasts two to three days, and then slowly decreases as repair is established, finally reaching normal again on complete recovery. If the animal be fatally poisoned, the lipase remains high until death on the fourth or fifth day.

[331] The test has been applied clinically by Whipple in a limited number of cases. A case of eclampsia showed a very high plasma lipolytic activity and at death showed hæmorrhagic portal liver necroses. Pneumonia, peritonitis, leukæmia, and various infections show an increased lipase, at times more than double the normal. Early stages of liver cirrhosis show a high lipase while late stages may, unless complicated with some liver necrosis, show a low lipase. A normal content was found in pernicious vomiting, uræmia with convulsions, in jaundice and obstructive jaundice of months' duration.

Ghedini's Ferment Test.

Within the current year Ghedini[46] has proposed a new test which is based upon the presence in the blood serum of a ferment which he claims arises in the liver cells and which is capable of converting glycogen into maltose, isomaltose, and glucose. In short, this must be a test for two blood ferments, diastase and maltase. Diastase varies tremendously in normal sera, consequently, *a priori,* this in itself would vitiate the test. Sufficient evidence has not been presented to establish the liver as the sole source of the ferment or ferments involved.

General Criticism of Functional Tests.

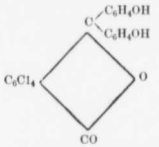
With the exception of the urobilinogen test, none of these deal with functions which can be said with certainty to be specific of the liver, since the muscles play a large rôle in carbohydrate metabolism, and the kidney, according to recent work of Van Slyke,[47] possibly participates in the conversion of amino acids into urea. The results of the tests seem to be inconstant, with the possible exception of the urobilinogen test, which is positive in most mild diseases of the liver. However, it only indicates the existence of liver injury and gives no conception of its extent.

Technical difficulties are encountered in some of the tests. The administration of large amounts of carbohydrates leads to nausea, vomiting, and diarrhœa, all of which vitiate the test. Considerable chemical training and equipment are

necessary to carry on the work in relation to the nitrogenous [331] metabolism, while large quantities of blood (50 cc.) are necessary for the fibrinogen studies.

Since the tests most used clinically have lacked a quantitative side they have proven of much less value from the standpoint of prognosis than similar studies in relation to the kidney. They have indicated only the presence of disease, but not the extent of involvement. Furthermore, the lack of clinical and autopsy data in the various publications detracts from their value, since one cannot form conclusions concerning the value of the findings in the individual cases.

PHENOL-TETRACHLOR-PHTHALEIN.



This compound was first prepared by Orndoff * and Black,[46] of Cornell University, in 1908. Its pharmacological properties were studied by Abel and Rowntree [49] in 1909. "Its physical and chemical properties present such similarities to those of phenolphthalein that one is surprised to learn that there are certain well-marked pharmacological differences between them. Like phenolphthalein, it is an odorless, tasteless, crystalline compound, insoluble in water and forming deeply colored hydrolizable salts with alkalies. Its ionization constant has not yet been determined, but its avidity as an acid cannot be far removed from that of phenolphthalein, inasmuch as solutions of its salts (Na or K) are promptly decolorized on the addition of serums or by contact with animal tissues. In this respect its salts differ in no way from those of phenolphthalein. The two compounds have, on the whole, a very similar pharmacological action."

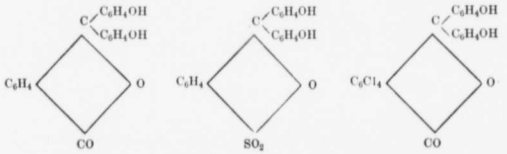
* It is with great pleasure that we take this opportunity of expressing our gratitude to Professor Orndoff for his kind response to our repeated requests for the phenol-tetrachlor-phthalein used in this and other studies.

[332] From the pharmacological studies of Abel and Rowntree[4] it was learned that phenol-tetrachlor-phthalein itself was non-irritant locally, but that solutions of its alkali salts administered subcutaneously act as decided irritants unless they are highly diluted since "such salts formed as they are by neutralizing a very weak acid with a very strong base are strongly hydrolyzed in aqueous solution and hence act upon the tissues like solutions of caustic soda." It was further learned in animal experimentation that the tetrachlor body has a very low toxicity; that it exercises no hemolytic influence; that it does not affect the coagulability of the blood; that, associated with its rapid intravenous injection, there occurs a fleeting drop of blood pressure which is followed by a slight increase (15 to 25 mm. Hg.) lasting 10 to 20 minutes, provided large injections are given; that it possesses no bactericidal or antiseptic properties; that it does not influence the rate of flow of either pancreatic juice or bile; that it appears in the bile first as a conjugated body and later in its free form, that in moderate quantities, following its subcutaneous administration in olive oil or its intravenous injection as a disodium salt, it escapes from the body only in the bile, the amount that passes into the intestines in other secretions being so minute that it can barely be detected; that a small amount is re-absorbed from the large intestine and that administered in a dose of 0.4 gm. in olive oil subcutaneously it exhibits laxative properties.

Further work showed that clinically the drug administered in olive oil displayed definite laxative characteristics, but that its low solubility in oil, necessitating a large bulky injection, stood in the way of its general adoption in this connection.

The effect of slight changes in the chemical formula of some of these phthaleins upon their pharmacological behavior, especially as to the channel of their excretion, is exceedingly interesting. Phenolphthalein given in moderate quantities subcutaneously in oil or intravenously as the disodium salt is excreted both in the urine and in the bile. The replacement of the CO by an SO_2 group yields phenolsulphonephthalein for which the kidney is the chief organ of excre-

tion, while the substitution of the hydrogen atoms of the [332] phthalein radical of phenolphthalein by four chlorine atoms gives phenol-tetrachlor-phthalein, the excretion of which is specific to the liver.



The specificity displayed by the kidney in the secretion of phenolsulphonephthalein together with its tinctoral properties which are ideally adapted for quantitative work, led to the introduction of this body as a renal functional test in which connection it has proven of the greatest value prognostically and diagnostically, and from the standpoint of treatment.

The striking specificity displayed by the liver towards the excretion of this dye suggested to one of us (R.) the possibility of utilizing the drug as a functional liver test, the underlying principle involved being identically that concerned in the phenolsulphonephthalein test of kidney function, *e. g.*, the specific excretion of a dye by a single organ and the decreased capacity for its excretion consequent upon lowered function resulting from disease.

With this idea in view the normal quantitative excretion was investigated and determined in rabbits to be from 30 to 45 per cent of the amount injected. The possibility of utilizing tetrachlorphthalein as a test for liver function was suggested to Dr. G. H. Whipple, who very kindly applied the test to a series of dogs suffering from experimental liver lesions. These preliminary tests showed a marked decreased excretion to exist in disease. A simultaneous clinical and experimental study has been carried on, the results of the experimental work being reported in this number of the BULLETIN by Whipple, Peightal and Clark.

[332] METHOD OF PREPARING SOLUTION FOR INJECTION.

The preparation injected is an aqueous solution of the disodium salt prepared as follows:

2.5 gm. of phenol-tetrachlor-phthalein are placed in a 200 cc. Erlenmeyer flask with 5 cc. of 2/N NaOH solution and 45 cc. of freshly distilled water. This is boiled for 20 minutes under a reflux condenser. The solution is filtered into a 100 cc. flask, when it is ready for use. This gives approximately a 5 per cent solution which is almost isotonic with the blood.

The solution is an intense purplish red color. It will not keep for more than a few days since the phthalein is precipitated by CO_2 from the air. Even when CO_2 is excluded some precipitation still occurs from the loss of the alkali through union with the silicates of the glass container. In the event of only a small amount of precipitate, sterile filtration can be carried out and the resulting solution used for injection, provided a fresh standard for comparison is prepared.

METHOD OF ADMINISTRATION.

Arbitrarily 8 cc. of this solution, approximately 400 mg. of tetrachlor-phthalein has been selected. This amount is sufficient to give a most intense purplish red color to 20 litres of water. Its administration in health is never followed by the appearance of the dye in the urine,* and this amount insures in health an intense color in the final preparation of the fæces which is used for the quantitative determination.

The dye is administered intravenously by gravity with antiseptic and aseptic precautions and with the usual intravenous technic. The funnel and system are filled with freshly
[333] distilled water and after the flow is well established the phthalein solution is added. Fifty to 100 cc. of water are used and the phthalein solution is washed in with freshly distilled water until the fluid entering the vein is colorless. Ten to 15 minutes are required for its administration. Physi-

* In health the dye has been recovered in the urine of a normal patient following injection of 0.5 gm.

ological salt solution may be preferable to distilled water for [333] use in this injection.

Collection of Materials for Study.

Active purgation is instituted prior to administration of the dye and throughout the time of observation, usually by means of compound cathartic pills. The stools are collected for 48 hours, the urine for 24 hours. In the event of little or no fæces being obtained enemata are used, but unless the normal amount of dye is recovered, the test must be discarded, since low findings under these conditions could not be accepted.

Method of Determining the Amount of Phthalein in Stools.

The total 48 hours fæces are placed in a 2 L. bottle and diluted with water to 1 or 1.5 L. depending on their amount. This is placed in a shaking machine for from 5 to 20 minutes. Without allowing time for sedimentation 1/10 of the total is placed in a 1 L. flask and to this is added 5 cc. of 40 per cent NaOH which causes the mixture to take on a dirty red color. Dilution is made with water to 1 L. A stopper is inserted and the mixture thoroughly shaken. One hundred cubic centimeters of this preparation is placed in a 200 cc. flask, 5 cc. of saturated basic lead acetate added, resulting in a decolorization of the mixture and the throwing out of a heavy lead precipitate which carries down all of the pigments, leaving a clear colorless supernatant fluid. Five cubic centimeters of 40 per cent NaOH are added; this again elicits the red phthalein color, but does not redissolve the other lead pigment combinations. In certain instances 5 cc. of NaOH at this point are not sufficient to elicit the maximum intensity of red and more should be added until the maximum is reached, but not sufficient to free the other pigments from their insoluble lead combination. The contents of the flask are made up to 200 cc., shaken, and a small part filtered off, or the solution is allowed to stand five minutes, when in many cases a clear red supernatant

[333] fluid ready for estimation can be decanted off. This solution is compared in the Rowntree and Geraghty modification of the Autenrieth Königsberger colorimeter with a 20 mg. to a litre solution of disodium salt of tetrachlor-phthalein (*e. g.*, 0.4 cc. of the original solution to 1 L. plus sufficient NaOH to insure maximum color). With these dilutions the amount of dye present is indicated directly in per cent.

When the amount recovered is below normal, it is advisable to add 2 to 3 cc. more alkali to the 200 cc. preparation and redetermine, thus insuring that the maximum color has been elicited. The addition of large quantities of alkalies is undesirable, since it sets free the other pigments, rendering the solution yellowish red instead of purplish red.

Not more than ten minutes are required to carry out the test after the fæces are removed from the shaker.

Where difficulty is experienced on account of the quality of the color, the following procedure, which may prove of some value in certain instances, may be utilized. After the addition of about 10 cc. of 40 per cent sodium hydroxide, the fæces are made up with water to one litre. To 1/10 of this is added 5 cc. of sodium hydroxide and water up to one litre. Of this 100 cc. is placed in a 200 cc. flask and to it 5 to 10 cc. or more, of a calcium chloride mixture * is added until the best quality of color is elicited. Dilution is made to 200 cc., the mixture is allowed to stand from one-half to 24 hours, a small amount of the supernatant fluid is filtered off, and read against the standard.

In our earlier methods an attempt was made simply to dilute the fæces, filter off and determine the amount present, but quantitative determination is usually impossible in this way on account of the large amount of coloring matter present in the mixture. Later basic lead acetate was used and the precipitate collected on a filter, extracted repeatedly with hot alkaline alcohol and the alcohol diluted to the proper extent, alkali added and determinations made. This method

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* $CaCl_2$ 90 gm.
Conc. NH_4OH 10 cc.
Water 50 cc.

was time consuming, required much alcohol, and the extrac- [333]
tion of tetrachlor-phthalein was never complete. Finally the method presented above was devised.

Accuracy of Method.

A number of procedures were utilized to determine the degree of accuracy of the method and to determine what part the personal equation plays in regard to it.

Is the total dye substance recovered? Accurately measured amounts of the original solution of the disodium salt were added to the fæces, thoroughly mixed by one member of our group, and determined by another who was unfamiliar with the amount added. In certain instances independent readings were made by the entire group. The results are as follows:

Table I.

Number	Amount added	Amount recovered		
		B	R	H
I	25 %	.....	23.5%	.....
II	12.5%	.....	12 %	.....
III	12.5%	12 %	12.5%	12.5%
IV	9.4%	8 %	10 %	10 %
V	25 %	23.5%	23 %	22.5%
VI	18.8%	17 %	19 %	17 %

Since only an aliquot portion of the fæces is used for the determination, the necessity of justifying this procedure seemed advisable. This was done as follows: The technic was performed on several fractions by one and readings made on the final solution by the three members of the group. The results in per cent are shown in Table II.

Table II. [334]

Number	B	R	H
I	16 %	14 %	16 %
II	16 %	15 %	17 %
III	17.5%	15.5%	16 %
IV	16 %	14 %	15.5%
V	17 %	14.5%	17 %
VI	16.5%	15 %	17 %
VII	16 %	13.5%	15 %

[334] From the table it will be seen that differences in reading the same solution may occur where various individuals are making the readings, R. reading constantly lower than B. or H., the difference, however, never being greater than 2.5 per cent.

Simultaneously it is seen that slight differences occur in different fractions, as evidenced by III and VII, the latter being lower according to all three observers. Here again, however, the difference is only slight.

It was also considered advisable to check the readings on various fractions at the point where lead acetate is added. The following table shows a series of readings of different fractions:

TABLE III.

Number	R	B	H
I	29 %	30 %	29 %
II	28.5%	30 %	28 %
III	29 %	29.5%	28.5%
IV	28.5%	29.5%	28 %
V	28 %	29.5%	27 %
VI	28.5%	29 %	30 %
VII	29.5%	29.5%	29.5%

No destruction of the dye occurs after the stools are collected, so that immediate determination is not necessary. The following table indicates the stability of the drug.

TABLE IV.

Patient	First determination	Time elapsing	Second determination
P.	54%	1 week	55 %
M.	18%	1 "	20 %
L.	47%	5 "	45 %
McC.	31%	5 "	33 %
S.	28%	7 "	32 %
G.	33%	12 "	33 %
B.	26%	15 "	24.5%
A.	26%	19 "	23 %

No preservatives were used so that decomposition of the dye does not apparently result from bacterial infection. Slight differences in the readings can be explained possibly by differences in the standards used for comparison, since in the first instance

each test was made from the standard prepared from the solution injected, whereas all of the later readings were made against a single freshly prepared solution. [334]

It is evident, therefore, that the test, though not absolutely quantitative, gives reliable results approximately correct, and that dependence can ordinarily be placed upon its findings, errors of more than 5 per cent being rarely encountered. Difficulties may arise at times, as will be seen later.

Undesirable Features of the Test.

The collection of total fæces for 48 hours is the most difficult part of the technic to control. It certainly constitutes an objectionable feature of the test. Simple as it may seem, even in the best institutions, except under special provisions, it is difficult to find a corps of attendants capable of carrying out proper collections. Despite all precautions, in four instances some of the fæces was lost in collecting. In these cases no drug at all, or a small amount only (at most 10 per cent), was recovered, the patients showing neither signs nor symptoms of liver involvement. Repetitions within a week in each instance revealed a normal, or practically normal excretion. Careful questioning of patients and attendants showed in one or two instances that losses undoubtedly had occurred.

In two other cases, both myocardial decompensation, repetition of the test within a week showed a tremendous increase in the dye output. Hesitation is felt in claiming that the increase was entirely due to improvement in liver function, although both cases were *in extremis* at the time of the first test and clinically in fair condition at the time of repetition. Until other such cases are encountered where more certainty exists in relation to total collection, losses in collection cannot be excluded as the cause of the low output in the first instance.

The collection over 48 hours has a second objectionable feature. The excretion of the drug occupies but 12 to 18 hours in health, consequently 48-hour collections are apt not to show minor grades of injury so well, since the continuous secretion of smaller amounts of the dye over longer periods, 24 to 36 to 48 hours, may bring the total output close to normal.

The quality of red color obtained in certain instances con-

[334] stitutes the third objectionable feature of the test. This objection is minimized by the method now utilized. However, with the best technic the color finally obtained may in a considerable proportion of cases (10-20 per cent) exhibit yellowish red or brownish red qualities instead of the purple red desired. Such determinations are less accurate, but only in rare instances does the color constitute a very serious difficulty.

In myocardial insufficiency with feeble circulation localized thrombosis of the veins at the point of injection may occur. This has been encountered in ten instances in this series. Slight local pain together with resistance offered to the palpating finger was noted. Thrombosis, however, was not encountered except in myocardial insufficiency, marked anæmia, or where advanced phlebosclerosis was present. The introduction of large quantities of fluids is inadvisable in the presence of a weak myocardium and consequently in this connection great dilution cannot be utilized.

The fate of the unrecovered portion is unknown. Apparently, however, no destruction of the drug occurs after its entrance into the intestinal tract, since the amount of drug recovered in a dog's fæces corresponds closely to that recovered directly from a permanent biliary fistula following the same dosage.

The test is inapplicable where obstruction to the biliary passages exists and is, therefore, limited in its application.

[336] The possibility of utilizing the time required for the disappearance of the drug from the blood after its administration is being tried in the hope that some of these difficulties may be surmounted.

The Results of the Test.

Eighty determinations of liver function have been made in 67 patients. The series contains normal controls and various types of liver injury.* The test was applied in 24 cases in

* We wish to express our thanks to Dr. Ernst Zueblin of the University of Maryland Hospital, to Drs. Boggs and Snowden of Bay View Hospital, and to the Medical and Surgical staffs of our hospital for the opportunity of studying the clinical material.

which the livers were believed to be normal. The amount of [336] drug excreted varied from 30 to 52 per cent, as will be seen in Tables V and VI. In one constipated patient only 24 per cent was recovered.

Cases in Table VI are considered as normal controls, since the excretion is normal with one exception, a case of typhoid (third week) in which focal necrosis cannot be excluded. The average output in afebrile normal 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 48 hours.*

Dogs with biliary fistulæ furnished some interesting data in relation to the rate of normal excretion of the drug. It appears in the bile in its free form regularly within 10 to 15 minutes following the intravenous administration of 100 to 200 mg. The same time is required in human beings, since, in the one case studied after operation, the drug was present in the bile after 15 minutes. The largest amount recovered from dogs was 55 per cent. The maximum excretion is quickly reached, since in one instance 27 per cent was recovered during the first 6 hours. In health excretion is complete within 16 to 20 hours.

The dye output is independent of the quantity of the bile excreted. Following the injection of the same amount of phthalein into the same dog more dye was recovered in 8 cc. in one instance than in 80 cc. of bile in another instance. This is analogous to the independence between the amount of sulphonephthalein excreted and the quantity of urine.

Influence of Fever.

Pyrexia *per se* has no effect upon liver function, as will be seen from Table VI. Case Q. T. was an acute febrile condition with temperature 104° to 105° F. at the time of the test, and case A. B., a chronic one, the temperature reaching 104° F. every day for over a month, yet both showed a normal phthalein output. Case I. B. is discussed above.

*** 48-hour collections are necessary, since in several instances an appreciable amount of dye (8 to 10%) was recovered in the second 24 hours.**

TABLE V. NORMAL CONTROLS.

No.	Name.	No.	Diagnosis.	Age—yrs.	Date—1913.	Per cent. in faeces.	Urine.	Remarks.
1.	S. H.	.....	Normal	27	1–28	30	..	
2.	A. B.	.....	Normal	25	1–28	30	..	
3.	B. E.	87296	Convalescent typhoid	22	2–15	42	..	Temperature normal for 1 week.
4.	C. McC.	87584	Splanchnoptosis	32	2–22	39	..	
5.	F. B.	87617	Orthostatic albuminuria	17	2–22	31	..	
6.	A. L.	87810	Neurasthenia	45	2–28	52	..	
7.	A. A.	87907	Diabetes	48	3–5	40	..	
8.	M. M. C.	87809	*Chronic tuberculosis	44	3–19	*22–33	..	Afebrile 1 week; earlier 22%.
9.	J. M.	88157	Neurasthenia	60	3–19	52	..	
10.	D. W.	.....	Convalescent pneumonia	27	6–10	24	..	Afebrile 1 week.
11.	L.	.....	Convalescent malaria	22	6–10	48	..	Afebrile 6 days.
12.	L. F.	89350	Rheumatic fever convalescent	24	5–29	30	..	Afebrile 1 week.
13.	C.	.....	Pulmonary tuberculosis	..	6–13	39	..	Afebrile.
14.	W.	.....	Fracture of femur	..	6–17	42	..	
15.	K.	.....	Fracture of femur	..	6–17	34	..	
16.	A.	.....	Gunshot wound	..	6–20	40	(1)	
17.	B.	.....	Fracture	..	6–20	35	(2)	500 mg. injected.
18.	M.	.....	Gonorrhœal arthritis	..	6–20	34	..	

(1) + Slight. (2) + Considerable.

TABLE VI. FEBRILE CASES.

No.	Name.	No.	Diagnosis.	Age—yrs.	Date—1913.	Per cent. in stool.	Urine.	Remarks.
19.	G. S.	87326	Pulmonary tuberculosis; pleurisy with effusion	43	2–7	43	..	99–102°F.
20.	J. F.	86802	Pulmonary tuberculosis; pleurisy with effusion	34	2–7	40	..	99–102°F. for 2½ months.
21.	I. B.	87671	Typhoid fever	14	2–28	27	..	15th day of fever.
22.	S. T.	88038	Acute lobar pneumonia	18	3–10	39	..	Fifth day of disease temperature 104–105°F.
23.	A. B.	87794	Acute tubercular pleurisy with effusion	28	3–19	43	..	Continuous fever 104°F. for over 1 month.
24.	B. K.	.....	Acute rheumatic endocarditis	30	3–19	40	..	Temperature 103°F. for 1 month.

TABLE VII. ANAEMIA.

No.	Name.	No.	Diagnosis.	Age—yrs.	Date—1913.	Per cent. in stool.	Urine.	Hb.	R. B. C.
25.	C. R.	88350	Hypernephroma	56	3–29	41	..	28	1,600,000
26.	O. K.	88692	Secondary anaemia; hemorrhoids	21	4–24	35	..	21	2,680,000
27.	J. S.	88675	Pernicious anaemia	20	4–23	18–20	..	31	1,700,000
28.	W. S.	88825	Secondary anaemia	45	4–27	28	..	23	2,700,000
29.	H.	.....	Gastric carcinoma	38	5–24 6–10	14 24	..	20	2,300,000
30.	L. F.	.....	Gastric carcinoma	39	6–10	20	..	22	2,800,000

In severe grades of secondary anæmia a normal, or practically normal, output may be encountered, as in cases O. K. and W. S., Table VII. From these cases it is justifiable to conclude that secondary anæmias of slow development must be of an extreme grade before liver function is affected. Experimental evidence indicates, however, that acutely developing severe secondary anæmia does influence the phthalein output, as will be seen from the following protocol.

Female Dog. 18.5 Kg.

5- 3-13. Excreted 35 per cent tetrachlorphthalein.
5- 9-13. Bled 640 cc. The following morning Hb. 64 per cent. R. B. C., 4,800,000. Injected 200 mg. phthalein.
5-12-13. Hb. 75 per cent. Phthalein recovered 41 per cent.
5-13-13. Bled 600 cc.—ether anæsthesia. The following morning Hb. 48 per cent. R. B. C., 3,840,000. Phthalein injected.
5-16-13. Hb. 50 per cent. Phthalein recovered 30 per cent.
5-18-13. Bled 650 cc.—ether anæsthesia. The following morning Hb. 42 per cent.
5-20-13. Hb. 42 per cent. Phthalein recovered 15 per cent.*
5-26-13. Bled 600 cc. The following morning Hb. 30 per cent. R. B. C., 2,400,000.
5-29-13. Phthalein recovered 13 per cent.
6-12-13. Phthalein recovered 27 per cent.
7- 7-13. Hb. 90 per cent. R. B. C., 5,586,000. Phthalein injected.
7- 9-13. Phthalein recovered 39 per cent.

A second dog responded in the same way, the phthalein decreasing from 50 per cent to 10 per cent, at which time the Hb. was 30 per cent and the R. B. C. below 2,000,000. This dog, however, had been accidentally inoculated with sarcoma which was unexpectedly discovered from microscopical study of the liver, the dog dying on the table during the last bleeding.

There exists a striking analogy in the influence of secondary anæmia on liver and on kidney function, as will be seen by comparing the above protocols with experiments previously reported by Rowntree and Geraghty[51] on the influence of anæmia on kidney function.

* 57 per cent of sulphonephthalein was recovered in two hours. This indicates only a slight reduction in kidney function.

The two cases of anæmia secondary to gastric carcinoma [336] show decreased function. However, metastasis cannot be excluded in either instance. In severe phenyl hydrazine anæmia in dogs Whipple saw but little influence on liver function. In the single case of pernicious anæmia a decreased output was found.

From such a limited number of cases no conclusions can be drawn except that secondary anæmia must be of an extreme grade before the excretion of the dye is decreased. The experimental results suggest the necessity of more observation along these lines.

Hepatopathies.

Thirty-seven cases exhibiting signs or symptoms of abnormalities of the liver have been investigated, the series including enlargement dependent upon cardiac disease, cirrhosis, carcinoma, amœbic abscess, luetic hepatitis, cholecystitis, and enlargement associated with leukæmia. A detailed description of the history and clinical findings of each of these cases, together with the phthalein output, is appended. Table VIII shows the results of the test in these cases.

Myocardial Insufficiency. [338]

Eighteen of the hepatopathies were associated with some degree of myocardial insufficiency. In nine the phthalein output was normal. Five cases showed marked involvement of function as indicated by the test and in each instance the low output was associated with an extreme grade of broken compensation, whereas the break in the nine cases already mentioned was much less severe. In two instances a subsequent test a week later, at which time the cardiac condition was improved, revealed a marked increase in the phthalein excretion, although hesitation is felt, as intimated above, in ascribing this difference between the two findings entirely to restoration of cardiac compensation.

Of the other four cases, one with a 21 per cent output (I. B.) had miliary tuberculosis which affected the liver, one (M) in moderate decompensation excreted 20 per cent,

TABLE VIII. PATHOLOGICAL LIVERS. HEPATOPATHIES.

No.	Name.	No.	Clinical diagnosis.	Age—yrs.	Date—1913.	Per cent. in stool.	Urine.	Remarks.
31.	C. H.....	87440	Myocardial insufficiency; acute endocarditis; tuberculous polyserositis.	47	1–7	7	..	Autopsy.
					2–14	18	..	
					4–26	15	..	
32.	T. A.....	87515	Arteriosclerosis; chronic nephritis; mild myocardial insufficiency.	39	2–5	28	..	
33.	R. S.....	87589	Myocardial insufficiency; arteriosclerosis.....	36	2–15	9	..	
34.	M. L.....	87653	Myocardial insufficiency; mitral insufficiency and stenosis; adherent pericardium.	48	2–22	33	..	
35.	P. G.....	87770	Myocardial insufficiency; aortic and mitral insufficiency.	23	2–28	42	..	
36.	C. G.....	87747	Myocardial insufficiency; chronic bronchitis; emphysema; cirrhosis of liver?	66	2–28	33	..	
37.	R. B.....	87855	Myocardial insufficiency; arteriosclerosis.....	45	3–5	8	..	Small specimen of stool.
38.	C. G.....	88093	Myocardial insufficiency; myocarditis; acute endocarditis.	51	3–15	35	..	Autopsy.
39.	J. F.....	88071	Myocardial insufficiency; mitral stenosis and insufficiency.	40	3–15	33	..	
40.	B. S.....	88324	Myocardial insufficiency; mitral insufficiency and stenosis; aortic insufficiency.	27	3–24	33	..	Died 4–12. No autopsy.
41.	E. G.....	88884	Myocardial insufficiency; dilated aortic arch; syphilis; chronic nephritis?	42	4–27	32	..	
42.	J. J.....	.....	Myocardial insufficiency; aortic insufficiency; dilated aortic arch; syphilis.	43	5–12	5*	..	Autopsy 6–15–13.
					5–19	24	..	
43.	T. G.....	89247	Arteriosclerosis; myocardial degeneration; chronic nephritis	52	5–17	30	..	
					5–24	28–30	..	
44.	I. W.....	89144	Myocardial insufficiency; arteriosclerosis.....	48	5–22	28	..	
45.	I. B.....	89301	Miliary tuberculosis; tuberculous pericarditis (adherent); myocardial insufficiency.	26	5–27	21	..	Autopsy.
46.	S. R.....	89417	Myocardial insufficiency.	33	5–24	7	..	In severe cardiac break.
					6–3	33	..	In good clinical condition.
47.	R. P.....	.....	(1) Myocardial insuffic...					

								In good clinical condition.
47.	R. P....	(1)	Myocardial insufficiency	..	4–28	35	..	
48.	M....	.....	Myocardial insufficiency	40	6–13	20	..	In moderate cardiac decompensation.
49.	J. N.....	88072	Cirrhosis of liver	52	3–10	23	..	Normal fibrinogen; clinically well, admitted only for test.
50.	D. M.....	(2)	Cirrhosis of liver	56	3–26	6	..	Special precautions in collecting specimens.
51.	W. G.....	(1)	Myocardial insufficiency; cirrhosis of liver	..	4–28	43	..	Died about 3 weeks later. No autopsy.
52.	K. Fischer....	(3)	Carcinoma of stomach; metastasis to liver	48	3–19	8	1.5%	Autopsy.
53.	A. Hepburn...	(2)	Carcinoma of gall bladder	67	4–22	20	..	
54.	E. S.....	88424	Carcinoma of stomach with metastasis	33	3–31 4–8	6* 24	.. ..	Unsatisfactory specimen of stools.
55.	G. D.....	.....	Carcinoma of stomach with metastasis to liver	72	....	14	..	
56.	M. S.....	87656	General abdominal carcinomatosis	40	3–5	39	..	
57.	J. T.....	89781	Carcinoma of liver	45	6–20	7	(4)	Collection for 30 hours.
58.	M. B.....	87983	Suspected amoebic abscess of liver	27	3–10	33	..	Explored; no abscess found.
59.	J. T.....	(1)	Amoebic abscess of liver; drained	45?	4–28	23	..	
60.	F. R.....	88825	Hepatitis; tuberculous peritonitis (?)	40	4–27	30	..	Unimproved on discharge.
61.	E. P.....	88861	Splenomegaly; perihepatitis (?)	19	5–10	23	..	Discharged; condit'n unchanged.
62.	J. McC.....	89082	Tuberculous peritonitis (?); syphilitic hepatitis (?); mitral insufficiency.	52	5–17 6–10	31 32	.. ..	
63.	J. K.....	89439	Acute cholecystitis	56	5–29	28–30	..	Discharged; well.
64.	H. A.....	89593	Tuberculous peritonitis (?); liver cirrhosis (?)	52	6–7	22	..	Discharged; condit'n unchanged.
65.	E. T.....	(2)	Syphilis of liver; syphilitic endocarditis; mitral insufficiency.	33	4–22	18–22	..	
66.	G. S.....	(2)	Syphilitic hepatitis (?); amyloid liver (?); pulmonary tuberculosis.	27	4–22	40	..	Autopsy.
67.	R. S. P.....	.....	Lymphatic leukaemia	..	6–13	55	..	

(1) University Hospital. (2) Bay View. (3) Surgical No. 31832. (4) +Slight.

[338] while two others (T. A. and I. W.) were practically normal (28 per cent).

It is therefore evident that liver function as indicated by the test only becomes seriously affected in those cases in which the myocardial insufficiency is extreme. This is in striking analogy to the condition of renal function as indicated by sulphonephthalein,[52] for only in the cases of extreme cardiac decompensation or passive congestion, clinical or experimental, is the output of phthalein appreciably decreased. The first evidence of cardiac improvement is also associated with a prompt return of renal function to normal.

Cirrhosis of the Liver.

Two cases, typical clinically in every respect, have been studied. One, D. M., was *in extremis* at the time of the test, showing both toxic and obstructive symptoms. His output was only 6 per cent and no dye appeared in his urine. Death occurred two months later, but no autopsy was obtained. The other case, J. N., had been under observation for years. Six years earlier, he had 272 litres of ascitic fluid removed. For some years, however, he has been practically free of symptoms, carrying on his usual work. The patient considers himself well and exhibits but few residues of his former disease. The output, 23 per cent, is well in keeping with his present clinical condition.

Cirrhosis possibly existed in two other cases, W. G. and H. A. The former clinically looked like cirrhosis, but myocardial insufficiency was also present. A normal output was found. The patient died three weeks later, no autopsy being obtained. The existence of cirrhosis in the other patient, H. A., with a 22 per cent output, is very questionable.

The limited number of cases and the absence of autopsy data allow of no conclusions concerning the excretion of the drug in cirrhosis.

Carcinoma of the Liver.

Three verified cases of liver carcinoma showed a decreased function. In one, K. F., the output was only 6 per cent. This patient came to autopsy, the destruction of liver tissue

being very marked, together with a uniform central necrosis involving about two-fifths of each lobule. The other patients showed 7 and 14 per cent excretion respectively, the liver involvement being marked on exploration. H., with cancer of the gall bladder, excreted 20 per cent. This patient is still living. [338]

In one patient, E. S., suffering from carcinoma of the stomach, 24 per cent was recovered. No metastases were visible on exploration.

In one case of general abdominal carcinomatosis without liver involvement, M. S., there was no decrease in phthalein output.

Amœbic Abscess.

A week after the institution of drainage in a case of amœbic abscess of the liver (W. G.) the test was applied and 23 per cent recovered, the patient at this time being in a good clinical condition. A second suspected case showed a normal function. This case was explored by Professor Halsted and no abscess was found.

Miscellaneous Liver Cases.

Three of these cases were very similar clinically, exhibiting an unexplained ascites. Luetic hepatitis and tuberculous peritonitis were suspected. Two showed a normal function, while 22 per cent was recovered in the other case in which liver cirrhosis also had been suggested as a clinical diagnosis.

One case of cholecystitis showed a normal function. E. P., with a diagnosis of splenomegaly and perihepatitis, excreted 23 per cent, while from E. T., with luetic hepatitis and myocardial insufficiency 18 to 22 per cent was recovered.

G. S., in whom an amyloid and luetic liver was diagnosed clinically, had a normal excretion. The patient later died of his pulmonary tuberculosis and at autopsy the liver change present was chronic passive congestion with some atrophy.

The highest phthalein output in this entire series was encountered in a case of lymphatic leukæmia with enlarged liver.

Unfortunately it has been possible to apply this test only

[338] to a limited number of diseased conditions. There still remain a number of diseases, for instance uræmia, eclampsia, pernicious vomiting, septicæmia, peritonitis, and the like, associated with intoxication and depression of functional activity in which the results of the phenoltetrachlorphthalein test may be of interest prognostically.

The number of cases studied is too small to permit of far-reaching conclusions. However, the constant findings in health, the decreased output in liver disease, the analogy between the effect of anæmia and myocardial insufficiency upon kidney and liver function as indicated by the sulphonephthalein and the tetrachlorphthalein tests, the results of the test in experimental liver lesions, and the established value of sulphonephthalein, based upon the same principle as the test in kidney diseases, all indicate that the excretion of tetrachlorphthalein will be useful in the estimation of the functional capacity of the liver.

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APPENDIX.

(25.) No. 88350. C. R., age 56, male, colored.

Clinical diagnosis: Hypernephroma (rt. kidney). Metastases. Myocardial insufficiency. Chronic nephritis. Uremia. For eight months difficulty on urination with passage of blood. Much strangury. On admission: Extreme emaciation, slight dyspnœa. Heart enlarged with systolic blow. Liver dulness from fifth rib to 8 cm. below costal margin in right mamillary line where edge is indefinitely felt. Not tender. Below liver in right flank is felt a round tumor, probably kidney. No edema of feet. At

[339] time of test under rest in bed liver dulness had gone up to 2 cm. below costal margin. Blood examination: Hb., 28 per cent; R. B. C., 1,600,000. March 29, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 41 per cent. Death, April 4. *Autopsy:* 3901. Hypernephroma of kidney. Dilatation and hypertrophy of heart. Chronic passive congestion of lungs. Cloudy swelling of viscera, etc. Liver weighs 2300 gm. Liver. Microscopical section. The lobules show central congestion, pretty extensive hyaline necrosis, probably not over 48 hours old. The lobulation is regular.

(31.) No. 87440. C. H., age 49, male, colored.

Clinical diagnosis: Tuberculous polyserositis. Acute endocarditis. Weakness, loss of weight, shortness of breath, gradual swelling of legs and abdomen. On admission presented signs of a myocardial break. Liver, hard, firm, smooth, to umbilicus. R. B. C., 3,000,000; Hb., 35 per cent. At time of second test conditions practically those shown at autopsy. Progressive emaciation, asthenia, anemia, persistent ascites. February 14, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 18 per cent. April 26, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 15 per cent. *Autopsy:* 3915. Tuberculous peritonitis, cloudy swelling of viscera, fibrous myocarditis, cardiac hypertrophy and dilatation, syphilitic aortitis. Liver weighs 2150 gm. The microscopical section shows subacute diffuse hepatitis with increase in connective tissue in all parts of each lobule and considerable deformity of liver architecture. Wandering cells of every type and scattered tubercles can be found. The liver cells show atrophy and degeneration as well as distortion.

(32.) No. 87515. T. A., age 39, male, white.

Clinical diagnosis: Arteriosclerosis, chronic nephritis. Symptoms for about one month: Palpitation, dizziness, smothering, sensations. At time of test, heart 14 cm. to left, 5 cm. to right. Systolic puff at apex. Aortic second sound loud. Liver dulness from fifth interspace to two fingers' breadths above costal margin in right mamillary line. Bases of lungs clear. Blood pressure, 200. Nothing to indicate any abnormality of liver except perhaps slight recent temporary chronic passive congestion of liver, not present at time of test. Blood examination: Hb., 90 per cent; R. B. C., 5,000,000. February 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 28 per cent. Discharged March 13, 1913. Improved.

(33.) No. 87589. R. S., age 36, male, colored.

Clinical diagnosis: Myocardial insufficiency. Arteriosclerosis. Pleurisy with effusion. Two previous admissions within past six months in badly broken compensation. At time of test, ortho-

pnœa, fluid in right chest below angle of scapula. Edema of legs. [339]
Heart, 15 cm. to left, pulse rapid (110). Liver, firm, reaches about palm's breadth below costal margin. Tenderness over it. On discharge three weeks later, no dyspnœa, edema or ascites, but liver still a palm's breadth down, no tenderness. Impression: Evidently permanent induration of liver from prolonged decompensation with additional acute passive congestion at time of test. Blood examination: Hb., 60 per cent; R. B. C., 4,100,000. February 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 9 per cent. Discharged March 9, 1913. At no time any toxic symptoms to indicate hepatic insufficiency.

(34.) No. 87653. M. L., age 48, male, white.

Clinical diagnosis: Myocardial insufficiency, mitral insufficiency and stenosis, adherent pericardium. Acute polyarthritis 12 years ago. Bronchitis, dyspnœa on exertion, palpitation, and precordial pain for past four winters. Comes in for these symp- [340]
toms. Transient hemiplegia (embolus?) five weeks ago. At time of test, heart 12.5 cm. to left and 4.5 to right. Aortic diastolic, apical systolic and presystolic murmurs. Positive Broadbent. Border of heart dulness moves 4 cm. Lung descends slightly over cardiac flatness. No ascites or edema of extremities. Râles at lung bases. Liver felt ¾ cm. below costal margin in mamillary line but no definite edge. Impression: Perhaps slight permanent liver induration from prolonged chronic passive congestion. (No note of condition of liver on discharge.) Nothing to indicate marked chronic passive congestion of liver or fibrosis. Blood examination: Hb., 85 per cent; R. B. C., 4,400,000. February 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Discharged March 17, 1913. Improved.

(35.) No. 87770. P. J., age 23, male, white.

Clinical diagnosis: Myocardial insufficiency. Aortic and mitral insufficiency. Right hydrothorax. Admitted eight months previous for acute polyarthritis. History of attack six years previously. Present complaints: For three days pains in legs, back, elbows, shoulders, fever and cough. At time of test, no dyspnœa or cyanosis. Right hydrothorax. Left lung clear to base. Heart 14 cm. to left and 4 cm. to right. Aortic diastolic and mitral systolic murmurs. Pulse 80. Liver dulness to costal margin; edge not felt. No edema of legs. No fever. Impression: No indication of chronic passive congestion of liver at time of test or of any chronic fibrosis. Blood examination: Hb., 84 per cent; R. B. C., 4,632,000. February 28, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 42 per cent. Discharged April 3, improved.

[340] (36.) No. 87747. C. G., age 66, male white.

Clinical diagnosis: Chronic bronchitis, emphysema. Cirrhosis of liver (?). Admitted in December, 1910. Diagnosis, chronic myocarditis. For six years shortness of breath on exertion. Winter cough. Pains in epigastrium since 1907, occasional nausea and vomiting. Findings on previous admission: Obesity, emphysema, chronic bronchitis, cardiac arrhythmia, no cardiac enlargement, no edema. Liver dulness from sixth rib above to 7 cm. below costal margin in mamillary line. Liver hard and not tender, edge not felt. On present admission: Chronic bronchitis, emphysema, cardiac dulness perhaps a little wide. Heart regular. No edema or ascites. Liver: Dulness to just below costal margin. Surface firm and hard, edge not felt. Impression: Liver pushed down by emphysema. Possible slight induration secondary to old myocardial condition. No definite evidence for cirrhosis. Blood examination: Hb., 87 per cent; R. B. C., 4,300,000. February 28, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Discharged March 3, 1913. Improved. In good condition three weeks later.

(37.) No. 87855. R. B., age 45, male, colored.

Clinical diagnosis: Myocardial insufficiency. Arteriosclerosis. Chronic nephritis. For four years dyspnœa and cough. Six months before admission swelling of abdomen and legs. Nausea and vomiting two weeks. At time of test, dyspnœa, edema of lungs, heart 17.5 cm. to left and 4.5 to right. No murmurs. Liver four fingers' breadth below costal margin in right mamillary line. Firm, tenderness over it. Edema of ankles. On discharge no myocardial insufficiency. Ten days before liver dulness two fingers' breadth below costal margin; edge not felt. Impression: At time of test marked recent stasis in liver. Probably some chronic induration of liver from prolonged myocardial insufficiency. Blood examination: Hb., 80 per cent; R. B. C., 5,500,000. March 15, 1913, injected 380 mg. Amount in urine, 0. Amount in stools, 8 per cent. Small specimen stool.

(38.) No. 88093. C. G., age 51, male, white.

Clinical diagnosis: Myocardial insufficiency, myocarditis, acute endocarditis, pulmonary and renal infarctions. Thrombosis of left iliac veins. Indefinite spell of edema of feet two years ago. No symptoms until two weeks ago, when he had dyspnœa, pain in side, and swelling of legs. At time of test, moderate dyspnœa; no edema or ascites; liver indefinitely felt three fingers' breadth below costal margin. On admission four days before, edema of legs, dyspnœa and cyanosis. Heart 16 mm. to left and six to right. Liver from fifth interspace to 7 cm. below costal margin. Edge readily felt, rounded and firm, surface smooth.

Subsequently developed an active endocarditis with fever, leucocytosis, infarctions. Died April 19. Impression: At time of test acute chronic passive congestion had practically cleared up. No evidence of chronic induration. Blood examination: Hb., 91 per cent; R. B. C., 4,300,000. March 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 35 per cent. Death. *Autopsy:* 3909. Thrombosis at site of injection. Liver 1900 gm. Surface slightly roughened. Typical nutmeg liver. Dark almost black central zones and yellow opaque looking partial zones. Liver. Microscopical section shows evidence of extreme passive congestion with central atrophy and fatty degeneration. There is some increase in connective tissue about the margins of the lobule, not, however, a definite cirrhosis. [340]

(39.) No. 88071. J. F., age 40, male, white.

Clinical diagnosis: Myocardial insufficiency. Mitral stenosis and insufficiency. Acute and chronic bronchitis. Emphysema. Two previous admissions within past year with broken compensation and large tender liver. On admission March 10, 1913, dyspnœa, cyanosis, enlargement of heart 16 cm. to left and 5 cm. to right; cardiac murmurs; no edema of ankles; general bronchitis; no ascites. Liver dulness from fifth interspace to 4 cm. below costal margin where it is indefinitely felt. At time of test, only slight dyspnœa, no edema or ascites, slight cough. Liver felt 3 cm. below costal margin. Edge not distinct. Impression: Slight clearing chronic passive congestion. Nothing to indicate red atrophy of liver. Blood examination: Hb., 77 per cent; R. B. C., 5,200,000. March 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Discharged much improved.

(40.) No. 88324. B. S., age 27, male, white.

Clinical diagnosis: Myocardial insufficiency. Mitral insufficiency and stenosis. Aortic insufficiency. Pulmonary infarctions. Acute polyarthritis seven years ago. Three months ago, cough, blood-tinged expectoration, dsypnœa, palpitation. Four to five weeks of swelling of legs. On admission: Enlarged heart with murmurs. Diffuse bronchitis and edema of lungs. Ascites, edema of legs. Dyspnœa. Liver edge indefinite, felt 3.5 cm. below costal margin. Tender over it. Test four days later: Condition essentially same but less marked. Five days later sudden rise of temperature. W. B. C., 13,000. Jaundice. April 12, collapse, death. Impression: At time of test moderate acute passive congestion of liver. Nothing to suggest any chronic changes. Blood examination: Hb., 86 per cent; R. B. C., 5,000,000. March 29, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. No autopsy. Thrombosis at site of injection.

[340] (41.) No. 88884. E. G., age 42, male, colored.

Clinical diagnosis: Myocardinal insufficiency. Dilated aortic arch. Syphilis. Chronic nephritis. History of cardiac failure for only six months. On admission: Orthopnœa, anascarca, dilated heart, gallop rhythm, liver not made out an account of ascites. At time of test, firm liver edge palpable three fingers' breadth below costal margin. Same symptoms as on admission but less marked. Impression: Moderate recent chronic passive congestion of liver and no evidence of chronic lesion. Blood examination: Hb., 75 per cent; R. B. C.. 6,600,000. April 27, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 32 per cent. On May 7, liver no longer felt. Symptoms have cleared up.

[341] (42.) J. J., age 44, male, colored.

Clinical diagnosis: Myocardial insufficiency, syphilis, aortic insufficiency. Very severe break in compensation. General edema; edema of lungs. Dilated heart. Very large tender liver. Several previous breaks. In extremis at time of both tests. April 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 5 per cent. May 19, 1913, injected 300 mg. Amount in urine, 0. Amount in stools, 24 per cent. *Autopsy:* 3946. Diag.—Syphilis, aortitis, aortic stenosis and insufficiency, myocarditis, chronic passive congestion of lungs and abdominal viscera, etc. Liver weighs 1220 gm. The microscopical section shows well marked passive congestion with central atrophy, obviously of long duration. The liver cells in many lobules have completely disappeared, leaving only a thickened reticulum. The lobulation is slightly irregular. Fatty degeneration appears in the middle zone. About one-half of the parenchyma cells nearly normal. Some of the lobules show the bile canaliculi distended with yellow, hyaline plugs. This condition is present in the central portion of the lobules, and absent in the periphery.

(43.) No. 89247. T. G., age 52, male, colored.

Clinical diagnosis: Arteriosclerosis, myocardial degeneration, chronic nephritis. Shortness of breath, palpitation, nycturia, transient swelling of feet and ankles for five months. Examination: Relative cardiac dulness 17 cm. to left, 5.5 to right, arrhythmia. No myocardial insufficiency. Liver dulness to one finger's breadth above costal margin; edge not felt. No evidence of liver disease. Blood examination: Hb., 72 per cent; R. B. C., 4,600,000. May 17, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 30 per cent. May 24, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 28-30 per cent. Thrombosis at site of injection.

(44.) No. 89149. I. W., age 48, male, colored.

Clinical diagnosis. Mitral insufficiency. Arteriosclerosis. Old mitral insufficiency. History of a break in 1910. Now for past

two months, dyspnœa, cough, palpitation. Examination: R. C. [341]
D., 15 cm. to left in sixth interspace, loud systolic murmur, slight edema of lungs, none of ankles. Liver to costal margin; edge not definitely felt. Nothing to indicate liver injury. Blood examination: Hb., 78 per cent; R. B. C., 5,000,000. May 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 28 per cent.

(45.) No. 89301. I. B., age 26, male, white.

Clinical diagnosis: Miliary tuberculosis. Tuberculous pericarditis. Liver not below costal margin. Edge not felt. Slight irregular fever. Blood examination: Hb., 60 per cent; R. B. C., 5,200,000. May 27, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 21 per cent. *Autopsy:* 3941. Tuberculous pericarditis. Miliary tuberculosis of lungs, liver and spleen. Ascites, hydrothorax, chronic passive congestion of viscera, etc. Liver weight 1775 gm. The microscopical section shows well marked passive congestion with atrophy of the central portion of the lobule. About two-fifths of the parenchyma is involved in the central atrophy. There is little fatty degeneration. The margin of the parenchyma is normal.

(46.) No. 89417. S. R., age 33, female, colored.

Clinical diagnosis: Myocardial insufficiency, syphilis, aortic insufficiency. At time of first test marked broken compensation with anasarca. Edema of lungs. Liver hard, tender, down almost to umbilicus. At second test condition improved but still hard liver a palm's breadth below costal margin. Impression: Probably marked nutmeg liver. No signs of hepatic insufficiency. April 24, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 7 per cent. May 8, 1913, Amount in urine, 0. Amount in stools, 33 per cent.

(48.) J. M., age 40, male, colored.

Clinical diagnosis: Myocardial insufficiency, syphilis, aortic insufficiency. Several previous breaks. At time of test slight edema of ankles and lungs, dyspnœa, enlarged heart. Liver four fingers' breadth below costal margin and hard. Impression: Moderate induration of liver. No signs of hepatic insufficiency. June 19, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 20-22 per cent.

(49.) No. 88072. J. N., age 52, male, white.

Clinical diagnosis: Cirrhosis of liver. *First admission in* 1907: Long alcoholic history. At that time for 19 weeks dropsy, "misery in stomach," and constipation. Blood in stools. Tapped six times before admission, one "gallon" removed each time. Heart and lungs clear. Liver edge 2.5 cm. below ensiform. Edge un

[341] even and firm. Ascites and edema of legs. Tapped 27 times between March, 1907, and October, 1907. Total of 272 L. removed Discharged. Improved. Abdomen still slightly swollen and some edema of legs. No fever, leucocytosis, drowsiness, or any signs of hepatic toxæmia. Symptoms due apparently more to portal obstruction than to liver insufficiency. *Second admission, June, 1911.* Meanwhile tapped three to four times, but no other symptoms. Felt well. Returned on account of increase in size of abdomen and sharp pains below costal margin. Slight jaundice for one year. Heart and lungs clear. Liver edge 3 cm. below costal margin. Tenderness in gall bladder region, with rigidity of recti. Increased dulness in gall bladder region. Slight jaundice. Movable dulness in flanks. W. B. C., 14,000. Irregular fever up to 100° F. No note of tapping during this admission. Discharged July 5. Temperature normal, feeling well, no shifting dulness. Levulose test by Dr. Churchman. Positive on 100 gm. *Third admission.* Recalled to have test made. Good health since 1911. Complains only of occasional slight dyspnoea. Is able to work. Abdomen pendulous, walls soft and flabby. Relative hepatic dulness begins in fifth interspace and absolute hepatic dulness in sixth interspace. Dulness to 3 cm. below costal margin in right mamillary line. Edge felt firm but regular. No ascites. No dilated superficial veins. No edema of extremities. Heart and lungs clear. Urine clear. No fever. Impression: Undoubted cirrhosis of liver. Never any symptoms to suggest hepatic insufficiency except perhaps on second admission. Symptoms due to portal obstruction which at present is perfectly compensated. Blood examination: Hb., 75 per cent; R. B. C., 4,500,000. March 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools. 23 per cent. Fibrinogen content of blood by Dr. Whipple normal.

(50.) Bay View. D. M., age 56, male, white.

Clinical diagnosis: Cirrhosis of liver. Shortness of breath 20 years. Periodic edema of ankles. Markedly alcoholic. For three years, swelling of abdomen and epigastric pains. At time of test general bronzing. Patient is torpid and dull. Liver, 4 cm. below costal margin in right mamillary line. Superficial veins dilated. Caput medusæ. Edge of liver firm. Spleen palpable. Very slight ascites. March 26, 13, injected 400 mg. Amount in urine, 0. Amount in stools, 6 per cent. No autopsy.

(52.) Surg. No. 31832. K. F., age 48, female, white.

Clinical diagnosis: Carcinoma of stomach, metastases to liver. For two months chills, sweating, fever, pain in epigastrium, radiating to right shoulder, vomiting and loss of weight. Liver dulness from third interspace. Firm, smooth rounded liver edge palm's breadth below costal margin. Surface smooth. *Exploration:* Liver enormously enlarged, studded with large carcino-

matous nodules. No symptoms of hepatic insufficiency. No gly- [341]
cosuria. March 19, 1913, inected 400 mg. Amount in urine 1.5 per cent. Amount in stools 8 per cent. *Autopsy:* 3903. Carcinoma of pylorus. Metastases to liver. Atrophy and focal necrosis of liver parenchyma with fatty degeneration. Practically entire liver tissue involved. The microscopic section shows numerous tumor nodules. Medullary cancer. Liver lobules show central, [342]
fatty degeneration and scattered areas of hyaline necrosis. In some areas these areas of necrosis are very extensive; in other lobules absent. The liver parenchyma adjoining cancer growth shows extreme atrophy and fatty degeneration.

(53.) Bay View. A. H., age 67, female, white.

Clinical diagnosis: Carcinoma of gall bladder. Cholelithiasis. Six or seven attacks of jaundice in past 40 years. Two weeks before admission—weakness, loss of appetite, jaundice. Examination: Emaciation, moderate jaundice, large mass, firm and rounded, from right costal margin down to 4 cm. below level of umbilicus (gall bladder?). Liver edge well felt; smooth, normally firm. Wassermann reaction 100 per cent +. Blood examination: Hb., 55 per cent. April 22. 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 18 to 20 per cent. Two and one-half months after onset jaundice more intense than ever.

(54.) No. 88424. E. S., age 33, male, white.

Clinical diagnosis: Cancer of stomach (metastases). For two months attacks of vomiting, nausea and pain following about two hours after eating. For past week vomitus bloody. Lost 80 pounds in three months. Examination: Emaciation; anemia; firm, nodular, transverse mass in epigastrium, thought by some to be liver, but finally was thought to be stomach or omentum. Liver dulness only to costal margin. Edge not felt. Blood examination: Hb., 38 per cent; R. B. C., 3,600,000. March 31, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 4 per cent. Stools unsatisfactory. April 8, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 22 per cent. Good specimens. *Exploration:* Carcinoma of stomach, metastases in glands and omentum. Liver smooth, no nodules made out (Finney). Death.

(56.) No. 87656. M. S., age 40 (?), female, colored.

Clinical diagnosis: Carcinoma of cervix uteri. One month before test general abdominal carcinomatosis found on abdominal exploration. At time of test some ascites; irregular nodular masses. Impression was that none of these were connected with liver, that dulness came to costal margin and that edge was not felt. Blood examination: Hb. 40 per cent; R. B. C., 4,300,000. March 5, 1913, injected 400 mg. Amount in urine, 0. Amount in

[342] stools, 39 per cent. Discharged April 10, 1913, without marked change in condition.

(57.) No. 89781. J. T., age 45, male, white.

Clinical diagnosis: Primary cancer of liver. For two months weakness, loss of weight, abdominal pain. *Exploratory laparotomy:* extensive inoperable primary cancer of liver. At time of test (post operative) great weakness and emaciation. Hb., 88 per cent. June 20, 1913 injected 400 mg. Amount in urine, trace. Amount in stools, 6 to 7 per cent.

(58.) No. 87983. M. B., age 27, male, white.

Clinical diagnosis: Suspected amebic abscess of liver. Ill about two months. Septic fever up to 102° F. W. B. C., 12,000. Liver dulness from fifth interspace to 6 cm. below costal margin in right mammillary line. Edge blunt, round. Surface smooth and tender. Careful *exploration* March 19 by Dr. Hulsted "was negative, with the exception of the enlargement of the right lobe of the liver, and the finding of a few adhesions between the right lobe and the dome of the liver." The peritoneum at "the lower portion of the right lobe which presented in wound was very soft and almost fluctuant." Blood examination: Hb. 75 per cent; R. B. C., 4,000,000. March 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Death. No autopsy.

(60.) No. 88925. F. R., age 40, male, colored.

Clinical diagnosis: Hepatitis, periostitis, syphilis, tuberculosis (?) tuberculous peritonitis (?) and perihepatitis (?). Ascites of obscure origin, large hard spleen. No evidences of collateral circulation. Liver just felt at costal margin, indefinite, not hard. Impossible to tell extent of anatomical liver change. No clinical signs of hepatic insufficiency. Blood examination: Hb., 40 per cent; R. B. C., 2,600,000. April 27, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 30 per cent. Case not followed after leaving hospital.

(61.) No. 88861. E. P., age 19, male, colored.

Clinical diagnosis: Tuberculosis (eye test). Splenomegaly. Liver easily felt one finger's breadth below costal margin; edge smooth and firm. Spleen easily felt; edge firm and sharp. Diagnosis not clear; chronic malarial infection suspected. No parasites found. No clinical signs of hepatic insufficiency. Blood examination: Hb., 90 per cent; R. B. C., 5,000,000. May 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 23 per cent.

(62.) No. 89082. J. McC., age 52, male, white.

Clinical diagnosis: Tuberculous peritonitis? Hepatitis? Syphilis (w). Mitral insufficiency. Arteriosclerosis. Symptoms: For about a month weakness, shortness of breath, abdominal pain,

swelling of feet. On admission, mitral murmur, heart 11 cm. to left, liver one finger's breadth below costal margin; edge not felt, edema of legs, ascites. Diagnosis not clear; most likely cause of findings is myocardial failure, perhaps with chronic peritonitis. No symptoms of hepatic insufficiency. Blood examination: Hb., 60 per cent; R. B. C., 4,400,000. May 17, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 31 per cent. June 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 31 per cent. [342]

(63.) No. 89439. J. K., age 56, male, colored.

Clinical diagnosis: Acute cholecystitis. Previously well. Acute onset with nausea, pain below right costal margin. Rigidity of upper right rectus, slight icterus. Leucocytosis, 22,000. Rapid recovery. Blood examination: Hb., 70 per cent; R. B. C., 4,000,000. May 29, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 30 per cent.

(64.) No. 89593. H. A., age 52, male, white.

Clinical diagnosis: Tuberculous peritonitis (?). Cirrhosis of liver (?). For six months increasing weakness and abdominal pain, with gradual ascites. Hemorrhoids 8 years. Emaciation, anæmia, ascites, paracentesis—cloudy, brownish fluid, specific gravity 1017. Liver felt almost at umbilicus; surface irregular, firm, and slightly tender. June 3, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 22 per cent.

(65.) Bay View. E. T., age 33, male, colored.

Clinical diagnosis: Syphilis of liver, syphilitic endarteritis, mitral insufficiency. Very large liver reaching to level of umbilicus in right flank, slightly irregular, and knobbed. Slightly tender. No other masses. Ascites. April 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 18 to 22 per cent.

(66.) Bay View. G. A. S., age 27, male, colored.

Clinical diagnosis: Syphilitic hepatitis? Amyloid? Pulmonary tuberculosis. Definite primary and tertiary lesions with positive Wassermann reaction. Two months before admission: swelling of legs, shortness of breath, cough and expectoration. Examination: Ascites, liver very large, smooth, not tender, does not pulsate, 8 cm. below costal margin. Moderate, irregular fever up to 101° F. in afternoon. Hb., 75 per cent. April 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 40 per cent. Autopsy: B. V. 41. Liver.—Microscopical section shows well-marked passive congestion, with central atrophy involving about ⅓ of each lobule, where the liver cells have undergone advanced atrophy, and in some instances even complete death. The sinusoids are engorged with blood. The liver lobulation is quite regular. Kidneys show advanced chronic nephritis. Lungs.—Bronchiectasis and organizing bronchopneumonia.