Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Liver Functions

INDEX

I. LAST WEEK

Date: January 20, 1939

Place: Recreation Room
          Powell Hall

Time: 12:15 to 1:30 P.M.

Program: Movie:
          "Reactions in Plants
           and Animals"

          Announcements

          Carcinoma of the Vulva
              J. L. McKelvey
              C. E. McLennan

          Discussion
              K. W. Stenstrom
              J. C. Litzenberg
              W. T. Peyton

Present: 144

                    Gertrude Gunn,
                    Record Librarian

              * * * * *

II. MOVIE

     Title: "Moose Hunters"

     Released by: A Walt Disney Short

              * * *

III. ANNOUNCEMENTS

     1. E. STARR JUDD LECTURESHIP
         in Surgery will be given by
Dallas B. Phemister, Professor and Chair-
man of Department of Surgery, University
of Chicago, Wednesday, February 1, at
8:15 p.m., Medical Sciences Auditorium.
Subject, "Pathogenesis of Gall Stones."

     2. INSTITUTE FOR MEDICAL LIBRAR-
         IANS, Center for Continuation
Study, January 30 - February 1. Over
80 medical record librarians from all
sections of the United States will attend
the course. The chairman of the program
is Sister Patricia, St. Mary's Hospital,
Duluth.

     3. DR. WILLIS H. THOMPSON,
         Instructor in Pediatrics, Gradu-
ate of University of Minnesota Medical
School, class of '29, who has been con-
nected with the department of pediatrics
since graduation, will leave for Tennes-
see, Saturday, January 28, to take a
new position. He has been appointed
State Instructor in Pediatrics by the
Tennessee State Medical Association.
His duties will be to hold a lecture
and clinic in an outlying district once
a week for 10 weeks. In addition to his
formal teaching, he will be available
for pediatric consultation with local
physicians. The course of instruction
will last two years. In a previous two
year course in Obstetrics, given by Dr.
Frank E. Whitacre 1334 physicians at-
tended. There were 53 teaching centers.
In addition to his medical program, Dr.
Thompson will give lay lectures in child
hygiene. The circuits are laid out in
various sections of the state at differ-
ent times of the year, depending upon
road conditions, weather, and concentra-
tion of physicians. Dr. Whitacre, who
taught the course in Obstetrics is now
on his way to China to become a member
of the staff of the hospital in which Dr.
John McKelvey was located before coming
to Minnesota. In the previous course in
Obstetrics, the Tennessee State Medical
Association was assisted with funds from
the Commonwealth Fund, Tennessee State
Health Department, Vanderbilt University,
and University of Tennessee.

This is a well deserved promotion for
Tommy. We have found him invaluable
in the post-graduate construction pro-
gram at the Center for Continuation Study.
We know the physicians of Tennessee will
obtain a great deal of valuable informa-
tion from him. Pediatrics is a sub-
ject which is widely practiced, and the
developments in this field have been
such that much new material can be pre-
sented. During his years at Minnesota,
Tommy has made scores of friends who
will regret his going. We wish him
success in his new undertaking, and
hope that he will come back to see us
from time to time.
          Good-bye, Tommy -
                    Good Luck!

IV. THE CLINICAL INTERPRETATION

OF LIVER FUNCTIONS

C. J. Watson
W. H. Hollinshead

It is very difficult to evaluate the functional and pathological state of an organ such as the liver. Hepatic activity embraces metabolic, excretory, detoxifying, and synthesizing functions. Students of liver functions have shown repeatedly that the determination of one function does not indicate the general status of the whole organ. The compensatory and regenerative powers of the liver are remarkable. It has been shown experimentally that regeneration of the liver occurs rapidly and completely after as much as 70% of the organ has been removed. It should be born in mind in this connection that a mild but diffuse cellular injury may be followed by distinct evidence of functional impairment whereas large areas of the liver may be replaced by tumor without this occurrence of functional derangement, simply because the remaining liver parenchyma, although perhaps small in amount, is relatively normal. This constitutes a difficulty which must confront any test seeking to detect liver disease by means of measuring functional capacity. This is reflected in the large number of liver function tests that have been devised. Many have been discarded as worthless. A few of the more valuable methods are reviewed in this paper.

Bilirubin Excretory Function

A cardinal symptom of liver disease is jaundice. The work of Mann, Bollman, and Magath (1) on hepatectomized dogs showed clearly that the liver was the excretory organ for bilirubin. Hyperbilirubinemia may be expected in three general types of disturbances or combinations of disturbances. 1. Where bilirubin is produced in excess of the capacity of the normal liver cell to excrete it. 2. Where the liver cells are damaged so that they can not excrete the normal amounts of bilirubin coming to

them. 3. Where obstruction of the bile passages causes regurgitation of bilirubin into the blood stream. Rich (2) has divided jaundice into two types.

1. Jaundice associated with intact bile canaliculi-retention, or hepatocellular jaundice. This group includes hemolytic jaundice, and in addition all types of jaundice in which the disturbance is limited to hepato cellular function (mild cardiac, araphenamine, or sulfanilamid jaundice are examples). The outstanding features are delayed or indirect Van den Bergh reaction, absence of bilirubin in the urine.

2. Jaundice associated with regurgitation of bile into the lymph spaces and thence into the blood. Regurgitation may be due to: (1) increased intrabiliary pressure because of obstruction with eventual rupture of bile canaliculi, or (2) damage of the ampullary portions of the bile capillaries with increased permiability and leakage of bile back into the lymph spaces. This group includes jaundice of cancerous and calculous origin and jaundice due to severe liver damage. The outstanding features distinctive of regurgitation are: direct, prompt Van den Bergh reaction, bilirubinuria, pruritis.

The degree of jaundice does not always correspond to the degree of retention or regurgitation. Bilirubin formation is directly related to blood destruction. Blood destruction may be markedly diminished as in severe post hemorrhagic anemia.

The icterus index is a simple method of indicating the degree of bilirubinemia. It is a measure of the yellowness of a given serum as compared with a standard solution of potassium bichromate. In rare instances the icterus index may be misleading as for example in the presence of carotinemia. Ehrlick's diazo reaction as applied to the plasma by Van den Bergh is specific for bilirubin. The Van den Bergh reaction may be used quantitatively, but in this clinic it is customary to employ it only in a qualitative way (in the distinction of retention and regurgitant jaundice, as mentioned

above). The icterus index is quite satisfactory for quantitative clinical purposes if the blood samples are taken fasting, and if patients are always scrutinized by the clinician for the presence of carotenemia (yellow plams of hands and soles of feet, absence of yellow sclerae).

Bilirubin normally present in the serum gives an indirect Van den Bergh reaction and is present in amounts varying from 0.1 - 1.0 mgm. per 100 cc. of blood.

If the bilirubin level (icterus index) is determined at frequent intervals during the course of a case of jaundice and plotted as a curve, it will usually have a certain form depending on the underlying cause of the jaundice. Complete biliary obstruction as a rule is associated with a rapidly rising curve and a high plateau. In obstruction due to stone, a rapid rise with a gradual fall is common, or as is frequently the case if partial obstruction persists and especially if complicated by biliary cirrhosis, a low plateau results. The icterus index in at least 90% of cases of calculous jaundice, remains at all times below 100, while the converse is true in jaundice due to cancerous biliary obstruction. As a rule severe acute parenchymal damage is associated with a rapid rise and a rapid fall if recovery occurs. More chronic forms of parenchymal disease are associated with low fluctuating curves. Each small rise signifies an acute episode of active liver damage, or a period of increased blood destruction with persisting liver dysfunction.

Urobilinogen Disposal:
                    enterohepatic circulation.

When bilirubin reaches the colon it is acted upon by bacteria and reduced to urobilinogen. This in turn is partly excreted in the feces and partly reabsorbed into the portal circulation. Normally the reabsorbed fraction returns to the liver and is probably reutilized at least in part in the formation of hemoglobin. A small amount is reexcreted in the bile, so that there is a constant enterohepatic circulation of urobilinogen. A very small fraction escapes into the general circulation and is excreted by the kidney (less than 3 mgm. in 24 hours).

In the presence of hepatic disease, varying fractions are not reutilized or excreted by the liver, and enter the general circulation. Urobilinogen accumulates in the blood and is excreted in the urine in excessive amounts. Heightened excretion of urobilinogen in the urine is almost a constant accompaniment of hepatic disease. There are exceptions to this which must be considered.

The amounts of urobilinogen which reach the liver are directly related to the amounts of bilirubin excreted into the bowel and the rate of reabsorption of urobilinogen from it. Where there is complete biliary obstruction, no bilirubin reaches the bowel, and, consequently, no urobilinogen can be formed. This is the case in carcinomatous obstruction of the extra hepatic bile ducts. In this instance the absence of urobilinogen from the urine is not an indication of normal liver function. In calculous jaundice, with its characteristically changing degree of obstruction, the amounts of urobilinogen in the urine varies with the degree of hepatic dysfunction, but may be small even in the presence of a damaged liver, if the amounts of bile permitted to enter the intestine are greatly reduced. At times urobilinogen is absent from the urine with varying degrees of obstructive jaundice due to stone and rarely with high grade regurgitation jaundice due to cirrhosis. Here the determination of the urobilinogen in the feces is important. If markedly reduced, then the presence of urobilinogen in the urine is even more significant of hepatic dysfunction. This is particularly true in cases of acute and chronic parenchymal liver disease.

If bile is excreted in excessive amounts the urobilinogen in the bowel is increased and the amount absorbed is proportionately much greater. Here even the

relatively more normal liver is unable to handle the large amount of urobilinogen coming to it in the portal blood; urobilinogen consequently appears in the urine in excessive amounts. This reveals the necessity of determining, whenever possible, the ratio of the amount in the feces to that in the urine.

All forms of hemolytic jaundice are associated with increased urobilinogen excretion in the feces. Liver function in some cases is so efficient, however, that urobilinogen does not appear in excess in the urine.

Bilirubin and Stercobilin Tolerance Tests

In many cases of mild liver disease the reserve power of the liver is adequate to excrete the amounts of bilirubin which come to it. However, if an additional burden is thrown on the excretory function of the cells by artificially increasing the amounts of bilirubin in the blood, evidence of impaired excretory ability appears. Following the work of Von Bergman and Ellbott on the excretion of intravenously injected bilirubin, Harrop and Barron (3) described a bilirubin tolerance test which is a test of the excretory function of the parenchymal cells of the liver. According to Soffer's (4) modification, the equivalent of 1 mgm. per kilo. of body weight of bilirubin is injected intravenously. Normally there should be less than 6% retention after 4 hours. Bilirubin would seem to be an ideal substance for testing the excretory function of the liver. Many investigators believe that the bilirubin tolerance is the most delicate of any single liver function test. Our experience with this test has been small. Its chief disadvantage is that it can not be used in the presence of even slight hyperbilirubinemia. Another objection is the cost of bilirubin. ($15.00 per gram at present.)

The stercobilin tolerance test is probably at least as delicate and somewhat more easily applicable. Crystalline stercobilin, isolated from hemolytic jaundice feces is used. Although studies are in progress to determine the best means of carrying out this test, the following procedure is in use at the present time.

Fifty mgm. of the crystalline material are injected intravenously. The urine is then collected for 24 hours, the first six hour portion being saved separately. The normal individual excretes less than 5 mgm. of the injected amount. Both in the normal individual and in patients with liver disease except where renal insufficiency is also present, all or nearly all, of the fraction appearing in the urine is excreted within the first 6 hours. The only contra-indication to the test is the presence of increased native urobilinogen in the urine. This is a contra-indication only in the sense that the test is unnecessary in such instances, since the presence of increased urobilinogen is already an evidence of liver dysfunction. This procedure can be used in the presence of hyperbilirubinemia and in fact may prove particularly valuable in cases of complete biliary obstruction where no native urobilinogen is formed in the bowel and where the determination of native urobilinogen is of no value insofar as the study of liver function is concerned. There are also cases of diffuse liver disease associated with marked diminution in the outflow of bile where the test is especially applicable.

Case 1   Age 30.

History of marked painless jaundice of 6 weeks duration. The onset was characterized by fever, general malaise, and constipation. The third day abdominal cramps developed. On the 6th day the patient noticed dark urine. Following this he was semicomatose for several days. During this time severe jaundice developed. The icterus index reached 160. The urine was "beer brown" and the stools acholic. The stools later became moose and bulky, but again became more normal when fats were eliminated from the diet. The jaundice persisted.

When admitted, the patient was deeply jaundiced. There was evidence of weight loss. (He had lost about 30 pounds). The liver was moderately enlarged and firm. The spleen was enlarged. There were numerous excoriations of the skin.

Laboratory data: Hemoglobin 74%; 3,680,000 red blood cells; 7,600 leukocytes; 62% neutrophiles; 38% lymphocytes. The M.C.V. was 109.5 cubic micra (normal 87 - 94 cu. micra). The blood urea nitrogen was 11.7 mgm. percent. The blood sugar was 96 mgm. %. The total blood cholesterol ranged between 259 and 308 mgm. per 100 cc. of blood. The icterus index was 147. The Van den Bergh prompt direct. The 24 hour urine contained from 0.9 to 1.3 mgm. of urobilinogen. The average daily output of urobilinogen in the stool over a four day period was 11.8 mgm. The galactose tolerance test was negative - 0.8 grams of sugar were excreted. Following 50 mgm. of crystalline stercobilin intravenously, 29.2 mgm. of urobilinogen appeared in the urine. Small amounts of bile, many pus and epithelial cells were present in the duodenal drainage. A diagnosis of a cholangitic type of catarrhal jaundice was made.

This type of hyperbilirubinemia is seen in extensive hepato-cellular damage. Because only small amounts of bilirubin entered the bowel, the formation of native urobilinogen was decreased as indicated by the quantitative urobilinogen determination. This in itself did not indicate liver dysfunction. However, the urobilinogen tolerance test indicated definitely abnormal function. The galactose tolerance test was of no value in this case.

Case 2.   Age 48

Admitted because of painless enlargement of the liver of about four months duration. No other complaints. The liver was very irregular and nodular. The edge extended 10 cm. below the right costal margin. The spleen was not palpable. Primary or metastatic malignancy was believed to be the cause of the hepatomegaly. No primary tumor was found in the gastro-intestinal or urinary tract or in the lungs.

The routine laboratory tests were normal. Urinalysis was negative including the test for melanin. The icterus index was six with an indirect Van den Bergh. There were .48 mgms. of urobilinogen in the urine. There was no retention of bromsulfalein. The Takata-Ara test was negative. The urobilinogen tolerance test resulted in the excretion of 7.5 mgm. of urobilinogen in the urine.

The patient was discharged with a diagnosis of malignancy, possible primary, of the liver. He returned four months later in a terminal condition. Autopsy revealed primary carcinoma of the pancreas with extensive metastasis in the liver, and no biliary obstruction.

In this case the slight abnormal stercobilin tolerance test was the only early indication of abnormal liver function.

Porphyrin Excretion

It has been shown that many disturbances of the liver are associated with increased coproporphyrin excretion in the urine. Garrod (5) first noted the relationship between hepatic dysfunction and the amounts of urinary porphyrin. Van den Bergh and his co-workers (6) believed that the largest amounts of coproporphyrin were found in the urine in cases of obstructive jaundice. Although Franke (7) was unable to confirm this, he found large amounts of porphyrin in the urine in acute catarrhal jaundice and subacute liver atrophy. Urinary porphyrin is increased in portal cirrhosis and chronic passive congestion. The work of Franke would indicate that prophyrin excretion is an extremely delicate test of liver function. He found that a diet including meat fat and bacon caused an elevation of urinary porphyrin. The consumption of as little alcohol as is contained in 6 glasses of beer or 40 cc. of cognac was followed by a definite increase in the 24 hour excretion of porphyrin. He attributes this to liver dysfunction.

Inconstant porphyrin excretion has been observed in pernicious anemia and hemolytic icterus. This is comparable to the variation in urobilinogen excretion observed in these diseases and is probably related to varying liver func-

tions.

As yet relatively little attention has been given to the study of the urinary coproporphyrin in relation to hepatic disease. There is much reason to believe that this topic deserves considerable further attention.

Excretory function as tested by means of dye retention

Among the dye tests of liver excretory functions, bromsulphalien is the most widely used. The test was originally described by Rosenthal and White (8). It consists of injecting the dye intravenously in a dosage depending upon the body weight of the individual. The amount of dye present in the serum at the end of a given period is determined by transverse comparison of the serum with standard tubes in a colorimeter.

Bromsulphalien is excreted by the liver through the biliary passages into the gastro-intestinal tract. Obstruction of the bile ducts will produce a prolonged retention of the dye in the blood stream. This does not necessarily represent liver dysfunction. This test should not be employed in instances of clinical jaundice where the Van den Berth reaction is direct or biphasic.

Mills and Dragstadt (9) have recently offered evidence which would indicate that the removal of bromsulphalien from the blood stream is brought about chiefly by the activity of the reticulo-endothelial system of which the Kupffer cells of the liver constitute an important fraction. According to them a disturbance in the removal of dye reflects some impairment of function in this system of cells.

The bromsulphalien test is most apt to yield positive results in cases where the liver damage is diffuse and extensive, as in portal and biliary cirrhosis. Less satisfactory results are obtained in primary or secondary malignancy of the liver. Snell, however, feels that the diagnostic value of the dye test in demonstrating metastatic malignancy can not be overlooked. He states that a relatively moderate hepatic involvement will produce a significant degree of retention. Magath found that retention of dye occurred in 96% of cases in which there was evidence of parenchymal hepatic injury.

The chief value of the bromsulphalein test is in cases of liver disease without jaundice. There is only a very rough quantitative relationship between the degree of retention of the dye and the extent of liver damage. In general the degree of retention of the dye is of prognostic significance. In any particular case that is followed over an extended period of time with this test, the results will indicate whether the hepatic lesion is becoming more extensive or is regressing.

Rarely does low grade retention occur without evidence of hepatic disease. According to Soffer (2a) this is true in about 15% of normal individuals.

In a similar way, a large number of other dyes have been used to test the excretory function of the liver. Rose bengal is commonly used. Recently Asorubin S has proved of value. The results, however, appear to be no better than those obtained with bromsulphalien. We have had no experience with dyes other than bromsulphalien.

Tests involving carbohydrate metabolism

One of the most important functions of the liver is its capacity to maintain the blood sugar at a normal level. As is to be expected, the liver attempts to conserve this function to the end. Only in the most advanced hepatic injury is hypoglycemia rarely seen. It may be present in the terminal stage of acute yellow atrophy. However, the diseased liver loses some of its power to hold glycogen. Hypersensitivity to insulin is frequently seen in various types of diffuse hepatic disease, indicating a low glycogen reserve. Many observers have noticed that in severe diabetes, the glycosuria is much easier to control following the onset of obstructive jaundice or cirrhosis. In this connec-

tion it is interesting to note that Soskin divides diabetics into two types on the basis of liver function: 1. The juvenile type in which rapid variations in blood sugar level with tendency to frequent hypoglycemia when insulin is being given. Soskin believes liver function good in this type. 2. The senile type in which the diabetes is usually more easily controlled, with less marked and less rapid variations in blood sugar level. In this type Soskin considers the liver to be relatively inefficient. Newburgh (10) and his co-workers have recently reported several cases of hepatic disease in which the main symptoms were due to hypoglycemia. In these cases there was a disturbance of both glycogenesis and glycogenolysis. With improvement of the hepatic disease the carbohydrate metabolism became normal.

Althousen and Stockholm (11) have shown experimentally on rats that the oral or intravenous administration of equal amounts of dextrose at the normal absorption rate led to an approximately equal deposition of glycogen in normal livers and in livers damaged by phosphorus. On the other hand, by increasing the amounts of dextrose given intravenously over the maximal rate of intestinal absorption, the deposition of glycogen in the normal livers was increased over that in the damaged livers. This would indicate a disturbance of glycogenesis.

Levulose and galactose have been widely used in the study of hepatic disease. McLean and de Wesslow (12) found that in contrast to other sugars, ingested levulose produced little if any increase in the total blood sugar level. Spence and Brett (13) found that marked hyperglycemia did, however, occur in cases of liver disease of various types and suggested a levulose tolerance test.

Many investigators have used the levulose tolerance test. The normal standards of various authors differ. There is still some doubt as to what should be taken as the criteria of normality. There is considerable argument as to whether the variations in the total blood sugar following the ingestion of levulose, or the variations observed in the blood

levulose alone are more significant. Spence and Brett (13), Kimball (14), and Hurse (15) feel that the determination of the total blood sugar is satisfactory. Stewart and Davidson (16) and Rivore (17) and his co-workers believe that the determination of the blood levulose level is a more reliable method. In reporting his experience in over 1000 cases Hurst believes that the levulose tolerance test is a reliable measure of hepatic efficiency. He found the test particularly useful in cases of toxic hepatitis, so-called alcoholic hepatosis, amebic hepatitis, acute catarrhal cirrhosis. He considers that a combined one and two hour rise of over 35 mg. in the total blood sugar, following ingestion of 40 gm. of levulose, is pathognomonic of liver disease.

The results of the levulose tolerance test correspond fairly closely with those of the similar test in which galactose is used. Levulose appears to have the advantage in chronic parenchymal liver disease such as protracted hepatitis, or cirrhosis, while galactose is undoubtedly of chief value in detecting acute diffuse liver disturbances.

Mild diabetic tendencies, chronic pancreatitis, and arteriosclerosis tend to give inaccurate results with both tests.

Galactose seems to be the best sugar for measuring the carbohydrate metabolism of the liver. It is practically unutilized by any other tissue but the liver. There is no renal threshold for the excretion of galactose. Galactose utilization is unaffected by the activity of any of the endocrine glands. Mann and Magrath (18) found that the injection of galactose failed to have any effect in combating the hypoglycemia following hepatectomy in dogs. Mann was able to recover from the urine more than 80% of the injected galactose in these dogs. Shay, Schloss, and Bell (19) demonstrated that galactose failed to prevent hypoglycemia in human subjects previously given insulin in doses sufficiently large to produce hypoglycemia. As originally introduced by Bauer (20) this test was to distinguish obstructive

from intrahepatic jaundice. The excretion of more than 3 grams of galactose in the urine following the ingestion of 40 grams of galactose is considered a positive test. Its use as a liver function test, however, is distinctly limited. Banks, Sprague, and Snell (21) investigated 127 instances of various types of jaundice using the galactose tolerance test. They obtained 62% positive results in intrahepatic jaundice (catarrhal, cinchophen, and arsphenamine). In 16 cases of biliary and portal cirrhosis only 3 yielded positive figures. One third of all types of obstructive jaundice yielded abnormal figures. From this they concluded that obstructive and toxic or infectious jaundice cannot be distinguished with any considerable certainty by the test, but that it yields valuable corroborative data in doubtful cases. Rosenberg (22) reported uniformly positive results in acute and subacute intrahepatic jaundice, and negative results in chronic intrahepatic jaundice. He was able to distinguish intrahepatic from obstructive jaundice only in the acute stages. White (23) found the test positive as a rule in acute catarrhal jaundice and acute toxic hepatitis, diseases in which diffuse liver cell damage predominates. He obtained negative results in chronic liver diseases (chiefly cirrhosis). Shay and Fieman (24) concluded that the test was most reliable when performed early in acute jaundice. Our results with the galactose tolerance test are in agreement with this conclusion.

Protein Metabolism

Frequently protein metabolism is significantly affected in liver disease. Mann (25) and his co-workers have shown: that following total removal of the liver, the formation of urea ceases. With the drop in blood urea, there is a coincidental rise in the amino-acids of the blood. Very small amounts of liver tissue are necessary for the normal formation of urea. Clinically a drop in urea and a rise in amino acids is demonstrated only towards the end in patients with acute yellow atrophy.

Many investigators have noticed changes in the serum proteins during the course of liver disease. Kerr, Horwitz, and Whipple (26) depleted the plasma proteins in dogs by plasmapheresis and noted a delayed regeneration of proteins when the liver was damaged by phosphorus or chloroform. Mann and Magath (25) found a decrease in the total protein content of the blood with a tendency towards a reversal of the albumin globulin ratio in dogs with experimental cirrhosis. Myers and Keefer (27) in a recent review found that in chronic hepatic disease there is frequently a lowering of the plasma proteins, particularly of the albumin fraction. At the same time there is a tendency towards a reversal of the albumin globulin ratio. Tumens and Bockus (28) determined the plasma proteins in 45 patients with various types of acute and chronic hepatic disease. Hypoalbuminemia was the most common alteration. It was present at some time or other in every case of chronic advanced liver disease and in most cases of obstructive jaundice. They found an elevation of the globulin fraction and a reversal of the albumin globulin ratio frequently but not as constantly as the lowering of the albumin value. Significant alterations are usually observed in portal cirrhosis, biliary cirrhosis, and other types of chronic diffuse liver disease due to toxic or infectious agents. Changes have been observed in Banti's syndrome. Tumens and Bockus have reported lowering of the blood albumin in 3 patients with metastatic malignancy of the liver. Serum protein determination may be of diagnostic value in obscure conditions associated with hepatosplenomegaly. A tendency towards a lowering of both the plasma albumin and globulin has also been observed in acute catarrhal jaundice, cinchophen and arsenical jaundice and acute chloroform poisoning.

Reduced protein intake is probably not sufficient to explain the above alterations.

A positive Takata Ara reaction is apparently based upon alterations in the quantity and possibly the nature of the serum proteins (29) - (30). It is usually positive when the serum albumin

globulin ratio is reversed. It is
also frequently positive in acute hepato
cellular disease. This may indicate
abnormal synthesis resulting in an
alteration in the nature of the proteins.
This test is of definite value in the
diagnosis of cirrhosis of the liver where
it is almost always positive. A negative
test casts distinct doubt on the diag-
nosis of cirrhosis. The test is not,
however, specific for liver disease, as
it may be positive in a number of other
conditions in which the plasma proteins
are altered, notably pneumonia, chronic
renal disease, and others. An increase
in the serum globulin fraction is usually
associated with an increased erythrocyte
sedimentation velocity. A rapid sedi-
mentation rate is to be expected where
such an alteration in the serum protein
exists.

Lipid Metabolism

Hypercholesterolemia is usually ob-
served in obstructive jaundice. The
reason for this is not perfectly clear.
Probably it is due to the regurgitation
of bile into the blood stream.

In jaundice due to parenchymatous liver
disease, the cholesterol level of the
blood is frequently low. This is un-
doubtedly a reflection of liver function.
Tannhauser and Schaber (31) observed a
drop in the cholesterol esters of the
blood in hepatic cell damage. They attri-
buted this to a disturbance in the
synthesis and hydrolysis of cholesterol
by the liver. Epstien and Greenspan (32)
have observed significant changes in the
cholesterol partition in parenchymatous
liver disease and attach diagnostic and
prognostic value to these observations.

The level of the blood cholesterol is
influenced by variation in the function
of several of the endocrine glands. To
be of diagnostic value studies of the
blood cholesterol and cholesterol parti-
tion must be restricted to cases with
jaundice.

Normally and in uncomplicated obstruc-
tive jaundice, the cholesterol ester value
in the blood is 50 to 70% of the total
cholesterol. In hepato cellular injury

this value decreases. The more acute
and severe the process is, the lower
the ester value will be. The ester
value remains low if the outcome is
fatal. The total cholesterol is de-
creased to a lesser degree. With im-
provement a rise in the ester value is
seen, and hypercholesterolemia is fre-
quently observed. This may persist for
some time after complete healing. Shay
and Fieman (33) correlating the degree
of bilirubinemia and the cholesterol
partition concluded that a rising bili-
rubin value accompanied by a falling
blood cholesterol value and an even
more rapid decrease in the cholesterol
esters is usually of severe prognostic
import. This picture is associated with
severe toxic or infectious hepatitis.
It may intervene in the course of ob-
structive jaundice when cholangitis
develops. There seems to be a diver-
gence between the total blood choles-
terol and the degree of hyperbilirubine-
mia but a close inverse relationship
between the changes in the blood bili-
rubin and the cholesterol ester ratio
is usually seen. Changes in the blood
cholesterol - cholesterol ester ratio
occur to a more marked degree and with
greater frequency in acute hepatic
disease. We have had little experience
with the cholesterol partition but be-
lieve that it merits further study.

Blood and bone marrow changes in liver disease

Anemia is very commonly associated
with liver disease. Obviously chronic
bleeding - especially from the gastro-
intestinal tract is responsible for many
cases observed. The association of
jaundice and bleeding is particularly
common. However, if bleeding is exclud-
ed there remains a high percentage of
cases of liver disease with anemia.
Wintrobe (34) studied 132 cases and
found anemia present in 77.3%. Rosen-
bert (35) reports anemia in 87% of 62
cases. Macrocytic anemia was present
in about 1/3 of Wintrobe's cases. Macro-
cytosis is observed in 50% of all types
of cirrhosis (36). Schalm (37) reports
macrocytic anemia in acute parenchymal
liver injury, in one case of Weil's dis-
ease, and in several instances of ob-

structive jaundice due to stone or neo-
plasm. Macrocytic anemia has been ob-
served experimentally in amimals following
hepatic injury.

The degree of anemia due to liver
disease is usually mild and the macro-
cytosis is not great. Wintrobe found
the mean erythrocyte count to be
3,490,000 and the average mean corpus-
cular volume to be 104 cubic micra (nor-
mal 82 - 94 cubic micra) in his cases.
The variation in the size of the red
corpuscles is equal to that found in per-
nicious anemia of a similar degree of
severity. In liver disease, particularly
in cirrhosis, a leukopenia with a rela-
tive lymphocytosis is not rare. Usually
there is a slight increase in the number
of reticulocytes. Rosenberg found an
average of 2.4% reticulocytes in his
series with a variation of from 1,1 to
18%. This is indicative of active hemo-
poisis. In many cases there is increased
blood destruction as indicated by in-
creased pigment excretion. At times a
hemolytic type of anemia may be the most
striking feature of the disease. There
is a direct relationship between the
rate of blood destruction, the degree of
hyperbilirubinemia and the number of
reticulocytes. Rosenberg found reticulo-
cytosis more frequently in jaundiced in-
dividuals. It has been suggested that
the presence of hyperbilirubinemia favors
the formation of hemoglobin from the
excess of bile pigment present. Insofar
as the anemia itself is concerned, it may
be that a slight degree of liver insuf-
ficiency is even an asset to these individ-
uals (retention of pigment).

The bone marrow is active or definitely
hyperplastic in this type of anemia. So
far as can be determined from the few
studies yet available, the bone marrow is
of normoblastic type, differing fundament-
ally from pernicious anemia in this re-
spect. Unlike pernicious anemia, the
typical neutrophile is not found either
in the blood or bone marrow. Achlorhydria
may or may not be present.

The large cell size associated with
leukopemia and hyperplastic bone marrow
indicates interference with blood cell
maturation. Improvement of the anemia

may occur spontaneously irrespective
of the liver disease. Remission may
follow intramuscular liver therapy.
Improvement is characterized by an
increase in the number of reticulo-
cytes. There seems to be no deficiency
in the formation of the intrinsic
factor. The intrinsic factor has been
demonstrated in the stomach contents.
The presence of a macrocytic anemia
should suggest impairment of liver
function.

The hemolytic macrocytic type of
anemia is frequently associated with
splenomegally. The spleen is undoubt-
edly the seat of overactive blood de-
struction. Splenectomy has been fol-
lowed by beneficial results.

Miscellaneous Tests

The liver is particularly concerned
in the removal of toxic substances
from the blood and in rendering them
physiologically inert. The conversion
of indol to indoxyl sulphate and the
conjugation of cholic acid to form
bi'le salts are examples of this pro-
cess. Many methods have been devised
to test this function but have for
the most part proved unsuccessful.
The hippuric acid test is considered
by some to be of value. Originally
a kidney function test, Bryan (38) sug-
gested that it might be applicable as
a test of liver function. Quick (39)
has pointed out that the results de-
pend largely upon the rate at which
the liver can supply amino-acetic acid.
If kidney function is normal, the rate
of excretion of hippuric acid can be
correlated with hepatic function. The
test is valueless when kidney function
is impaired.

Case 3   Age 63

On admission 8/12/38, he complained
of constant dull pain in the right
upper quadrant, mild anorexia, and
about 10 pounds weight loss since May,
1938.   There was a history of drink-
ing heavily at one time. Physical
examination revealed a slight icterus.

The liver edge extended 7 cm. below the costal margin. The liver surface was firm and finely nodular. The spleen was enlarged and firm. There was no ascites.

A clinical diagnosis of cirrhosis of

the liver was made. This patient has been followed for several months. During this time progressive liver damage has occurred, as born out by the laboratory studies.

	8/17/38	11/28/38
Hby	78%	63%
Rbc		2,600,000
Wbc	9400	7800
Pmn	76%	73%
Lymph.	24%	27%
Mcv.	99 cubic micra	141 cubic micra
Mch.	30.6 micro mgm.	41 micro mgm.
Protein	6.6 grams	5.4 grams
Alb.	2.9 "	2. "
Glob.	3.6 "	3. "
Alb/glob.	.8	.7
Ict. Index	13	56
Van den Bergh	indirect	prompt direct
Urobilinogen in urine	38.9 gmg.	22.1

The bromsulphalien retention is 40 - 50% at the end of 30 minutes. The galactose tolerance test is negative. The levulose tolerance and hippuric acid tests are positive. Takata-Ara test is strongly positive.

Beteeen 8/17/38 and 11/28/38 ascites occurred and persisted requiring repeated paracentesis.

There has been a progressive anemia with a change from a normocytic to a macrocytic type and a tendency towards hyperchromasia. The albumin globulin ratio has become slightly less. These are evidences of progressive liver damage.

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V. GOSSIP

The third annual course in Hospital Administration under the chairmanship of R. M. Amberg, Superintendent, University of Minnesota Hospitals, has been in session at the Center for Continuation Study since Monday, January 23. It will close Saturday afternoon, January 28. The attendance has been the largest of any course in medical or hospital education (88). The members have come from Minnesota, Wisconsin, North and South Dakota, Montana, Iowa, Ohio, and the Philippines. The majority are women, which is in accord with the sex distribution in this field. Their time has been completely occupied from morning until night. The instruction has consisted of lectures, field trips, round table conferences, and moving pictures. Today is their third trip to the University of Minnesota Hospitals. They were here on Monday afternoon for a demonstration of nursing procedures, on Tuesday evening for an operating room demonstration by Misses Halverson, Fuller, and Smitka; today they are our guests at staff meeting, following a short tour of Powell Hall. Following the meeting, they will witness a demonstration of blood transfusion by Dr. Harry Hall in Todd Amphitheatre at 1:30. At 2:30 they will be taken on a trip thru the pediatric division and the patients' library. Dr. Arthur C. Bachmeyer, Director of the University of Chicago Clinics, and Dr. Melville H. Manson, Associate Division of Rural Hospitals, Commonwealth Fund, New York, are the special guest instructors this morning. Their discussions were concerned with "Trustee Problems in the Small Hospital" and "Professional Staff Education." Drs. Bachmeyer and Manson will conduct a round table at the Center for Continuation Study, following tea at 4:00. The Administrators have apparently enjoyed their week with us, and we were delighted to be their host. After the course for Hospital Administrators, there will be a three-day session for Medical Record Librarians starting Monday, January 30. There will be courses in February for Hospital Dietitians and Medical Social Workers. As the program in hospital education unfolds, it is intended that it should follow the same pattern as medicine. It has been estimated that there are nearly 40 fields of interest in medicine and approximately 20 - 25 in the hospital field. The hospital subjects include administration, nursing, medical records, out-patient department, laboratory service, operative room service, obstetrical service, radiologic service, radiologic service, pharmacy, admissions, business administration, hospital construction and plant maintenance, housekeeping, laundry management, purchasing, food service, insurance, personnel relations, public relations, etc. In the field of nursing alone there are many subdivisions (education, head nursing, operating room supervision, out-patient nursing, pediatric, medical, surgical, obstetric, gynecologic, ophthalmologic, and otolaryngologic, public health, school, etc. It will take some time to develop all of these post-graduate fields, but it is obvious now that there will be a demand for all these types of instruction. In the more specialized fields, the courses will probably be three days in length, although developments may bring about a uniform six-day course. Hospital trustees are becoming interested in the plan of providing an annual budget for staff education. Studies by the Commonwealth Fund of special interests in medicine indicate the complexity of developments. Some of the medical subjects are medicine, surgery, obstetrics, obstetrics and gynecology, pediatrics, ophthalmology, ophthalmology and otolaryngology, otolaryngology, dermatology, neurology, psychiatry, neuropsychiatry, orthopedics, urology, diagnostic roentgenology, pathology, anesthesiology, physical therapy, neurosurgery, metabolic diseases, peripheral vascular disease, plastic surgery, thoracic surgery, malignant disease, oral surgery, radiation therapy, communicable disease, human serum, venereal disease, respiratory disease, surgical anatomy, goiter surgery, cardiology, electrocardiography, endocrinology, traumatic surgery, tuberculosis, gastroenterology, hematology, surgical pediatrics, allergy, surgical anatomy, and others. The universities are ideally suited for bringing interested groups together for post-graduate courses. The educational resources of such institutions are greater than any other social agency. Contrary to prevailing opinions, practical instruction which involves saving of time, labor and materials, can be obtained in these centers. President Coffman predicted the day would come when all professional peo-

ple would return to a center at regular intervals to receive advanced instruction. It looks as if it is nearer than most of us have realized. Those who have been delegated the responsibility of alloting public funds should keep in mind the challenge which the Universities have accepted to further the training of the "trained" members of society.