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So-called liver death""

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SO-CALLED "LIVER DEATH"

by

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INTRODUCTION

For many years, pathologists have been endeavoring to explain the origin of a variety of liver changes that accompany or are terminal to widespread or local disease within the abdomen. This association has been so commonly observed and the relationship exhibited so casually that it has not aroused the interest it ordinarily should have.

This paper will deal primarily with gallbladder disease and those patients who are expected to have a comparatively simple operation, but who never seem to completely recover from the operation, develop a high temperature, coma and die within 36 to 48 hours after the operation.

The concept of disease of the biliary tract which includes involvement of the liver as well as the gall-bladder is of relatively recent origin. Courvoisier in 1890 published one of the earliest papers on the subject and reported a mortality of 16 per cent following operation on the biliary tract. In 1934, Hener reported a mortality of 6.6 per cent in more than 35,000 operations and Graham, speaking for himself and associates, reported a mortality of 0.4 per cent following simple cholecystectomy and two per cent on operations on the common bile duct.

This striking reduction in the collective and in-dividual surgical mortality can be attributed to the

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surgeon's comprehension of the inseparable association of the liver and gallbladder in cases of disease of the biliary tract, plus the commendable habit of modern physicians on analyzing their own results and especially their failures.

As soon as such an analysis was begun on this sort of case, it was found that the operation was done to restore health and not as an emergency, and that these cases fell into three distinct groups.

The immediate mortality factors include hemorrhage, shock and embolism, while the delayed factors include peritonitis and complications of the respiratory tract. But, in a certain group of cases, the significance of which Charles Gordon Heyd was apparently the first to comprehend, none of these factors operate. The patients, for the most part, are not desperately ill, the majority present an unusually good surgical risk. Many of them die too soon to be explained on an infectious basis and too late for hemorrhage or shock, while a certain group in whom death is deferred exhibit no clinical evidence of infection or pneumonia. Post mortem throws no light on the subject because it eliminates all the usual causes of death.

Heyd grouped his patients as follows:
Group 1. The patient is frequently obese and gives a history of long-standing disease of the biliary tract.

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He is a good risk and has no organic defects, that can
be demonstrated. Cholecystectomy or cholecystetomy in
combination with appendectomy is easily done. There is
however a delayed recovery from the anesthetic; a semi-
comatose state ensues, which is followed by carphology,
coma and death from 24 to 48 hours following the operation.
Hyperpyrexia is the outstanding symptom in this group.
Group 2. The patient has jaundice, and there is often a
history of a previous operation on the biliary tract.
He is not so satisfactory a risk as the patient in group
1, but, he cannot be considered a poor risk. Operation
which may range from cholecystectomy to choledochostomy
is not extraordinarily difficult. Convalescence is satis-
factory for from 36 to 48 hours. Then the patient becomes
irritable and nervous; there is pronounced and abrupt
vasomotor collapse, and death ensues from 24 to 48 hours
later. Hyperpyrexis is again a feature.
Group 3. The patient exhibits calculous cholongeitis
and sometimes pancreatitis and more rarely there is a
pancreatic malignant disease. The seriousness of his
condition is realized, but he is properly prepared and
he does not, all things considered, present a bad risk.
Operation may be cholecystostomy, choledochostomy and
cholecystenterostomy or the creation of an external
biliary fistula. Convalescence is good for the first
five or six days; the jaundice decreases and the patient

considered on the road to recovery when suddenly,
somnolence ensues, which passes into coma, death is only
a question of time. In this group of cases, a deferred
renal factor is apparent beginning as oliguria and fre-
quently progressing to complete anuria, in contrast to
the first two groups in which the most striking thing
is hyperpyrexia.

In 1926 Cave reported three cases in a group of
35 deaths which seemed to belong to Heyd's group 1.
Stanton in 1930 reported fifteen fatal cases from one
hundred hospital records which seemed to fall in this
same group. Many men have reported cases since the
work of the above two men and in all, 95 such cases
have been reported.

The problem of the so-called "liver death" was soon
to assume a wider significance and not the least inter-
esting feature of it is the manner in which the significance
of previous observations on apparently unrelated or at
least irrelevant subjects is coming to be realized. In
1927 Furtwaengler from Clairmonts Clinic in Zurich, intro-
duced an entirely new element into the situation by
reporting the case of a young woman who, after an auto
accident, presented precisely the same picture as the
fatal cases in Heyd's group 3. Helwig and Orr in 1932
reported a similar case, but they, as well as Furtwaengler,

overlooked the fact that in Stanton's report just such a case had been reported although their patient was referable to Heyd's group 1. Stanton gave no postmortem observations, but in Furtwaengler's and in Helwig and Orr's cases autopsy revealed, in addition to the expected traumatic necrosis of the liver, high grade bilateral necrosis of the cortex of both kidneys.

Willard Bartlett Jr. in an extensive paper on the subject of renal complication following infection of the biliary tract, emphasized the renal factor in these cases. The majority of the cases which he reported are not in my opinion entirely germane to this discussion, for the reason that no operation was done in some instances, while in others, renal disability was demonstrated before operation.

In 1911 Clairmont and Von Haberer, after reporting five cases of renal failure following operation on the biliary tract, three of which were fatal, attempted to produce anuria experimentally by ligation of the common bile duct. Excretion of dye showed some impairment, but the experiments were unsuccessful. In the same year Steinthal noted anuria on the fourth day after operation on the common bile duct and autopsy revealed acute tubular degeneration of the kidney. He considered the anesthetic had precipitated the fatal result. In 1922 Parham and Walters reported several cases of patients dying of renal

insufficiency after operation on the biliary tract.
Ravdin, in 1929, in writing on the subject of vasodepressor
substance in the liver after obstruction of the common
bile duct, recalled that Ronsahoff in 1908 endeavored
to explain the shocklike states which occasionally
supervene after such operations. Connell, in 1931, and
again in 1934, linked the problem of "liver death" with
sudden postoperative death associated with high temperature
cases of which were reported by Gibson, Johnson and
Brewer in 1900, Candon and Ebrenfreid in 1912, Moschcowitz
in 1916 and Martin in 1928. Reports of 26 such deaths
were collected by Cutting in 1931, but he, like all
previous writers endeavored to explain them simply as
due to heat stroke, with climatic conditions as the
probable underlying cause. Dr. John Duncan published an
article in 1935 on Hyperpyrexia Following Surgical
Operations. He called attention to five postoperative
deaths which he believed were due to spells of torrid
heat during the summer. The deaths were not due to sepsis
and careful laboratory investigations did not reveal any
other causes. He found that the clinical picture con-
formed closely to ordinary heat stroke such as is seen
in non-surgical patients exposed to very high temperatures.
He pointed out that the operating rooms are often
excessively and unnecessarily hot, and the patient is

often exposed additionally to the radiation of heat from operating lights, that the atmosphere is humid from escaping steam, damp linens, wet dressings et cetera. An additional factor is dehydration either from loss of blood in the operating room, or the withholding of fluids during convalescence, both of which decrease sweating. The patient, he points out, may also have been given atropine or scopolamine and under all these conditions a perfect situation is developed for heat stroke.

In comment, may I say that heat stroke as such no doubt does occur and surely an ideal situation is set up for its occurance, but heat stroke does not explain the so-called "Liver Death" because he reported no liver or kidney changes which are the outstanding or only findings in the deaths under discussion.

There seems to be a tendency for more recent writers to extend this field not only to deaths following operation on the biliary tract and death following trauma to the liver, but also deaths occuring after such widely different conditions as burns, drug poisoning and intestinal ob- struction. Connell writing in 1934 definitely retracted the statement he made in 1931 that death with hyperpyrexia was noted only after operation on the biliary tract.

It might be well at this point to specify the changes which are uniformly noted in these patients at sutopsy. In none of them is there any anatomic or infectious

explanation for the death. In group 1 and 2 of Heyd's
classification, the organs are normal except for the
liver which shows diffuse toxic changes progressing in
some cases to degeneration and actual necrosis. Usually
the only other finding is slight congestion of the kidneys.
In group 2, on the other hand, they found, of course,
trauma to the liver with liver necrosis and a marked de-
gree of renal damage which is chiefly tubular degeneration
which ranges from granular changes to actual necrosis and
sequestration of cells. In other words, the cases fall
into two distince clinical and histological groups. The
first group of cases show hyperpyrexia and death soon
after operation with degenerative change in the liver as
the main picture. In the second group, the picture is
of uremia, deferred death and there are postmortem changes
of a degenerative character in the kidneys as well as
liver. There apparently is a wide disparity of figures
or impressions concerning the incidence of "liver death".
The majority of writers have mentioned isolated cases,
but Stanton reported fifteen which he was able to locate
personally from his study of hospital records, and he
thinks that several other cases should be considered
under the heading. Hever, apparently a man of a great
deal of surgical experience, says he has never seen a case
of cholecystitis without jaundice which could not be

explained in some other way. It seems the important
thing is not the exact incidence of the condition, but
that when it does occur, it is invariably fatal and thus
seems a worth while complication to study.

ROLE OF LIVER FUNCTION TESTS

Graham in 1918 published his observation that in
every case of cholecystitis there is an associated
hepatitis. He noted that the inflammation was more
marked in the right lobe and seems to be an infection
of lymphatics around the intrahexatic bile channels.
This work was corroborated by Heyd. He says that, "It
is significant that there is no anatomic block in the
lymphatics between liver and gallbladder, the lymphatic
channels passing uninterruptedly from gallbladder to
liver and from liver to gallbladder. The lymphatic
channels from the area of the cystic duct and calots
triangle is along the common duct to the under surface
of the pancreas. Surely the association of pancreatitis
and gallbladder disease is not without its effect on the
reparative power of the patient." Graham thinks that in
cases where jaundice is associated without any obstruction
to the bile duct, it is probable that the jaundice is
due to an obstruction of the intrahepatic bile ducts
caused by the inflammation.

Earlier workers were more concerned with kidney
function prior to an operation on the gallbladder, but
later workers are more concerned with liver function
prior to operation. In a sense the liver is more important
to life than the kidneys in that we cannot live more than

a few hours without the liver, but we can live for about one week without any kidney function.

Kidney function can be measured relatively easily, but liver function is difficult to determine. All the functions of the liver are not known and those which are known cannot be measured. One would probably be amazed to learn how often a damaged liver plays a part in the cause of death.

Tetraiodophenolphthalein has been used to measure liver function and is based on the livers ability to change that substance into phenoltetraiodophthalein. It was found that this substance not only visualized the gallbladder, but also stained the serum upon addition of a little alkali. Therefore, the substance could be used to study the liver function. This substance could not be expected to study all the functions of the liver, but could be used to study the ability of the liver to concentrate that particular substance. It is comparable to studying the excretory function of the kidneys.

A few years back before understanding the significance of this dye to study liver function, they had four unexpected deaths after simple cholecystectomy. The deaths occured in patients who were apparently good operative risks. At autopsy, in none of these patients, could a satisfactory cause for death be found other than a badly

damaged liver. In seeking a possible explanation of the tragedies, all the particulars of the cases were reviewed and found that all had had a high retention of the dye. In a normal individual, there is a retention of from 10 to 15 per cent within half-an-hour. Two of the four patients just mentioned had retentions of 90 per cent, one of 70 per cent and the fourth of 60 per cent. The significance of these findings is striking, especially when they found those patients who did not have high retention of dye went through the operation in fine shape. Additional support of the belief that these patients had serious hepatitis was shown by the fact that at operation, Graham had removed a piece of liver and on microscopic section showed extensive hepatitis. In other words, there seemed to be a very definite correlation between the high retention of dye and hepatitis.

After discovering the relationship between retention of dye and safety of operation, a point was made not to operate on patients who showed a high retention of dye. Instead of operating, the patient was put at rest on a high carbohydrate diet. This was done to insure a high storage of glycogen in the liver, since it is well known that the liver depends to a large extent on the amount of glycogen in the liver. If the patient could not

tolerate much glucose by mouth it was given intravenously.
An adult of average size was given 100 grams of glucose
in 24 hours.

An arbitrary standard of 50 per cent was set as the
basis of operation. Experience showed that in those
patients with a retention of 90 per cent, it could be
brought down to 30 per cent by the treatment outlined.

In the three years prior to using this test, the
operative mortality was six per cent in 216 cases. Since
using the test, the rate is 0.5 per cent.

Hospital mortality after cholecystectomy for three
years preceding phenoltetraiodophthalin:

Year	Cases	Deaths	Per Cent
1925	78	4	5.1
1926	63	7	10.1
1927	75	3	4.0
Total	216	14	6.5

For three years during which test has been used:

Year	Cases	Deaths	Per Cent
1928	90	0	0
1929	68	0	0
1930	66	1	1.5
Total	224	1	0.5

There was only one case in which they refused to operate
during the years 1928 to 1930 and that patient had
myocardial damage.

Not all deaths due to operation on the biliary tract
are due to hepatic function. Some are due to pneumonia,
cardiac complications, etc. It seems possible, though,
if a patient has a badly damaged liver to start with

his chances of surviving are less because he is more susceptible to post-operative complication. Stanley Eiss says it is a common finding that pathology of the liver does not parallel the pathology of the gallbladder. One may have a slight hepatitis with marked cholecystitis or visa versa. If the liver then is already damaged to a greater or lesser degree before operation, is it not reasonable to expect liver function to become still more impaired by the strain of anesthesia, trauma and esposure. That this is the case is indicated by the occurance following gallbladder operations of unexpected deaths not due to any of the usual causes.

Special attention was called to this type of case by Cave in 1926 who reported 575 cases of gallbladder operations in which there were 35 post-operative deaths and in three of which, the usual causes of death-- hemorrhage, peritonitis, pneumonia and embolism were all excluded. In these three cases, the main symptoms were a rapid rise in temperature and pulse. These patients were considered good operative risks, the patients were not jaundiced and there was no particular technical difficulties. All had prolonged chronic cholecystitis and calculus.

The liver as Judd says, has a "multiplicity of metabolic functions", it is concerned with metabolism

of carbohydrates, protein and fats; with production of
bile and fibrinogen, and with detoxification. "Probably
no one text can be relied upon to measure true liver
function."

The Mayo Clinic uses one of the dye-retention tests
and the Van den Bergh test as routine before operation.
Others prefer to use the icteric index to the Van den Bergh
test as it also depends upon bile pigment formation and
is simple to use.

Boyce writing in 1939 gives high praise to the
Quick hippuric acid test of the detoxifying functions
of the liver which is a simple almost universally
applicable test. The synthesis of hippuric acid, as
Quick notes, is a process of detoxification, brought
about by the conjugation of benzoic acid and glycine.
There is no store of preformed glycine in the body, but
the liver has a maximum hourly synthesis which cannot
be increased in the absence of an exogenous source. The
rate of the synthesis of hippuric acid is, therefore,
governed by the physiologic ability of the organ to pro-
duce glycine. This ability is adversely affected in
certain types of liver damage, and the output of the
hippuric acid is proportionally decreased. The test is
thus based upon a normal and very important physiologic
process, it puts no strain upon the liver, and it requires

no elaborate laboratory equipment and no skilled personnel for its performance. Quick has recently devised an intravenous modification of the text, to be employed when oral administration of the benzoic acid is unwise or impossible. The results of this test are usually corroborated by operative and postmortem findings and that it is of value in demonstrating latent hepatic damage before clinical signs are evident.

When Charity Hospital started to use this test in hepatic and biliary disease, they expected to find many cases in which impairment of liver function would be evident, and they did. When, shortly afterward, they began to apply it to thyroid disease, they expected to find many cases in which liver function was impaired, and they did. They were surprised to find how great the impairment was. Function averaged only 58 per cent of normal in both the toxic nodular and the toxic diffuse type. They were considerably surprised to find that in nontoxic diseases, the liver was also impaired. It averaged only 83 per cent of normal in the simple diffuse type and 78.8 per cent of normal in the simple nodular variety.

The Quick hippuric acid test showed poor liver function in several cases, for no apparent reason. Simple operations were done as appendectomy and herniotomy

and liver function in these cases were found to fall as much as 21 per cent under ethylene anesthesia, 25 per cent under ether and 49 per cent under spinal. The liver did not return to normal at the end of the seventh day and frequently had not returned to normal at the end of the 14th day. The safety of the various anesthesia has no part in this discussion. It was merely put in to show what happens to normal subjects.

CLINICAL DATA

Boyce and McFetridge began a study of one hundred cases of "gallbladder deaths" occurring in New Orleans Charity Hospital and found that 23 or almost 25 per cent fell into the class so-called "liver deaths", and gives the following data concerning these cases.

Group 1A Death within 48 hours, with hyperpyrexia. There are six cases in this group and their age range was 38 to 68 years with an average range of 53 years. Three of these cases were very obese. All had a long history of biliary tract infection, but none were acutely ill and all were thought to be good surgical risks. None of these cases had jaundice, but two were found at autopsy to have calculi. Ether anesthesis was used in five cases, spinal in one.

Group 1B Death within 72 hours with hyperpyrexia: There are five cases in this group with an age range of 24 to 58 years making an average age of 39 years. Two were obese and two had lost considerable weight during the illness. All had chronic infections of several years duration. One had jaundice, one had previously undergone cholecystostomy, and at operation, four were found to have stones. In one case the gallbladder was hydropic, and in another case there was marked hepatitis, but the condition of the liver was not reported in most cases.

As a matter of comment, it would be well to point out at
this point that Boyce says there was marked hepatitis,
but he does not go into a detailed account of this
hepatitis or how he determined the extent of hepatitis.
Ether was used in two of these operations, and two were
given spinals. These patients all had a fair recovery
for 24 to 48 hours, then developed hyperpyrexia of 105
to 107 degrees (by axilla), but no other symptoms than
an increasing pulse rate. In all these cases, the post-
operative carbon dioxide combining power indicated
acidosis, ranging from 24 to 38 volumes per cent. In
all the cases in this group and in group 1A in which
autopsy was done the picture was the same, i.e., degener-
ative change within the liver and some congestion of the
kidneys.

Group 1C These patients had a fairly normal course for
four or five days, then developed hyperpyrexia and death
within 24 hours. There are two cases in this group.
Both the cases in this group who were respectively 23
and 48 years old presents good surgical risks. Both
had long histories of long-standing biliary trace disease,
one had jaundice and exhibited stones. Ether was used
in one case, ethylene and ether in the other. Convalescence
was smooth for the first four or five days, and then the
clinical course was the same as in groups 1A and 1B.

The late death naturally brings up the question of peritonitis, but there was no such finding at autopsy. In both cases, autopsy revealed some apparent renal factor. One patient voided only once during the last 26 hours of life, the quantity not being recorded. In the other case, the patient voided involuntarily. In one case the CO_2 combining power was 42 volumes per cent and the N.P.N. previously within normal limits rose to 50 milogram per cent at death. In both cases only partial autopsy was permitted, a histological examination of the kidneys was not made, but damage to the liver cells was verified. Group 2. These patients had a smooth recovery for from five to ten days, then developed oliguria, progressing to anuria with symptoms of uremia, but an absence of hyperpyrexia noted in group 1. There were four cases in this group with an age range from 32 to 49 years with an average age of 42.4 years. They had the usual history of gallbladder infection. Two had jaundice and calculi, but all were thought to be good surgical risks. One gallbladder was hydropic and one showed a small patch of gangrene. Ether was used in one case, ethylene and local infiltration in one and spinal anesthesia in two cases. All had a smooth recovery at first and then a turn for the worse. Oliguria, progressing to anuria dominated the picture and death was due to uremic

coma. There was a rise in the N.P.N., and the urine
showed albumin and casts. At autopsy, degeneration of
the liver, parenchyma accompanied with necrosis of the
convoluted tubules of the kidneys was found.

Group 2B Cardiorespiratory collapse in from 60 to 92
hours was the outstanding feature of these cases of which
three are reported. They had the usual history of long
standing biliary tract disease. The age range was from
24 to 52 years with the average age of 44.5 years. One
patient was obese. In from 60 to 92 hours, cardiorespiratory
collapse with clear evidence of vasodepression was ap-
parent. One patient had repeated convulsions. The
carbon dioxide combining power of the blood ranged from
22 to 74 volumes per cent. In one case, the non protein
nitrogen was 74 mg. per cent and in another 120 mg.
Oliguria was a striking feature in the two patients who
lived the longest. In all these cases, death ensued in
from three to six days. After the collapse, there was
no response to any measures aimed at correcting the blood
chemistry. There was no autopsy report of these cases.

When one attempts to analyze these cases, it is
evident immediately that they fall into two groups histo-
logically and clinically speaking, yet there is no obvious
common factor to explain the fatalities. The age range
was wide, varying from relative youth to old age, so that

renal lesion cannot be a reasonable explanation in all cases because renal lesions of this sort are seldom described in youth. Anesthetic cannot be blamed because all types were used. Some of the patients were obese, half of them were not and a few were thin. The pathologic process was seldom serious enough to make operation difficult, or to present a bad risk patient.

Heyd thinks that pancreatic surgery is sometimes characterized by this same syndrome, so Boyce investigated the deaths after operation on the pancreas for several years back in the Charity Hospital and no deaths with hyperpyrexia were recorded. There were four deaths in which there occurred the sort of deferred death with renal damage which has been discussed. The cases Heyd speaks of are placed in a Group 3. There were four cases in this group with ages ranging from 22 to 62 years. Two were obese. Operation was performed in three cases as an emergency measure immediately after admission, and one patient had previously undergone cholecystostomy. All of these patients presented as good a surgical risk as pancreatitis goes, except for one exception. Spinal anesthetic was used in all the cases, the operation in-cluded simple exploration, drainage of the pancreas, cholecystostomy and cholecystectomy and appendectomy. The outstanding feature of the clinical course in all

instances was deferred oliguria progressing to anuria and associated with typical changes in the blood chemistry, chiefly a rise in non protein nitrogen, which in one reached 66 mgm per cent and in another 92 mgm per cent. Postmortem was done and found in addition to pancreatic disease, degenerative changes in the liver cells and tubules of the kidneys as found following operation on the biliary tract. Boyce believed that trauma to the liver may produce a similar hepatorenal syndrome, so such deaths were investigated. The cases which presented this syndrome fall into two distince classifications corresponding to groups 1A and 2A following operation on the biliary tract. These two groups will be called 4A and 4B.

Group 4A This includes three cases following gunshot wounds and one following an automobile accident. The age range was from 8 to 32 years with the average age of 22.3 years. Exploration under ether anesthetic was done immediately in three cases and six days after admission in one case. After marked jaundice had developed, three cases died within 24 to 36 hours of the injury with an axillary temperature of 105 to 108 degrees while the fourth case had hyperpyrexia promptly following operation and no true peritonitis could be found in any case.

A case that came into the Nebraska University Hospital will be reported here. A white, rather obese,

married female age 28, gravida three came into the
University Hospital complaining of:

1. Sharp shooting pain in right upper quadrant and ex-
tending to the back and behind the right shoulder inter-
mittently for three weeks. She had had her first attack
one year before and had to have hypodermic injection at
times for pain.

2. She had been jaundiced at times with the attacks of
pain.

3. Nausea and vomiting with each attack, she was very
nauseated on admission and restless.

4. Inability to eat during the past three weeks because
of nausea and vomiting. She stated that she had been
free from attacks for the past year until three weeks
before entrance to hospital when she had about one attack
per day. Her blood pressure was 125/90, and physical
examination revealed nothing other than marked tenderness
in the upper right quadrant, no rigidity or masses.

Progress notes:

November 3rd: Cholecystectomy done. Liver found to be
small and tucked up under the costal margin. Surgeon
experienced mechanical difficulty in removing gallbladder.

November 4th: At one A.M. pulse became more rapid and
patient vomited. The interne felt the patient might be
bleeding so she was given morphine gr$\frac{1}{4}$, a Wanganstein

suction inserted and an ice cap was placed on the abdemen,
the foot of the bed elevated and five per cent glucose
in normal saline intravenously was given. She was then
given neoprontosil in case she might have an infection.
Her temperature rose steadily, respiration became shallow
and pulse was poor. She was given adrenalin and caffein
grs. $7\frac{1}{2}$ every four hours. Her temperature rose to 106
degrees at ten A.M. Nitroglycerine and sodium nitrite
were given along with 50 per cent glucose intravenously.
Temperature ranged around 106 degrees all day.

November 5th: Patient was disoriented part of the time.
Temperature came down to 102 degrees, but developed
twitchings of muscles of the hands. Carbon dioxide and
oxygen were started.

November 6th: Temperature was 100^2 degrees rectally.
Treatment outlined above was continued. Condition not
much better in spite of temperature drop. Patient
irrational, repeated phrases over and over again. Com-
plained she was unable to see or keep her eyes fixed.

November 7th: Temperature around 99 degrees all day.
Mental condition little changed except that she recog-
nized her husband at times. Was violent at times and
had to be restrained.

November 8th: Temperature about the same, pulse better
quality. Rales heard in the bases of both lungs. Mental
condition about the same.

November 9th: At 4:30 A.M. patient was gasping for
breath and became very cyantic. Adrenalin and caffein
given. She was pronounced dead at 4:45 A.M.

A postmortem was done and no sign of hemorrhage or
infection was found. All organs were essentially normal
except the liver and kidneys. The liver lobules could
not be made out except directly around the veins and
arteries. The cells had lost their shape and continuity.
There was a loss of nuclei and cytoplasm. Diagnosis was
focal necrosis and fatty degeneration of the liver.

The kidney tubules were swollen and contained non
cellulor debris. The glomeruli were swollen and the
capsules practically obliterated.

This case would fall into Heyd's group two cases,
except for the fact she lived longer than 72 hours.
However, considering the postoperative course and post-
mortem findings, it can definitely be classed as a "liver
death". Going back and reviewing this patient's history
we see that she came into the hospital following a three
weeks illness during which time she had considerable
nausea and vomiting, and consequently her liver store of
liver glycogen was naturally low or depleted. Considering
this fact along with the fact that she must have had some
hepatitis as most authors agree is present when cholecystitis
is present and add to this, surgical trauma, the effect
of the anesthetic and the lowering of the liver temperature

from exposure during the operation, we then get a clue
as to the cause of this death. A liver function test
was not done on this particular person, but had one been
done, it would probably have been below 50 per cent.
Going back now and trying to postulate how this death
might have been prevented, we must refer to Graham's work
on liver function tests. Had a liver function test been
run and found to be low, the patient should then have
been put on a high carbohydrate diet as Shearer outlines
until the liver function was well above 50 per cent. We
must also consider that this patient was vomiting for
three weeks before ever entering the hospital. This
period of delay must have likewise had its effect on
depleting the liver of reserve glycogen. Early surgical
treatment in all cases of cholecystitis which do not
respond promptly to medical treatment is advocated in
order to prevent gross liver damage.

This case bears out Heyd's contention that if the
patient lives long enough, there will be characteristic
kidney changes. This patient lived longer than the
majority of so-called "liver death" cases and did show
marked kidney changes. It is evident, from these case
reports that after operation on the biliary tract, after
operation on the pancreas and after traumatic necrosis
of the liver, there may occur a typical syndrome in
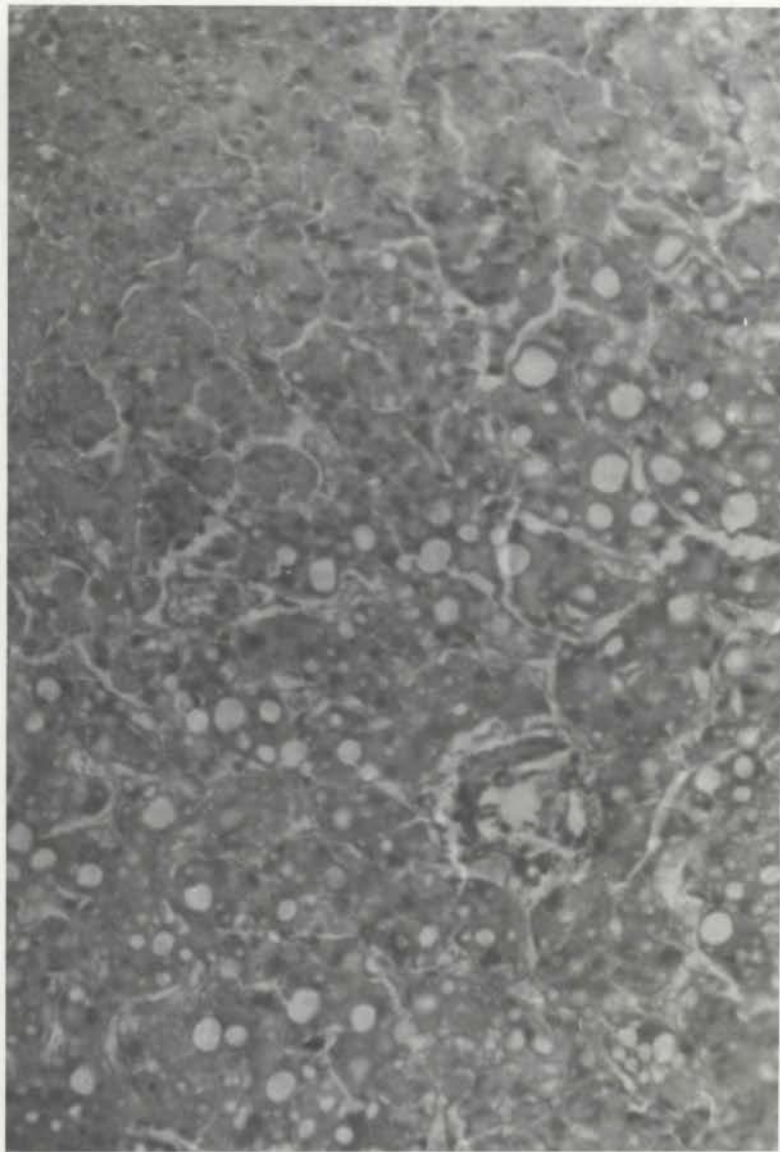
Microscopic section under high magnification,
from patient who died in the University Hospital
presenting the so-called "Liver Death" syndrome.
Picture by courtesy of J.P.Tollman M.D.
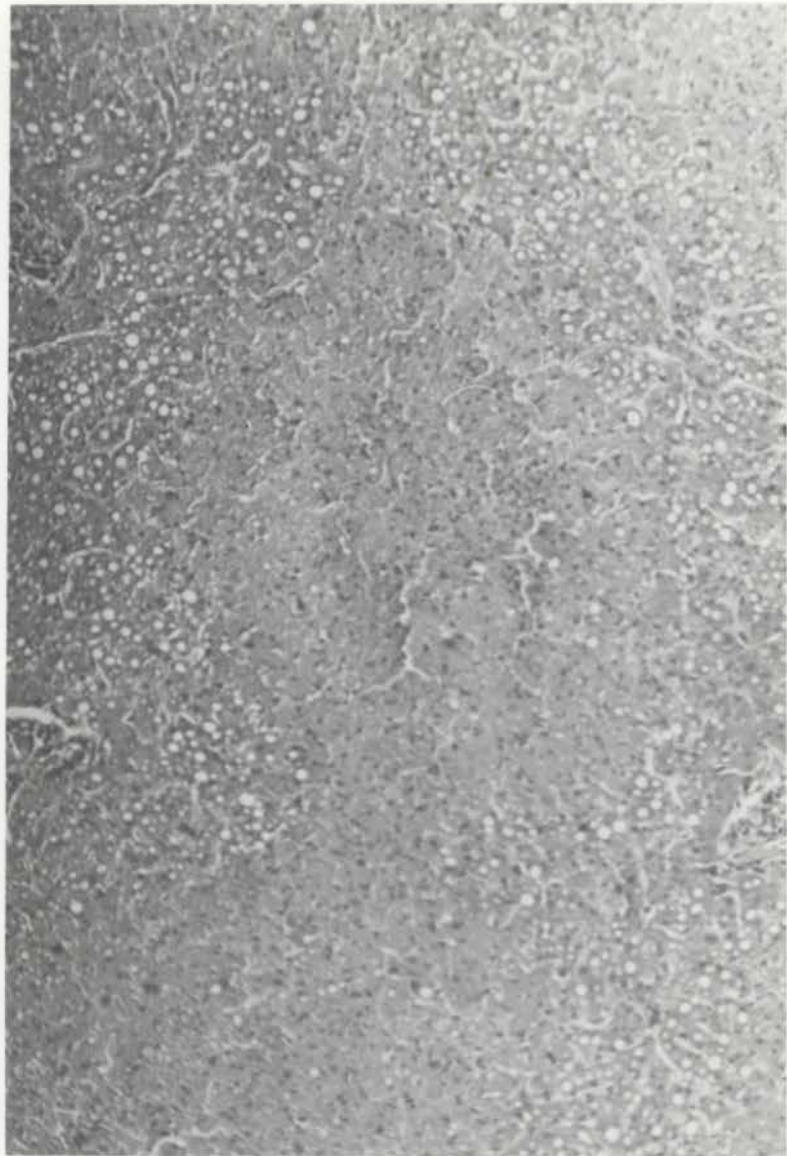
Microscopic section, under low magnification,
from kidney of patient who died in the University
Hospital presenting the so-called "Liver Death"
syndrome. Picture by courtesy of J.P.Tollman M.D.
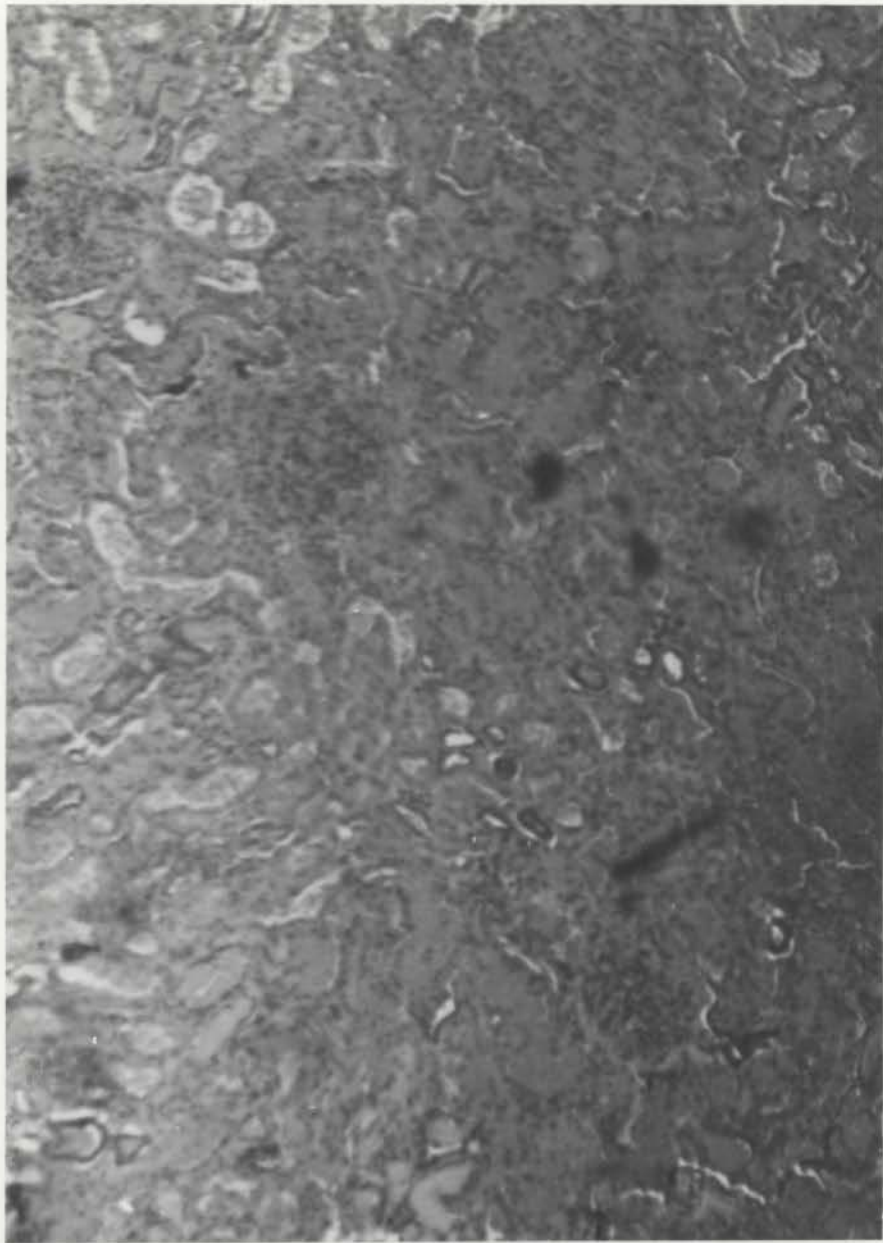
Microscopic section from kidney of patient who
died in the University Hospital presenting the
so-called "Liver Death" syndrome. Picture by
courtesy of J.P.Tollman M.D.

which death occurs promptly, with hyperpyrexia as the
outstanding feature, or occurs later with renal symptoms
as the outstanding feature. The first group of cases
showed at postmortem that the pathology was chiefly
limited to degenerative changes within the liver,
associated with slight degenerative changes in the con-
voluted tubules of the kidneys. The only marked difference
between death following operation on the biliary tract
and those following trauma to the liver is as Helwig and
Orr pointed out, that in the case in which death follows
traumatic necrosis of the liver, the degenerative changes
within the liver are limited to the traumatized area,
whereas in true hepatic disease, they are widespread.
The damage to the kidneys, however, is widespread in
both traumatic and pathologic states.

EXPERIMENTAL DATA

With the idea in mind of trying to reproduce the Pathological and Clinical syndrome outlined in the clinical cases, many men have done various types of work on experimental animals which will be reviewed at this time. These processes, they have endeavored to reproduce by the following methods.

1. Traumatic necrosis of the liver

2. Various types of interference with the hepatic and portal circulation

3. Obstruction of the biliary tree

4. Obstruction of the biliary tree with later release of the obstruction

5. Intraperitoneal and intravenous injections of extracts made from the liver of animals in which the biliary tree had been obstructed and later released

6. Injection of the same extracts of animals in which previous damage to the liver had been produced by the use of carbon tetrachloride mixture.

7. Intraperitoneal injection with the extract of the liver of a patient who died with hyperpyrexia 32 hours after cholecystectomy.

8. Implantation of normal liver into the peritoneal cavity as done by Mason, Dragstedt and Andrews and Hidina.

9. Intraperitoneal injection of extracts of normal liver, as done by the above men.

10. Intravenous injection of the same extracts.

All the animals that were used in these experiments
were grossly normal animals which had normal renal
function as proved by urinalysis and by studies of blood
chemistry. They measured the 24 hr. output of urine for
several days to obtain the average for each animal.

All experiments were done under aseptic conditions
and the liver extracts were made under the same con-
ditions. Anesthesia was variously a light ether narcosis
or local analgesia for all experiments except two in
which veterinary pentobarbital sodium was used. None
report any evidence of toxicity following the use of
any anesthetic.

1. Traumatic Necrosis of the Liver as done by Boyce and
McFetridge

The abdomen was opened through an upper right rectus
incision, and various manual and instrumental methods
were employed to traumatize the liver substance without
fracture of the capsule. If the capsule was broken and
intraperitoneal hemorrhage occurred, the animal was
discarded. In all cases, there was more or less evidence
of shock after the injury, and in a few cases death
followed promptly. In the animals which survived, there
was noted a diminution in the 24 hourly output of urine
with the appearance of albumin, casts and R.B.C. and an
insignificant rise in amount of blood nitrogen. Within

from seven to ten days after the injury, these symptoms disappeared, and the animal seemed normal in all respects.

They felt that they had not produced enough hepatic damage to reproduce the traumatic or pathologic renal damage responsible for the hepatorinal syndrome. Helwig and Schutz did similar experiments on dogs and rabbits and reported the same difficulty and the same absence of positive renal signs in the animals which survived the immediate period of shock.

2. Various Types of Interference with the Hepatic and Portal Circulation.

Sutton believes that this condition may be due to accidental ligation of the hepatic artery during the course of the operation. Thoresk believes that 33 per cent of patients have collateral circulation or accessory circulation which may be a source of danger during operation. He found in dissecting 29 unselected cadavers that there was wide variation in the course and distribution and branches of the hepatic artery. In 50 per cent of the cases, the hepatic artery was in such close relationship to the cystic duct that it might easily have been injured during a cholecystectomy.

To demonstrate this circulatory theory, fourteen dogs were chosen and a cholecystectomy and ligation of the hepatic artery was done on each of them. Six of the

dogs developed a high temperature and died. All six showed diffuse disorganization of the liver cords and many areas of focal necrosis. In the eight surviving dogs, which did not show this rise in temperature, injections of a bismuth suspension or a starch mixture were given which demonstrated adequate collateral circulation. In these livers, there were areas which showed disorganization of the liver cords but no necrosis. Sutton found that the ones which lived were the animals with collateral circulation.

Direct injury to the hepatic vessels is a frequent possibility and there might be accidental legation or trauma initiating thrombosis.

3. Obstruction of the Biliary Tree

In some animals, the common bile duct was ligated and divided, and the distal end was buried; in others the same experiment was combined with cholecystectomy, with an idea of securing a more rapid rise of pressure. In all cases, anomolies of the biliary passages were searched for and due account taken of those found. A very deep jaundice promptly developed in all animals so treated, but the urinary findings were practically unaltered, as was the blood chemistry. Such deaths as did occur were quite clearly due to infection and there was no evidence in any case of damage to the liver or kidneys as had been expected.

4. Obstruction of the Biliary Tree with later Release
of the Obstruction

In the animals which survived the obstruction just
described and where there was no evidence of infection,
the obstruction was continued for from twelve to twenty
days. Then the abdomen was reopened and the obstruction
released by means of an external biliary fistula. For
this purpose a specially devised cannula was used which
was stopped by a screw and by this method it was hoped
that the obstruction could be created or released at
pleasure. Because of medical difficulties, however, this
did not prove successful.

In all cases the clinical course was the same following
release of the obstruction. There was a prompt decrease
in jaundice associated with increasing anorexia and death
within from 72 to 96 hours of those animals which were
not killed when their state was terminal. There were
also noted oliguria which promptly progressed to anuria,
together with the appearance of albumin, casts, and red
blood cells in the urine and a rise in the amount of non
protein nitrogen.

In all cases, examination after death showed no evi-
dence of peritonitis. Only faint traces of jaundice were
apparent. The liver was greenish and slightly enlarged,
and there was no gross evidence of the accumulation of bile.

Histological examination of the liver and kidney revealed precisely the same changes noted in human subjects following "liver death". In the liver, the periportal areas showed no significant changes. There was no evidence of cholangeitis or biliary stasis, but there were central areas of degeneration, with vacuolation and fragmentation of the muclei of the liver cells. In some cases, there was noted the deposition of a peculiar, homogeneous, red staining material the nature of which, although not clear from the hematoxylin and eosin stain, was undoubtedly hyaline. In all cases, the central area of the liver showed actual necrosis of the liver cells, without significant changes in the architecture of the portal fields. In all cases, the kidneys showed engorgement of the blood vessels, interstitial hemorrhage and tubular degeneration. Boyce feels that from this group of experiments that the renal changes found at autopsy in such cases, whether clinical or experimental, are the end result, not of the obstruction, but the release of the obstruction. Hepatic changes of some degree are, as has been stated, the constant accompaniment of all degrees of cholecystitis, but whether the extreme hepatic changes noted in such cases are the result of the original obstruction or of the release of the original obstruction has not yet been definitely proven. Boyce,

however, feels that they are aggravated by the surgical procedure which releases the obstruction and that the renal changes are positively precipitated by it.

5. Intraperitoneal and Intravenous Injections of Extracts Made From the Livers of Animals in Which the Biliary Tree Had Been Obstructed and Later Released

Boyce now took the livers of the animals so treated which had died or which had been killed when their condition was terminal, put the liver through a small grinding machine under strict aseptic precautions. The substance thus obtained was extracted with physiologic solution of sodium chloride sterile distilled water and with alcohol and the extracts injected into normal animals intraperitoneally and intravenously. The dog given the alcohol extract intravenously died promptly, undoubtedly as the result of alcoholic poisoning, since they discovered the lethal dose was miscalculated. All the other dogs survived and showed no clinical laboratory evidence of pathological changes other then temporary vasodepression following the intravenous injection of the extracts. Boyce feels these experiments failed because the extracts were not sufficiently concentrated. The vasodepression is an interesting notation in light of work done in 1929 by Ravdin. He feels that the early period at which hepatic secretory suppression occurs in animals in which

the gallbladder has been removed is due to the anatomic structure of the liver. Its dense fibrous capsule does not permit rapid distention. In an organ composed mainly of cells as the liver is, there is not sufficient space for extensive expansion when the ducts are occluded without encroachment on the parenchyma and the vascular bed. The increased intra-acinar pressure causes damage to the liver cells, but the portal retardation contributes still more to this and may be the decisive factor. Rous and Larrimore have shown the effect of portal retardation in rabbits. In these animals, replacement of the damaged parenchyma with connective tissue occurs shortly, while in dog and man this is prolonged.

It may be that damage to the cells either liberates certain toxic substances or further elaborates them, or that the cells store these and the restoration of the normal blood flow carries them out of the damaged cells into the circulation. This theory is based on the knowledge that hepatic shock does not occur in a patient as long as the obstruction is in place, but occurs after the obstruction is released. Whether during the period of obstruction the liver stores the substance through an inability to detoxify or excrete them, or whether they are the result of cell destruction is not known.

As to the role histomine might play in liver shock

cannot be easily determined and it is not known whether histomine is present in the living cell as such or whether it is released after death of the protoplasm. Some authors think that it is present as such and escapes after death due to the destruction of the cell wall and enables it to escape. It may be that histomine is liberated from the necrosed cells of the liver and it is this substance that causes death.

If it is the histomine that is repponsible, then an extract from an animal with a normal liver should produce the so-called "liver death" just the same as the extract from a liver which is damaged by hepatitis. This, however, is not the case according to Boyce and rather explodes the histomine theory.

6. Injection of the same extracts of Animals in which Damage to the Liver had been Produced Previously by the Administration by Stomach Tube of a Combination of Carbon Tetrachloride, Cottonseed Oil and Alcohol

Carbon tetrachloride is a substance which has been proved, experimentally and clinically, to cause various degrees of necrosis of the liver. Few animals died promptly and those which survived were given intraperitoneal injections of the extracts just described. In a few cases albumin casts and red blood cells appeared in the urine, accompanied by an insignificant rise in the amount of non protein nitrogen, but in no case was the damage

terminal or permanent. They concluded that they did not damage the liver enough to bring about the first stage of the hepatorenal syndrome, or that they allowed so long a time to elapse between production of the hepatic damage and the injection of the liver extract that full regeneration of the damaged liver cells had occurred. The inadequate concentration of the extracts is another factor to be considered.

7. Intraperitoneal Injection of the Extract of the Liver of a Patient who Died with Hyperphyrexia 32 Hours After Operation on the Biliary Tract

A woman died with the classical picture of Heyd's Group one deaths. The liver was ground and an extract made with distilled water and alcohol and this extract injected into dogs intraperitoneally. All dogs died within 72 hours of the first injection. All showed casts, albumin and red blood cells in their urine.

Autopsy on the dogs given the alcohol extract showed no significant changes, but the dogs given injection of the saline and the watery extract, there was marked parenchymatous degeneration of the liver cells, with similar degenerative changes in the convoluted tubules of the kidneys as well as marked engorgement of the renal blood vessels and interstitial hemorrhage. Since this is the precise picture exhibited by patients

who died of this hepatorenal syndrome, there seems no question that there was some substance in the extract made from this liver that produced the histological changes in the dog.

8. Implantation of Normal Liver into the Peritoneal Cavity

There were no significant findings following the implantation of normal liver into the peritoneal cavity.

9. Intraperitoneal Injection of Normal Liver

This experiment was also carried out by Mason, Dragstedt and Andrews and Hrdina. All their dogs died within seven to 18 hours with autolytic peritonitis. These experiments were repeated and incubated, concentrated extracts of normal liver was used. All the dogs in this experiment lived and showed no reaction of any sort, temporary or permanent, except for a slight immediate reaction after the injection, which is to be expected. This experiment proved again that normal liver and diseased liver do not cause the same pathological processes, but why lethal results were not obtained with the other experiments cannot be determined.

10. Intravenous Injection of Normal Liver

These injections produced no clinical or laboratory results of any sort and need no detailed discussion.

SUMMARY OF EXPERIMENTS

Traumatic necrosis of the liver to a sublethal degree, and obstruction of the biliary tree failed to produce in experimental animals the hepatorenal syndrome seen in human patients after operation on the biliary tract. Obstruction of the hepatic circulation produced similar changes when done by one man and none when done by another. The experimental production of autolytic peritonitis, as well as the intraperitoneal and intravenous injection of the extract of normal liver, proved irrelevant to this discussion.

On the other hand, the release of experimentally produced obstruction promptly initiated a clinical course and a postmortem picture, gross and histologic, precisely similar to the clinical postmortem picture, observed in human subjects who die under the same conditions after operation on the biliary tract. Injection of various extracts made from the liver of these animals failed to produce the same picture in the other animals, chiefly because errors in concentration of the extracts. However, the same picture was reproduced by the injection of the saline and watery extract of the liver of a human patient who died suddenly after cholecystectomy with hyperpyrexia.

COMMENT

As repeated over and over again by all men writing on the subject of cholecystitis, there is in all cases of biliary tract disease an associated hepatic state. Whether it is antecedent or consequent is still a matter of dispute and makes no special difference in this discussion. It can, however, in certain instances be of enormous significance. The moment such a liver is altered by surgical release of the obstruction, however slight and trivial, the obstruction may have seemed, it becomes progressively more severe which brings one sharply up against the fact that the very means adopted to relieve the disease may kill the host, a situation analogous to operation for intestinal obstruction for instance, in which the release of the obstruction often permits a fatal onrush of toxic intestinal contents into the still undamaged area of the bowel. This state of affairs is over and above all the complications of operation, the risk of anesthesia, surgical trauma, changes of temperature and the anatomic changes consequent on the removal of the gallbladder from the bed of the liver.

The effect of the anesthetic, for instance, depends on the agent employed and the amount of damage to the liver already present. Rosenthal, Bovine and others, chiefly with dye tests have shown that ether causes a definite although transitory impairment of hepatic

function, rarely lasting longer than 24 hours, while others think that when there is already a certain amount of hepatic and renal damage, the anesthetic cannot help but cause more embarrassment. However, ether cannot be blamed for all "liver deaths" because other anesthetics were used in patients who died with the so-called "liver death".

Surgical trauma needs little discussion, because it is clear that the amount of trauma will be greater with an unskilled surgeon than when a skilled surgeon is operating.

Another point which cannot be ignored is that even the slight exposure attendant on merely opening the abdomen reduces the temperature of the liver, as Crile has shown, from 1.5 to 3 degrees. Crile has also shown that for every one degree drop in temperature there is a decrease of some ten per cent in its chemical activity.

If these things are true of the normal liver, it should be even more likely to occur in the diseased liver.

There are no accurate tests for measuring liver function. The most accurate tests give only an approximation. It has not been shown that the amount of pathology in the liver is in proportion to the amount of biliary disease, but it is known that there is always some hepatitis and whether this is extreme or minimal cannot be determined.

The occurrence of events is something as follows:
The patient with or without gross obstruction of the
biliary tree has some degree of hepatic damage, but it
is not incompatible with life. So long as the liver is
put to no strain and stress other than that of ordinary
living, to which it has accustomed itself, so to speak,
it is quite capable of carrying on. When surgery is
undertaken, even under the most favorable condition, there
are introduced other factors, including the anesethetic,
the trauma of the surgical manipulation, the associated
drop in inter-abdominal temperature, and changes in
intrahepatic and biliary pressure, and with these new
factors, the liver, already the seat of a pathological
process, cannot cope. As a result, its function promptly
fails and the toxic substances which reach it in the course
of normal body metabolism are thrown off undetoxified.
Then the liver cells, as they become increasingly unable
to function, themselves undergo necrosis and themselves
discharge into the circulation some additional toxic pro-
ducts which originate in their own degenerating cellular
substance. The kidney, after which the liver is the
great detoxifying organ of the body, must take up the work
of the liver, purely as a matter of physiology, when the
detoxifying function of the latter organ fails. But, in
the kidney, the margin of safety is very small, and it is

not fitted to handle even the normal products of body metabolism, let alone, in addition the toxin liberated by the damaged liver cells. Therefore an overwhelming and lethal toxemia naturally ensues.

Bowman thinks that toxic products are excreted through the convoluted tubules. This has been established experimentally by the use of salts foreign to the blood, and would not the same process be operative with the toxic products of necrosed liver cells. The sensitive epitheluim of the convoluted tubules shows changes ranging all the way from slight granular changes to complete necrosis and sequestration, while the glomeruli remain practically undamaged. The clinical phenomenon is, as has been noted, oliguria which progresses to anuria, in spite of the undiminished if not actually increased fluid intake always forced on the patient in an endeavor to correct his perverted blood chemistry.

Boyce's personal opinion, which he thinks is substantiated by the clinical and experimental facts on the subject, is that the hepatic damage always precedes the renal damage and that if the patient who dies promptly with hyperpyrexia and shows hepatic changes at postmortem examination could be kept alive long enough he too would show precisely the same clinical and postmortem renal changes as the patient who dies later. The patient who

dies promptly undoubtedly has a more overwhelming toxemia

perhaps qualitative, but more probably quantitatively

than the patient who dies after cardirespiratory collapse,

while death which occurs after from two to 20 days is best

explained in the light of our present knowledge as due

to protein intoxication in contrast to the probable

anaphylactic reaction of early death with high temperature.

The patient who has a pre-existing hepatic damage, small

amounts of the toxic substances elaborated in the damaged

liver cells are released into his system, but he is

sensitive to the substance and can handle it. He cannot,

however, handle the massive amounts released postoperatively.

Furthermore, even though his damaged liver can stand the

strain and stress of ordinary life, it cannot withstand

the added strain and stress of surgical trauma and its

concomitants, and his kidneys, especially if they are in

anyway prediseased, as they often are in older individuals,

and has little or no margin of reserve.

Heyd, the first to consider "liver death" as a dis-

tinct postoperative entity in the diseases of the biliary

tract, expressed the belief that in the group 1 type of

death (with rapidly increasing hyperpyrexia, certain

deleterious substances are released at operation) the

whole mechanism suggesting complete and rapid cessation

of hepatic function, and that in the second group (death

with hypeypyrexia within 48 to 72 hours) there is a toxic innudation of the system and direct poisoning of the liver cells again with cessation of liver function. In the group 3, deferred death with renal symptoms according to him, death is due to throwing on an already damaged liver the burden of detoxifying and increment of deleterious products released by operation, the result being a progressive increase of hepatic dysfunction.

Heyd also advanced the theory which he admits is only speculative, that in the group of cases in which pancreatic disease is a factor, the underlying cause of death may be some pancreatic toxemia. Aside from the fact that the existence of a pancreatic toxin has never been demonstrated, this in no way explains the deaths in his own groups 2 and 3 which have no pancreatic damage.

Cave's idea is much the same i.e., that the sudden liberation of toxin from the liver or of pieces of chemically altered liver cells into the general circulation is responsible for the catastrophe. He mentioned as other possible causes the stirring up of infected bile in the intrahepatic ducts as the result of operative manipulation and the partial cessation of hepatic function caused by the shock of the actual removal of the external biliary viscus from its bed, with the resulting exposure of the surface of the liver. The latter consideration,

he says, is operative in fatal and nonfatal cases alike, and the toxic theory, while it is correct in its fundamental conception does not go far enough.

Walters and Parham emphasized the difference between hepatic and renal insufficiency in these cases in a report published in 1922. Willard Barlett Jr., inclined to emphasize the same distinction, stated that there is no evidence that hepatic cell damage serious enough to cause renal damage must precede the pathologic process in the kidneys, his idea being that infection of the bile passage and not some toxic phenomenon is the cause of the nephritis. This theory does not stand up because one should not disregard the hepatic factor which is apparent to some degree in all cases of biliary trace disease and then again as brought out in clinical data and experimental data, this syndrome occurred in cases of trauma to the liver, and where no infection was evident. Stanton, who was at first inclined to the theory of infection, changed his mind after encountering the same syndrome in traumatic necrosis of the liver in which the same syndrome was present and in which infection could not possibly have played a part. Stanton also thinks that if infection were the etiological factor in kidney damage, it would be seen many more times after operation than it is. Really, the incidence is very

small in proportion to that of infection.

Ransahoff noting the shocklike states which sometimes supervene immediately after operation on the common bile duct, advanced the theory that the cause is a sudden stretching or pulling forward of the structures in the gastrohepatic omentum, with consequent construction of the portal vein, but this, as Ravdin pointed out, is not an adequate explanation; it does not explain cases of deferred death, nor does it explain those cases in which the common bile duct is not handled. Ravdin, himself, advanced the vasodepressor theory which has already been discussed. Vincent and Sheen, as early as 1903, were able to extract from the liver a depressor substance, and Ravdin, working along this line, was able after experimental ligation of the common bile duct, to obtain a substance containing histomine and choline, both of which are notoriously vasodepressant in action. His theory is that an overwhelming amount of this substance is suddenly released at operation or, as Helwig and Orr pointed out, after trauma of the liver. Theoretically, the latter authors added, such a substance might cause sufficient vasodilitation to produce renal damage, but Ravdin does not think so. As he proved the amount of depression substance in jaundiced hepatic tissue is considerably in excess of the amount in unjaundiced

tissue, so the explanation is not particularly helpful in which disease of the biliary tract is not of extreme degree.

Wilensky advanced the idea that the initial lesion in the biliary tract produces a primary effect on the hepatic cells and a secondary effect on the renal apparatus, it being highly probable that in hepatic disease, some of the catobolic products of liver metabolism and the end products dependent on its injury have an effect on the kidney. Such an explanation, he says, covers the picture of uremia associated with the so-called cholemia of hepatic toxemia, but it does not provide, as does Boyce's theory, for the successive steps of injury extending from the biliary tract into the liver cells and thence into the convoluted tubules of the kidneys.

Helwig and his 6o-workers, Schutz, Kuhn and Orr, believe that there is some specific toxic liberated by the damaged liver cells which acts on the kidneys to cause tubular degeneration. They believe it is a specific toxin because no other organs are affected which is true in the majority of cases when a toxin is liberated in the blood stream. Boyce and McFetridge agree that it is a toxin, but disagree that it is a specific toxin. They think that the kidney is a normal excreting organ from the liver. The kidney after the liver is the great detoxifying organ

of the body, must take up the work of the liver, purely

as a matter of physiology, when the detoxifying function

of the latter organ fails. But, in the kidney, the margin

of safety is very small, and it is not fitted to handle

even the normal products of metabolism, let alone, in

addition the toxin liberated by the damaged liver cells.

Connell, writing in 1931, stated that the syndrome

of sudden death with hyperpyrexia, was not apparent after

any operation other than that on the biliary tract, but

he withdrew the observation, and mentioned it following

operations for ovarian cyst, uterine fibroid tumors,

chronic appendicitis, ventral hernia and fracture of

the skull. It is true that in at least one of these

patients, there was a former operation for biliary tract

disease, and it is also true that cranial injuries are

prone to produce high temperature reactions. Furthermore

in the 26 cases of postoperative heat stroke, reports

of which were collected by Cutting, only a few, as

Connell pointed out, followed operation on the biliary

trace, and there is little doubt that most of them in

view of present knowledge would fall into the category

under discussion.

CONCLUSION

It would seem that the most important consideration in regards "liver death" is that made by Graham who says, "Any patient with a damaged liver presents a questionable risk not only for operation on the biliary tract, but for any operation no matter how trvial it may be." Shearer has made the same warning and means there is no such thing as simple surgery. It has been oft repeated by every man who has done any work on this subject that wherever there is biliary tract disease there is also hepatitis to a certain degree and that all patients must be studied from the point of liver function just the same as routine urine and blood examinations are made. In other words, the ninety and nine patients must be given liver function tests in order to save the one that might be lost.

At present no test is available which will give anything but an approximate idea of the efficiency of hepatic function. The details of these tests is no concern of this paper, but it is reasonable to call attention to certain tests which are used. Graham thinks the best is iso-iodeikon and takes 50 per cent retantion as an arbitrary standard of safety for operation and without elaborate preparation he was able to reduce his mortality in simple cholecystectomy from six per cent in

216 cases to 0.4 per cent in 224 cases while in operation on the common bile duct his mortality fell from 7.7 per cent to two per cent. Regardless of how inaccurate a test may be, it is worthy of routine use when such results have been produced.

In the same connection, Boyce of Charity Hospital believes that the best test available at present is the Quick Hippuric test which seems to be a fairly physiological test and overcomes the objection to phenoltetraiodophthalein in that many men felt this substance itself damaged the liver.

Wilensky suggests that hepatic function be estimated in the light of renal function and that evidence of renal insufficiency in cholelithiasis and kindred diseases be regarded as presumptive evidence of hepatic insufficiency. This, however, does not seem reasonable in that renal damage is a late sequale of hepatic damage and would give no early evidence to hepatic insufficiency.

Shearer pointed out that pre-operative preparation is as important for the apparently good risk patient as for the bad risk patient. It should include according to indications a diet high in carbohydrates, fluids by all routes, dextrose as necessary, orally and intravenously, and calcium, not so much for control of hemorrhage as because Lawson, Minot and Robbins have shown that hepatic

damage caused by carbon tetrachloride is repaired more rapidly under this form of treatment.

The anesthetic should be chosen with care and ether avoided where hepatic damage is suspected.

Manipulation should be done with as little trauma as possible. Unnecessary and prolonged exposure of viscera should be avoided. Crile suggests diathermy to maintain body temperature, but this does not seem to have been generally accepted.

In that, experimental evidence has shown it is not the obstruction which causes the damage, but the release of the obstruction perhaps gradual decompression of the biliary tract would be worthy of adaptation. Ravdin describes a method which involves the drainage of small quantities of bile, from six to ten C.C., at intervals of 30 minutes for the first four days after operation.. He feels that in this time the liver has been able to re-adjust itself to the new pressure so that no sudden enlargement of the capillaries can occur. He gives no statistics, but states that since he adopted this plan he has had no postoperative hemorrhage or hepatic insufficiency. Of course, the methods requires personal nursing which in certain institutions would be impossible.

Mann, Helwig and Schutz suggested that it may be poor policy to suture the liver after cholecystectomy,

for fear of bringing about sufficient necrosis of the liver to release toxic products. He says the most profound changes are found in the region of the gallbladder.

Many writers have suggested that perhaps the patients well being would be better served by cholecystotomy than by cholecystectomy. This point is open to objection on many counts, but as Walton Martin pointed out in 1927, it does not predespose to hepatitis. He points out that in the era when cholecystostomy was the common practice, no reports were ever made in which the retention of even a grossly infected, drained gallbladder set up a chronic hepatitis.

Another point brought out by this work seems to be that early treatment of cholecystitis should be instigated. Surgery should be thought of early in the process to prevent the pathological process from continuing too long.

It is felt that this experimental and clinical study has definitely proven the cause and effect relationship between disease of the kidney and disease of the liver associated with or consequent on disease of the biliary tract, the so-called hepatorenal syndrome. This syndrome is not the result of the obstruction, but the release of the obstruction and the underlying cause is some toxic substance which in water soluble, released by the necrosed cells of the liver and the action of

which on the kidneys is not specific but simply a corollary
to an overtaxed normal physiological process, the ex-
cretion of foreign protein by the convoluted tubules.
The so-called hepatorenal syndrome is a pathological
process which is most marked and most dramatic after
operation on the biliary tree, but which may occur after
other operations as well.

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