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Albert S. Lyons, MD: The liver has always been considered an important organ. Its size alone would impress us. One noted physician whose name, perhaps, became the most famous in his lifetime, and afterward, so that I would say there are few whose name has exceeded his in recognition, was a clinical observer. He was an experimentalist, and he was a philosopher and thinker. And I would like to just summarize one of his summaries of the circulation, in which the liver played a role.

You see, the stomach, when it receives the food and digests it, and through the venous system, we now call the portal vein, carried this food to the liver. In the liver, the food was transformed in such a way so that blood was formed. Part of this food was so treated and broken down so that what came out was bile that went to the gall bladder, and another part was taken out to purify it, and through this venous system went to the spleen, and the watery parts of this complex were then through the veins brought to the kidneys, excreted as urine. Then this blood which was formed here in the liver, through the veins that we now call the hepatic veins, went to the right side of the heart, to the right ventricle, and there was pumped from the pulmonary artery to the lungs, and from the right heart blood went to the left heart through little openings in the septum between the right chamber and the left chamber.

Now, here, when the blood came here, it here became mixed with air, with the vital spirit which was inspired through the trachea and the bronchi and also from the lung, and through the pulmonary veins went into this left heart and here mixed with the blood which had been formed in the liver and gone to the heart over here. Now, here, from the left heart, it was pumped, it went all over the body, in fact went to the brain particularly, and here the blood was then transformed into a type of animal spirit, and then came down the nerves to the various parts that were innervated by the nerves.

Of course, this whole system ebbed and flowed the way respiration does, for each increase and decease, increase and decrease. And so you see that the veins carried nourishment which came originally from the stomach, carried to all organs. And each organ also received air or vital spirit through the arteries, and the psychic part or soul parts went to the same organs. We know even now that veins, arteries and nerves often run together. And this circulation of the blood was of course described by Galen, 2nd century AD.

Well, now, this was the concept for centuries, actually about 1,300, 1,400 years, until Harvey came along. But there are several lessons I think we can learn from this. We'll only mention one. For instance, if we had been there at the time that Galen – who didn't create this idea, [he] took the ideas of others, added his own, [he] was an observer, dissected animals, set up experiments. He was a clinician and observed the sick, and he was a profound thinker and disputed with the greatest minds of the day, and believe me, these were great minds by any

standard, including our own. And so if we had been there and he had presented this view, the question is, would we have accepted it? I think there's little question that we would have accepted it. We certainly notice that everyone else did, and through the centuries almost everybody did.

So, we ask ourselves, what do we do now? Well, we receive much of our information from articles written by others, and some of us take whatever our teachers tell us. And we even not only question, challenge, but object to many of the opinions of the empiricists of our day, those who are in practice and, on the basis of what they observe and what happens with the patients, come back and say things which apparently don't agree with many of the things we have been taught. In other words, we accept today's dogma, only we consider it truth.

It is certainly also a fact that debate does not determine the truth. For instance, Galen was able to out-argue anyone. The clarity of his mind, clarity of his expression, the wide knowledge he had, his own observations of experimental data, as well as of sick patients, [he] developed arguments that overwhelmed anybody else's. He must have been right.

Well, now we know that he wasn't right, that he was wrong. Will we be right or wrong, when we are looked at some centuries from now?

So, it's with this humility that we ought to approach the knowledge of our day. When it comes to today's knowledge of the liver, investigative, clinical, philosophical aspects, I can really honestly say it would be hard to find anyone who has more, or even equal to, that possession on which Dr. Fenton Schaffner has. He's a Professor of Medicine and Acting Director of the Department of Medicine [at Mount Sinai], as you know, but he's also an investigator, a reporter, and a practitioner, which he has been for years. Dr. Schaffner, tell us about the liver, will you?

Fenton Schaffner, MD: Thank you very much, Dr. Lyons. Ladies and gentlemen, I look upon myself as an evangelist more than anying else, trying to sell the liver around the world as something to be interested in, not only from the clinical point of view, but the investigative one as well. The request by Dr. Lyons to take the historical approach to this was to me a challenge, a bit, and one that I enjoy exploring.

In the presentation today, I would like to cover first a little bit about the development of the knowledge of the structure and function of the liver, a little bit about the therapy of disease up until at least the beginning of the 20th century, a bit about the contribution made either by Mount Sinai or by the people who have been associated with Mount Sinai, and finally, looking back at the historical review, extrapolating a bit to tomorrow.

Now, the liver has been looked upon through the ages as a means of foretelling the future, and I think this has little changed, except that instead of telling the outcome of a battle, we like to prognosticate by looking at the liver as to the outcome in a single individual. At any rate, the ancients, particularly the soothsayers, individuals who were called haruspexes or haruspeces - one being a haruspex – these individuals would sacrifice animals and hold up the liver to the light, and depending upon how the light fell upon it or how its color was, they would make predictions as to the future.

Well, scientific observation in this regard was really first catalogued by Aristotle, and he described the shape and variations in shape of the liver. But the much better group of bits of information were put together by Erasistratus, and his contributions were that he described the portal vein, hepatic vein, the common bile duct, and also coined the term parenchyma for the substance of the liver. That means that this is an old, old word, going back well over 2,000 years.

Dr. Lyons in his introduction told you a bit about Galen's contribution and this contribution was mainly the concept that the liver was the big blood forming organ and was central, in the circulation of blood played a central role, and this view lasted from the 2nd century to the 16th century. And the two men who did the most to start the revolution against the Galenic concepts were Vesalius, who studied the structure of the liver and said that what Galen had said couldn't be right because it wasn't built that way, and Harvey who said, not only wasn't it built that way but it [blood circulation] really didn't work that way, and demonstrated how it did work. These two greats of the Renaissance were responsible for the anatomical and functional development, the concepts of structure and function of the liver.

The 17th century saw the application of the microscope to the study of the liver, and the name Malpighi stands out, Malpighi working in Bologna. He was the one who recognized within the parenchyma, the lobule, and called it the lobule. He thought it was a glandular structure.

Then, the names of the greats of anatomy and physiology in old times contributed each a little bit here and there, and names like [Friedrich Ernst] Krukenberg and [Emil] Zuckerkandl and Johannes Müller and Sabourin and Ferrein and [FA] Henley and [Theodor] Schwann and Ducci [?] and [C. J.] Eberth – all made some contributions, and the list of names is long and from many different countries.

The one man who contributed probably the most in terms particularly of modern anatomy was an Englishman named [F.] Kiernan, and Kiernan was the one who really described the structure of the liver as we now appreciate it today, including the circulation, how this really worked. Most of the concepts of Kiernan have been born out into modern times.

As a matter of fact, there was very little new added until the late 1940s and 1950s, and the concepts that were described were that blood flowed into the liver via the portal vein, and via the portal veins was distributed into the parenchyma, and the parenchyma was periodically drained by hepatic veins. This places the parenchyma between various portal vein areas, drained by a hepatic vein branch, was considered the lobule, and in the center of the lobule was a central vein, the hepatic vein collecting system.

This concept has stayed, and most of you, except those who are students here, learned this concept. This is how the liver's put together. Well, apparently it isn't so, and there were two men in – both still living – in the United States who challenged this old concept. The first who did so was a man named Hans Elias, who was a zoologist and he was drafted, he was a refugee from Hitler's Europe and was drafted into the American Army. And as a hobby, [it was] really doodling, but he was quite an artist at this and the Army decided that the best place for him was in

illustration. So they wanted to know, they wanted him to make film strips of various diseases to teach medical corpsmen, and the first thing they had him do, since there was an enormous amount of hepatitis in those days, was to make a film strip on hepatitis.

He started to draw the liver and he realized that nobody knew what the organ really looked like, in terms of a three dimensional approach. And so Dr. Elias invented a field of stereo-morphometry and applied solid geometry to histology and discovered that liver cells, for instance, were not arranged in cords but were arranged in plates. And that the anatomy of the liver was like one of these rubber sponges, which you moisten postage stamps with, and the material in the sponge, the rubber part, was composed of plates or sheets. He called it a wall work or muralium, of liver cells, and that the spaces were the blood spaces. The concept of livers being in plates one cell thick has now been accepted, and this was a major contribution of Dr. Elias.

The second contribution came from another refugee from Hitler's Europe, but one who went to Canada instead of the United States, and that is Dr. [Aaron M.] Rappaport, who is in Toronto. Both of these men are professors of anatomy, Elias at Chicago Medical School and Rappaport at the University of Toronto. And what Rappaport had decided, on the basis of embryonal liver and on the basis also of comparative studies in other animals, and on the basis of injection preparations, was that the center of things was not the central vein but the portal vein. And he said the unit of the liver that counted was a pear-shaped area that extended out from the portal vein, the portal vein being its base, the apex being the central vein, and this view is being supported more and more. These represent the two major advances in structure in this century.

Now, the problem of function of the liver, bile flow, and [the] relationship of circulation to this is less, somewhat less, well understood than anatomy is. There's still a lot of argument going on as to the anatomy even of the various structures, at least in the biliary system. What do we call the various pieces?

The bile is excreted first into the tiny bile canaliculus, which has also been called capillary, and which was seen by Kiernan. For many years it was argued as to whether this was a separate tubule, with a tightness coat [?] to it, or whether indeed this was just a dilation between neighboring cells, and only the advent of electron microscopy some 16 years ago settled the question, and this was done mainly in the laboratories of France, at the Cancer Institute of Dr. Benhart [?], who was one of the leading pioneer microscopists in his day. Still is, still active. It was clearly shown then that the bile canaliculus is merely a dilation of the neighboring cells.

One of the anatomists of the early 19th century, late 18th century, was a man named [Ewald] Hering, who showed that there was a connection, a collecting system, for this bile canalicular network which extended between every neighboring liver cell, and this connection he called a canal, and it was named after him as the Canals of Hering, and this was the first cellular structure solely for carrying bile to the intestinal tract. These canals extended into the parenchyma and also extended back to the bile ducts in the portal tract.

The recognition that this was a tubular structure came later, came actually in this century, and the name for these structures is something that Dr. [Hans] Popper and I invented, namely, the

ductule. And that was about, almost 25 years ago now that we tacked this term onto it and it stuck. The function of this particular structure has been argued a good bit, and it is now recognized by some nice techniques, done by many people in different laboratories in the world, that not only is this biliary system a conduit, but that it acts on bile, altering its final concentration.

The blood flow studies also have been refined by modern techniques, electron microscopy, flow studies using thermistors and other electronic sensing devices, and we can now measure pressures in the hepatic venous system and the portal venous system. We can measure rates of flow by the application of principles used in measuring cardiac output. We can sample blood from various places in the liver, either percutaneously or even more easily by cardiac catheterization. Techniques that Cournand and Richardson applied to the heart can also be applied to the liver and are applied to the liver. And consequently, we have learned now a lot about structure.

And what about therapy: diagnosis, recognition of disease, and sort of modern approach, how did it get there?

Well, here again we have to go back to antiquity, because the ancients knew a little bit about treatment, and even in the *Corpus Hippocraticum*, which was about the 4th century BC, there were very clear, simple instructions as to how to open an hepatic abscess. There were a lot of admonitions connected to this, and some people said that you shouldn't do it; some said you should, and the difficulty was that the ancients were mixing up three different diseases which were common in the Mediterranean. One was the pyogenic abscess. The second was the amoebic abscess, and the third was the Echinococcosis cyst. And the difficulty that they were running into was with the Echinococcosis cyst mainly, and that was, they would open up the cyst a little bit with some trochar, and then the hydatids inside would plug up the hole, and they couldn't get them to unplug, and then, of course, they had obviously no asepsis and so – or antisepsis – and so infection was a problem.

The other therapeutic procedure that they knew and understood at that time was paracentesis, and the paracentesis was rather interesting. They believed that the best place to do the paracentesis was through the navel, and Erasistratus, who had done some of the anatomical work, was also a therapeutician at the time. He had written extensively about the navel paracentesis. However, he said that this therapy was really no good for liver disease, recognized at that time that this was nonspecific therapy, had nothing to do with getting the patient better, but was really related only to relief of symptoms.

Now, from the time of the ancients to the 19th century, there really wasn't much going on, from a therapeutic point of view. During the 19th century, there was again an attempt made at therapy, and there were six diseases that really people were trying to treat. One was a fatty liver, and in a way this was recognized, probably by Laennec is one of the early ones, and this is even where he got the word cirrhosis from, which just meant yellow, the yellow color of the fatty, cirrhotic liver that he observed. But, in addition, it was recognized that non-alcoholics could get yellow livers, although they were not as hard and obviously not cirrhotic, but it was recognized that this could be associated with TB, and even Addison recognized that fatty liver could occur in

the absence of TB and the absence of alcohol. He probably was looking at some diabetics in those days and didn't know that.

The differential diagnosis of cirrhosis, which the physicians of the last century tried to treat, was really made, again, by Kiernan, and here, where he separated it from cancer, that metastatic disease or other tumors could be separated from cirrhosis was done in the first third of the 19th century. Then the other differential diagnosis that was made at that time, about the same time and beginning really to a big extent in this country in the War of 1812, was the recognition that hepatitis and hepatic abscess weren't really the same disease. For a long while it was thought that they were only stages in the same disease, and fatty liver hepatitis and cirrhosis could even have been – fatty liver, hepatitis, and abscess - could have even been stages in the same disease.

I might say that that question still isn't absolutely settled yet, because there are some people who believe that this transition between hepatitis and abscess at least still occurs in amebiasis, and they may be right, but they may not be also. It's not clear.

At any rate, it was also thought that the initial stage of all of these lesions was hyperemia or congestion. It was very difficult to eradicate some of the earlier teachings of Galen in this regard. But what happened in the War of 1812 was repeated in the Civil War in the United States, and the Franco-Prussian War occurred also with large epidemics of viral hepatitis. In the Civil War, for instance, about four percent of both Union and Confederate troops had viral hepatitis – an incidence not much different from that in World War I in the American armed forces. It was called camp jaundice in those days. In those days also, the soldiers were kept on duty. Nobody bothered to look at their insides when they were killed in battle wounds. That occurred, autopsy of jaundiced soldiers killed in battle, was really not done until World War I, and that was done by Hans Eppinger, who was the teacher of Dr. Popper and was done on the Eastern Front. Eppinger, working in the army of Austro-Hungary, did the autopsies on the soldiers and found that hepatitis bore no relation to abscess and furthermore, bore no relation to the teachings of the 19th century, of Virchow and Rokitansky, particularly about catarrh of the duodenum. And so the concept of catarrhal jaundice, the foundations for laying it to rest began in 1916, '15 and '16. It took a while to get out of the literature in the United States, and when I was a medical student you could still see the term catarrhal jaundice in the textbooks we used. It was only World War II, with the tremendous number of cases we had, that really changed that.

At any rate, what was done from a therapeutic point of view with the abscesses was that it was recognized that you had to wall off the abscess to avoid the spillage of abscess content in the peritoneum and all sorts of scarification processes were suggested. And this was done with all sorts of chemicals of various kinds, the nature of which isn't even interesting anymore. The Echinococcosis disease was recognized as separate from the abscess and its etiology was recognized at the end of the 17th century, but it wasn't really until the 19th century that the lifecycle of the parasite was discovered and something was done about it. Despite the fact that much more is known today, our therapeutic attempts really are no better than that of the ancients. We still have big trouble with Echinococcosis disease, and in the same parts of the world, particularly around the Mediterranean.

Fashions in diseases come and go, and diseases are sometimes caused by fashions and one of these has been a liver disease, namely the so-called "corset liver" or "wandering liver." The very beautiful hourglass figures that the women had in the 19th century were due to the tight binding, and the compression of the ribs to make the nice hourglass waist would cause all sorts of distortions of the liver. And then, if somebody did a physical exam on these people, sometimes masses were felt in the abdomen. And, of course, the women would complain that they would have distress related either to eating or getting rid of the contents of the intestinal tract, and so it was suggested that surgery be performed on these "corset livers" and "wandering livers," and all sorts of pieces were chopped off in the name of making women better.

I think the change in fashion has taken care of this disease and even the "wandering liver," which wasn't really ptosis of the liver. It wasn't known what it was, but some of the famous surgeons were writing papers about removing livers that wandered all over the abdomen in those days. Fortunately, that has stopped too.

There are some therapies and therapeutic maneuvers that have gone out of style, and some that still remain, and two are deserving of comment. One is that it was felt that the various diseases were really due to an imbalance in these various fluids and fluxes that Dr. Lyons has described before. So one of the means of therapy was to remove various of the fluids by emetics, purges, phlebotomies, or leeches or cupping or whatever you wished, and it took a long time before this was really removed from medical thinking. There were, it was really left to the discretion of the physician whether he attributed more healing power to vomiting or more healing power to diarrhea, and he would base his therapy on just his own feelings in this regard. One shouldn't dismiss this altogether as a form of therapy, because as you know, if you hit yourself on the head enough it hurts terribly; it feels a lot better when you stop. And it is possible that this is the same role that some of these ridiculous treatments had in those days.

Now, it was also felt that while we can take things out, maybe we ought to put something in, and just as what you take out is an unpleasant procedure, what you put in should be relatively unpleasant. And so mineral waters were tried, and if any of you have ever gone to any of the spas, you'll find that the water is terrible. It is salty and usually it's laxative besides, and if you drink too much of it, you're really in trouble. There were people, important names like [Eduard H.] Henoch for instance, who advocated these water therapies, particularly for the fatty liver and the cirrhotic. Well, the spa therapy has persisted, not so much as a recognized medical approach, but really as part of social medicine. In Germany today, for instance, some of the spas are administered by a division of the government call Social Medicine, and they're very important political items, because what it means for the workers is a second and paid vacation in a nice place. This is not called vacation; you "go to take the cure" each year. And this is still being done. I can recommend that if you ever want to go to any of the spas of Europe, there are several liver ones, that you will eat well, and if you don't drink the water, you also will not tend to gain too much weight from just fluid retention, because of the saline content of this water.

There were names, however, of people who were skeptical even in the days when all this was starting and flourished. Virchow expressed contempt at this whole business. Johann Schönlein, whose name got hooked onto Henoch's when we talk about Henoch-Schönlein purpera.

Henoch was very much in favor of water, and Schönlein thought that everything that was done was nonsense, particularly the phlebotomies and cupping and leeches. Some courageous souls even tried smearing things on the livers, that is, doing a laparotomy and applying oils and unctions to the surface of the liver itself, which didn't last very long. There, we're very grateful to the body defenses for putting a quick stop to that. The recognition between alcohol and cirrhosis was really made probably by [Oskar] Minkowski working with [Joseph] von Mering in the later part of the 19th century.

Now, all of these points that I'm talking about were changed a good deal by the advent of the 20th century. Some of the surgery, like biliary tract surgery, was attempted in the 19th century. It all required the development of antisepsis by Lister and the application of the works of Pasteur, which took quite a while to become applied, with asepsis, before something could be done. And this really belongs to the 20th century. I don't really want to go into this in detail.

There are two advances in recent times that I would like to bring you first, before spending the last few minutes talking about what happened at Mount Sinai. The two advances belong to the 1960s and they are the recognition of Australian antigen by Baruch Blumberg in Philadelphia, and the development of hepatic transplants by Tom Starzl in Denver, now Denver, Colorado, before at Northwestern University in Chicago.

Just a word about Blumberg's discovery of the Australian antigen. He's a geneticist and was interested in tracing the wanderings and migrations of mankind over the surface of the earth, and he thought by checking various areas that he could see how the proteins became further and further apart genetically as man wandered around. And he tapped the serum bank at NIH in Washington, Bethesda and tested a whole bunch of serum and found that the blood of a hemophiliac at Mount Sinai here in New York reacted with the blood of an Australian aborigine and formed a precipitating antigen antibody reaction. And that's why he called it Australian antigen.

Our hemophiliac - who's still alive and whose blood we were using until he found out he could sell it for $75 a cc - he had had about 400 blood transfusions, and Blumberg had figured that this man, who held some kind of record, would really have more antibodies to more different kinds of protein than anybody else, and this is what he was looking for, common proteins. And this is what he found, and it took him three or four years to recognize that this was related to hepatitis. Now there's pretty good evidence that the Australian antigen, at least one form of it, is the virus that causes hepatitis, what we call serum hepatitis. It is now called hepatitis B and Australian antigen is hepatitis B antigen. This contribution was really very noteworthy and now gives us a handle with which to recognize these cases. It gives us a handle with which to study the epidemiology, and also gives us something to shoot for, to try to develop antiviral chemotherapy. Not ready yet, but at least people are trying.

The other advance - that is of liver transplants - has been an unspectacular one as far as publicity is concerned. There have been more liver transplants done than heart transplants, and survival has been much better. Survival up to three years is quite possible. Whether this is going to have any place in the future is not known. Interestingly enough, some diseases can be cured by

liver transplantation. Wilson's disease, for instance, cured when a Wilson's liver is removed and a new liver put in its place. Some diseases, the results are discouraging, like primary hepatic cancer, because metastases seem to develop even if the primary is removed. They may develop a year or two after, and then even the new liver is the site of metastases from the metastases, and so this doesn't work. We are not sure what is going to be the status as far as antigen, virus invections, whether this will go into the grafted liver or not. The answer is it appears to be.

Now, what about Mount Sinai's role? I haven't left much time for it. I just really want to mention it, and that doesn't mean it gets short shrift in terms of overall history, because Mount Sinai and the people associated with it had a very significant role. I first appreciated that about six or seven years ago when we found a patient who had a web in the inferior vena cava at the level of the diaphragm and had developed a Budd-Chiari syndrome from this web. We reported this in the *American Journal of Medicine*. But in looking up the literature, they found that the first case was described by a Canadian (Hopkins, London, Oxford) – Osler, described by Osler and the second case in the word's literature was described at Mount Sinai in 1902. So, we didn't even have the first case in our own hospital when we wrote this up.

Mount Sinai's contributions have, in general, been quiet ones like this all through the years. In terms of men, I think the one who has made the largest contribution of all through the years was Dr. [Isidore] Snapper, and he is still alive, a man in his middle 80s, sick, but still a remarkable man. As a medical student in Amsterdam, working with his chief [A. A. H.] van den Bergh, Snapper described the so-called van den Bergh reaction and it was published in 1912 [1913 – ed] as from van den Bergh and Snapper, describing direct and indirect reaction [of bilirubin?]. Snapper continued working with liver disease and was partly responsible for helping [Edgar] von Gierke describe this disease, von Gierke's disease, glycogen storage disease type 1. And Snapper devised some tests of liver function involving conjugation with glucuronic acid, and the interesting thing is that he worked with conjugation with glucuronic acid and he worked with bilirubin and he never put the two together, that his direction reacting bilirubin was really bilirubin glucuronide [?]. Whereas he had been working with conjugations of benzoic acid, with glucuronic acid, [it] just never occurred to him that the two belonged together.

The next name in liver disease that is important here at Mount Sinai was Dr. [Paul] Klemperer, and Dr. Klemperer's contribution to the liver, at least, was also made in large measure before he came here [in 1926] in that he described intrahepatic sclerosing cholangitis somewhere in the 1920s and wrote another paper here in New York.

Another man whose name must be mentioned in the list of those who made important contributions is that of Dr. Eli Moschcowitz. He was responsible for pointing out that the vasculature in the liver played an important role in the development of cirrhosis, and he was the one who developed the concept of angiogenesis, that is, into a scar, new blood vessels grew, and around these blood vessels was a stroma, and the scar was really kept, in part, because of the fibrous connective tissues' stroma around these newly developing vessels. And this concept was really ahead of its time, and is now regarded as one of the mechanisms contributing to the development of the septum in cirrhosis.

There's another man whose name has not survived much in the literature, but some of the people here may remember him, and that was Dr. [Edgar] Baron, and Dr. Baron in the middle 1930s, toward the end of the 1930s, '37, began doing liver biopsies, needle biopsies at Mount Sinai, before the Danes did and before the big epidemic had occurred in Scandinavia in 1938-39. [See *Arch Intern Med (Chic).* 1939;63(2):276-289. doi:10.1001/archinte.1939.00180190078005] He did this simple aspirating technique and looking at the cells he got out. The difficulty was that after doing some 40-odd, a couple of patients bled. Vitamin K was not – the supply mechanism – Vitamin K deficiency was not well understood. Prothrombin times were available, but they really weren't widely available and consequently, the whole procedure was dropped, only to be re-introduced by the Danes and later in the United States with the Vim-Silverman needle.

In recent times, there is an interesting study [by] Dr. [Max] Ellenberg and Dr. [Kermit E.] Osserman about the liver and shock. There are some studies of Dr. Gerber about migratory thrombophlebitis in the liver, and one of the other attendings was in on that, I don't remember. It may have been Dr. King – King and Gerber, I'm not sure.

Now, the groups studying the liver are several at the [Mount Sinai] Hospital. Dr. [Hans] Popper and myself [are] involved in continuing studies to try to piece together the story of cholestasis. We made the observation first in this hospital that intrahepatic cholestasis has the morphologic features, including ultrastructural features, as extrahepatic biliary obstruction, and this was in 1958. We have now been studying, continuing to study, cholestasis with intensive studies of bile acid metabolism, and there is even in this month's *Gastroenterology* two papers from our group about bile acid metabolism and cholestasis and its role in the development of cholestasis. But we are not the only group in the Hospital studying that. The Department of Surgery is also engaged in such studies with Dr. [Demetrius] Pertsemlidis. And bile flow is also being studied by other members of the GI group and including some of the people working with Dr. [Henry] Janowitz.

So much is continuing to go on, and hopefully Sinai's name will continue as a center for making contributions to the study of liver disease, and I hope to be able to be part of this activity for a while to come yet, and I would like to invite some of the others to participate with it. Thank you for this opportunity to review with you some of the background of the area in which I myself am interested.

[applause]

Lyons: Thank you very much. You covered all the history of man in a very short and lucid way. Are there any questions you may have of Dr. Schaffner or others here? As I recall, Dr. Baron did this on his own; he really got no help from anybody. He didn't even have equipment. He just kept poking away, and people were rather unhappy about the sticking of needles in various individuals, and so when he developed, when he had a few complications, that was all that was necessary. He had nobody who was his protector or supporter, so it all went down. Yes?

Q: I would like to know [inaudible]

Lyons: [Restating the question] Should we expect the equivalent of renal dialysis with respect to the liver, Dr. Schaffner?

Schaffner: Well, the support for the failing liver has been tried with the use of cross-circulation with other human beings, cross-circulation with cadaver livers, cross-circulation with animal livers, particularly pigs, exchange transfusion. And this is another item where Mount Sinai deserves very early credit, because in 1952 the first exchange transfusions for hepatic coma were done by the late Dr. Lou [Soffer? Schaeffer?], working with Dr. Snapper, and this was published in the *Annals of Internal Medicine*. And one of their patients survived. So this was done. Actually, none of these methods of therapy appear to be useful. The Dickinson [?] company is now trying to work on an artificial liver, which is a drum [?] through which the blood is passed and something removed. The difficulty is, we don't know what to remove, or add, and so they're having problems with this.

Dialysis does not work. And the latest is something that is being done in New York City, at NYU, devised by a colonel in the Army, Colonel Klebanoff, working in Texas, who washes out the body of all of its blood with iced saline albumen solution. It's called the saline washout technique. The patient is kept totally without blood for a period of about seven minutes. It takes that long to flush out everything, and then the patient is rapidly reinfused with warm blood from the blood bank. Whether this will have a role in the future or not, we don't know. So far we have been sending our patients down - as a matter of fact we sent one down this week - down to NYU for this procedure.

Q. You haven't said anything about the chimp transplants.

Schaffner: The question is about chimpanzee transplants. I think that this has been tried as a temporary holding measure, that is, putting in an auxiliary liver. The difficulty with the auxiliary liver, even if it is a human liver, is that it is very rapidly rejected, and the hope was that with diseases like viral hepatitis, where regeneration is so rapid - and recognize that the ancients realized the rapid regeneration - that this would permit, to buy some time till the normal liver took over again. It just simply doesn't work.

Q. [inaudible]

Schaffner: Question is relating to liver transplant in Wilson's disease. There was a young boy from New York, a patient of Drs. [I. H.] Scheinberg and [I.] Sternlieb at Albert Einstein, who was sent to Dr. Starzl in Colorado because the boy had increasing hepatic failure and it looked like he was going to die from his Wilson's disease. He had absent ceruloplasmin in his serum. They did the transplant, ceruloplasmin reappeared in his serum, and he lived for three years. He died mainly because of infection associated with the immunosuppressive therapy he was receiving. All the signs and symptoms of Wilson's disease had disappeared. As a matter of fact, this child was shown in several of the meetings. I saw him myself. He was a kid who did get three years of pretty comfortable living from the procedure.

Q. Any more comments on this history of liver biopsy?

Schaffner: Question relates to the history of liver biopsy. Well, there really are two main groups, three if you wish, involved with this and the first credit belongs to the Danes and Professor Poul Iversen. [He] was the chairman of the department of medicine at the hospital in Copenhagen and started the whole bit going. There were some men working with him, particularly Kaj Roholm, and a whole group at that time of the younger men in his department, most of whom are still alive and working today. Iversen is dead but the other men are still alive, and they developed an aspiration type needle. That is, they put it in with a rubber bulb section technique and just sucked out a piece of liver. It was a pretty big needle and a pretty gruesome looking affair, but it worked quite efficiently.

In this country, several people began applying the Silverman prosthetic biopsy needle to the liver, and this was in the early days of World War II, when we had this enormous epidemic [of hepatitis]. Our total incidence in World War II in the U.S. armed forces was a quarter of a million cases, and the liver biopsy was done then with the Silverman needle. The defects of the Iversen-Roholm needle, of which there were several modifications made around - and the best one was an English one by a man named [Richard] Terry, which was the needle we used here in this hospital for quite a while – was that it was too big and it was painful and almost frightened people to see the thing. The Silverman needle had the defect that it was a punch biopsy rather than aspiration biopsy. The needle was put in the liver, squeezed a piece together, and you ripped it out. The difficulty was that there was so much squeezing and so much distortion of the liver tissue that the biopsies were really not as informative as the sucked out pieces. This is why this fell into disuse.

The modern technique was invented by an Italian… [tape ends]