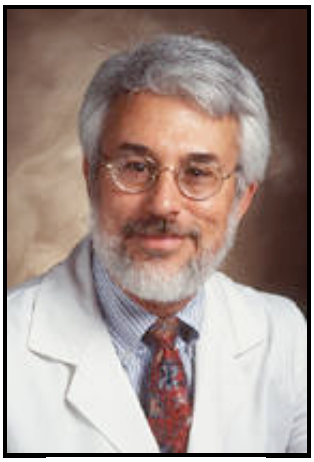
12th Annual Conference on Polycystic Kidney Disease, June 2001. Selected Talks.

Web presentation sponsored by an unrestricted educational grant from Sigma-Tau Pharmaceuticals

Polycystic Liver Disease
Part One of Two



Dr. Ron Perrone

Ronald D. Perrone, M.D.
Professor of Medicine, Tufts University School of Medicine, Associate Chief, Division of Nephrology, Associate Medical Director of the Kidney Transplant Program in New England Medical Center in Boston, Massachusetts.

CME-related Information

This talk is not presently accredited for Category 1.0 CME credit.

Program Objectives and Goals: The primary target audience is nephrology health care professionals. The educational objective is to understand the genetics of PKD as it pertains to liver cysts. Further goals are to understand the prevalence of liver cysts in PKD patients, the most common clinical problems that these cysts engender, and potential treatment options. Posting date: November 3, 2001.

No post-test nor evaluation form at present

Disclosure Statement: Dr. Perrone discloses no support relevant to the material being discussed. Web extension of this symposium is being provided through an unrestricted educational grant from Sigma Tau, Inc.
About the Speaker: Dr. Ronald D. Perrone, M.D. is Professor of Medicine, Tufts University School of Medicine, Associate Chief, Division of Nephrology, Associate Medical Director of the Kidney Transplant Program in New England Medical Center in Boston, Massachusetts.
HDCN CME Policies: See **this page**.

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Moderator:
This is the last session of the day, and I really hope that we can keep everybody awake and alert because this is a very, very important topic to many people who have filled this room today. My name is Rose Stephan; I am from Buffalo, New York. I am on the Friends Advisory Council and the Coordinator of the Western New York Friends Group. It gives me great pleasure today to introduce a member of our Scientific Advisory Council, who will speak to you today about cystic liver disease.

Dr. Ron Perrone is Professor of Medicine at Tufts University School of Medicine. He is the Associate Chief, Division of Nephrology, and Associate Medical Director of the Kidney Transplant Program at the New England Medical Center in Boston, Massachusetts. I hope you enjoy this session.

There will be a 15-minute question and answer session as soon as Dr. Perrone times that. Please don't forget to fill out your evaluation form that is on the back page. There will be a box left by the door for you to leave that in. It is very important for us. So enjoy your session. Let's give a hand for Dr. Perrone.

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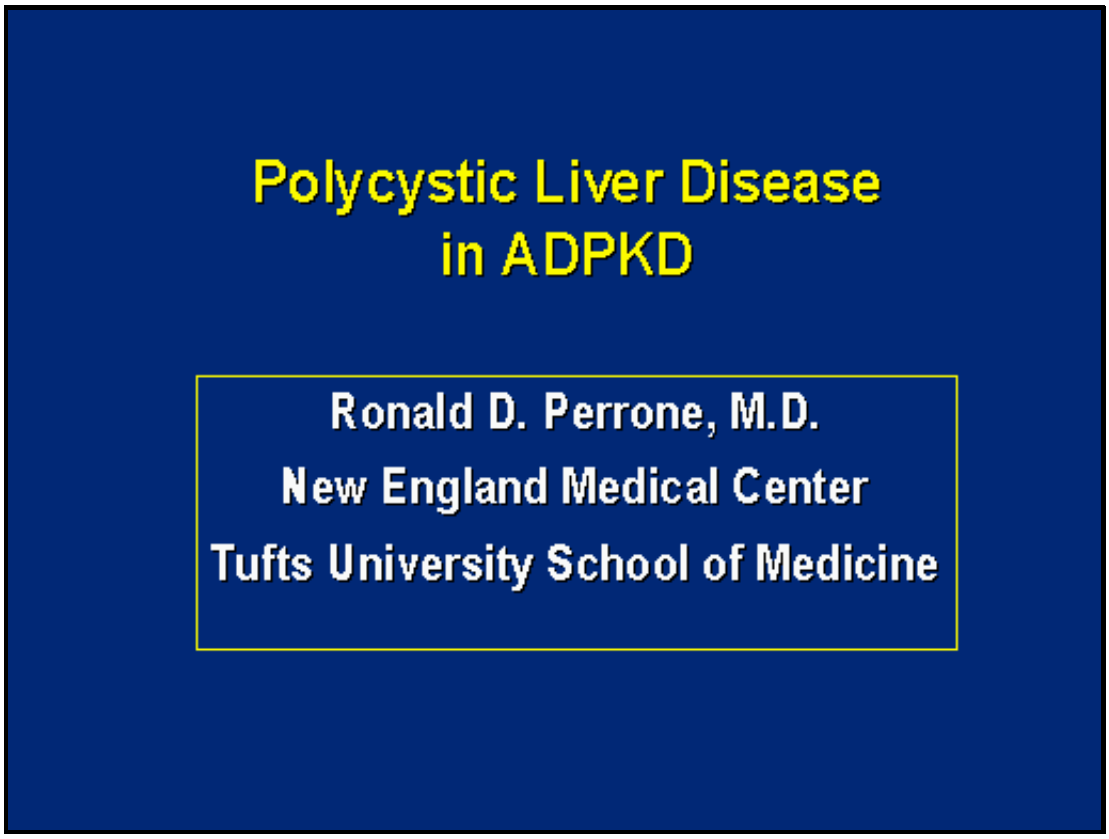

Dr. Perrone:

Introductory remarks
Thank you very much for the kind introduction. How many of you have never been to this conference before? I realize that the audience has a wide range of knowledge and experience in this area. I am going to, for the first few slides, review polycystic disease and then go quickly into the liver cyst manifestations.

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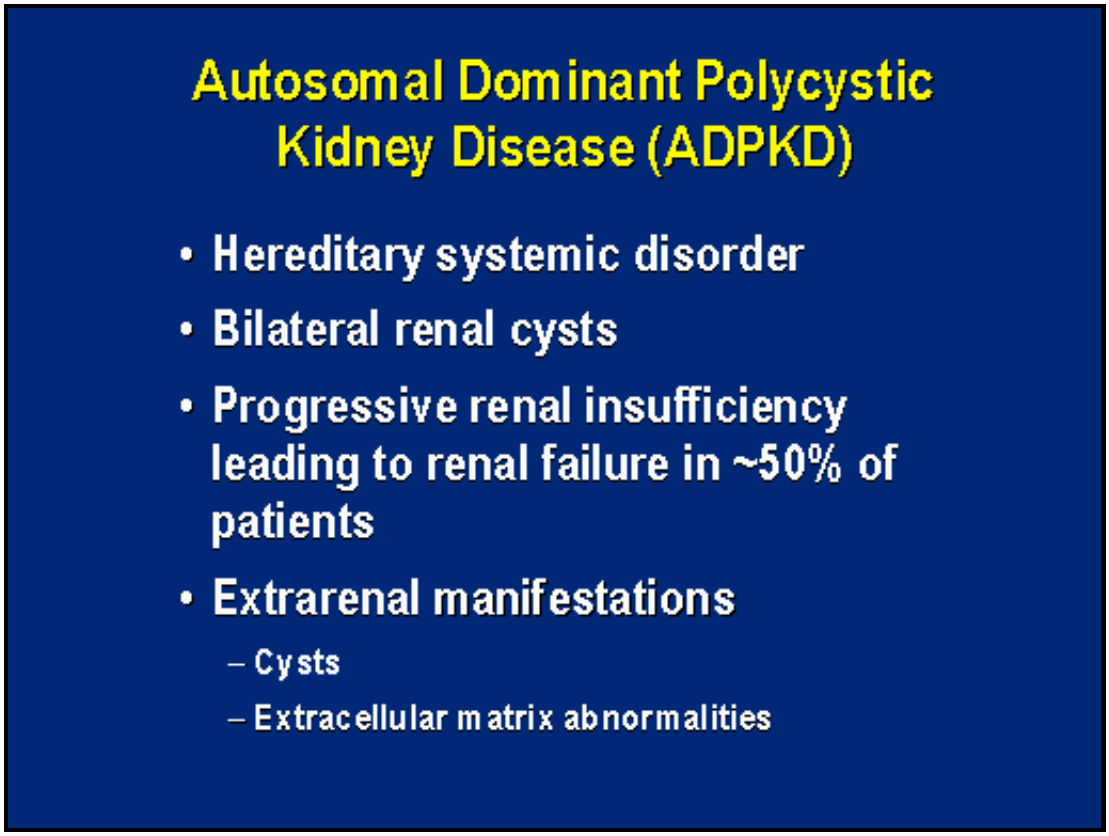

Autosomal dominant polycystic kidney disease (ADPKD)
Autosomal dominant polycystic kidney disease, as you know, is a hereditary systemic disorder. When we say "systemic", we mean that it affects the whole body potentially. The hallmark is cysts in both kidneys with kidney insufficiency leading to kidney failure in about 50 percent of the patients. In addition to the kidney problems with PKD, there are extrarenal or manifestations outside of the kidney. These include cysts and what are called extracellular matrix abnormalities. They are abnormalities in the proteins that hold cells together.

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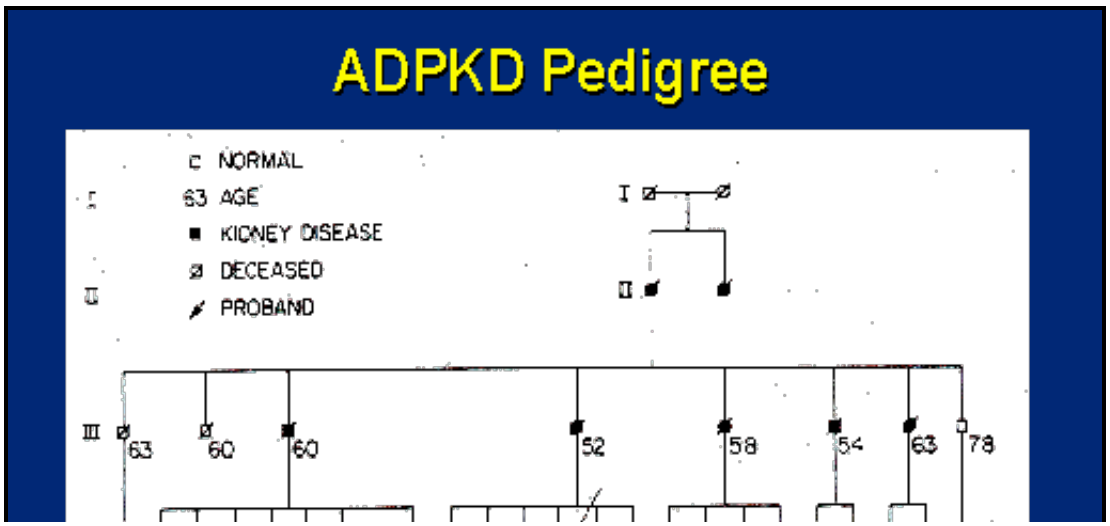

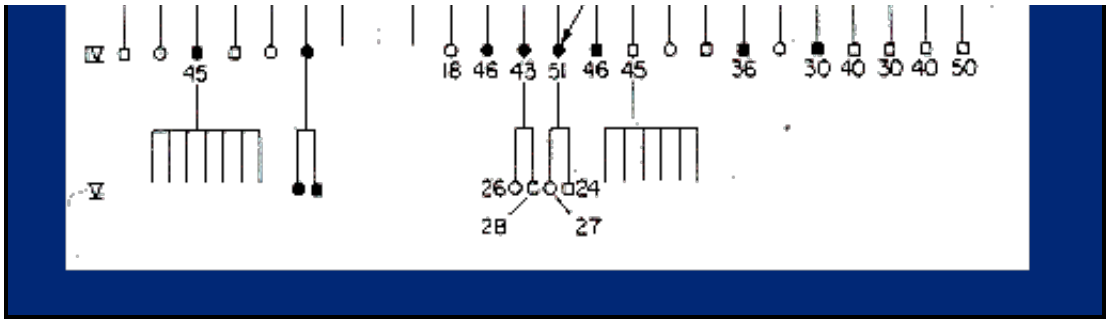

ADPKD pedigree
This is a pedigree, which I know many of you are personally familiar with, demonstrating the passage of the PKD genetic defect down through multiple generations, affecting siblings, parents, aunts and uncles, etc., etc.

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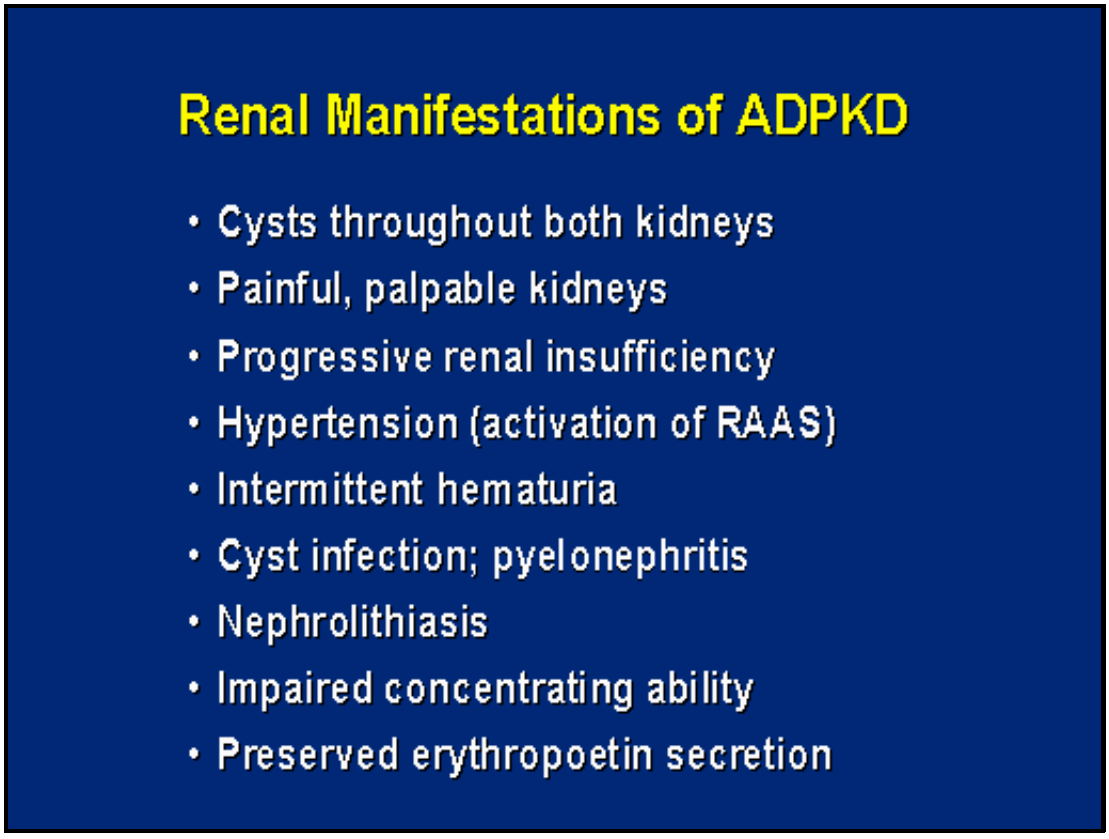

Kidney manifestations of ADPKD
Many of you are familiar with the kidney manifestations of PKD, and I will briefly review these because some of them at least that occur in the liver are also similar to these. Cysts are on both kidneys, painful, palpable--that means the doctor can feel them, loss of kidney function, high blood pressure, blood in the urine, cyst infection, kidney infection, kidney stones, impaired ability to concentrate the urine, and a preservation of erythropoietin secretion, known chemically by the drug companies as Epogen. These are the kidney manifestations of polycystic kidney disease, which are very important, but they are not the only manifestations of polycystic kidney disease.

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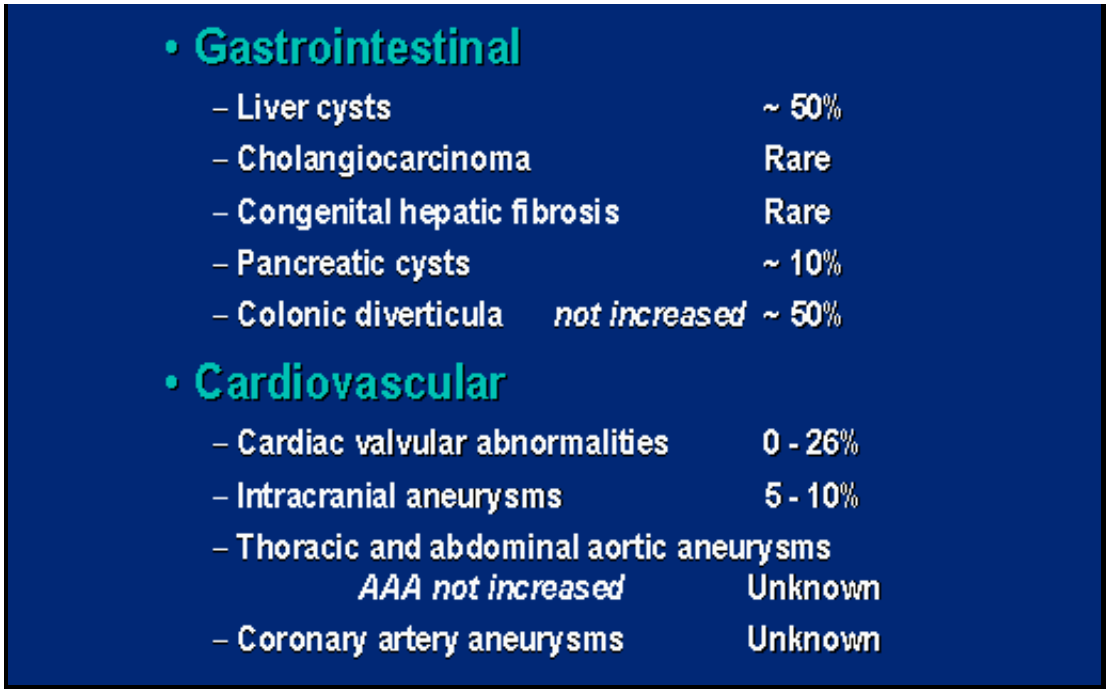

Extrarenal manifestations of ADPKD
I am going to list all of the extrarenal problems with PKD and show you where the liver cyst disease fits into the broad range of possible complications. Liver cysts on average affect about half of the people who have PKD. There are some very rare or unusual problems--cholangiocarcinoma is a cancer of the bile duct and the gall bladder, which is a very rare problem; hepatic fibrosis means scarring of the liver, and this is usually found in the recessive form of PKD and usually doesn't occur in the adult form, but there are some families that are affected by that; there may be cysts in the pancreas.

It was thought for many year that diverticula, or little outpouchings of the colon, were increased in PKD; and now more systematic studies show this is probably not the case.

Cardiac valve problems, intracranial aneurysms... there is a lot of noise outside. I will do my best to overcome that... very rarely aneurysms, which are enlarged or dilated areas of blood vessels, and these are part of the extracellular matrix or connective tissue abnormalities that occur in PKD.

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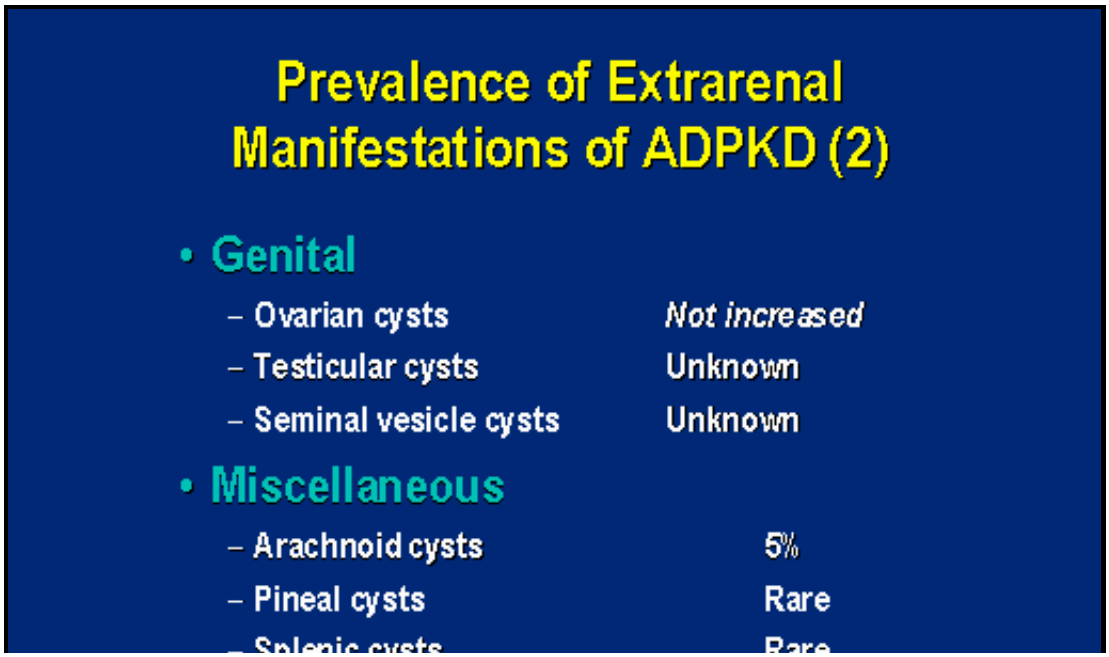

Extrarenal signs of ADPKD (cont..)
A mixed bag of other things, most of which don't cause any clinical problems--cysts in the testicles or the seminal vesicles; cysts in the membrane around the brain, called the arachnoid membrane; an then a few rare things. This very long, complicated term down here (dolichoectasia) just means abnormal stretching and elongation of some of the arteries in the brain. These are usually found incidentally when people are getting MRIs for other reasons.

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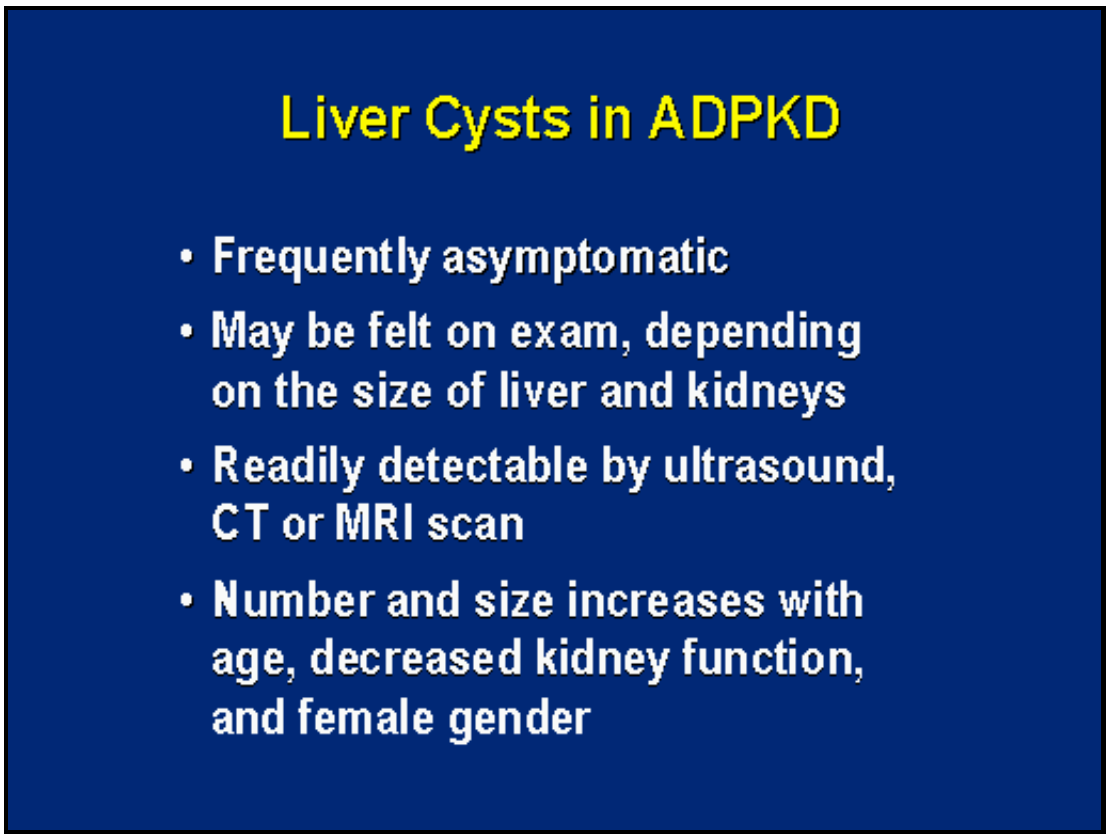

Liver cysts
That is the background. Liver cysts are found in many people with polycystic kidney disease. Most affected individuals will not have any significant issues with liver cysts throughout their whole life, but a minority of individuals can be affected in a very substantial way. Most people are asymptomatic. A doctor may feel the cysts on a physical examination depending upon the size of the liver and the kidneys. These liver cysts, just like the kidney cysts, are readily detectible by any imaging tests that a doctor could order, either an ultrasound, a CAT scan, or an MRI scan. The number and size increase with age. They increase as kidney function gets worse and affect women to a much more substantial degree than men.

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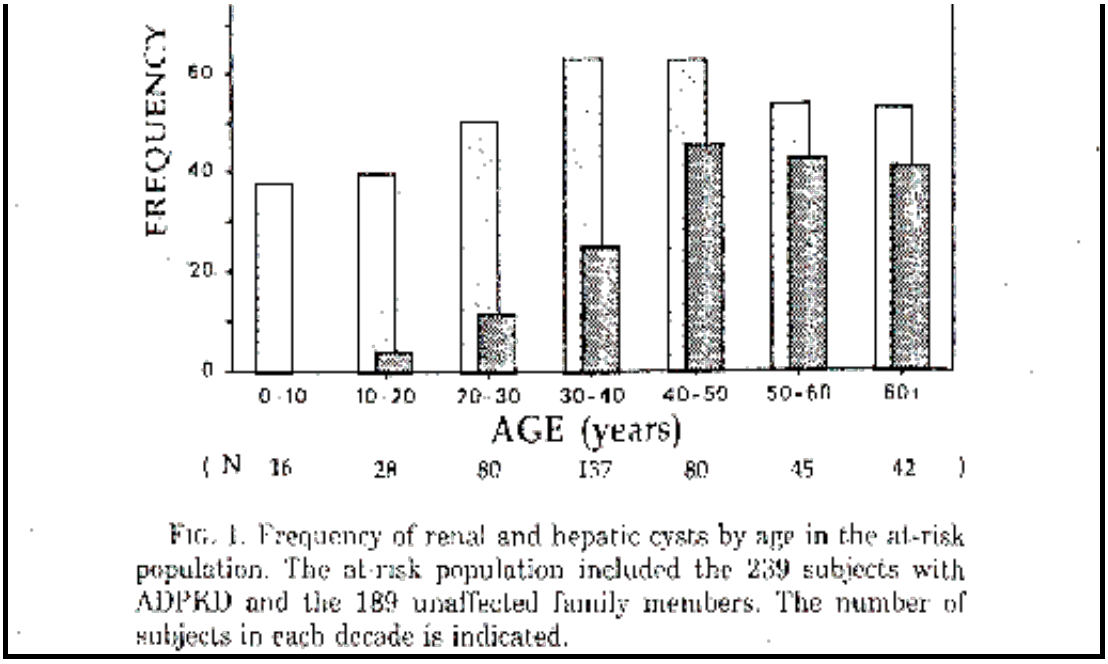

FIG. 1. Frequency of renal and hepatic cysts by age in the at-risk population. The at-risk population included the 239 subjects with ADPKD and the 189 unaffected family members. The number of subjects in each decade is indicated.

Source: Everson GT et. al., Hepatology. 1990 Apr;11(4):557-65.

Development of kidney and hepatic cysts as a function of age
This is a slide from the Colorado group, who have extensively studied polycystic disease in many families over a long period of time. This is the development of kidney and hepatic cysts as a function of age. These are individuals in polycystic families. What you see is over time... these are decades--0 to 10, 10 to 20... by the age of 20 to 30 and 30 to 40, about half of the individuals have developed kidney cysts, in the open bars. That is about what you would expect in a dominant disease. However, you can see that the liver cysts lag behind. It isn't until perhaps two decades later that half of the individuals have developed liver cysts. So for reasons that we don't understand, the liver cysts tend to develop more slowly than do the kidney cysts.

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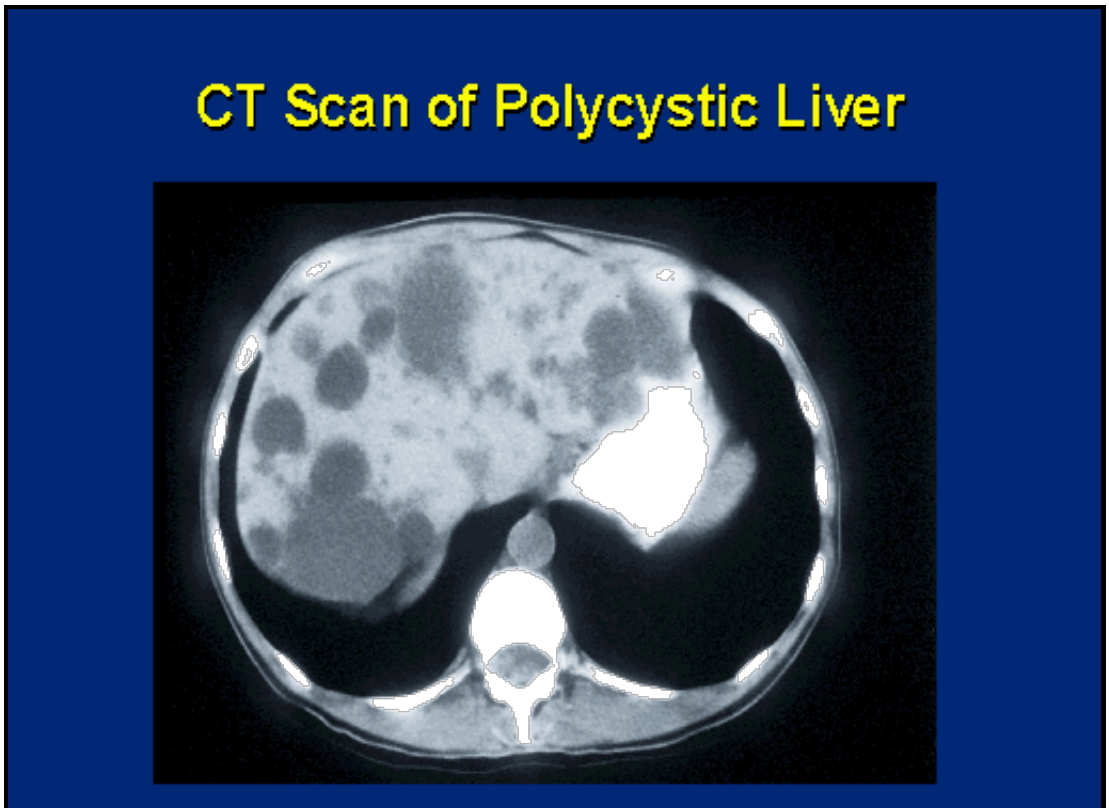

CAT scan of a polycystic liver
This is a CAT scan. It is basically a cross-section across the abdomen. It shows... this is the liver; this is the back of the individual, showing the spine. You can see these multiple spaces, these black openings here, represent multiple cysts throughout the liver of this individual. This woman had absolutely no symptoms referrable to her liver. She had a brother with PKD. She had an abdominal CAT scan for some other reason, and this was the finding. No pain, no bloating, no nothing. She just had these and they were there.

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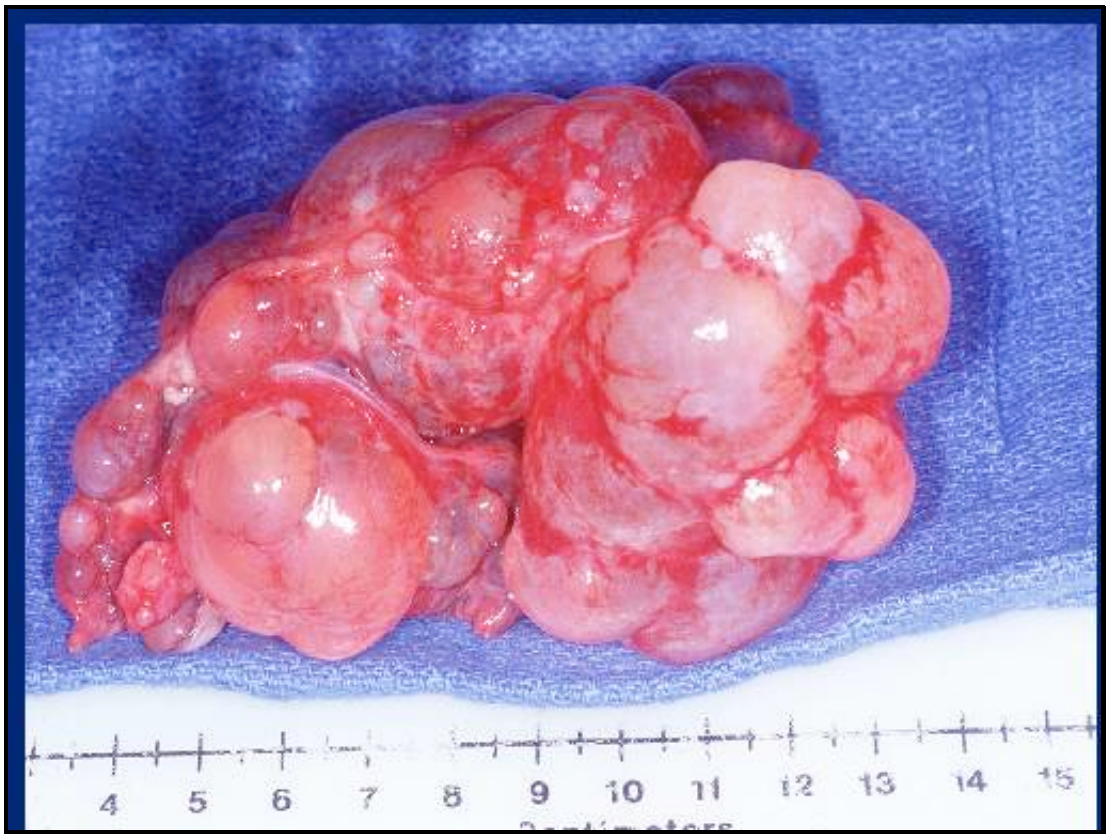

A piece of polycystic liver
This is a small piece of a polycystic liver that was retrieved from an individual who had part of his liver removed at the Mayo Clinic. You can just see these multiple, fluid-filled sacs. In this particular specimen, you don't see any normal liver tissue scattered throughout here.

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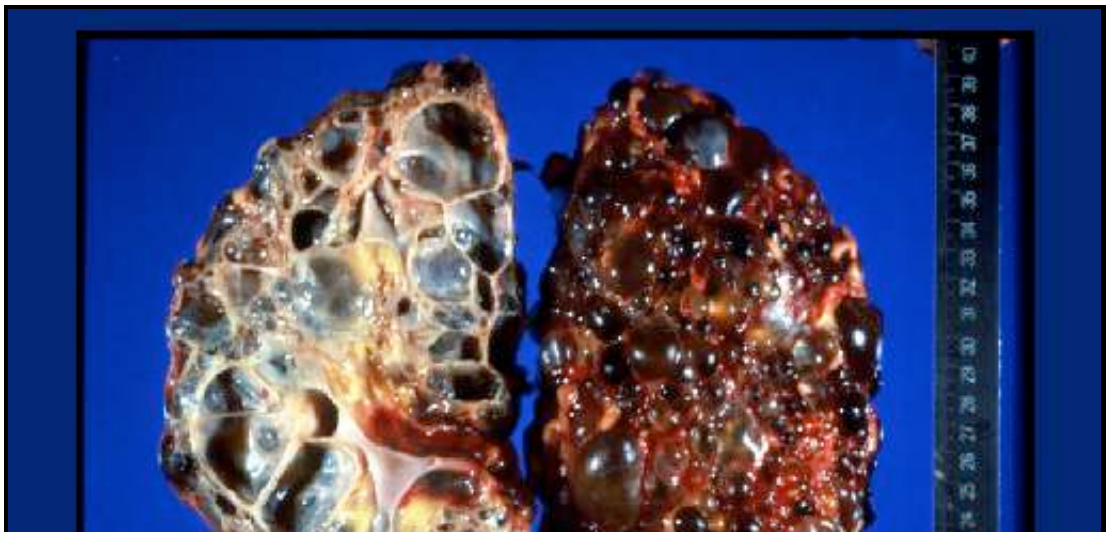

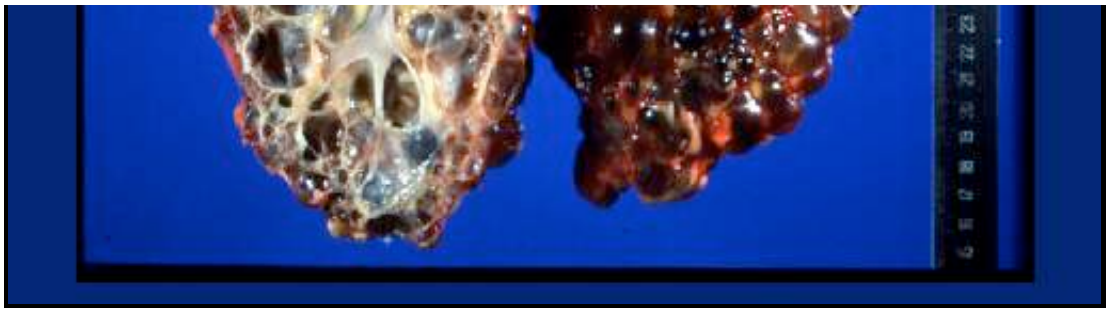

Two polycystic kidneys
Just for comparison, this is a picture of two polycystic kidneys. If you had a small piece of the liver or the kidney in your hand, you wouldn't be able to tell the difference. The cystic disease is really almost identical in both organs.

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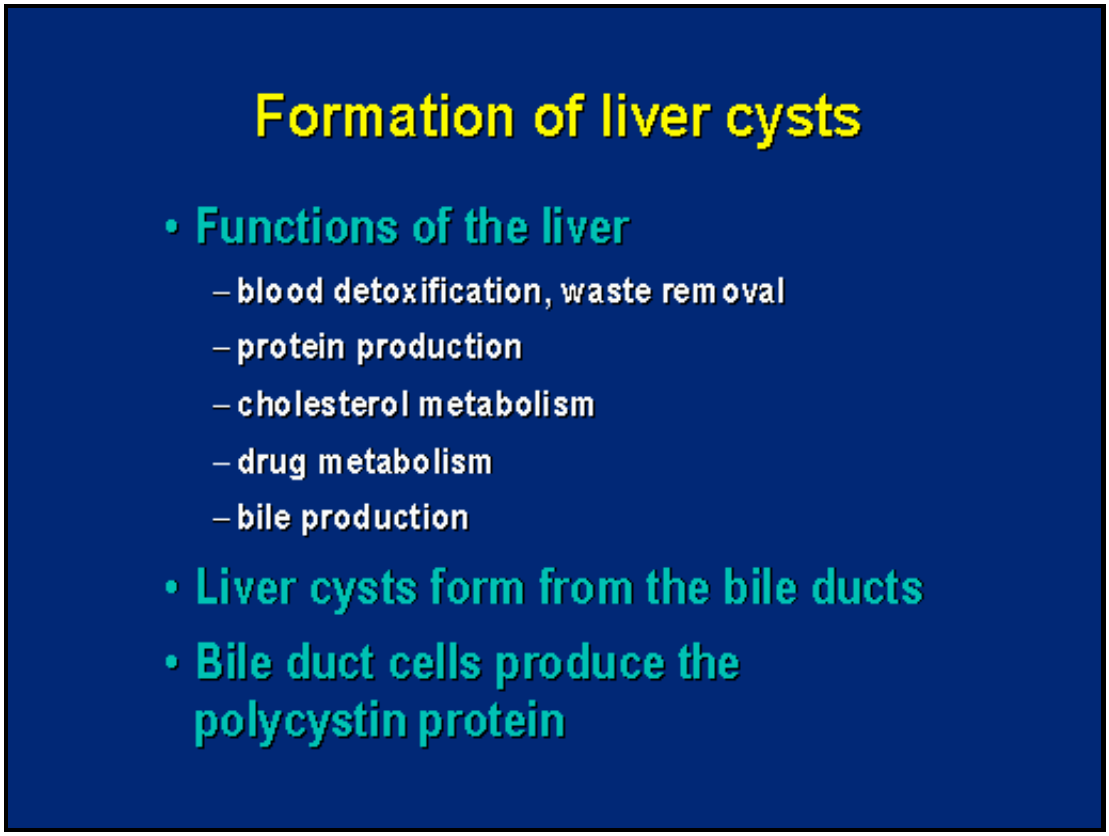

How liver cysts form
I am going to go into a little bit of detail about where the liver cysts come from and what we know about how they form. The liver has many different functions, including detoxifying the blood and removing certain kinds of waste products, making proteins, cholesterol metabolism, metabolizing drugs, etc.

One of the other functions of the liver is to make bile to help in the digesting of food. The bile is made in these cells, the liver cells, called hepatocytes. Then it goes through a series of tubes or ducts that gradually... you can imagine these small tubes branching and branching and eventually forming larger tubes that come out into one large bile duct that drains the entire liver. I will show you some direct evidence of this.

The liver cysts derive from these small bile ducts within the liver...so from these cells. It is interesting that the function of these cells is very similar to the function of cells in the kidney. Remember that the kidney filters the blood. The material that is filtered is acted upon by the tubules of the kidney to reabsorb things and to prevent excess fluids and salts from being lost. Interestingly the cells lining the bile ducts have the same sort of function.

They modify the bile after it is produced to make sure it is the right composition. Both the kidney cells and the bile duct cells are a site where polycystin protein is found. Again, the relationships are very similar.

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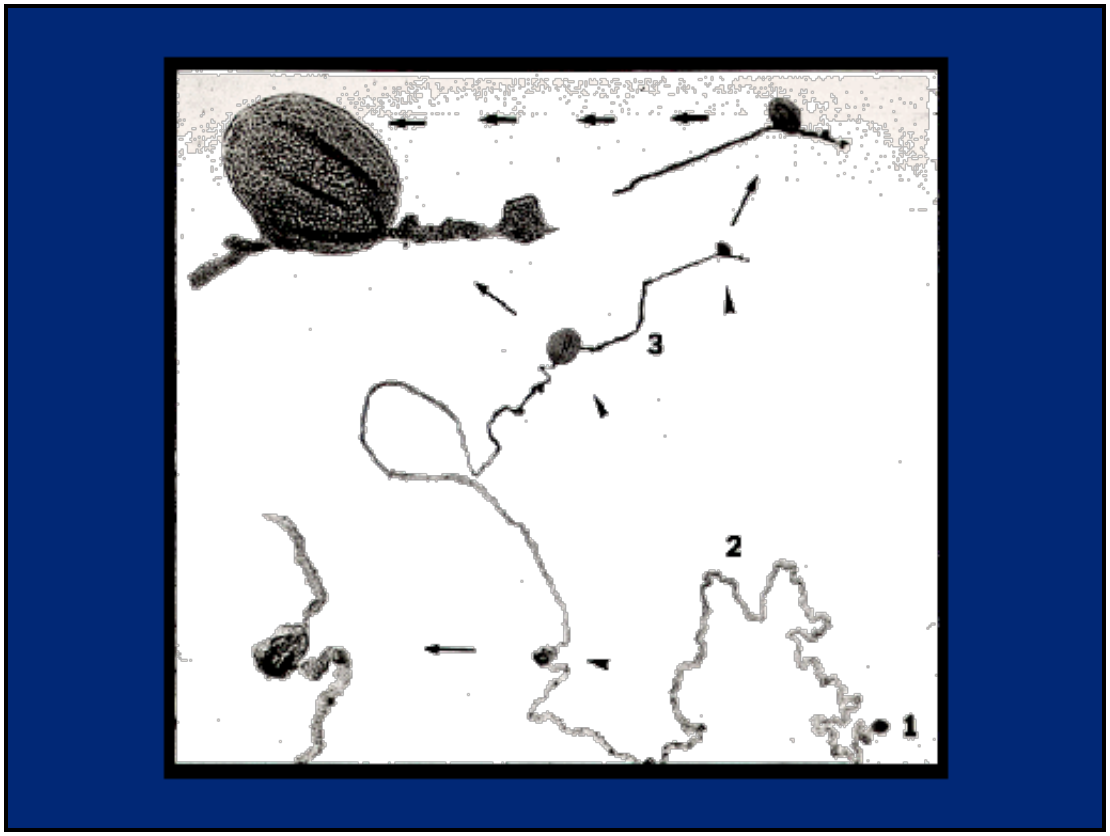

Source: Everson GT et. al., Kidney Int. 1978 Jun;13(6):519-25.

Early formation of kidney cysts in PKD
This is a slide showing the very earliest stage of formation of kidney cysts. The same thing happens in the liver, in the bile ducts, but I don't have a slide of that to show you. This is a photograph of a picture taken with a microscope. This is a kidney tubule. You can see that this is a microscopic cyst that is being formed and over time will progressively enlarge and separate from the tube that it is connected to. We think the same thing happens in the liver. The cysts begin as these microscopic outpouchings from these little bile ducts and progressively enlarge.

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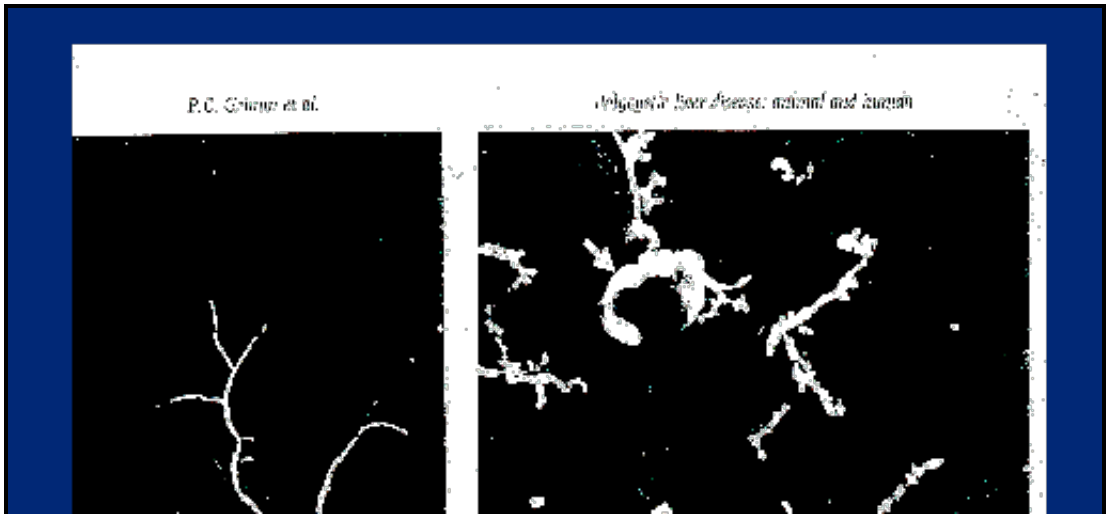

Source: Grimm PC et. al., J Exp Pathol (Oxford). 1990 Feb;71(1):119-31.

Bile ducts
This is from a study of humans: What was done was in the human liver the bile ducts were injected with a material that shows up white in this particular technique. You can see that this is a normal liver and a normal bile duct. These are fairly nice and smooth and taper down nicely, just like that branching I mentioned.

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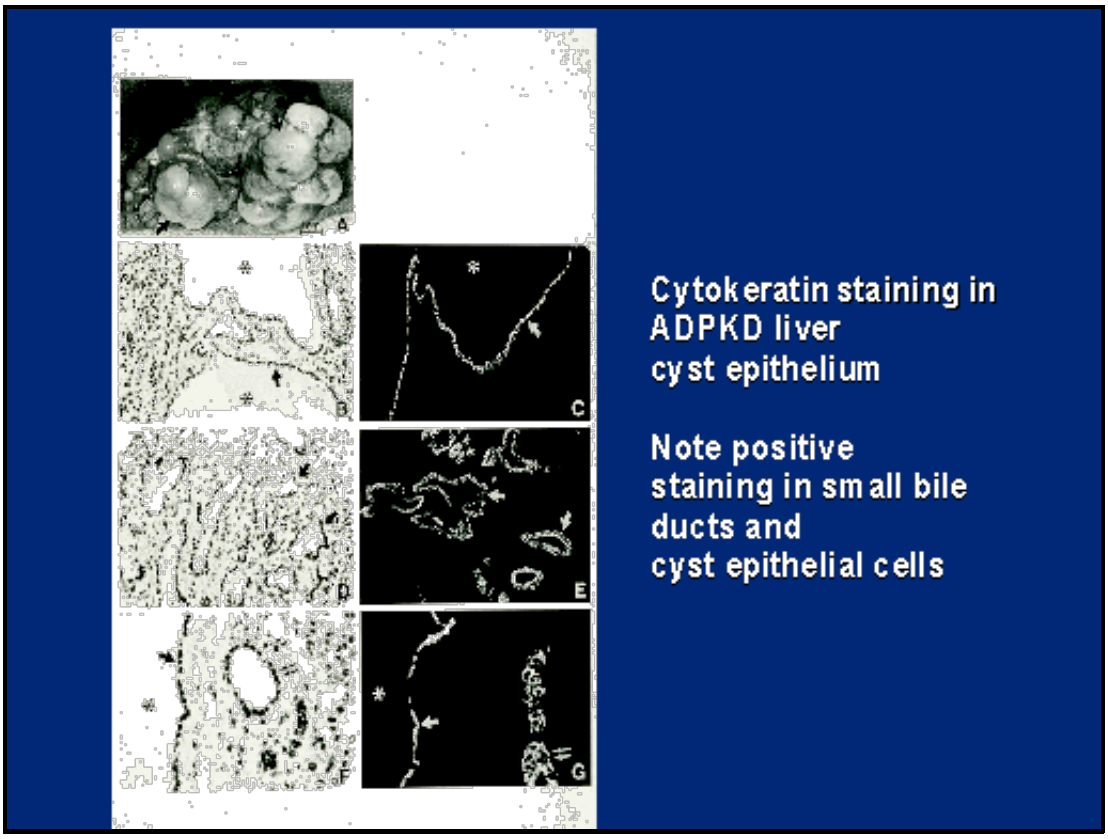

Source: Perrone RD et. al., Am J Physiol. 1995 Sep;269(3 Pt 1):G335-45.

Bile ducts in PKD
These are the bile ducts in an individual who had polycystic liver disease. You can see that these are all kind of enlarged or dilated. You can see these round areas, which represent the cysts beginning to form. It is the same thing over here. Just like in the kidney, some of these cysts don't communicate with the bile ducts. They've grown larger, they've separated off, and then fluid continues to be secreted inside, and they continue to enlarge.

This is again spending a little time on where these cysts are coming from. These are studies using a fluorescent marker technique, which shows up as white. This is the edge of a cyst, and these are the cells lining the cyst. The only other structure in the liver that lights up with the same marker are these little bile ducts.

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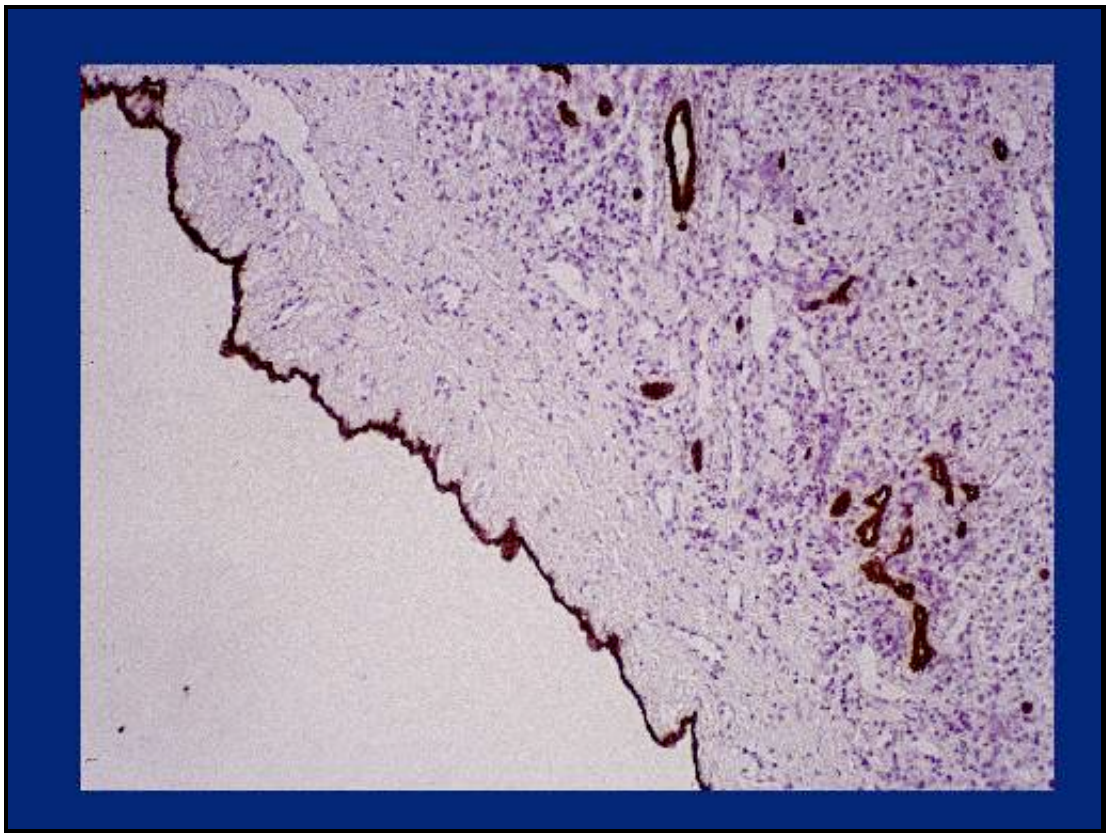

Origin of liver cysts in PKD
Using a slightly different technique, this is the lining of the cyst, showing the cells staining brown, and then these are the little bile ducts within the liver which have the same marker. So we have fairly conclusive evidence that these liver cysts come from these little bile ducts.

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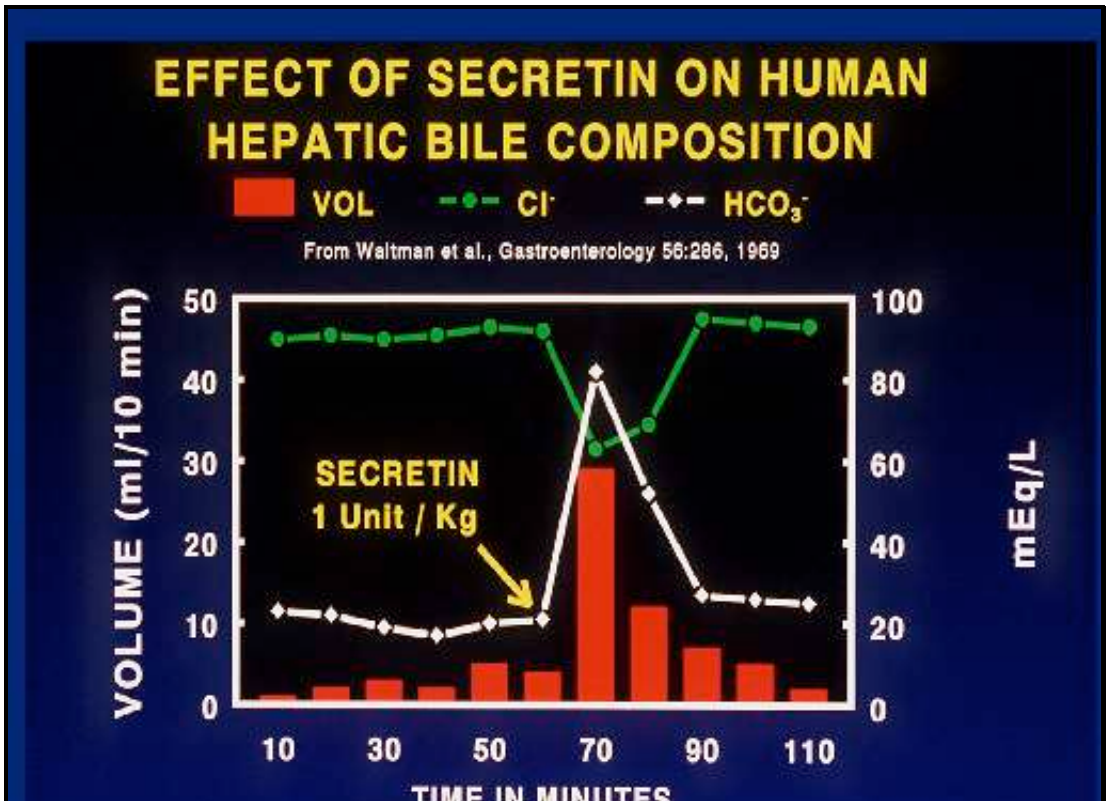

The effects of secretin of hepatic bile composition
Finally, I will show you some what I would call functional data, which might explain some of the symptoms that people tend to have. When you eat a meal, you need bile to help to digest the food. When you eat a meal, you make a hormone called secretin. What happens when you make secretin is that the volume of the bile goes up. That is indicated by this increase in the red bar. And the composition of the bile is changed. It has more alkali in it, which helps in the digestion.

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