Is liver cirrhosis reversible ?

Lecture by

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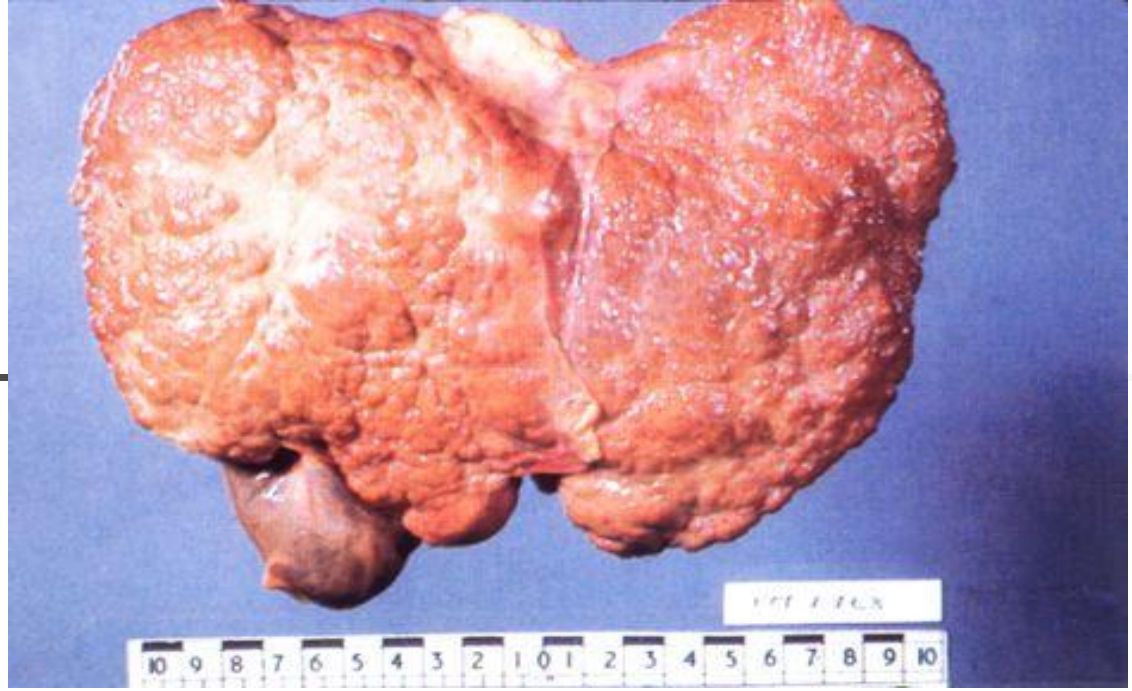
Cirrhosis: the final fibrotic stage

• Cirrhosis is a pathological condition involving the presence, throughout the liver, of **fibrous septa dividing the parenchyma into nodules.**

• It represents the common final stage of chronic liver damage of various causes: **viral, alcoholic, toxic, autoimmune, metabolic, or ischemic**.

• Its complications include refractory **ascites, variceal bleeding, encephalopathy, hyponatremia, and renal dysfunction.**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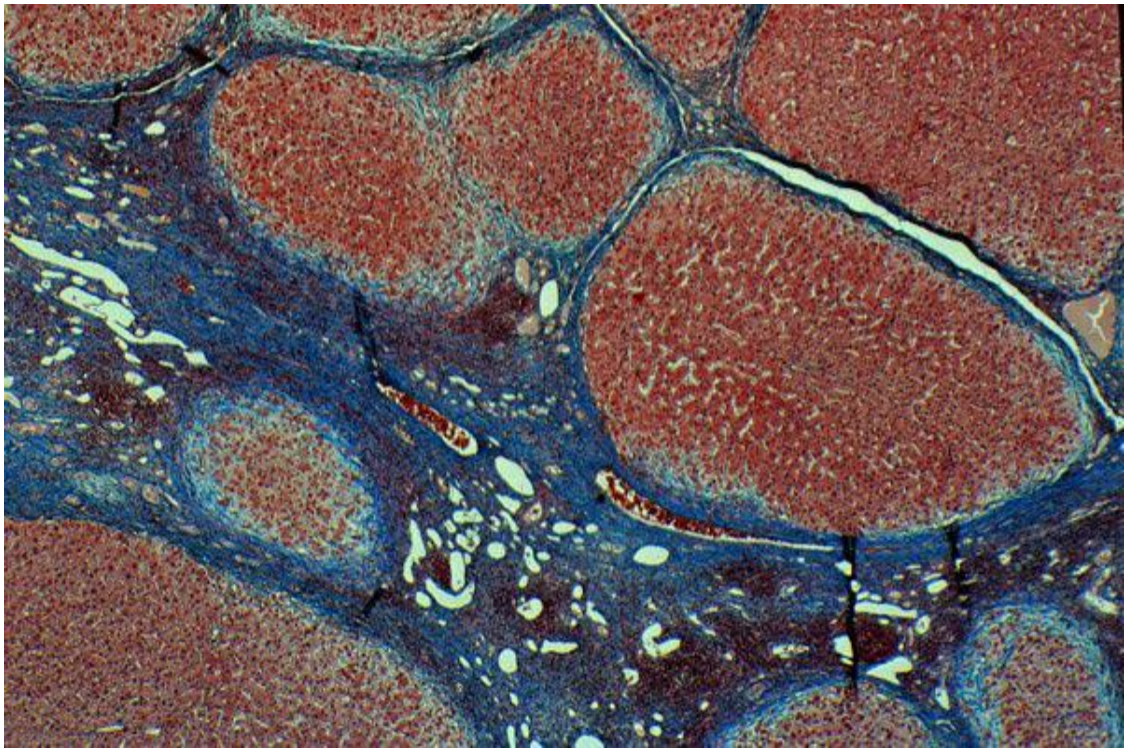


PATHOGENESIS OF CIRRHOSIS 1.

Three major mechanisms are central to the onset of cirrhosis:
cell death, ECM (extracellular matrix) deposition, and vascular modifications.

The fibrotic process is characterized by
- excessive deposition of collagen in the portal tracts and
- replacement of low-density type IV collagen with high-density types I and III collagen in the space of Disse, **causing sinusoidal capillarization.**

PATHOGENESIS OF CIRRHOSIS 2.

The morphogenesis of cirrhosis is related to the **underlying disease** and reflects the **topographic distribution of the liver damage** and the **contribution of different cells involved** in the fibrogenic process.

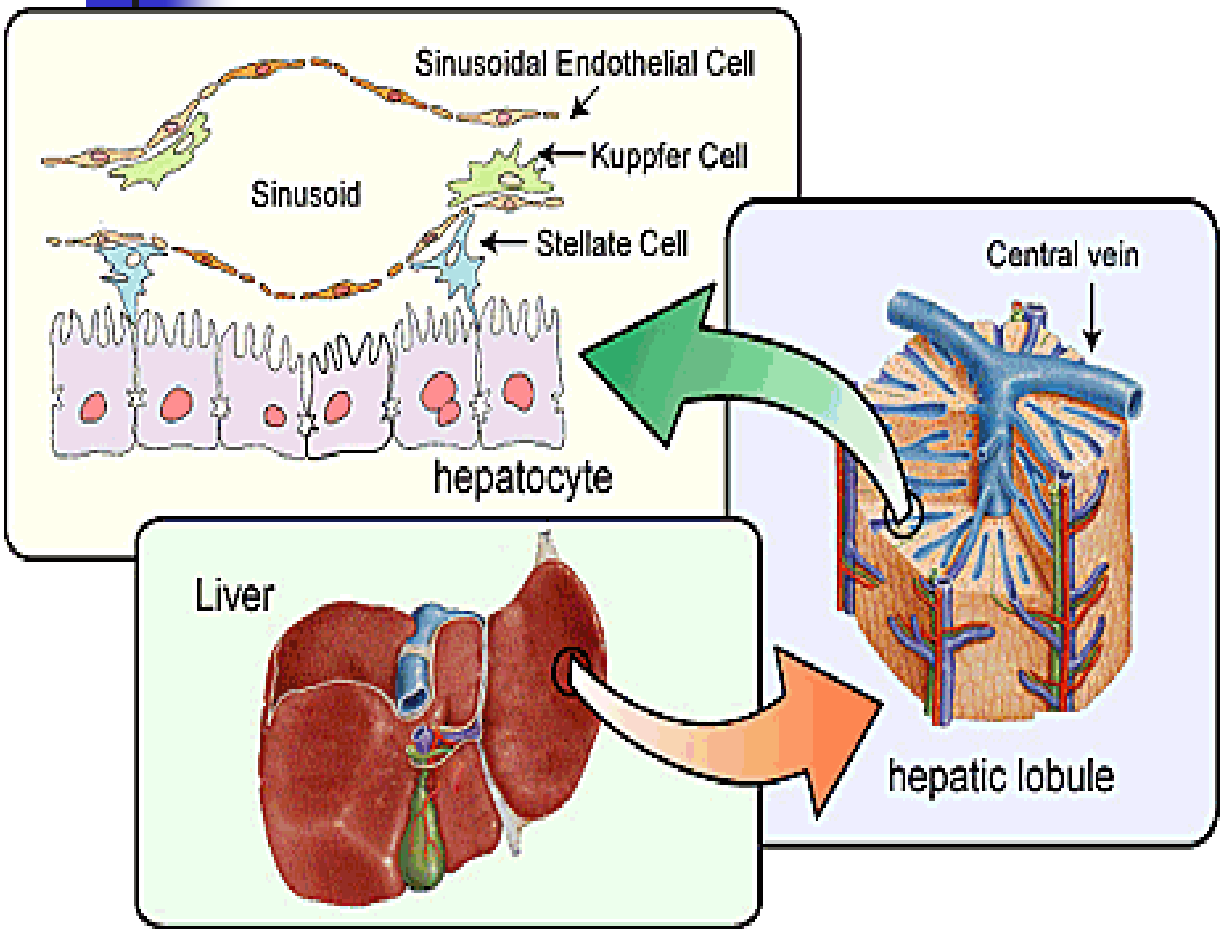
Biliary diseases: fibrosis in portal tracts - portal-portal septa.
Chronic viral hepatitis: interface hepatitis - portal-portal septa - necroinflammation - portal-central bridging necrosis - portal-central vein fibrous septa
Outflow disorders: central-central septa.
Alcohol: fibrosis surrounding groups of hepatocytes around the central veins is a key step.

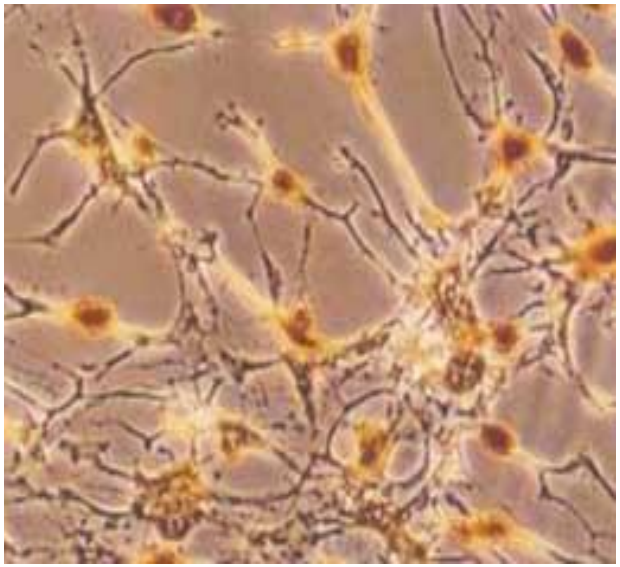
PATHOGENESIS OF CIRRHOSIS 3.

Regardless of the cause, **sinusoidal capillarization** is an early event, which inhibits metabolic exchange between hepatocytes and blood.

Further impairment is due to formation of **new intrahepatic vessels**, via **porto-portal** and **porto-central collaterals**, that shunt the blood away from the hepatocytes.

The hepatic stellate cell (HSC)



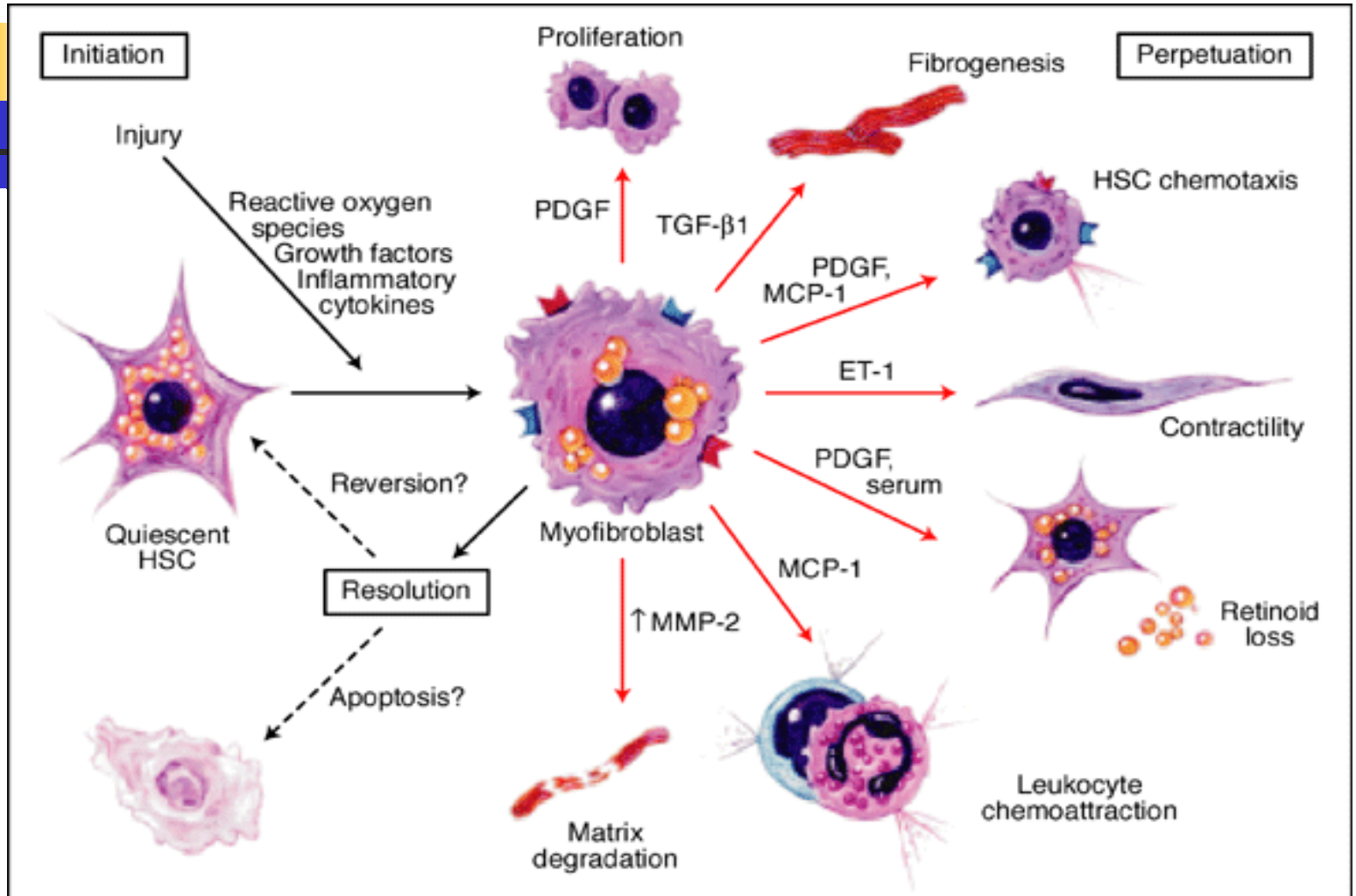


Cellular Effectors of Fibrogenesis

The **hepatic stellate cell (HSC)** is considered the key source of collagen. In the normal liver, HSC reside in a quiescent state in the space of Disse, between hepatocytes and sinusoidal endothelial cells.

In response to liver injury and the related production of cytokines, HSC undergo **transformation into proliferative, fibrogenic, and contractile myofibroblasts** (not found in the normal liver).

Functions of stellate cell



Phenotypic features of hepatic stellate cell activation during liver injury and resolution

Published in Expert Reviews in Molecular Medicine by Cambridge University Press 2003

Cellular Effectors of Fibrogenesis

The proliferation of myofibroblasts increases the number of fibrogenic cells. The direct fibrogenic activity of the myofibroblasts gives rise to a **dramatic increase in the synthesis and deposition of ECM**.

Myofibroblast contractility, primarily in response to endothelin-1, leads to increased portal resistance by **constricting individual sinusoids** and contracting the liver as a whole.

HSC produce tissue inhibitor of matrix metalloproteinases (TIMPs), which inhibits collagen-degrading matrix metalloproteinases.

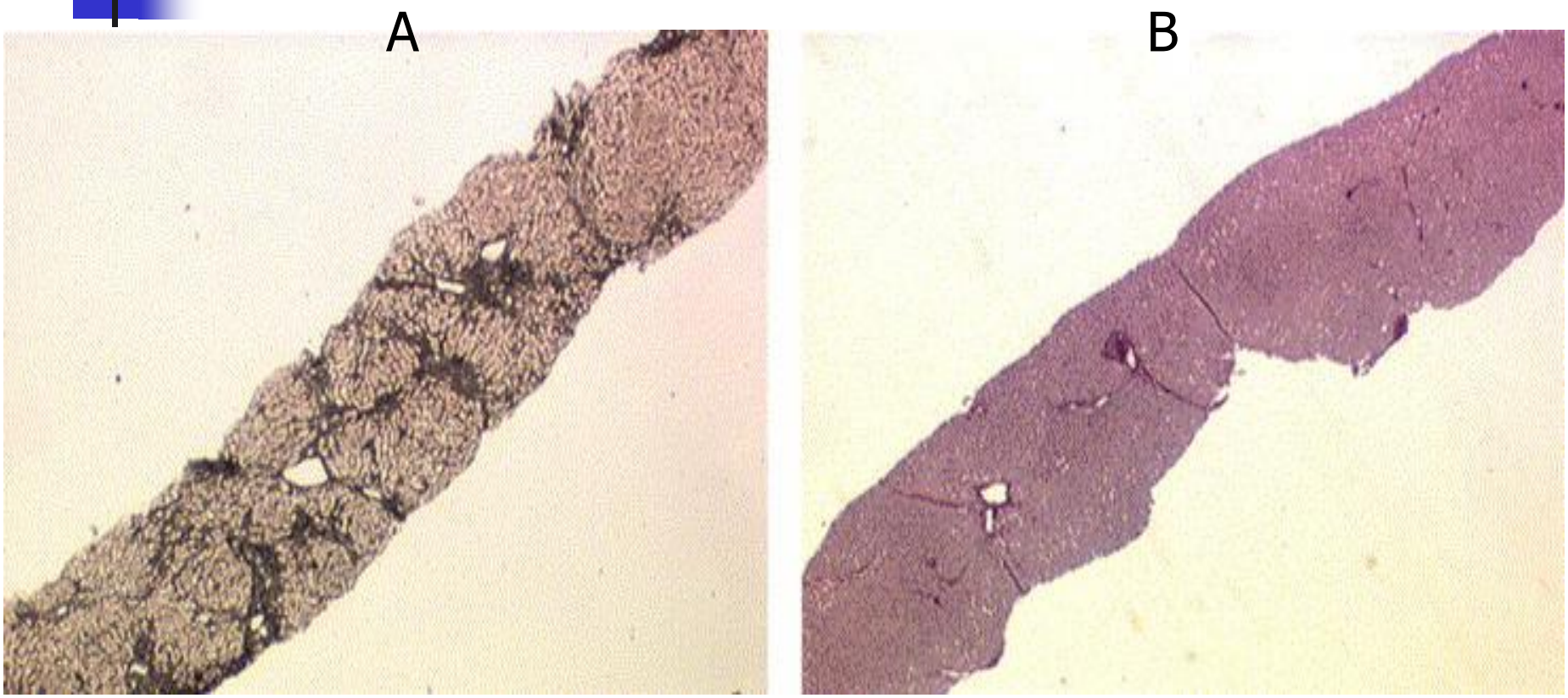
Mechanisms of Fibrolysis

In vivo activation of hepatic stellate cells by agents causing liver fibrosis can eventually lead to senescence of these cells.

The **senescent hepatic stellate cells** have been demonstrated to **limit liver fibrosis** by activating the immune system via interactions with the NK cells.

In rodents the **reversal of fibrosis** is **accompanied by** an increase in the **apoptosis of activated HSC**, which reduces ECM.

CIRRHOSIS REVERSAL IN CLINICAL PRACTICE



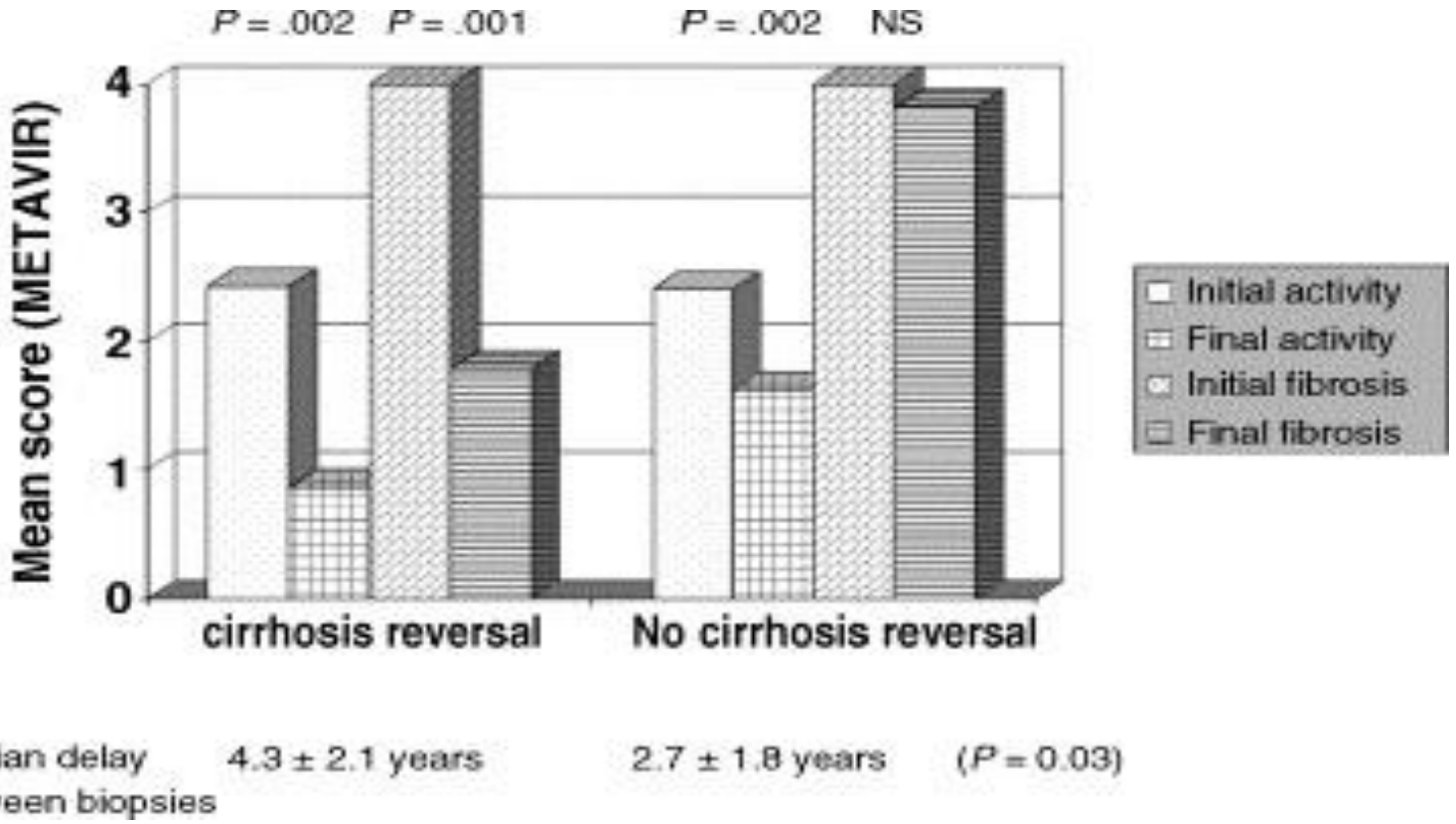
Illustrative microphotograph of the progression from cirrhosis (panel A) and to its reversibility (panel B) for the same patient after control of necro-inflammation.

CIRRHOSIS REVERSAL IN CLINICAL PRACTICE

Regression of fibrosis and cirrhosis has been documented in the entire spectrum of chronic liver diseases (i.e, in *alcoholic cirrhosis* after alcohol abstinence, in *autoimmune hepatitis* and *primary biliary cirrhosis* after effective immunosuppressive therapy, in *biliary obstruction* after surgical decompression, in *hemochromatosis* after iron depletion, in *hepatitis B and C* after antiviral therapy).

Reversal of cirrhosis is **more common among younger patients and in less severe cases** of cirrhosis.

CIRRHOSIS REVERSAL in chronic hepatitis C



Evolution of activity staging and fibrosis grading in the 2 groups of patients (pre- and posttreatment mean value of METAVIR fibrosis score).

Human Pathology Volume 37, Issue 12, December 2006, Pages 1519-1526

Specific Serological markers of fibrosis

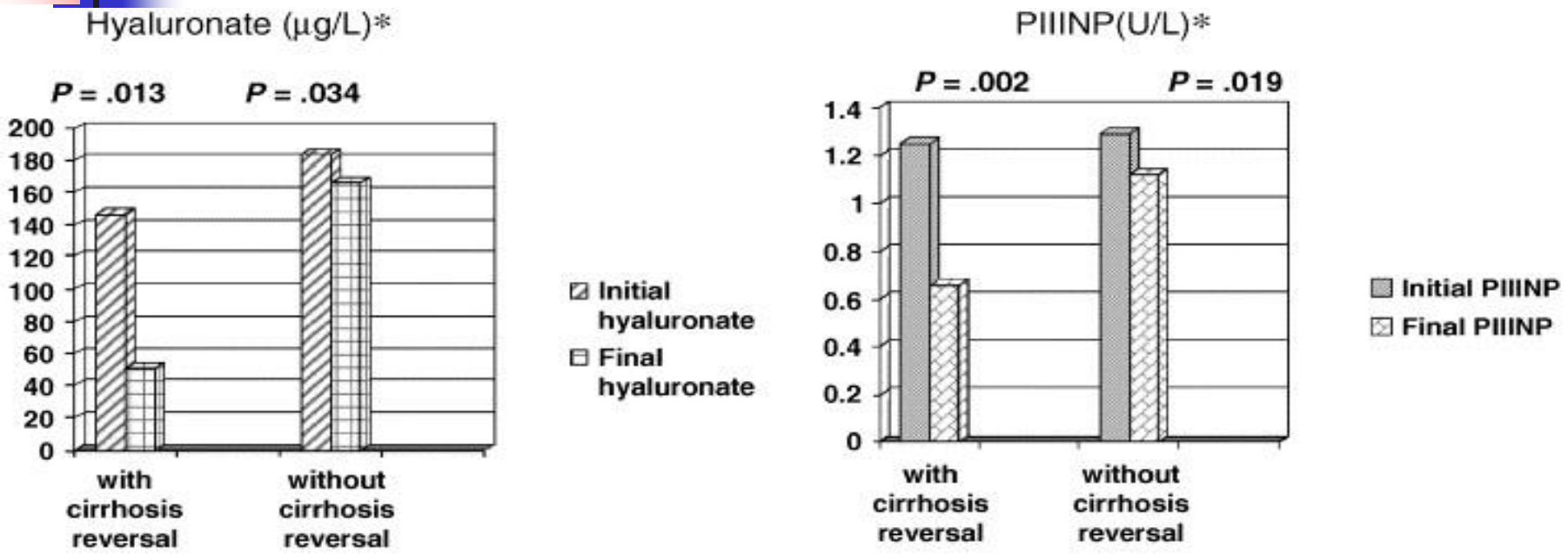
Several **glycoproteins** (hyaluronan, laminin, human cartilage glycoprotein 39)

The **collagens** family (procollagen III, type IV collagen and type IV collagen 7s domain)

The **collagenases and their inhibitors** (metalloproteinases, and tissue inhibitors of metalloproteinases)

A number of **cytokines involved in the fibrogenetic process** (in particular, TGF-β1, TNF-β)

CIRRHOSIS REVERSAL
Relevance of serological fibrosis markers



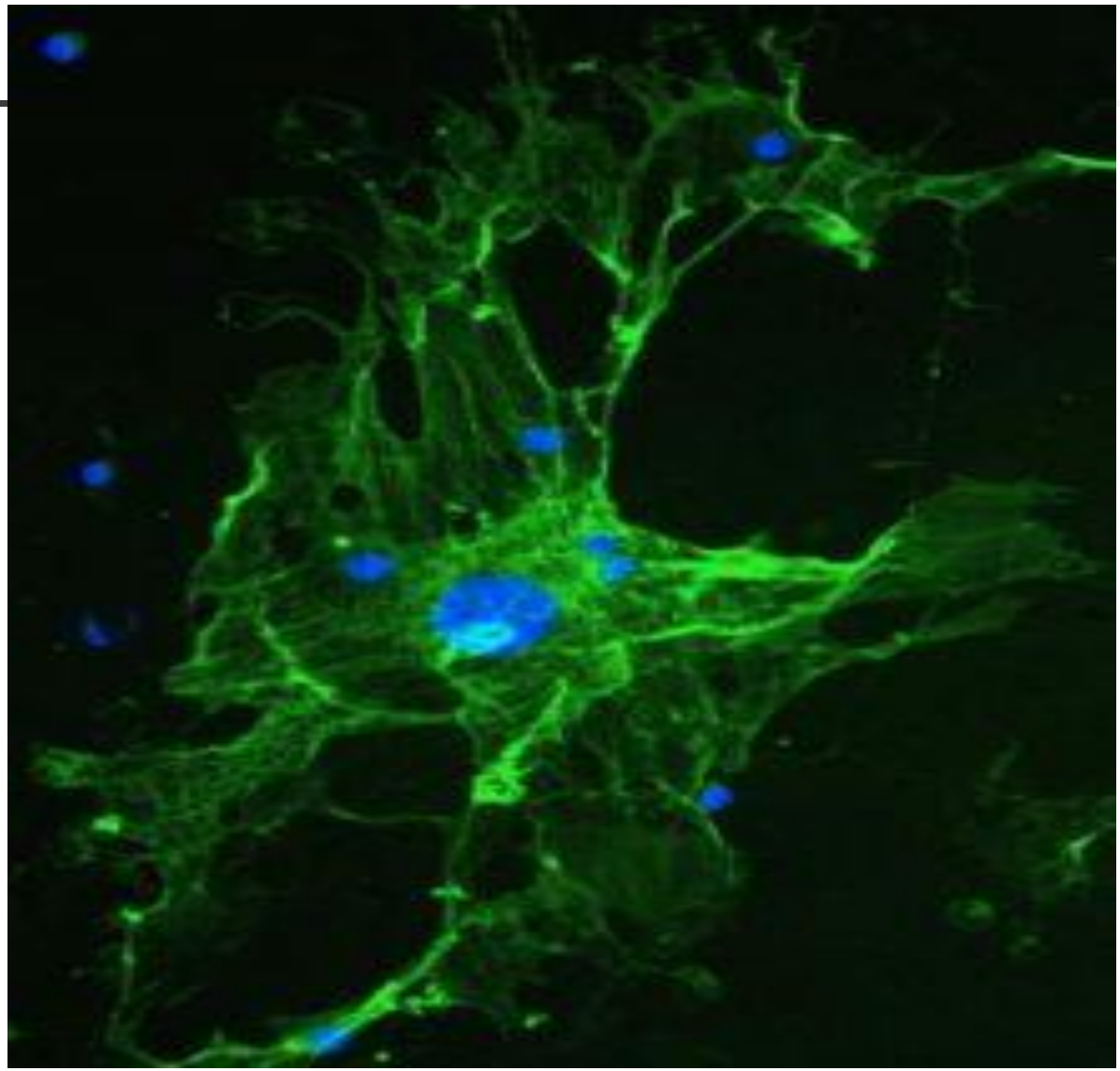
*Decrease in hyaluronate and PIIINP levels were more pronounced in the group with than without reversal (*P* = .36 et 0.002)

Variation of serum hyaluronate acid and serum type III procollagen peptide concentrations in patients with and without regression of cirrhosis. **Human Pathology** Volume 37, Issue 12, December 2006, Pages 1519-1526

Conclusions

1. Reversal of cirrhosis is more likely to occur in patients with a relatively short-lived history of disease and some preservation of liver function.
2. An improvement in or disappearance of, the underlying pathogen is a necessary condition for the reversal of cirrhosis.
3. Reversion of cirrhosis usually follows specific treatment but may also be a spontaneous event.
4. Reversal is probably **a slow process**, which starts soon after the pathogen has been removed/treated and may take several years
5. Future therapies may be specifically aimed at accelerating the fibrosis resolution processes.

Hepatic Stellate Cell reparing the liver



A hepatic stellate cell activated by the p75 Neurotrophin Receptor promotes repair in the liver. (mouse model)