History of Pathology Society
March 18, 2018

Disease and Environment: Liver Cancer

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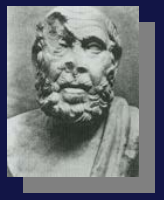
Nothing to disclose

Environmental agents incriminated in liver injury

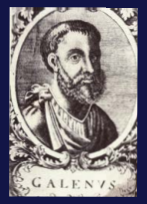
Amanita phalloides	DDT	Hexachlorobenzene	Polychlorinated biphenyls
Anabolic steroids	4,4'diaminodiphenylmethane	Hypoglycin	Ponceau-MX
Arsenicals	Dieldrin	Lead	Safrol
Benzene	Diethyl nitrosamine	Methylene chloride	Senecio
Beryllium	Dimethyl nitrosamine	Methylenedianiline	Styrene
Bush tea	Dinitrophenol	Mycotoxins (aflatoxin)	Tetrachlorethylene
Carbon tetrachloride	Dioxin	Organochlorine pesticides	Tetrachlorodibenxo-p-dioxin
Chlorinated naphthalene	Epichlorhydrin	Pethachlorophenol	Tetrachlorethane
Chromium	Ethionine	Perchlorethylene	Throrotrast
Copper	Ethylene dibromide	Phenobarbital	Toluene diisocyanate
Crotolaria	Galatosamine	Phenytoin	Trichlorethylene
Cyanide	Heliotropium	Phosphorus	Trinitrotoluene
Cycasin	Herbal remedies	Polybrominated biphenyls	Vinyl chloride

Understanding of cancer

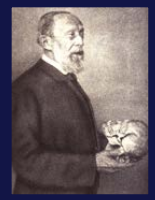


Hippocrates (46-377 BCE) **- introduces the word "cancer" or "carcinoma"**

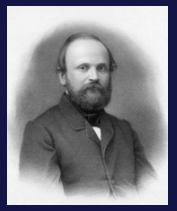
Galen (138-201) - "Scirrhus is a hard, heavy, immobile, and painful tumor; cancer is a very hard malignant tumor, with or without ulceration. Its name comes from the animal called the crab."



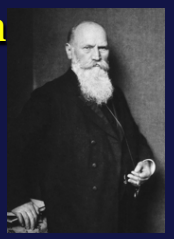
Virchow (1821-1902) - cancer arises as metaplasia of connective tissue; ***omnis cellula e cellula***



Remak (1815-1865) - skin cancer arises from the epithelium, not the connective tissue



Waldeyer (1836-1921) - carcinomas of internal organs arise from the epithelium; carcinoma spreads by direct extension and by embolism lymph and blood channels



Liver tumors and etiologic associations

Tumor	Etiology	Author(s), year
Hepatocellular carcinoma	Cirrhosis	Sabourin, 1881
	Hemochromatosis	Letulle, 1897
		Achard, 1911
	Hepatitis B	Prince, 1970
		Sherlock, 1970
	α-1-antitrypsin	Berg, Eriksson, 1972
	Androgens	Bernstein, 1971
Cholangiocarcinoma	*Clonorchis sinensis*	Katsurada, 1900
		Hou, 1956
Angiocarcinoma	Thorotrast	MacMahon, 1947
	Arsenic	Roth, 1956
	Vinyl chloride	Creech, Johnson, 1974
Liver cell adenoma	Oral contraceptives	Buam, 1973

Liver cancer, including hepatocellular carcinoma (HCC), accounts for 9.1% of all reported cancer deaths.

Liver cancer is the second most common cause of cancer mortality worldwide.

HCC incidence is the most rapidly rising of solid tumors in the United States.

Worldwide there >750,000 new cases/year with >250,000 deaths/year in China.

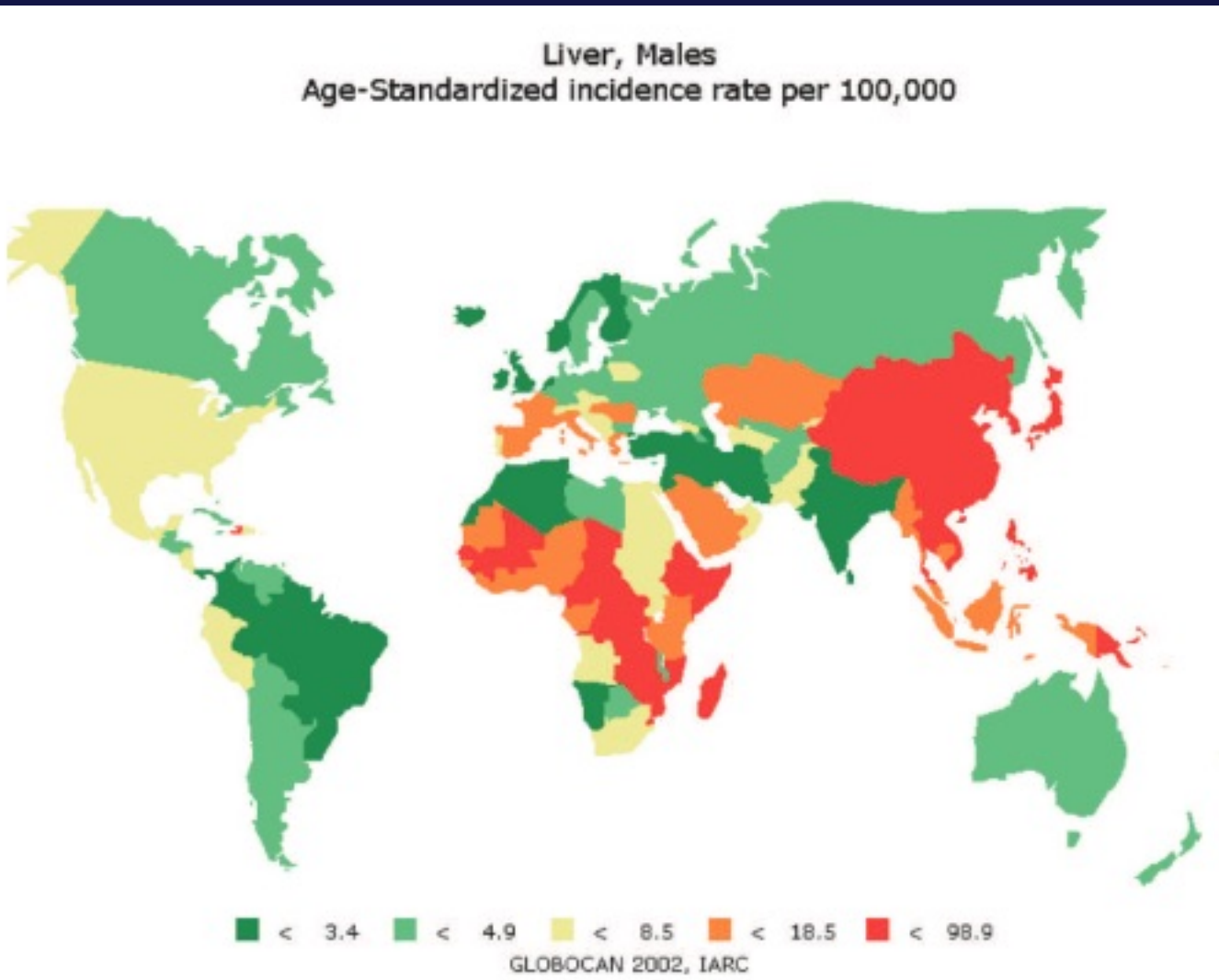
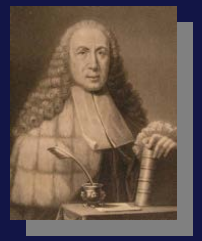


Fig. 1. Age-standardized incidence of liver cancer in men worldwide *(8)*.

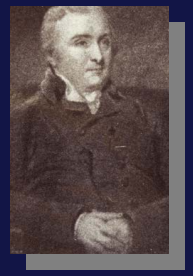
Primary carcinoma of the liver - historical background

- **Rigveda (~1500 BCE) - oldest Indo-European book, mostly hymns and verses - Hindu Sanskrit - alludes to malignant tumors**
- **Hippocrates (46-377 BCE) - introduces the word "cancer" or "carcinoma" as a descriptive term for all new tissue formations which could not be cured - distinguished "scirrhus," a hard type of tumor, from open "carcinoma" - classic descriptions of breast and skin cancers**
- **Aretaeus (1st or 2nd C) - regarded liver cancer as result of hepatitis**
- **Galen (129-210) - early description of liver cancer**
- **Morgagni (1682-1711) - founder of pathologic anatomy - described "steatomata" or "hard" tumors of the liver - first autopsy descriptions of cancers of the liver, almost certainly metastatic**



Primary carcinoma of the liver - Morgagni forward

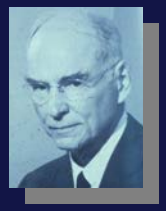
- **Matthew Baillie (1761-1823) - extended Morgagni's work - described "large white tubercles" in the liver, comparing them with "scirrhus" in other organs - could not distinguish neoplasia from tuberculosis, syphilis and other diseases**



- **Gaspard Bayle (1774-1816) - first clear description of cancer of liver - showed that "steatomata" of Morgagni and "white tubercles" of Baillie were true cancers, similar to cancer of breast - thought that metastasis represented a consitutional cancerous diathesis**

Primary carcinoma of the liver - histopathology

- Rudolf Virchow (1821-1902) - defined primary and metastatic
- Kelsch and Kiener (1876) - two cases of primary liver cancer
- Sabourin (1881) - benign primary liver tumors from malignant
- Hanot and Gilbert (1888) - classification of primary liver cancer (gross: "massive," "nodular," "cancer with cirrhosis" - microsopic: "trabecular epithelioma" "alveolar epithelioma")
- von Hansemann (1890) - incidence of primary liver cancer low
- von Heukolom (1894) - introduced term "adenocarcinoma" for primary liver cancer
- Eggel (1901) - modified Hanot/Gilbert to add "diffuse" - separated into two histologic types ("carcinoma solidum," "carcinoma adenomatosum")
- Katsusaburo Yamigawa (1911) - "hepatoma" and "cholangioma" (benign and malignant)
- Goldzieher and von Bokay (1911) - "hepatocellular carcinoma and "cholangiocarcinoma"
- Edmondson and Steiner (1954) - grading of hepatocellular carcinoma
- Hugh Edmondson (1958) - first AFIP fascicle on liver tumors



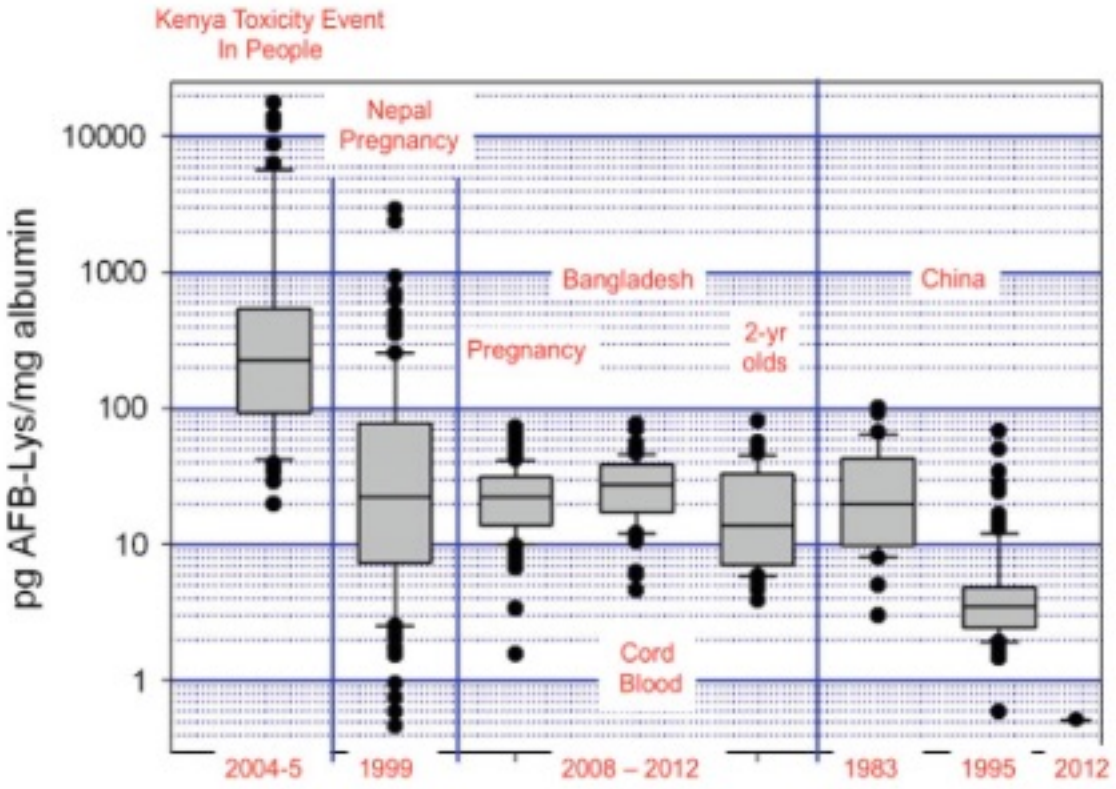
Environment: Aflatoxin

From fungal contaminant of peanuts, corn, rice, cottonseed, and other foods.

Geographical distribution in regions high in hepatocellular carcinoma.

The most potent experimental hepatocarcinogen.

Fig. 2.4 Range of aflatoxin exposure in different populations [162]



Biomarkers

Biomarker of exposure **– measurement of a specific compound of interest, its metabolite(s) or its specific interactive products in a body compartment or fluid, indicative of the presence of a biological response from exposure to an environmental agent.**

Biomarker of susceptibility **– indicator or metric of an inherent or acquired ability of an individual to respond to the challenge of exposure to a specific toxic agent.**

Groopman JD. Environmental carcinogens and risk for human liver cancer, in Carr BI (ed) Hepatocellular Carcinoma, Current Clinical Oncology, Springer Publishing, 2016.

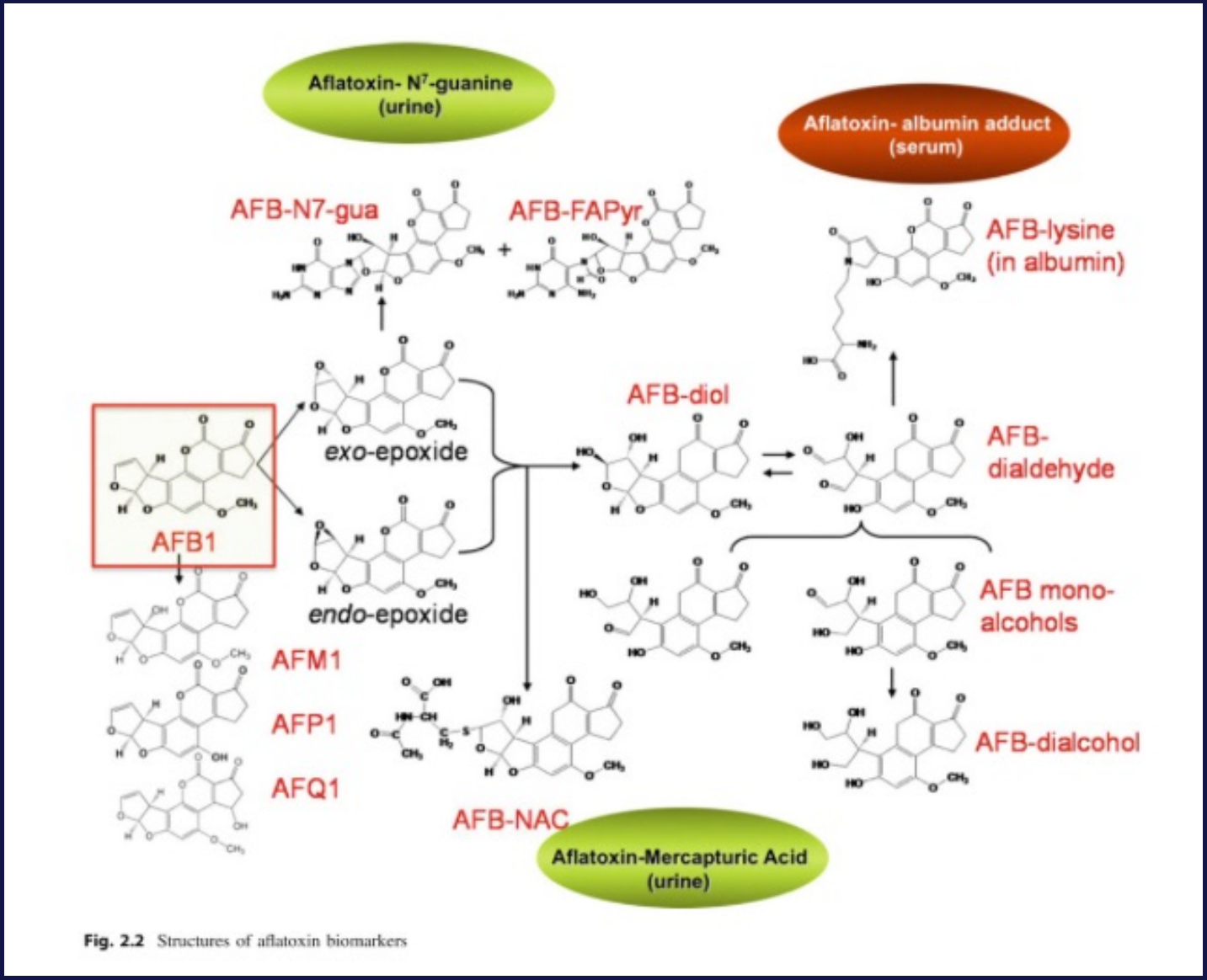


Fig. 2.2 Structures of aflatoxin biomarkers

Groopman JD. Environmental carcinogens and risk for human liver cancer, *in* Carr BI (ed) Hepatocellular Carcinoma, Current Clinical Oncology, Springer Publishing, 2016.

HCC incidence/mortality increasing in USA - why?

- HCV infection
- Influx of immigrants from HBV endemic areas (e.g. China, Taiwan, Korea, Vietnam)
- Increase in numbers of persons living with cirrhosis
- ? Obesity epidemic and diabetes mellitus
- ? HIV
- ? Increase in environmental carcinogens (e.g. aflatoxin)

Modified from El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Eng J Med 1999;340:745-750.

Don't forget the *internal* environment:

Worldwide, liver cancer is more common in men (~555,000/year) than women (~228,000) year.

In experimental models of aflatoxin carcinogenesis male rats have an earlier onset and higher incidence of cancer when compared to female rats.

Primary hepatic sarcomas

Year	*Author*	*Diagnosis*
1867	Hörup	Gemischtzelliges Sarkom
1868	Pintray	Polymorphozelliges Sarkom
1871	Lancereaux	Spindelzellensarkom
1885	Windrath	Kleinspindelzellensarkom
1885	Orth	Kleinspindelzellensarkom
1887	Rehn-Weigert	Sarkom
1888	Podrouzek	Spindelzellensarkom
1890	Arnold	Angiosarkom, polymorphzellig
1891	Puritz	Gemischtzelliges Sarkom
1893	Peyser	Angiosarkom
1894	Axtell	Kleinrundzellensarkom
1896	Walter	Angiosarkom, kleinovalzellig
1896	Bramwell, Leith	Spindelzellensarkom

Fischer W et al. *Leber* in Handbuch der Speziellen Pathologischen Anatomie und Histologie. Henke F und Lubarsch O (eds), Berlin, Verlag von Julius Springer, 1930.

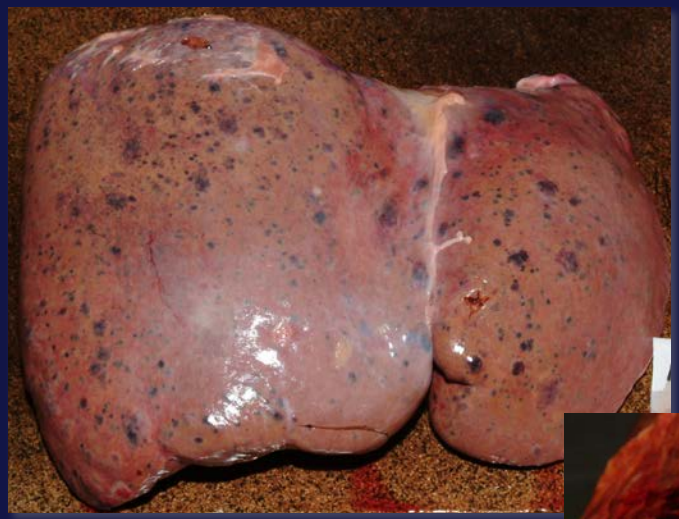
Hepatic angiosarcoma

- Rare
- 200-300 new cases worldwide annually
- Peak age 6th and 7th decades
- Exceedingly rare in children
  - Type 2 infantile hemangioendothelioma
  - Androgenic/anabolic steroids
  - ? arsenic exposure
- M:F = 3:1
- Very poor prognosis – no effective therapy
- k-ras mutation ~85%

Etiology of hepatic angiosarcoma

Physical/chemical injury	*Circumstances of exposure*	*Latency (years)*
Thorotrast (thorium dioxide)	Contrast medium for angiography	15-40
Radium	Needle implant for breast cancer therapy (1 case)	3
External radiation	Atomic bomb, Hiroshima (1 case), radiotherapy	35
Vinyl chloride	Manufacturing; in sprays using vinyl chloride as propellant	12-28
Inorganic arsenic	Insecticides; Fowler's solution; drinking water contaminant	6-33
Copper	Copper sulfate in sprays for vineyards (1 case)	35
Iron	Idiopathic hemochromatosis cirrhosis	?
Androgenic/anabolic steroids	Treatment of Fanconi anemia and other disorders	2-35
Contraceptive steroids	Birth control (1 case)	10
Diethylstilbesterol	Treatment of prostate carcinoma (1 case)	13
Phenelzine	Antidepressive – (1 case)	6

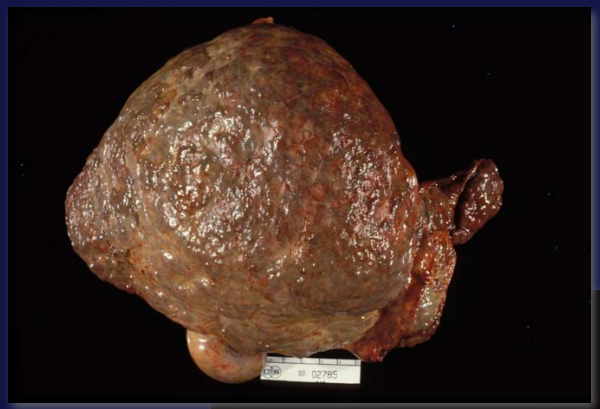
Angiosarcoma

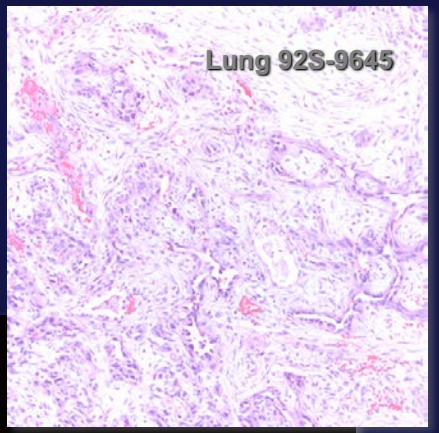


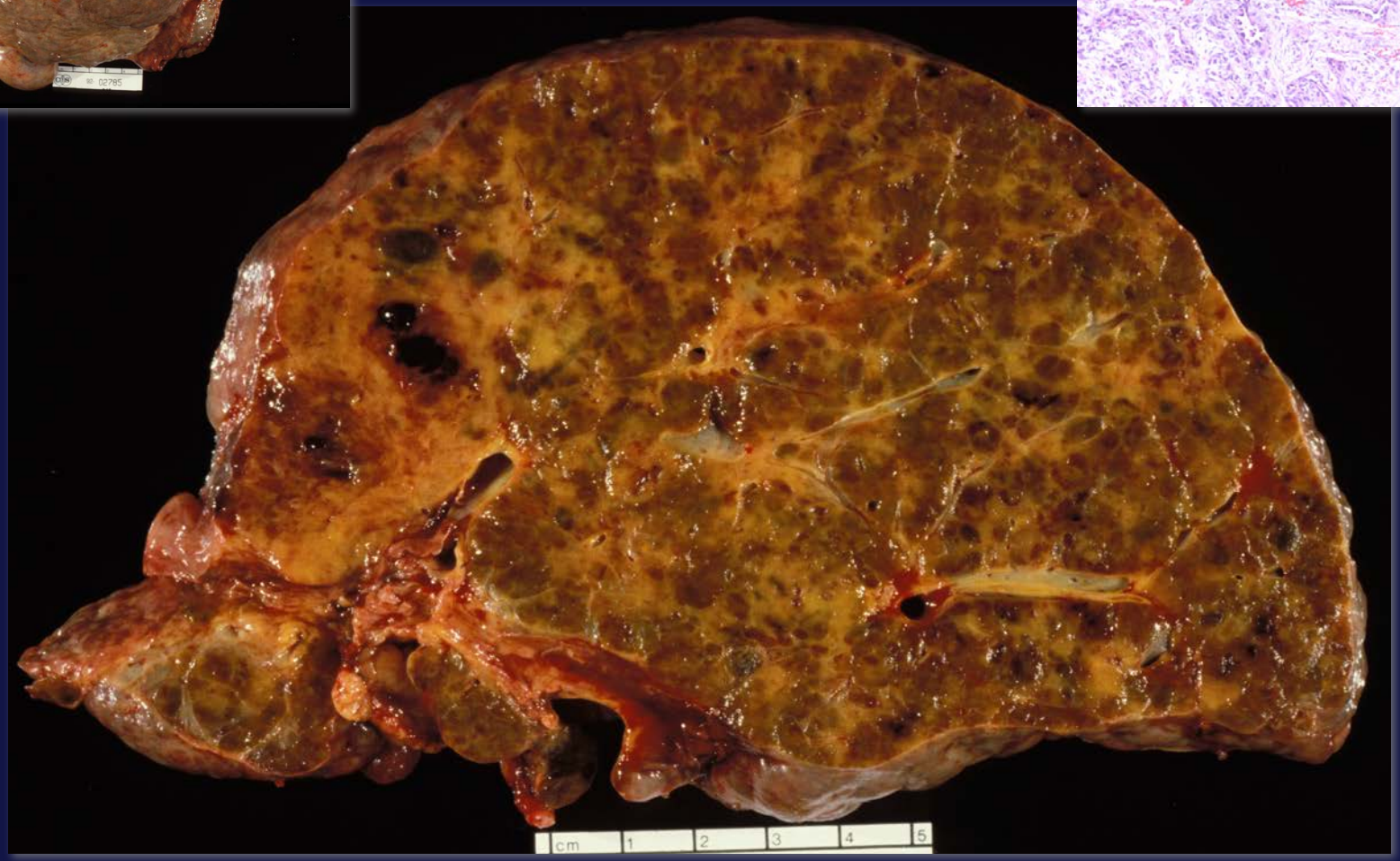
WM, 64 year old, vinyl chloride worker

Macroscopic features:

- Variegated
- Gray, tan and/or white tissue alternating with small and/or large hemorrhagic areas
- Blood-filled cystic spaces sometimes
- Reticulated pattern of fibrosis with vinyl chloride, thorotrast
- Cirrhosis uncommon (<20%)

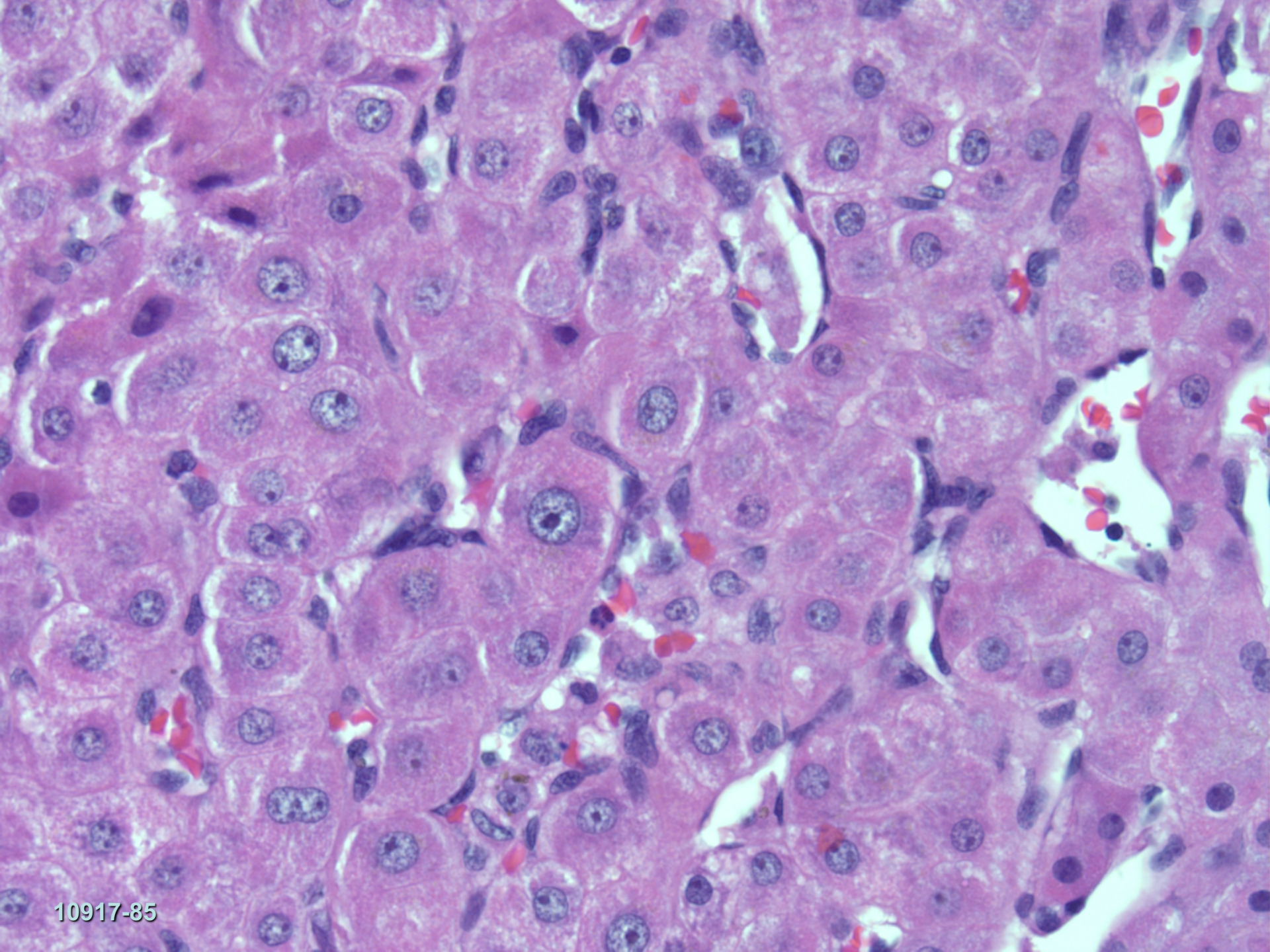






Clinical diagnosis: cryptogenic cirrhosis, no mass with imaging – died 3 months after surgery

How in the world did I miss that?


10917-85

Microscopic features - 1:

- Malignant spindle-shaped or irregular endothelial cells with irregular borders
- Lightly eosinophilic cytoplasm
- Hyperchromatic elongated and/or irregular nuclei
- CD31, CD34, F VIII, ulex, etc

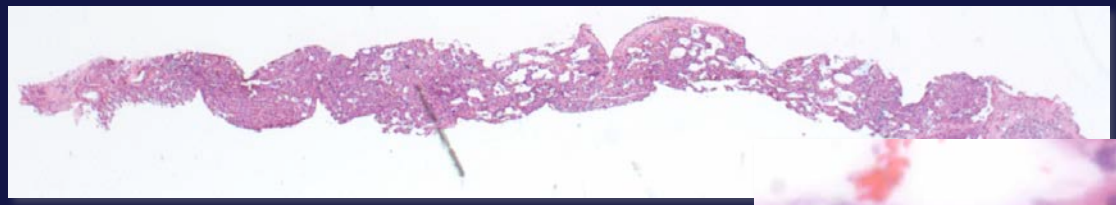
Microscopic features - 2:

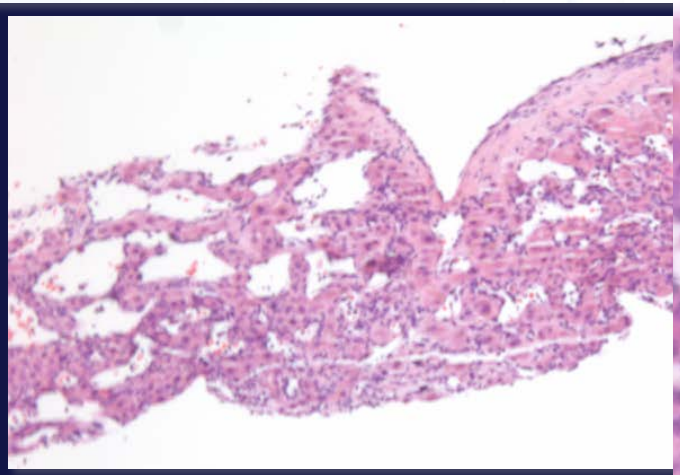
- Tumor cells grow along preformed vascular channels (e.g. sinusoidal spaces)
- Sinusoidal growth leads to liver plate atrophy and disruption
- Liver cell hyperplasia
- Larger vascular channels ("peliotic") and cavitary spaces develop
- Spaces lined by tumor cells – may have papillary/polypoid projections

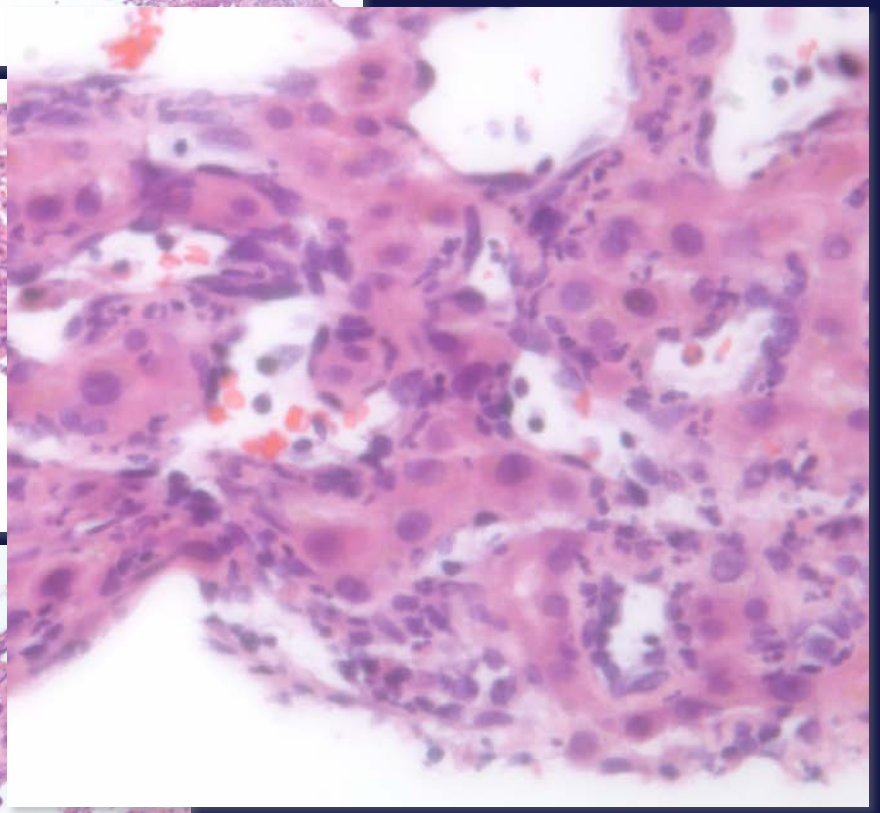
Microscopic features - 3:

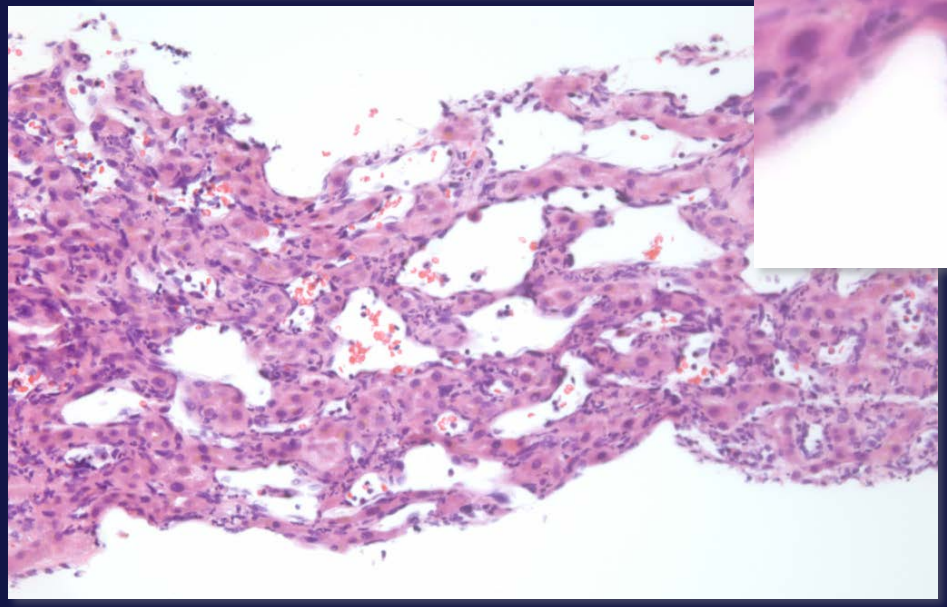
- Vein (THV, portal) invasion ⟶ obstruction
  - hemorrhage, infarction, necrosis
- Solid pattern resembes fibrosarcoma
- Hematopoiesis (especially Thorotrast related)
- May have simultaneous hepatocellular carcinoma or cholangiocarcinoma

Angiosarcoma





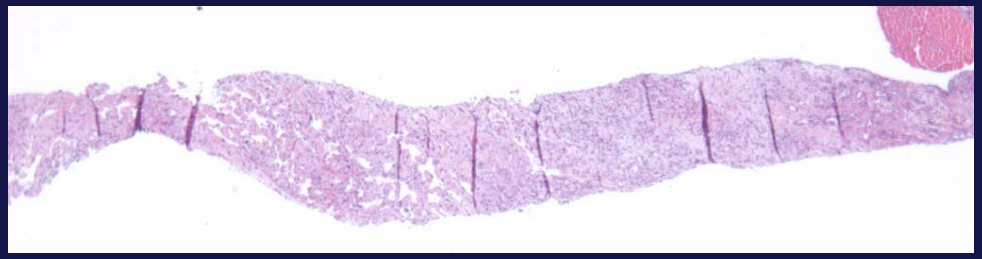


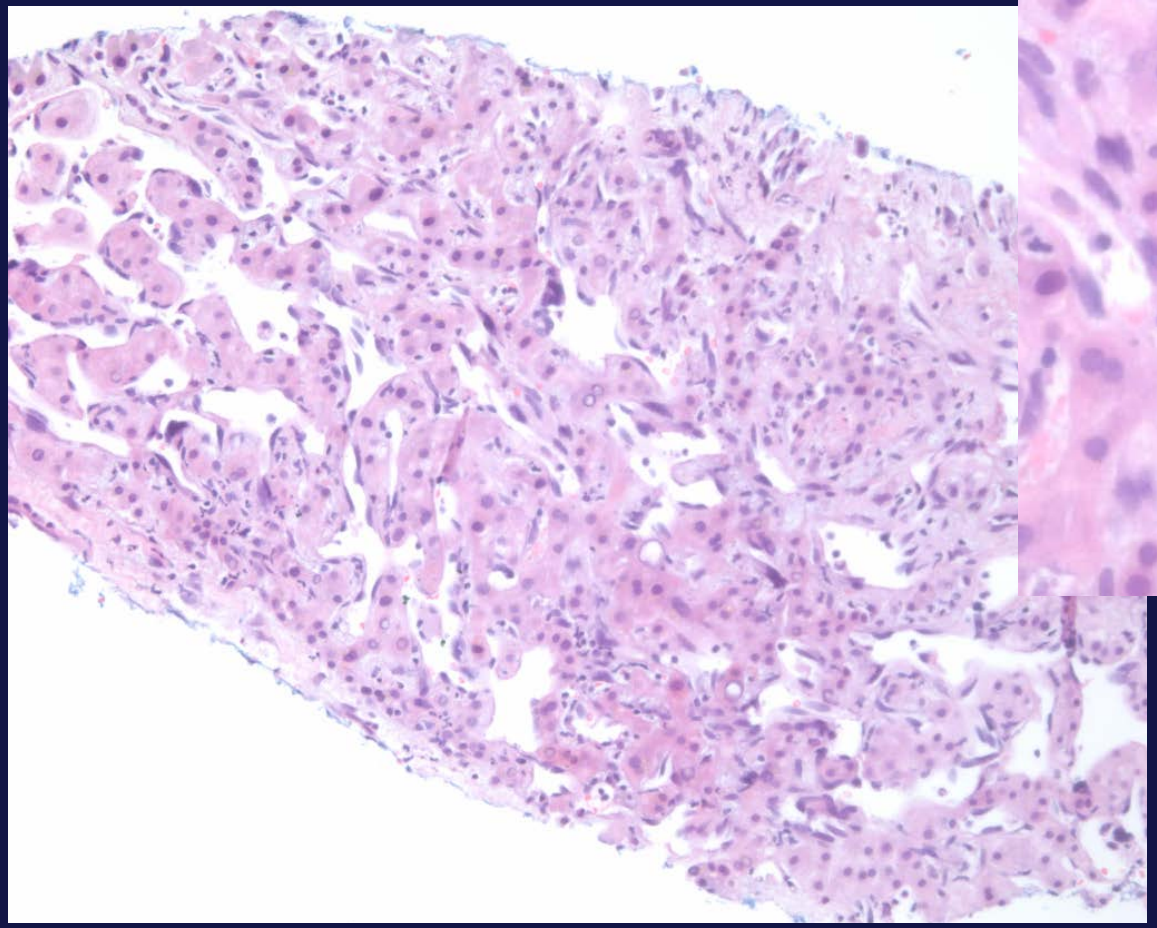


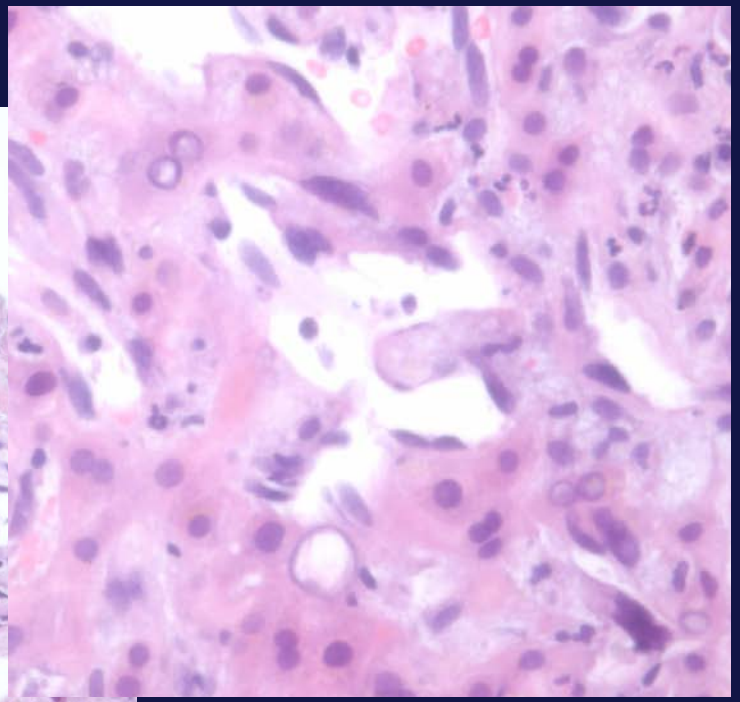
CR, 51 year old man, vinyl chloride worker

Proposed diagnoses:
? Peliosis, early adenoma
? Heart failure
? Hemangioma

Angiosarcoma

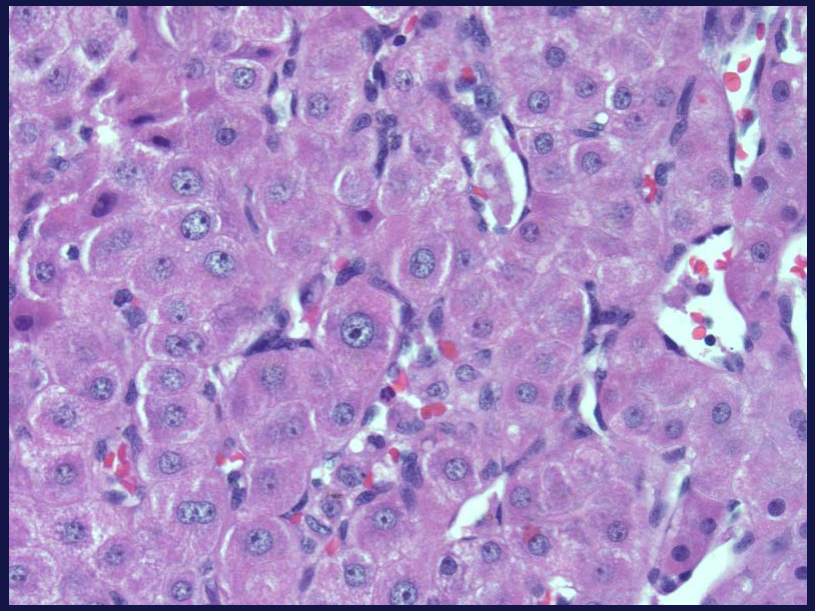
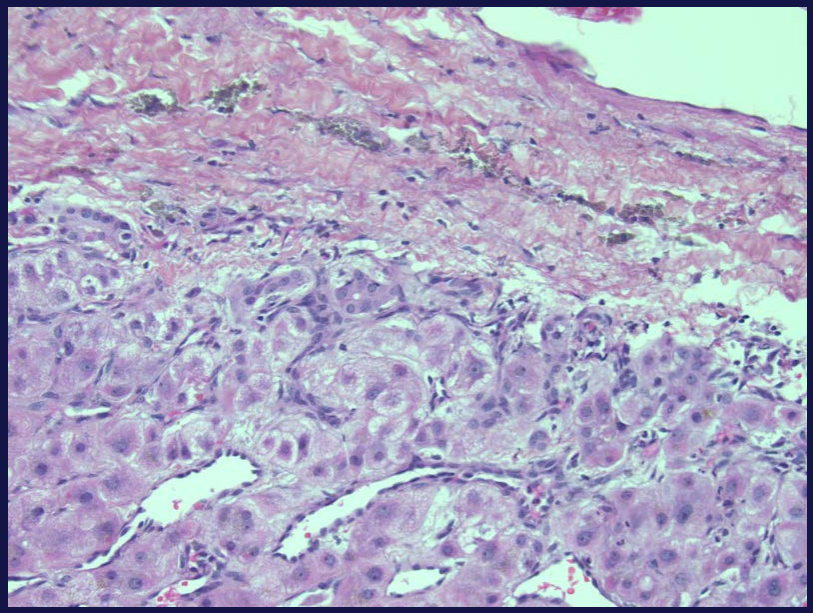
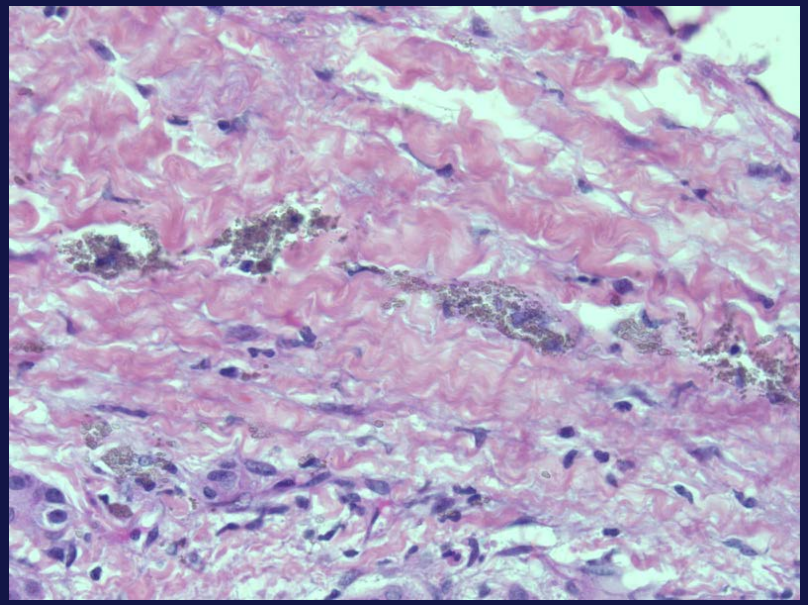
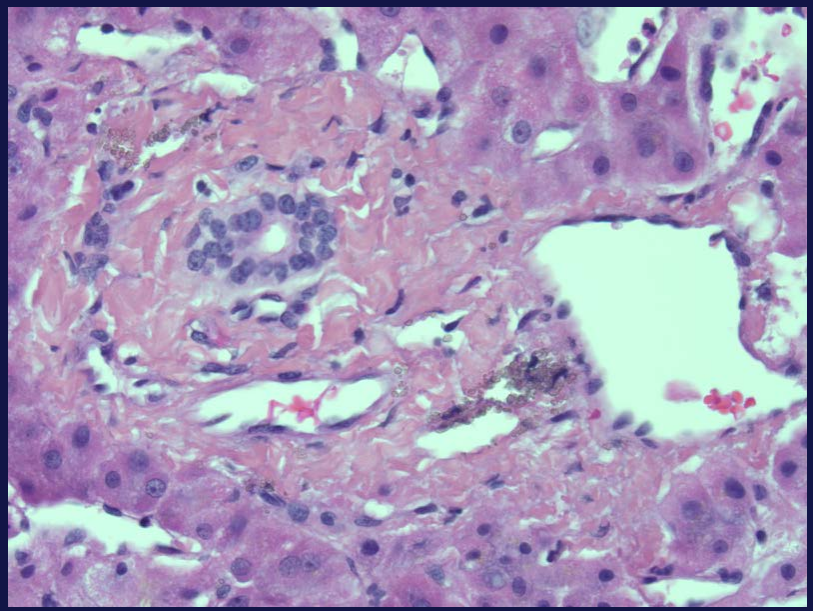






Original dx: Sinusoidal dilation, with long differential

JG, 69 year old man, vinyl chloride worker

66 year old woman – unexplained transaminase elevation
Thorium dioxide (thorotrast) [angiography ~25 years previously]

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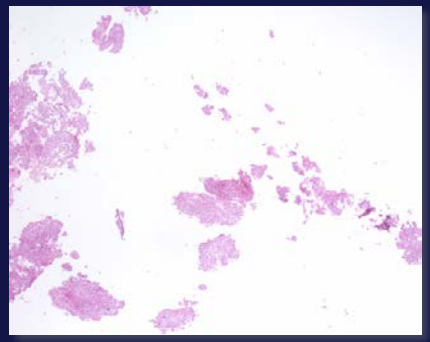
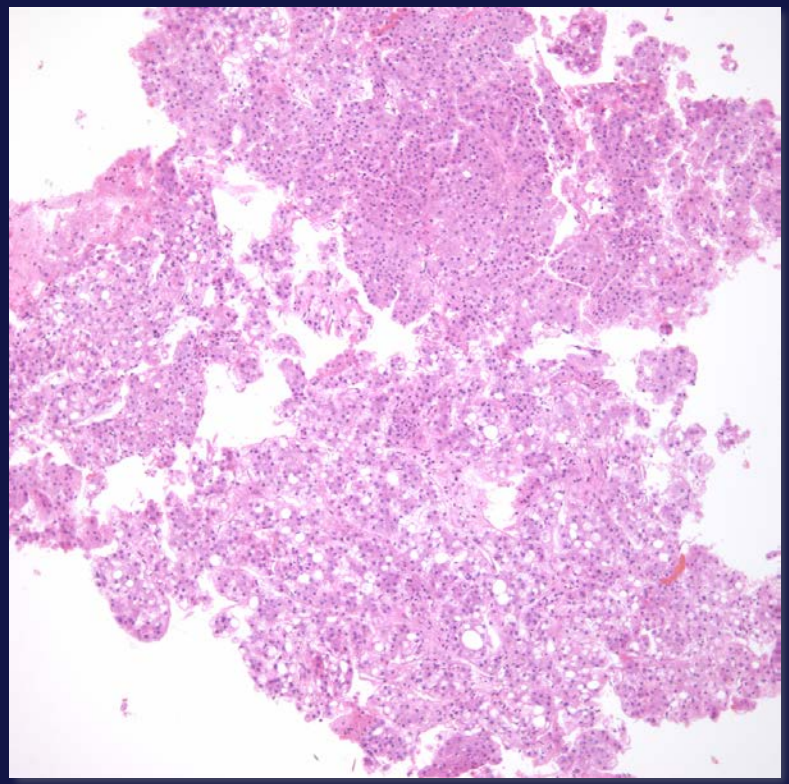
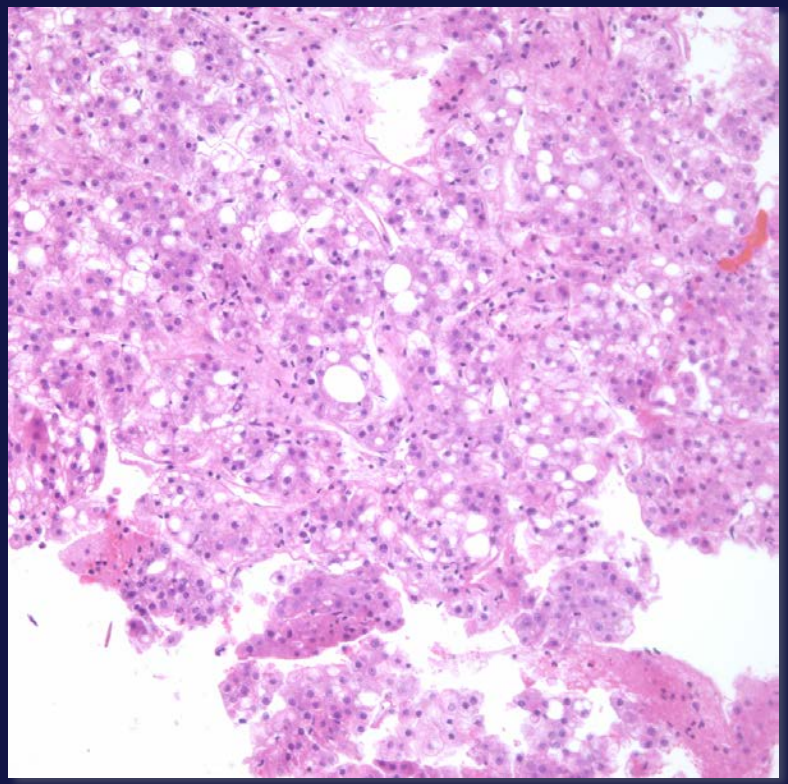
Hepatocellular carcinoma

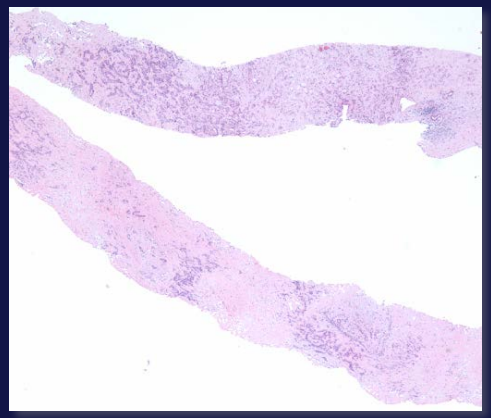


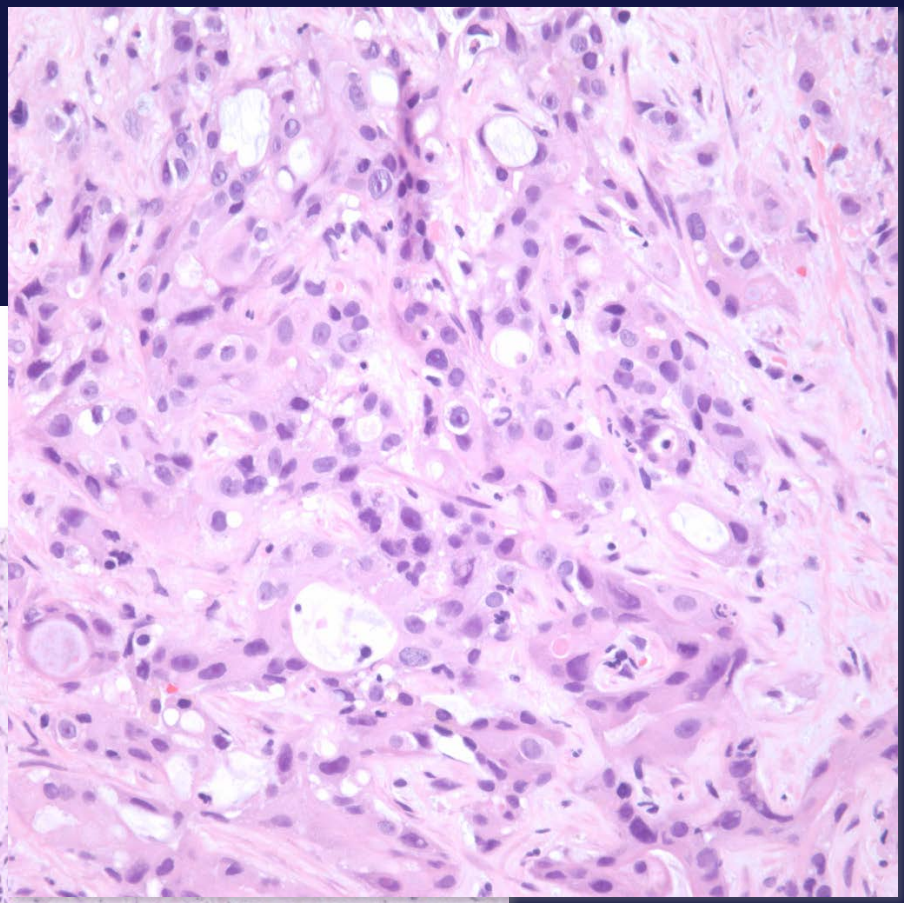


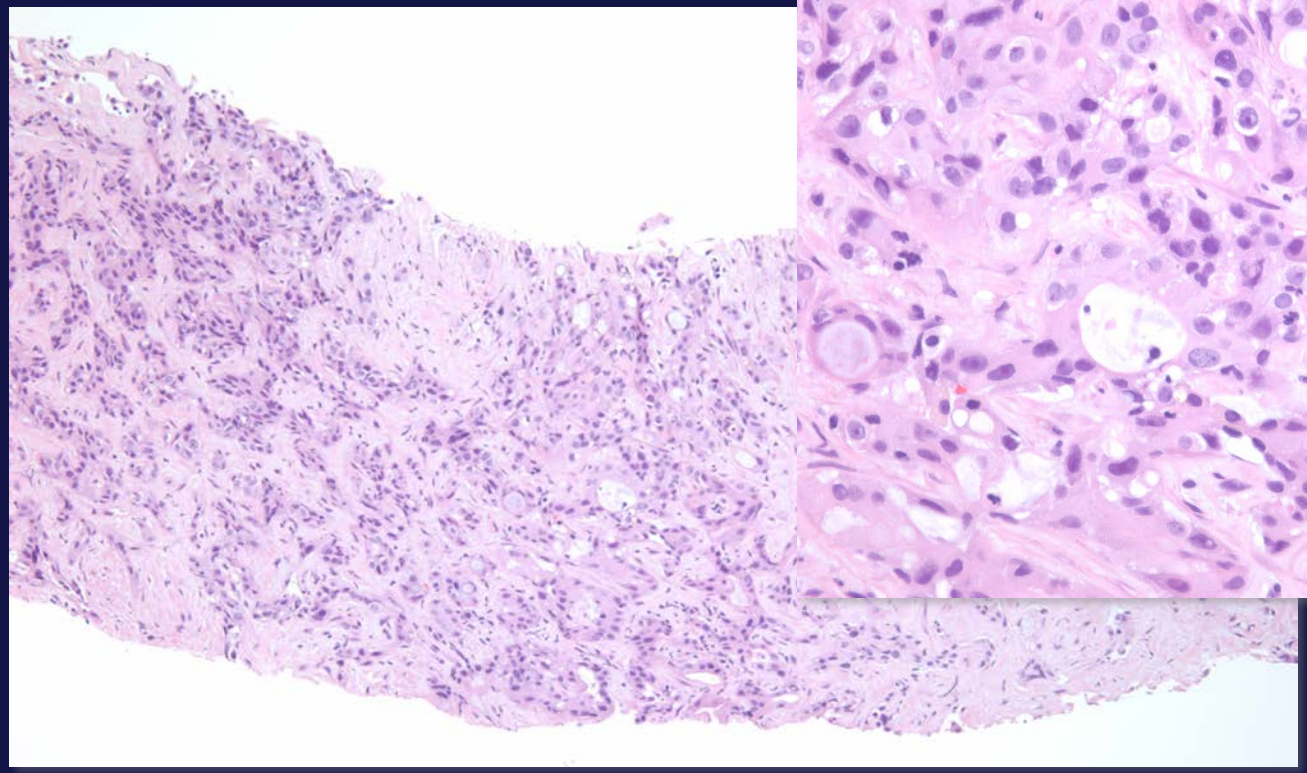


RH, 80 year old, vinyl chloride worker

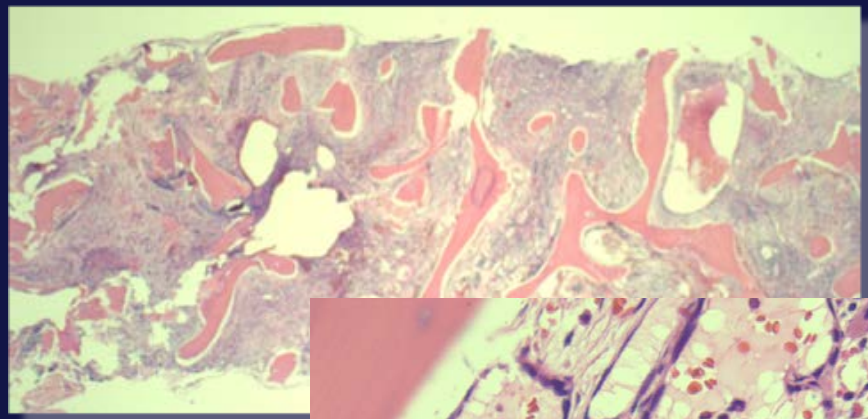
Cholangiocarcinoma

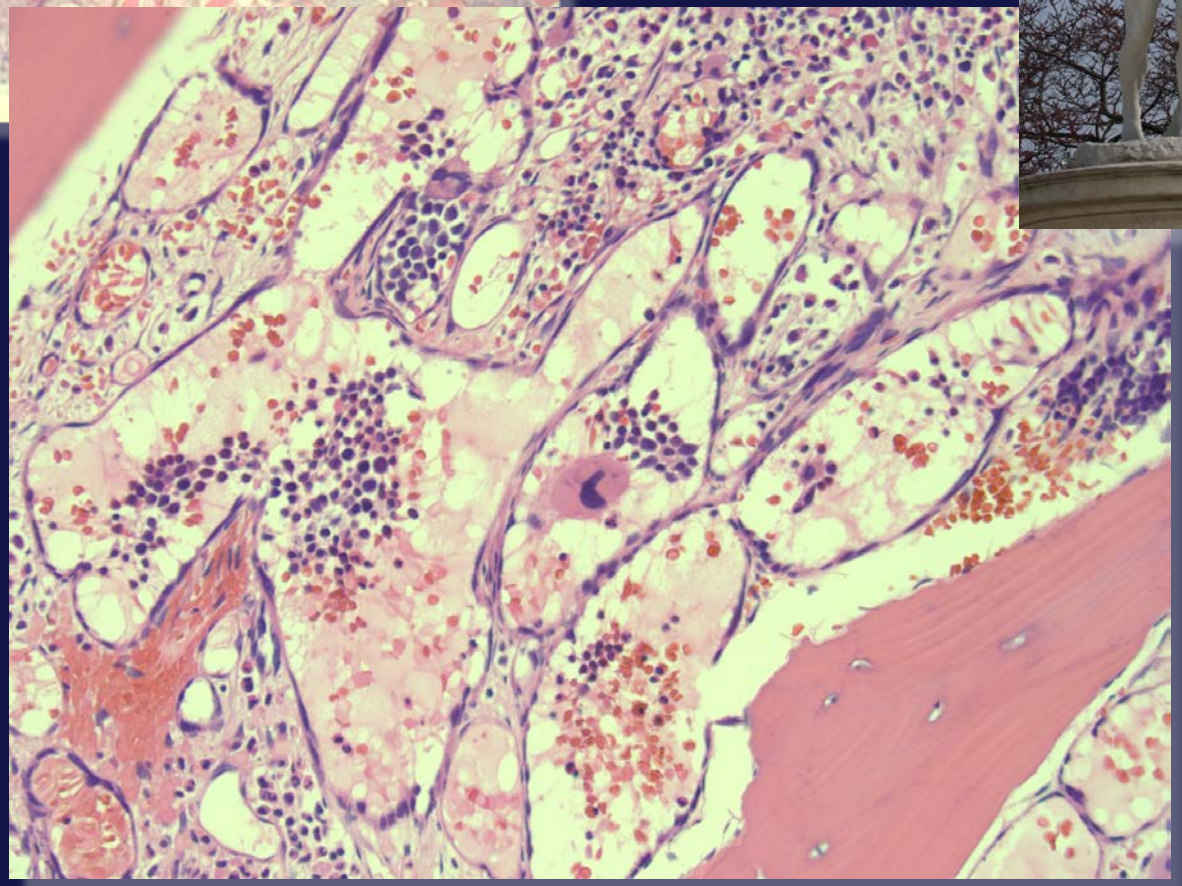




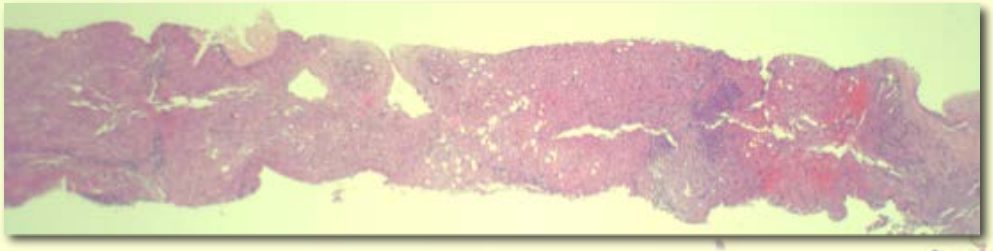


EP, 72 year old man, vinyl chloride worker

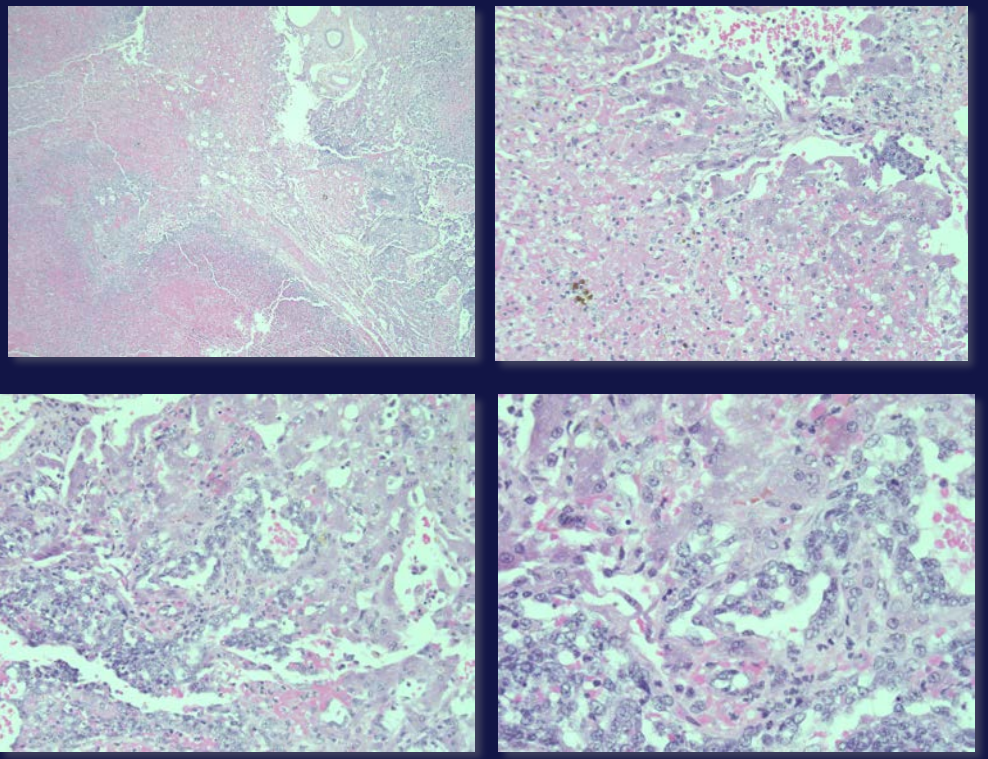




B-05-729 26 yom hypertensive, hypercholesterolemic, diabetic presented to ED with flank pain. WBC 23K, platelets 14K, Hgb 8, AST 249, ALT 152, AlPh 297.



S-05-28220 26 yom hypertensive, hypercholesterolemic, diabetic p presented to ED with flank pain. WBC 23K, platelets 14K, Hgb 8, AST 249, ALT 152, AlPh 297. Died 3 days after admission.



Cleo, 11 year old – (not a vinyl chloride worker)

Cleo

Angiosarcoma

Special Communication

Angiosarcoma of Liver in the Manufacture of Polyvinyl Chloride

Three reported cases of angiosarcoma of the liver serve as an alert to the probability that this condition may, in some instances, be causally related to employment in the manufacture of polyvinyl chloride resins.

J. L. Creech, Jr., M.D. and M. N. Johnson, M.D.

On January 22-23, 1974, a manufacturer of polyvinyl chloride and copolymers notified it's employees, the National Institute of Occupational Safety and Health, the Kentucky State Department of Labor, and the public, that three workers had died of angiosarcomas of the liver. These cases had as a common denominator employment in the manufacture of polyvinyl chloride resins.

A patient of one of the authors (J.L.C., Jr.) died on September 27, 1971 from an angiosarcoma of the liver. At that time the potential causal relation to the manufacture of polyvinyl chloride resins was not realized. Although other clinical manifestations of exposure to VCM were known (acroosteolysis), only one experimental paper[1] indicated that vinyl chloride may be a carcinogen. The tumors in rats that he described occurred primarily in the skin and were epidermoid in origin.

Eighteen months later on March 3, 1973, a second former employee in the Louisville plant died. Since he was not under our care, no connection was made that the two cases may have had a common origin. When a third patient died on December 19, 1973, the pathologist on gross examination diagnosed an angiosarcoma of the liver. Since all three patients were treated by different physicians, no relationship to exposure to polyvinyl chloride was surmised until the authors, recognizing the rarity of the tumor, and learning that all three had worked in the PVC plant, brought the matter to the attention of the company. Further search indicates that a fourth death from angiosarcoma may have occurred five years earlier (1968), but the death certificate shows primary liver tumor as the cause of death. (Clinical, epidemiologic, toxicological and occupational investigations are being vigorously pursued with regard to other employees who may have been similarly exposed.)

A brief resume of the first case under our care is presented. The history, clinical course, and pathologic findings are consistent with the others who died of angiosarcoma. These cases will be presented in a group and in more detail at a future date.

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Case Report

Patient one, a 36-year old white male, was hospitalized January 5, 1970 because of tarry stools.

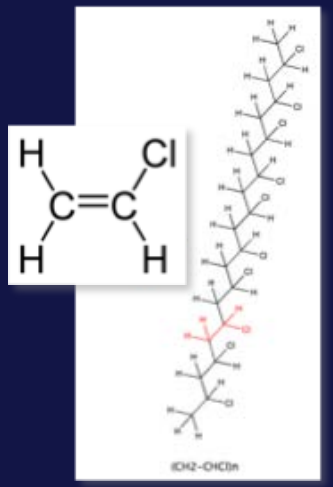
Occupational History.— The patient had been employed from November 1955 until his illness, except for two lay-offs of nine months in 1958 and six months in 1959, as a chemical helper and operator in the Louisville plant of B. F. Goodrich Chemical Company in the manufacture of polyvinyl chloride resins.

Present Illness.— At the time of admission the patient had no complaints except passage of tarry stools. Past history was negative except for an operation for hemorrhoids four years earlier. Physical examination showed pallor, and black stool on rectal examination. Liver and spleen were not palpable. Although upper G-I series was interpreted as normal, a tentative diagnosis was made of bleeding duodenal ulcer.

On diet and medication, the patient had no recurrence of

JAMA, 1974

Hepatic angiosarcoma - etiologic associations

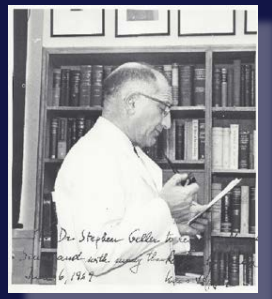


- Arsenic (vintners, Fowler's solution for psoriasis)
- Thorotrast (Thorium dioxide)
- Vinyl chloride (monomeric)
- Radiation – external, implanted
- ? Dioxin
- ? Copper-containing vineyard sprays
- ? Iron
- ? Steroids
  - ? contraceptive pills
  - ? androgenic/anabolic steroids
  - ? diethylstilbesterol
- ? Phenelzine (MAO inhibitor)
- ? Urethane
- Idiopathic

Development of Hepatic Angiosarcoma in Man Induced by Vinyl Chloride, Thorotrast, and Arsenic

Comparison With Cases of Unknown Etiology

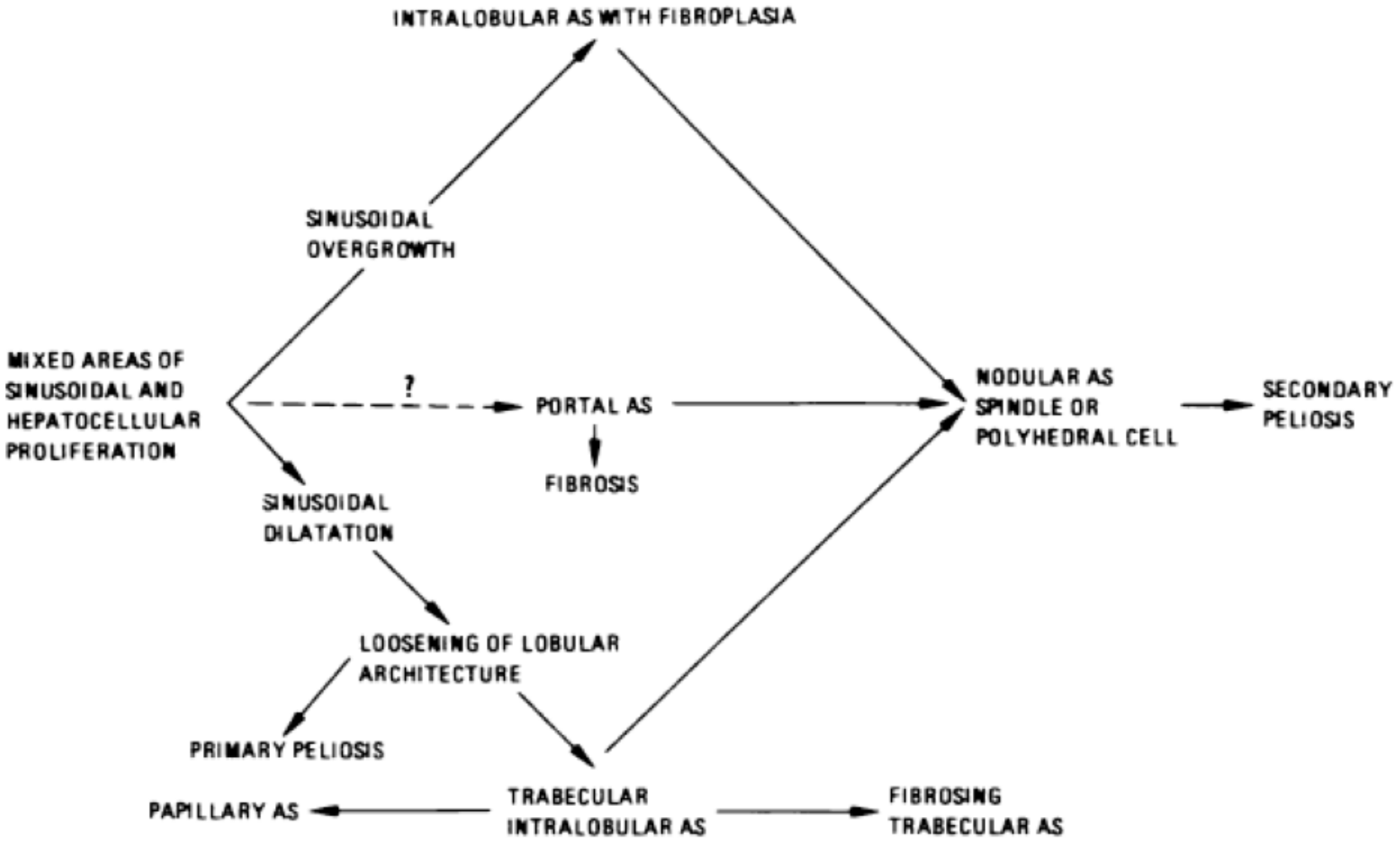
Hans Popper, MD, PhD, Louis B. Thomas, MD, Norman C. Telles, MD, Henry Falk, MD, and Irving J. Selikoff, MD



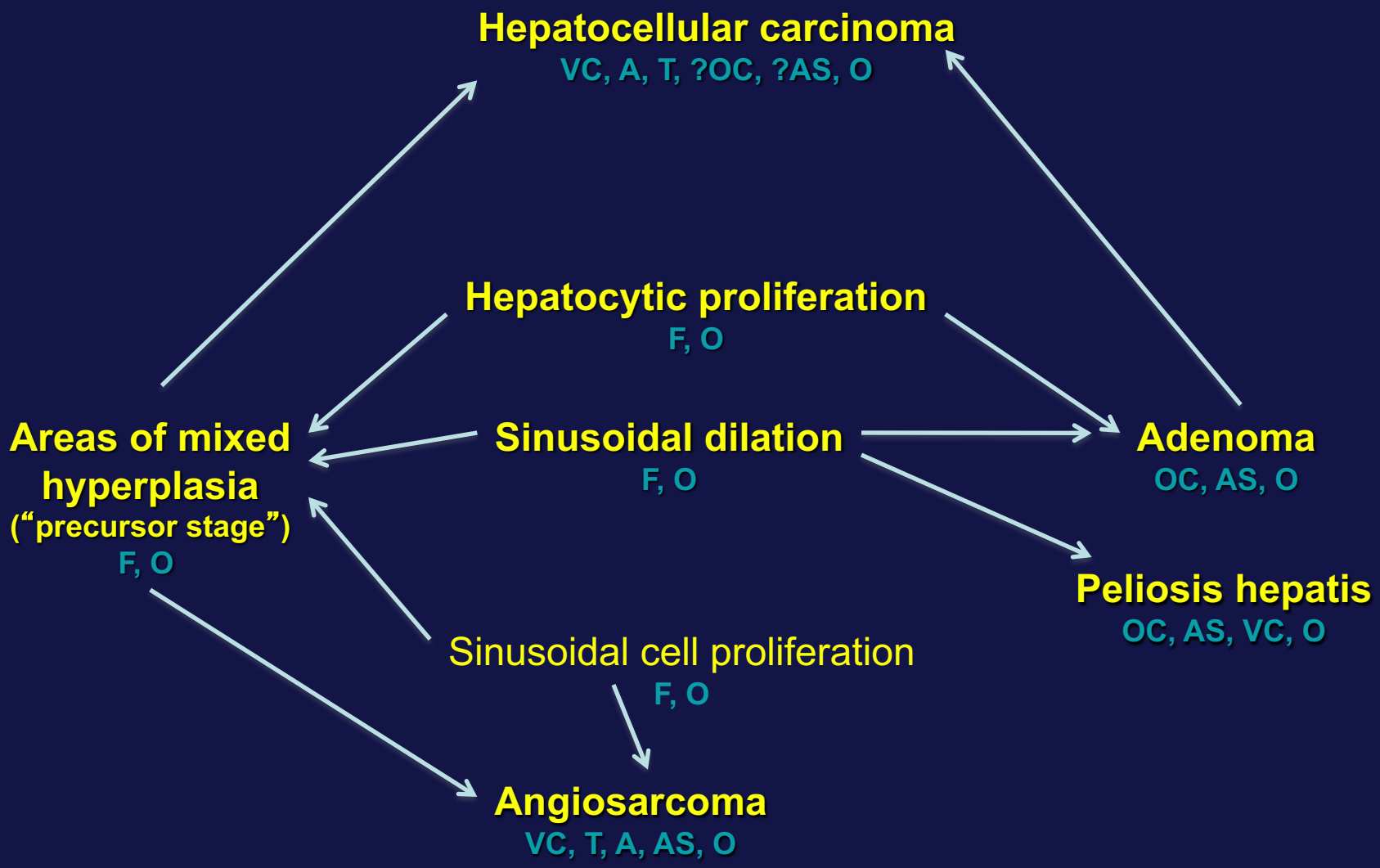
Examples of human angiosarcoma following exposure to vinyl chloride, Thorotrast, or arsenic (medicinal and industrial) and cases, including children, of unknown etiology were studied to establish diagnostic criteria and to study their evolution. The uniform evolution suggests an environmental factor also in the cases of unknown etiology, which may be established by epidemiologic studies. A precursor stage is characterized by areas of combined hyperplasia of hepatocytes and a variety of sinusoidal and perisinusoidal cells associated with excess of reticulin and with sinusoidal dilatation. The diagnostically useful picture in silver impregnations indicates reticulum formation by the perisinusoidal cells, presumably the lipocytes. The hepatocytic proliferation suggests a hepatocarcinogenic but usually not fully expressed potential. The mixed hyperplasia of the various sinusoidal cells proceeds to an overgrowth of angiosarcoma cells, presumably derived from endothelial cells. In early stages they are usually in contact with hepatocytes (intralobular growth). A trabecular arrangement results from loosening of the lobular plate arrangement by dilatation of sinusoids, leading to primary peliosis. With disappearance of the hepatocytes, various growth patterns develop, terminating in nodular, solid angiosarcoma composed of either spindle-shaped or polyhedral cells which undergo necrosis or hemorrhage (secondary peliosis). The interaction between hepatocytes and sinusoidal cells requires elucidation. (Am J Pathol 92:349–376, 1978)

THE RECOGNITION of the association between exposure to gaseous vinyl chloride during its polymerization to the common plastic polyvinyl chloride and the appearance of hepatic angiosarcoma[1] has increased the interest in this tumor. This concern was accentuated by its production in rodents exposed experimentally to vinyl chloride before the human lesion was recognized.[2] Until then, hepatic angiosarcoma had been considered rare in man, although it has been known that exposure to thorium dioxide (Thorotrast)[3] and inorganic arsenicals[4] may be followed by de-

Popper H et al. Am J Pathol 1978;92:349-378.



TEXT-FIGURE 1—Proposed schema of evolution of hepatic angiosarcoma (AS).



AS – androgenic-anabolic steroids; OC – oral contraceptives; VC – vinyl chloride;
A- arsenic; T- Thorotrast; F – all of these; O – others

Modified from Falk H, Popper H, Thomas LB, Ishak KG. Hepatic angiosarcoma associated with androgenic-anabolic steroids. Lancet 1979;2(8152),1120-1123.

TABLE I. HAS Cases, CDC Survey, 1964–1974. Distribution by Etiologic Status and Year of Death

Etiology	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	Total
Idiopathic	4	10	9	13	12	13	11	12	13	11	18	126
Vinyl chloride	1	–	–	–	3	2	1	1	–	3	1	12
Arsenic	1	–	1	2	1	–	–	–	–	1	–	6
Thorotrast	–	–	–	1	2	2	3	2	4	1	5	20
Androgenic-anabolic steroids	–	–	–	1	–	–	–	1	–	1	1	4
Total	6	10	10	17	18	17	15	16	17	17	25	168

Falk H, Caldwell GG, Ishak KG, Thomas LB, Popper H. Arsenic-related hepatic angiosarcoma. Am J Ind Med 1981;2:43-50.

Vinyl chloride (? arsenic, thorotrast) lesions in liver

- Fibrosis
- Portal
  - Portal vein wall
  - Intralobular
  - Capsular (most characteristic)
- Cholestasis, with bile plugs
- Hepatocyte proliferation
  - Nodules
- Endothelial cell atypia
- Sinusoidal dilation

Popper H, Thomas L. Alterations of liver and spleen among workers exposed to vinyl chloride. Ann N Y Acad Med 1975;246:172-194.

Constitutional genetic diseases leading to liver tumors*

Disease	Tumor type	Chromosome location	Gene
Trisomy 18	Hepatoblastoma	18	
Beckwith-Wiedemann	Hepatoblastoma, hemangioendothelioma	11p15.5	P57KIP2, others
Familial polyposis	Hepatoblastoma, adenoma, biliary adenoma, hepatocellular carcinoma	5q21,22	APC
Li-Fraumeni	Hepatoblastoma, undifferentiated sarcoma	17p13	P53, others
Glycogen storage I	Adenoma, hepatocellular carcinoma, hepatoblastoma	17	Glucose-6-phosphatase
Alagille	Hepatocellular carcinoma	20p12	Jagged-1
Hereditary tyrosinemia	Hepatocellular carcinoma	15q23-25	Fumarylaceto-acetate hydrolase
Familial cholestatic syndromes	Hepatocellular carcinoma, cholangiocarcinoma	18q21-22, 2q24	Fic-1, BSEP, [ABCB11]
Neurofibromatosis	Hepatocellular carcinoma, angiosarcoma, malignant Schwannoma	17q11.2	
Ataxia-telangiectasia	Hepatocellular carcinoma	11q22-23	ATM
Fanconi anemia	Hepatocellular carcinoma, fibrolammelar hepatocellular carcinoma	1q42, 3p, 20q13.2-13.3	FAA, FAC, BRCA 2
Tuberous sclerosis	Angiomyolipoma	9q34, 16p13	TSC 1, TSC 2

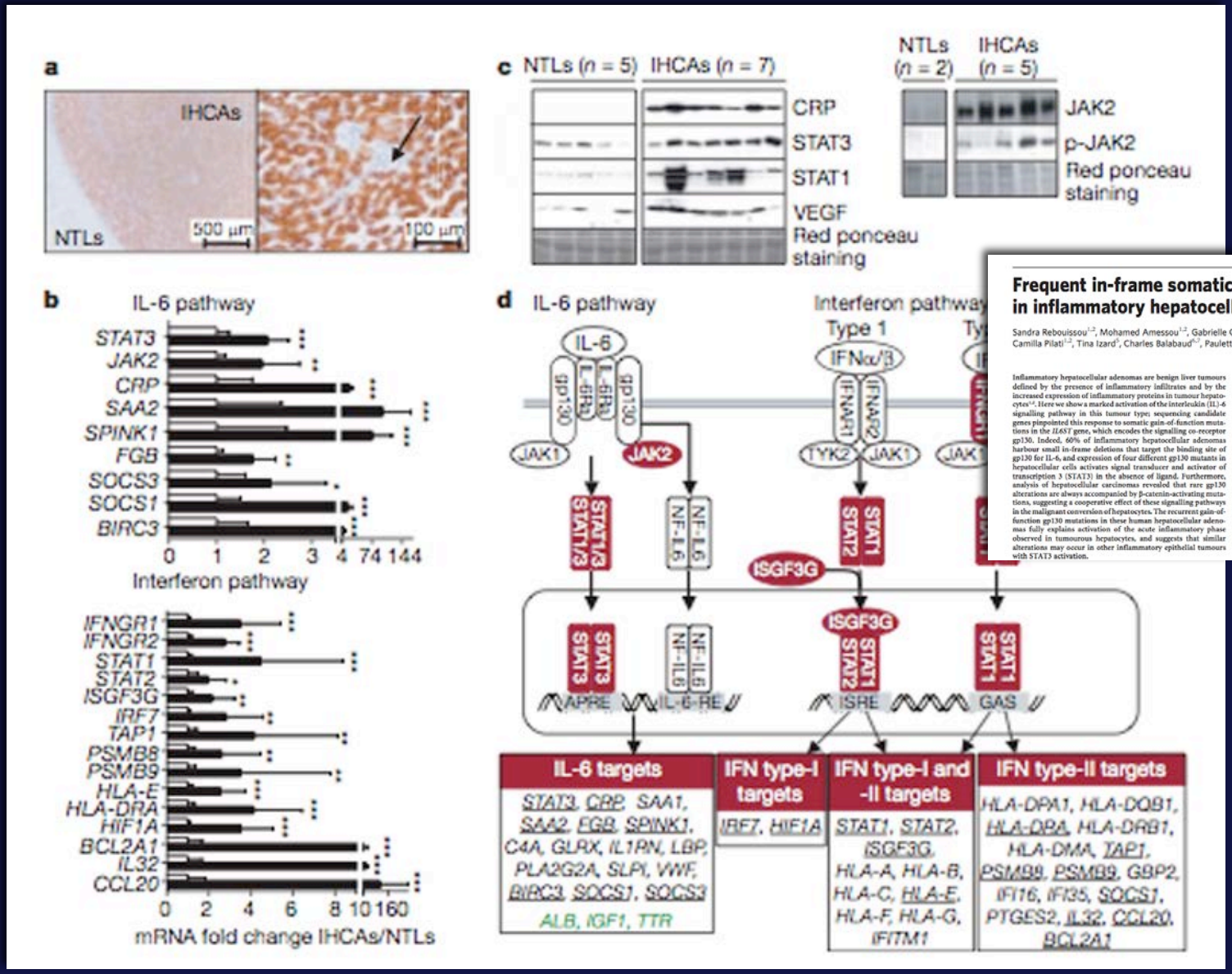
*Modified from Finegold MJ: Hepatic tumors in childhood, in Russo P, Ruchelli E, Piccoli DA (eds). *Pathology of Pediatric Gastrointestinal and Liver Disease*, New York, Springer-Verlag, 2004.

Hepatocellular carcinoma chromosomal abnormalities*

Region	*% of tumors affected*	*Abnormality*	*Method*
1p35-36	30	Loss of heterozygosity	Microsatellite markers
4q	70	9 copies	Comparative genomic hybridization
4q (12-13)	33	Loss of heterozygosity	Microsatellite polymorphism
5q (35-qter)	70	Loss of heterozygosity	Restriction fragment length polymorphism
6p	33	8 copies	Comparative genomic hybridization
	37	9 copies	Comparative genomic hybridization
8p	41	8 copies	Polymorphic markers
	64	Loss of heterozygosity	Polymorphic markers
8p 21.3-p22	45	Loss of heterozygosity	Restriction fragment length polymorphism
8q	60	8 copies	Comparative genomic hybridization
	77	Loss of heterozygosity	Polymorphic markers
11p	42	Loss of heterozygosity	Restriction fragment length polymorphism
13q	50	Loss of heterozygosity	Restriction fragment length polymorphism
	35	Loss of heterozygosity	Comparative genomic hybridization
	37	9 copies	Comparative genomic hybridization
16p	22	Loss of heterozygosity	Restriction fragment length polymorphism
16q	54	9 copies	Comparative genomic hybridization
16q 22-23	70	Loss of heterozygosity	Microsatellite polymorphism
17p	51	Decreased copies	Comparative genomic hybridization
17q	33	Increased copies	Comparative genomic hybridization
20p	37	Increased copies	Comparative genomic hybridization

*Selected examples from more than 35 documented chromosomal abnormalities

Modified from Finegold MJ: Hepatic tumors in childhood, in Russo P, Ruchelli E, Piccoli DA (eds). Pathology of Pediatric Gastrointestinal and Liver Disease, New York, Springer-Verlag, 2004.



Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours

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Inflammatory hepatocellular adenomas are benign liver tumours defined by the presence of inflammatory infiltrates and by the increased expression of inflammatory proteins in tumour hepatocytes[1,2]. Here we shows a marked activation of the interleukin (IL)-6 signalling pathway in this tumour type; sequencing candidate genes pinpointed this response to somatic gain-of-function mutations in the *IL6ST* gene, which encodes the signalling co-receptor gp130. Indeed, 60% of inflammatory hepatocellular adenomas harbour small in-frame deletions that target the binding site of gp130 for IL-6, and expression of four different gp130 mutants in hepatocellular cells activates signal transducer and activator of transcription 3 (STAT3) in the absence of ligand. Furthermore, analysis of hepatocellular carcinomas revealed that rare gp130 alterations are always accompanied by β-catenin-activating mutations, suggesting a cooperative effect of these signalling pathways in the malignant conversion of hepatocytes. The recurrent gain-of-function gp130 mutations in these human hepatocellular adenomas fully explains activation of the acute inflammatory phase observed in tumourous hepatocytes, and suggests that similar alterations may occur in other inflammatory epithelial tumours with STAT3 activation.

To resolve the underlying pathogenesis of these inflammatory lesions, a genome-wide transcriptome analysis of four IHCAs was compared to four normal liver tissue samples. Among the 285 genes significantly overexpressed in IHCAs (Supplementary Table 1), gene ontology analysis identified a strong enrichment for genes associated with inflammation and the immune response, accounting for 40% of the overall ontology terms significantly enriched (Supplementary Table 2). High levels of significance were found for genes involved in 'antigen processing and presentation of peptide antigen' ($P = 2.10^{-12}$) and 'regulation of the Janus kinase (JAK)–STAT cascade' ($P = 10^{-7}$; Supplementary Table 2). We confirmed this inflammatory signature in an additional 14 IHCAs with a clear activation of the acute-phase inflammatory response affecting both type-1 and type-2 acute-phase genes (Fig. 1b, c and Supplementary Table 3). Consistent with the known roles of IL-6 and JAK–STAT signalling in the acute-phase response[1,2], STAT3 messenger RNA and protein were significantly increased in IHCAs (Fig. 1b, c). IHCAs also overexpressed several effectors of type-1 and type-2 interferon signalling pathways (for example JAK2, STAT1 and STAT2) and their downstream targets (Fig. 1b, c). Collectively, these data suggest that IL-6 and interferon signalling are the main inflammatory pathways acti-

Rebouissou S et al. Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumors. e-pub, Nature. November 2008, 1-6

Diseases and Environment: Liver; some future directions

James Watson
Francis Crick

- **Continuing identification of molecular and immunohistochemical biomarkers**
  - **predict response to chemotherapeutic agents**
  - **identify targets, including metabolites, for new *in vivo* therapies, including preventatives**
- **Increasing use of genetic studies for diagnosis and prognosis**
- **Increasing biomarker specificity (serum, urine, other)**
- **New forms of non-invasive evaluation (e.g. imaging, spectral and other assays)**

Thank you for your attention