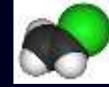
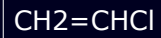


# Vinyl chloride-induced liver neoplasms

vinyl chloride monomer



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## History of vinyl chloride monomer (VCM) toxicity

1930's – 1940's: Acute effects on man

Narcotic effects (anesthesia)

Central nervous system (euphoria, dizziness, headaches, narcosis)

1950's – 1960's: **Acroosteolysis** (fingers)

Raynaud-like sd, scleroderma-like skin changes, osteolytic bands of distal phalanges

1970's: Carcinogenicity – liver disease

Experimental carcinogenesis<sup>1,3</sup>

In exposed workers

**Angiosarcoma of the liver (ASL)<sup>2</sup>**

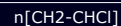
**Non-cirrhotic portal hypertension<sup>2</sup>**

Hepatocellular carcinoma (HCC) rare cases

1987 human carcinogen (group 1) linked to ASL<sup>4</sup>

2007 A causal relationship between VCM and HCC<sup>5,6</sup>

vinyl chloride monomer



vinyl chloride polymer



1. Viola P L et al. *Cancer Res* 31:316-522, 1971
2. Grech J L Jr, Johnson MN. *J Occup Med* 16:150-151, 1974
3. Maltoni C, Lefemine. *Environ Res* 7:387-405, 1974
4. IARC Monographs, Suppl. 6, 566-569, 1987
5. Grosse Y et al. *Lancet Oncol* 2007;8:679-80.
6. IARC Monographs. IARC 97, 112-422. 2008.

## History of vinyl chloride monomer (VCM) toxicity

Concentrations of VCM measured in manufacturing workshops<sup>1</sup>

Workers exposed to VCM vapours during autoclave cleaning (tank cleaners)

Year(s)	Concentration of VCM in air (ppm)
1945-1955	1,000
1955-1960	400-500
1960-1970	300-400
mi-1973	150
mi-1974	50
1980	5
1985	<1

(1 ppm = 2.59 mg/m<sup>3</sup>)

Contassot JC. EMC 16541 A<sup>20</sup>, 9-1990

### **1. VCM-induced angiosarcoma of the liver (ASL)**

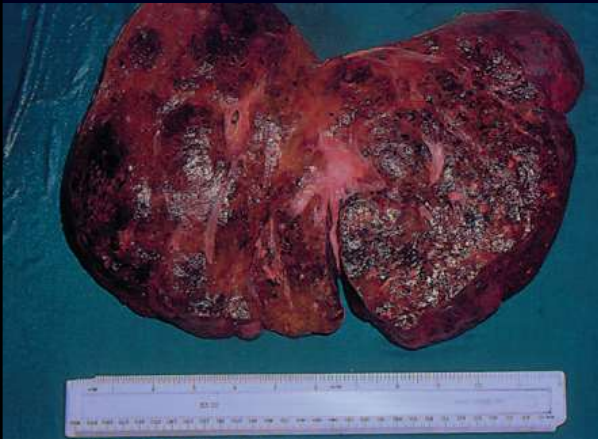
2. VCM-induced HCC\*

3. VCM-induced liver disease

HCC: hepatocellular carcinoma

**VCM-induced angiosarcoma of the liver**

**Morphology**

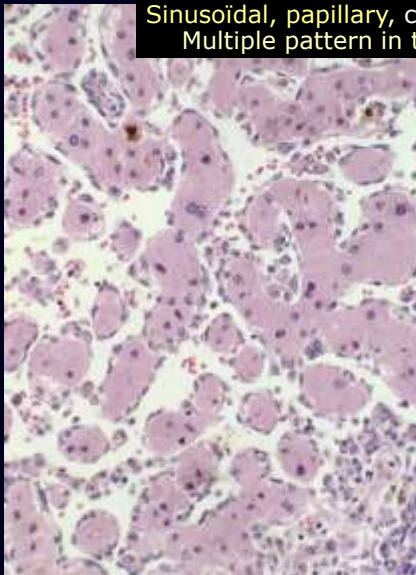


Multicentric tumor

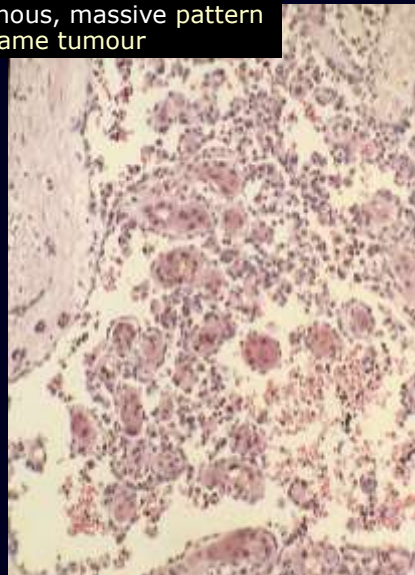
**VCM-induced ASL**

**Morphology**

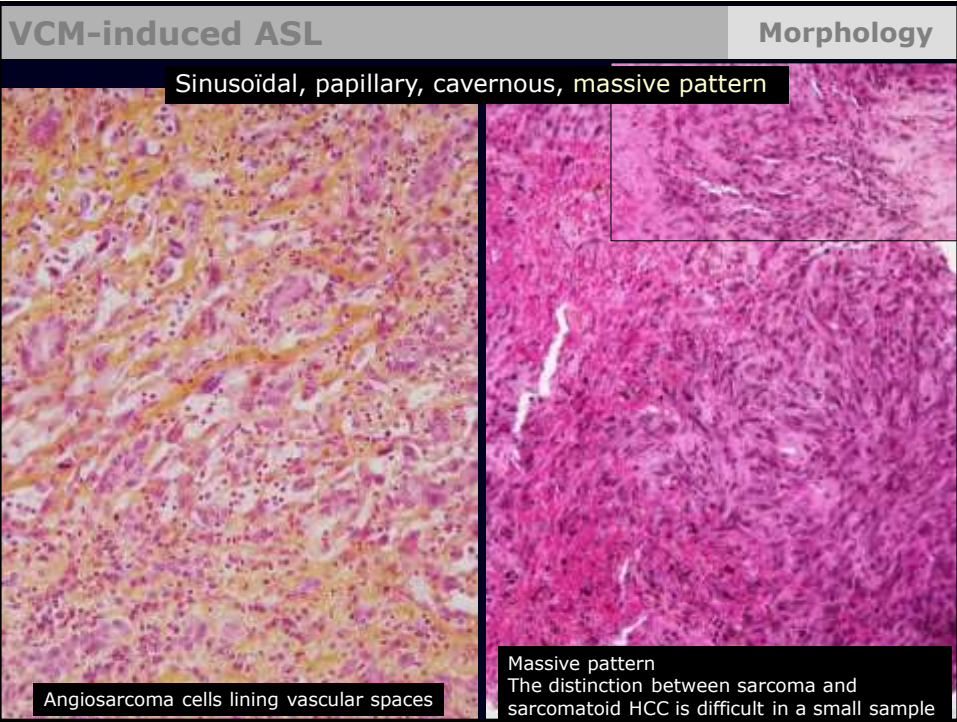
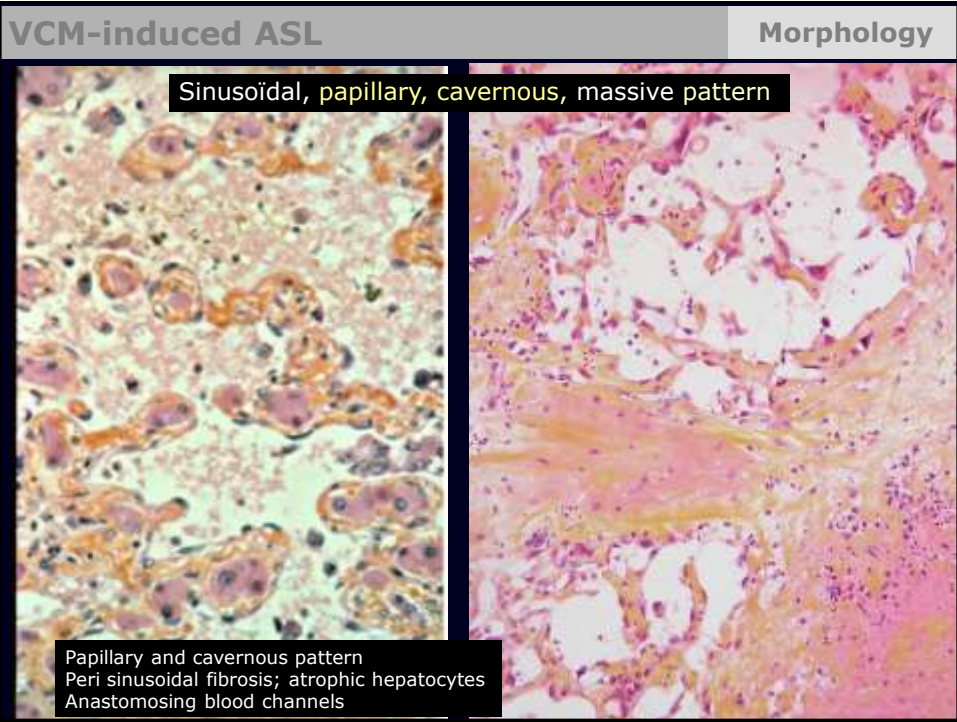
Sinusoidal, papillary, cavernous, massive pattern  
Multiple pattern in the same tumour



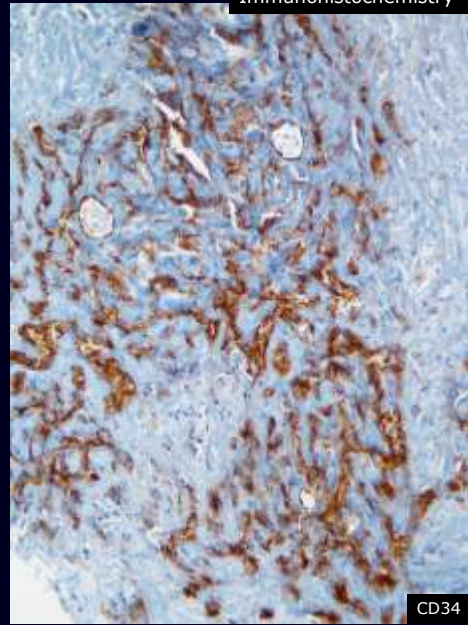
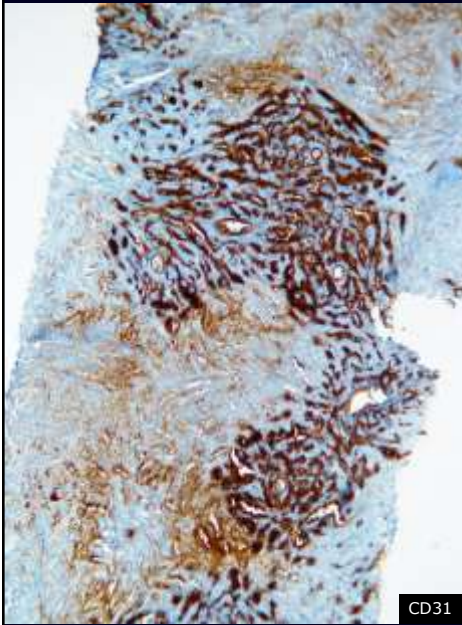
Scaffolding growth pattern along sinusoids surrounds hyperplastic hepatocytes  
Dilated sinusoids



Sinusoidal growth, with trabecular disarray (papillary pattern); Hyperplastic hepatocytes  
Anatomosing blood filled spaces







1. VCM-induced angiosarcoma of the liver (ASL)
- 2. VCM-induced HCC\***
3. VCM-induced liver disease: precursor lesions

HCC: hepatocellular carcinoma

## VCM-related HCC

## Introduction

2007, VCM a human carcinogen causally linked to HCC

Increased risk for HCC is not as great as the risk for ASL

Causal relationship difficult to tease out because of

The high incidence of HCC in non-exposed patients

Some cases were diagnosed as « liver cancer », without histology

Changes in non-neoplastic liver not available in most reported data



1. Grosse Y, et al. Lancet Oncol 2007;8:679-80.

2. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2008, 97:112-422.

## VCM-related HCC

## Documented reports of HCC combined HCC ASL

	HCC number	Fibrosis	"VCM-hepatopathy"
Fox 1977	2 <sup>a</sup>	/	/
Pialat 1980	1	/	/
Evans 1983	1 <sup>b</sup>	Noncirrh	Portal fibr; <i>Hyperplastic hepatocell nodules, 'in some instances, showing malignant transformation</i>
Langbein 1983	1	Noncirrh	Sinusoidal fibrosis, dilatation
Dietz 1985	2 <sup>c</sup>	Noncirrh	Sinusoidal fibrosis (n=1)/ fibrosis NOS
Leibach 1996	1	Noncirrh	Slight septal and portal fibr
Saurin 1997	2	Noncirrh	Case 1: Mild lobular and portal fibr; sinusoidal dilatation; diffuse steatosis Case 2: Bridging & portal fibr; sinusoidal dilatation; variable steatosis; <i>NHH, hyperpl endoth cells &amp; hepatocytes; Small-cell dysplasia,</i>
Du and Wang 1998	4	Noncirrh (2 out of 4)	/
Weihrauch 2000	18 <sup>d</sup>	Noncirrh 83%	interstitial and perivenular fibrosis; sinusoidal dilatation peliosis; moderate $\mu$ vesicular steatosis

NHH, nodular hepatocytic hyperplasia.  
EH, endothelial hyperplasia

a). one undifferentiated carcinoma, NOS. b) another case combined HCC ASL. c) previously published by Langbein d). Between 1981-1997

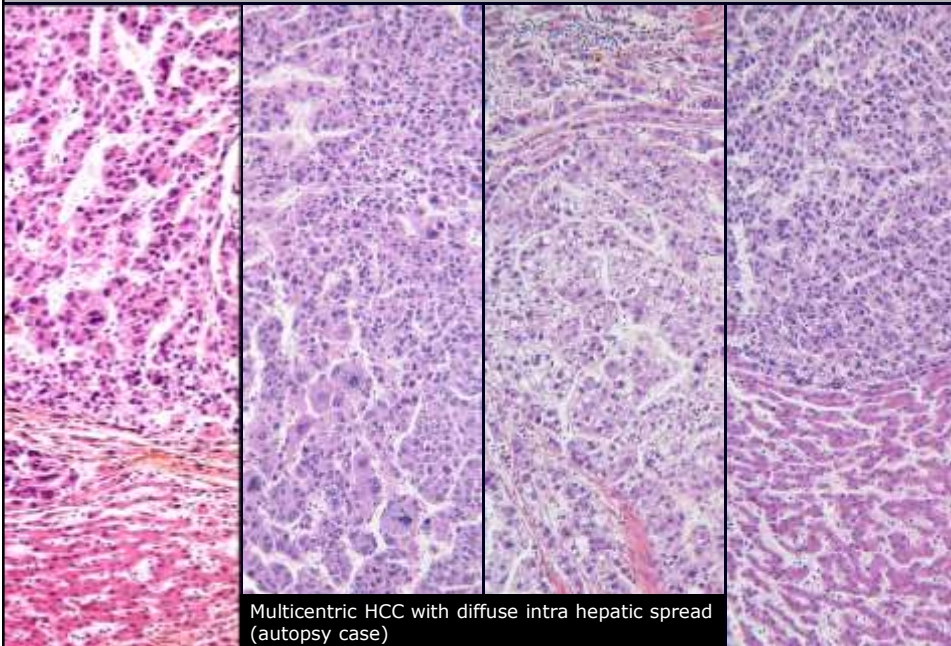
## VCM-related HCC

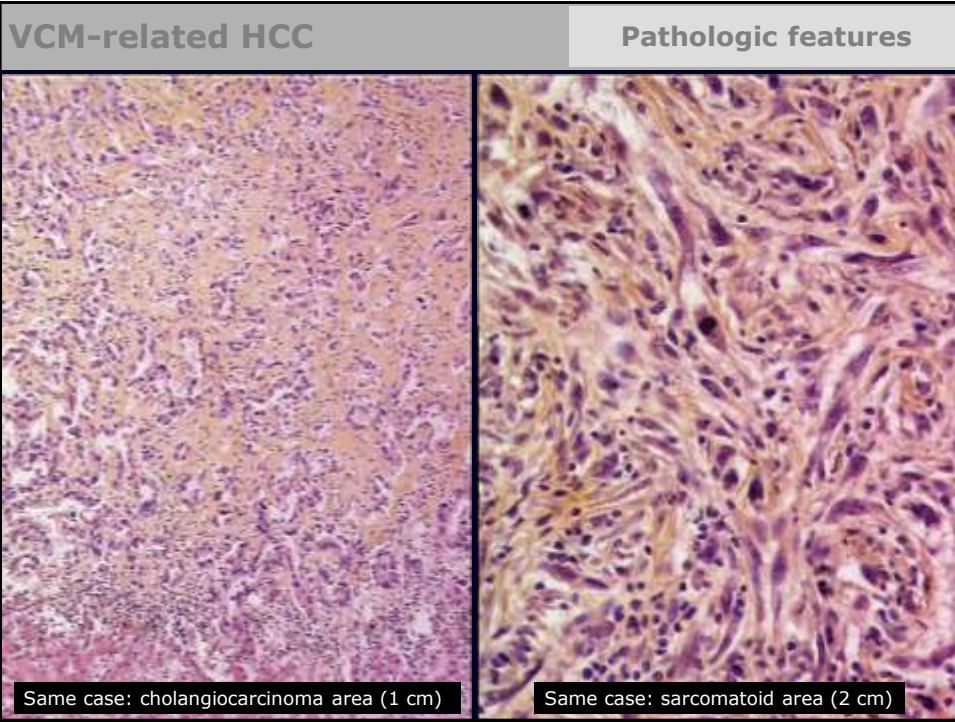
## Documented reports of HCC combined HCC ASL

	HCC-ASL number	Fibrosis	VCM-disease
Byren et Holmberg 1975	1	/	/
Gokel 1976	1	Noncirrh	Portal & septal fibr; capsular fibr
Evans 1983	1	Noncirrh	Portal fibr; <i>Hyperplastic hepatocell nodules</i>
Delorme 1978	1	Noncirrh	Portal, septal & sinusoidal fibr; sinusoidal dilatation; <i>reticulo-endoth cell dysplasia</i> ,
Tamburro 1978	1		
Koischwitz 1981	1	Cirrh	Portal & capsular fibrosis, no sinusoidal dilatation; imp siderosis; focal steatosis
Lelbach 1996	1	Noncirrh	Slight septal and portal fibr

## VCM-related HCC

## Pathologic features





1. VCM-induced angiosarcoma of the liver (ASL)

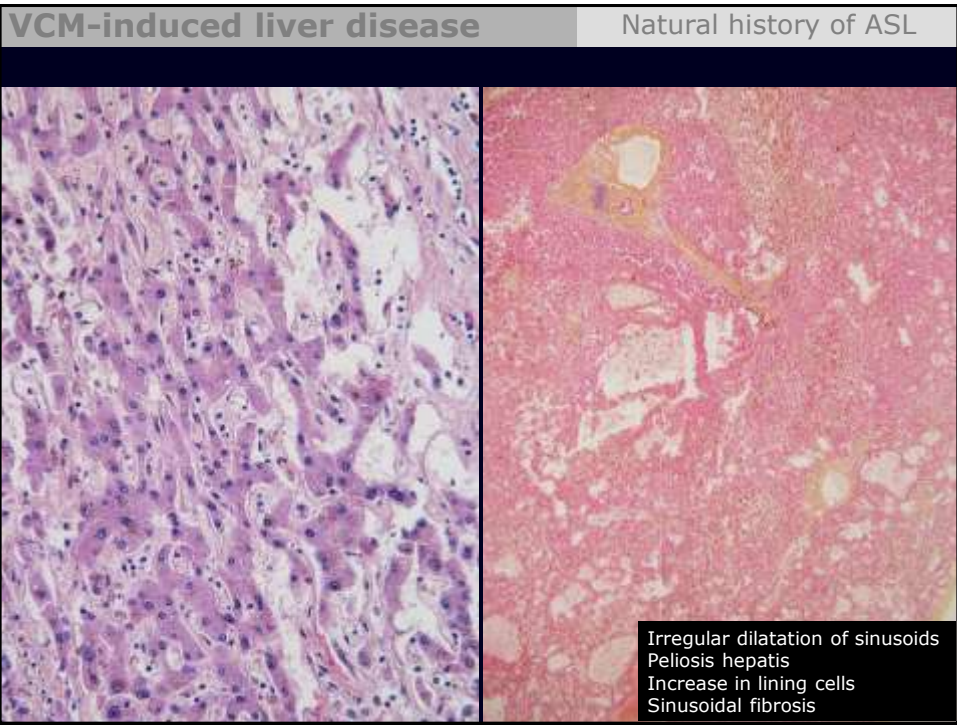
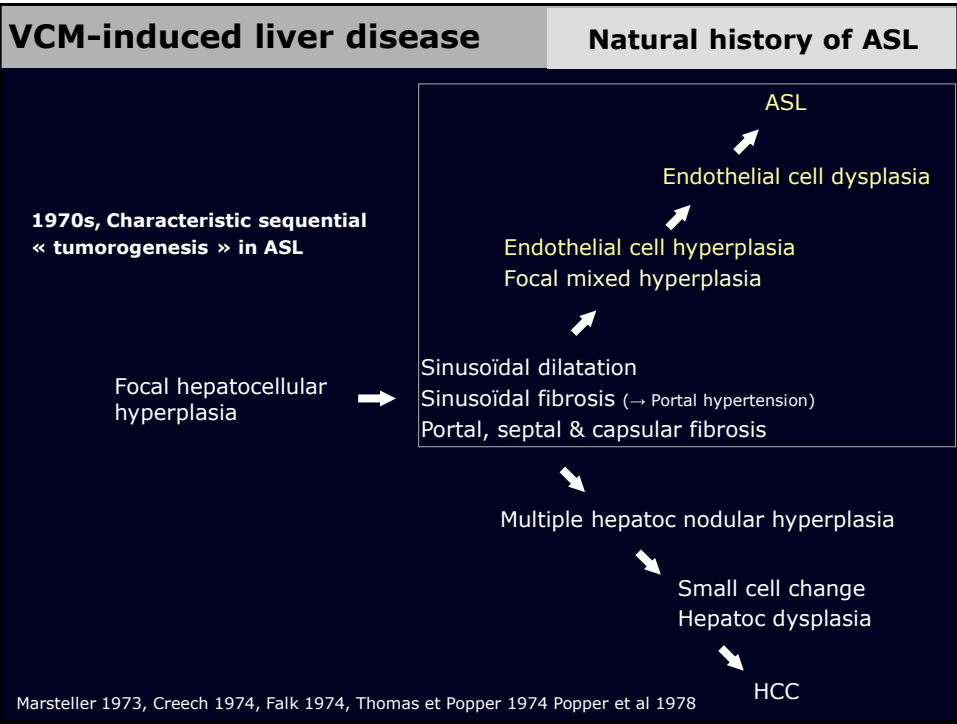
2. VCM-induced HCC

**3. VCM-induced liver disease**

Criteria for attributing both cancers to VCM exposure



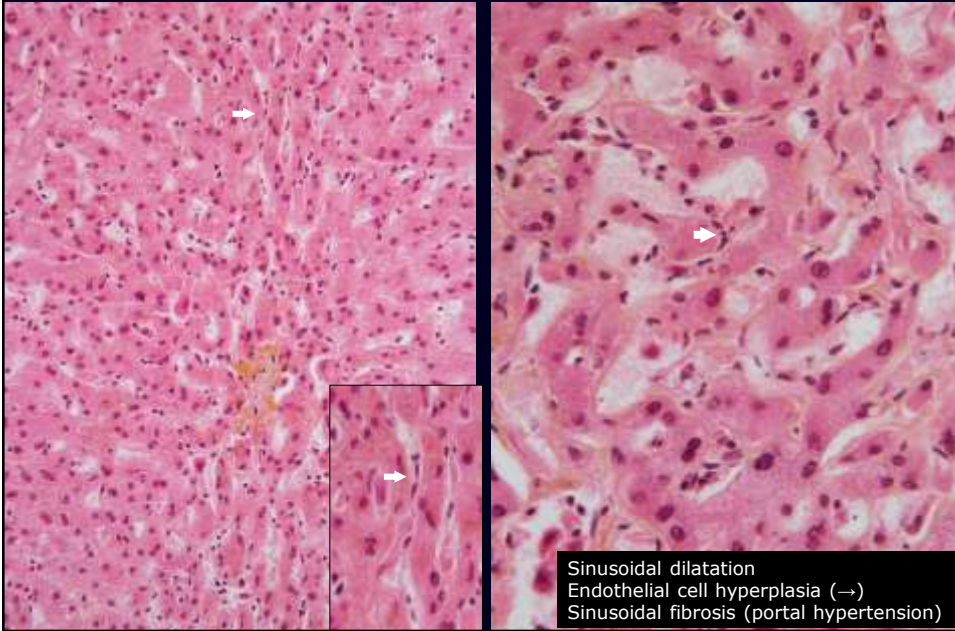




**VCM-induced liver disease**

Natural history of ASL

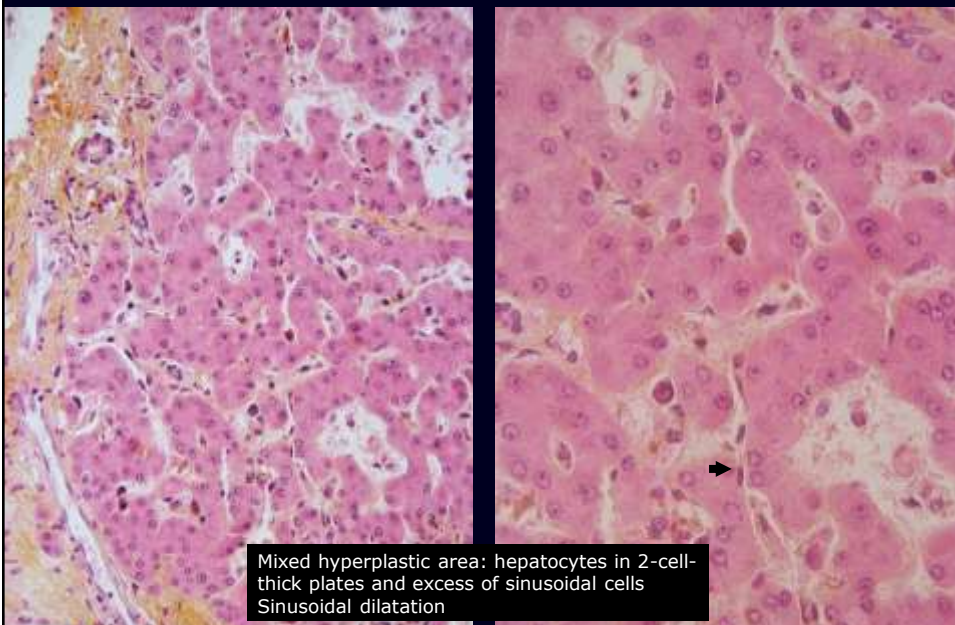
Endothelial cell hyperplasia – dysplasia - angiosarcoma



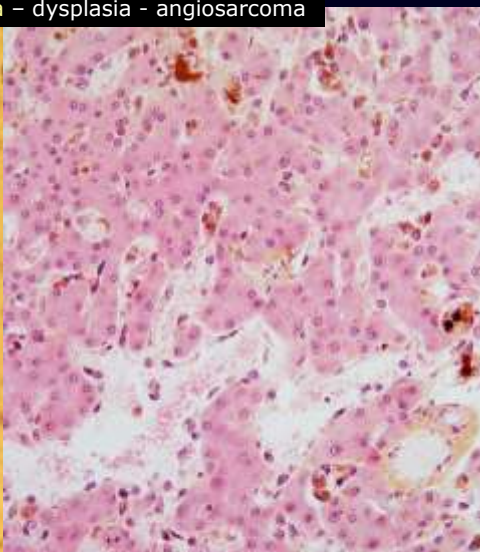
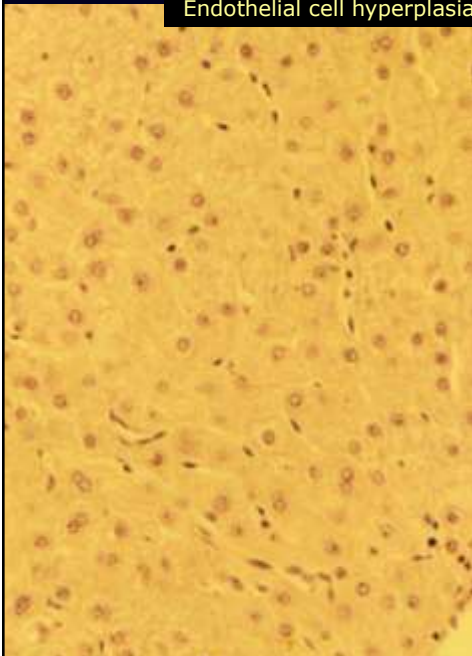
**VCM-induced ASL**

Natural history of ASL

Endothelial cell hyperplasia – dysplasia - angiosarcoma

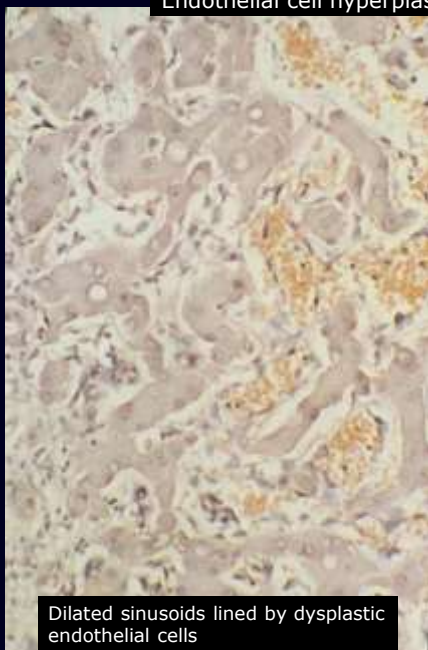


Endothelial cell hyperplasia – dysplasia - angiosarcoma

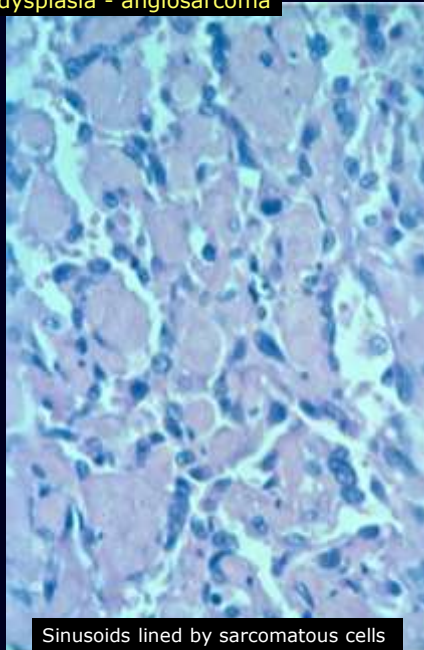


Irregular dilatation of sinusoids  
Mixed hyperplasia of hepatocytes (in 2-cell-thick plates) and endothelial cells  
Bile plugs in dilated bile canaliculi & Kupffer cells

Endothelial cell hyperplasia – dysplasia - angiosarcoma

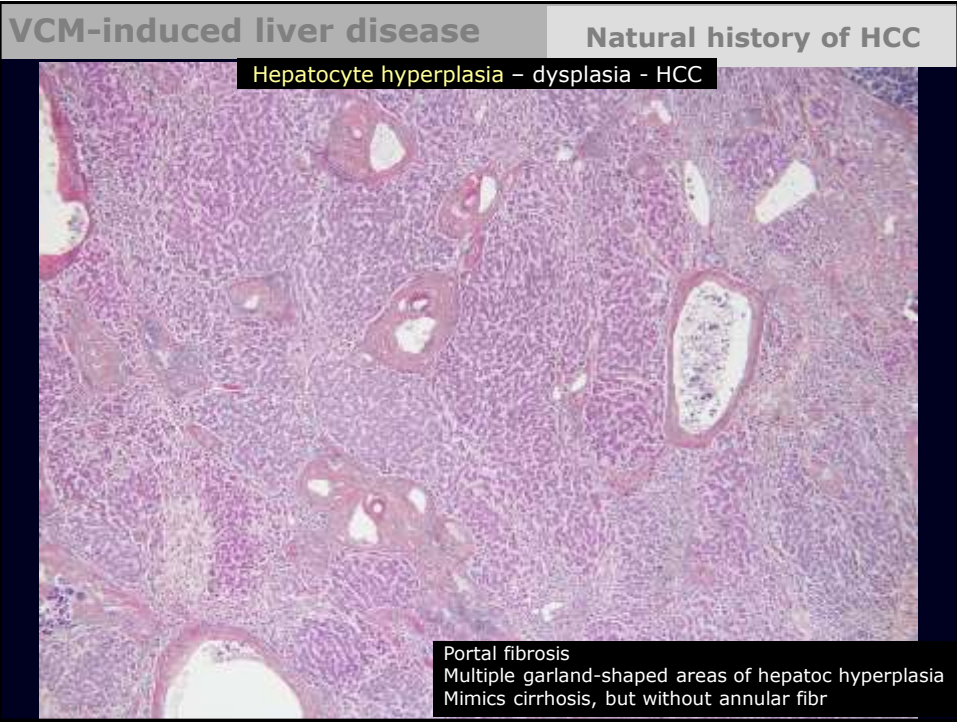
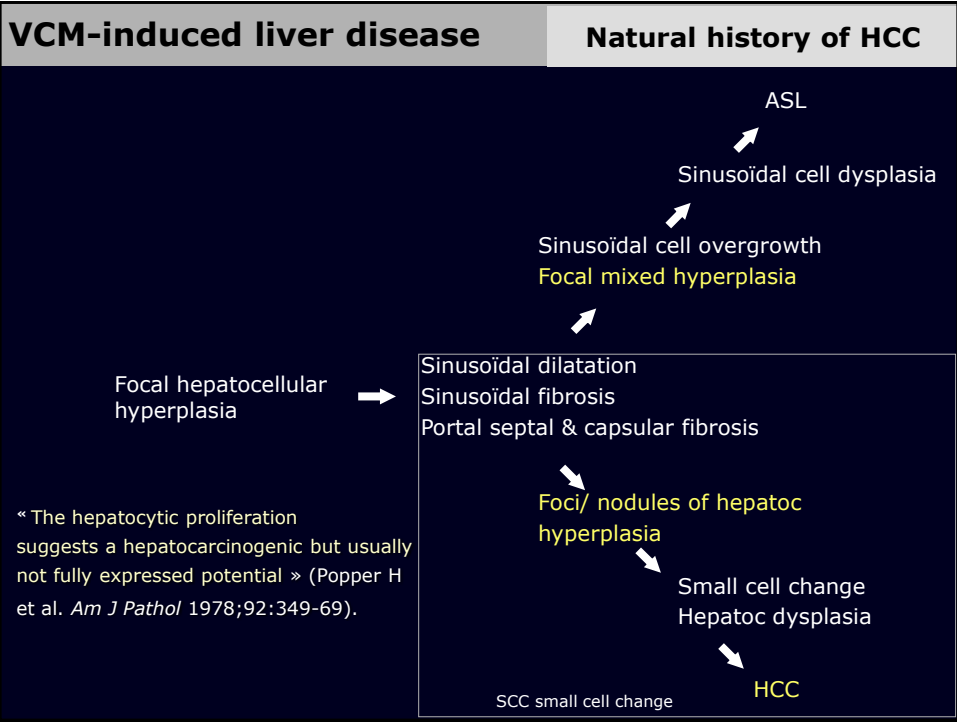


Dilated sinusoids lined by dysplastic endothelial cells



Sinusoids lined by sarcomatous cells







VCM-induced liver disease

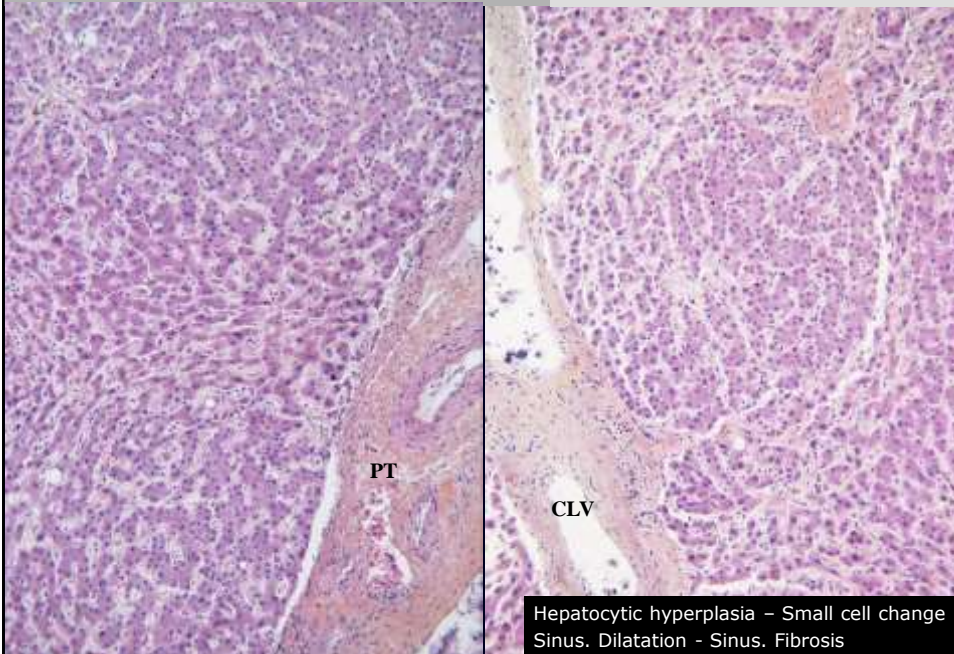
Natural history of HCC



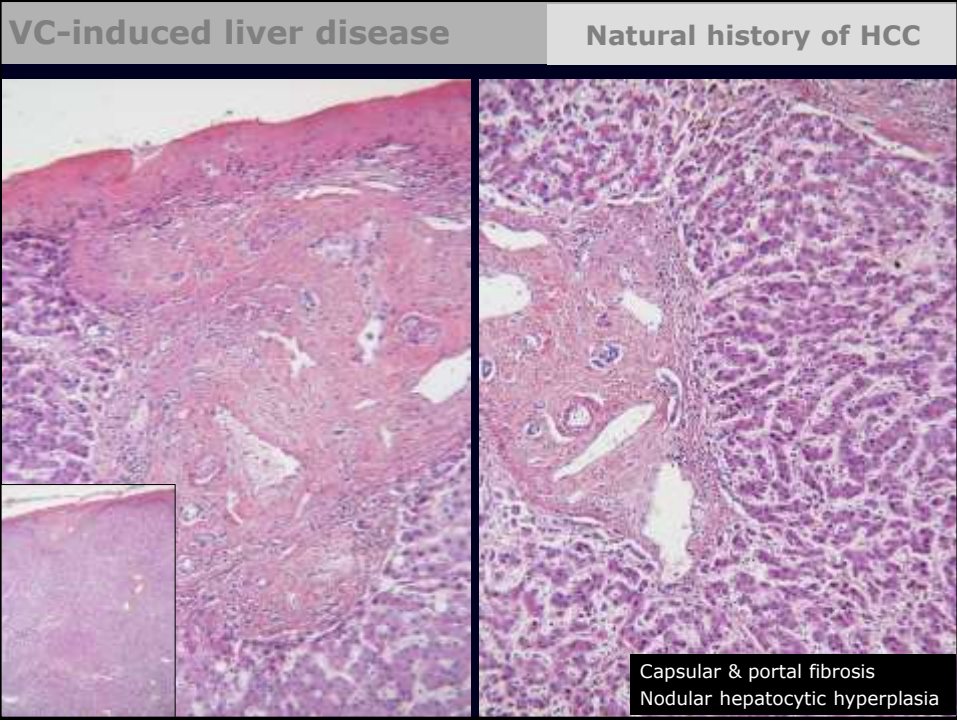
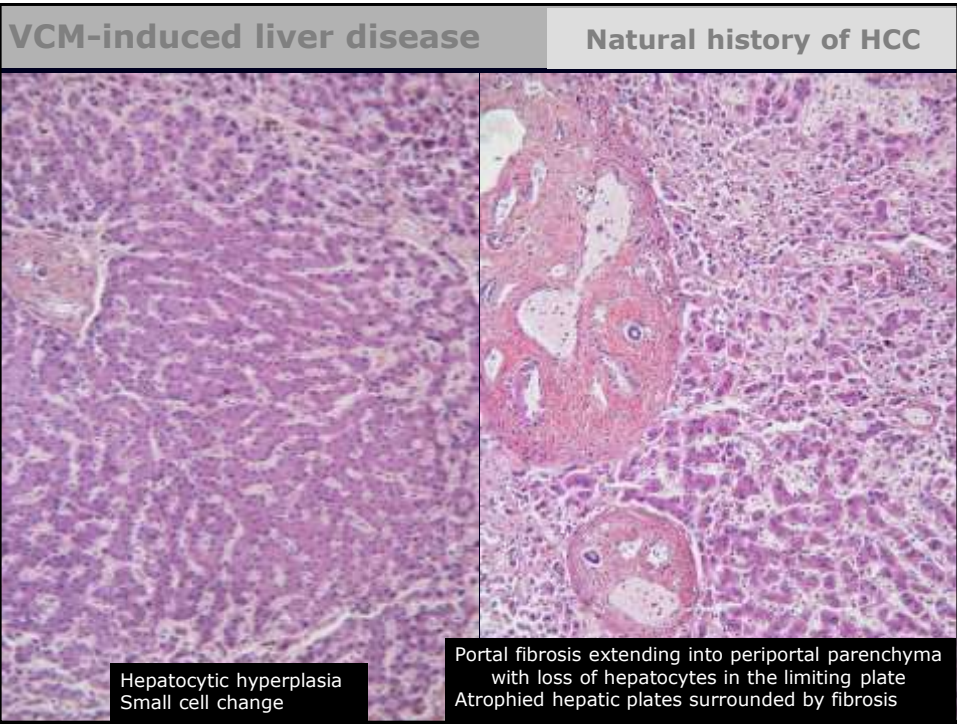
Areas of hepatoc hyperplasia

VCM-induced liver disease

Natural history of HCC



Hepatocytic hyperplasia - Small cell change  
Sinus. Dilatation - Sinus. Fibrosis

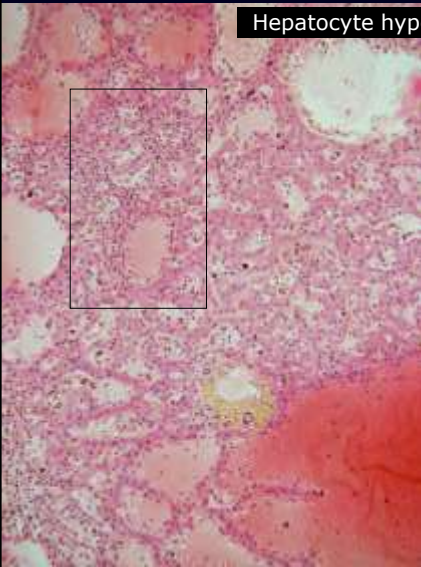




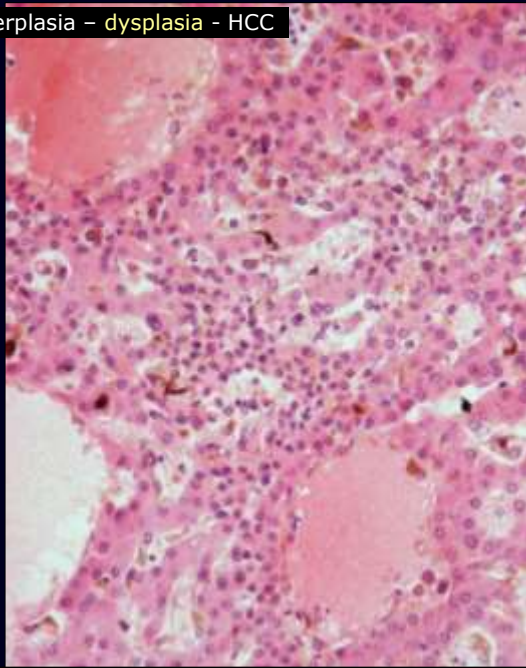
**VC-induced liver disease**

**Natural history of HCC**

Hepatocyte hyperplasia – dysplasia - HCC



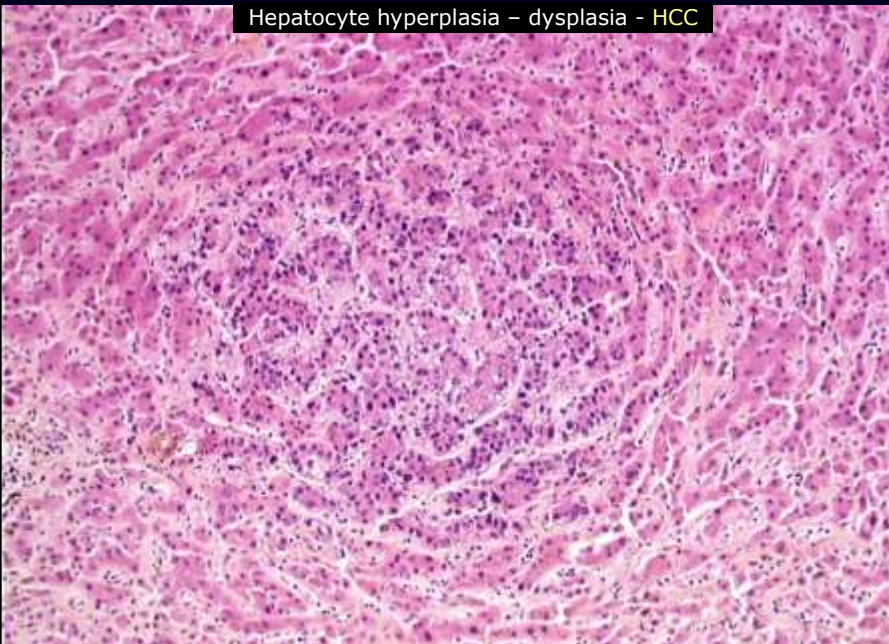
Small-cell change foci (noncirrhotic liver)  
Sinusoidal dilatation – Peliosis hepatis



**VCM-induced liver disease**

**Natural history of HCC**

Hepatocyte hyperplasia – dysplasia - HCC



## Conclusion

VC-induced liver cancers and disease: an exceptional human model of sequential chemical carcinogenesis

They occur in a fibrotic non-cirrhotic liver

3 hepatic target cells

Peri sinusoidal cells → sinusoidal fibrosis

Endothelial cells → angiosarcoma

Hepatocytes → HCC

K-ras codon 13 mutations<sup>1,2</sup>

in VC-induced ASL (53%) and nontumorous liver (13%)

In VC-induced HCC (33%) and nontumorous liver (17%)

Workers compensation

1. Weihrauch M et al. *Br J Cancer* 2001;84:982-9.

2. Weihrauch M et al. *Environ Mol Mutagen* 2002;40:36-40.