MEDICAL-GRAND-ROUNDS

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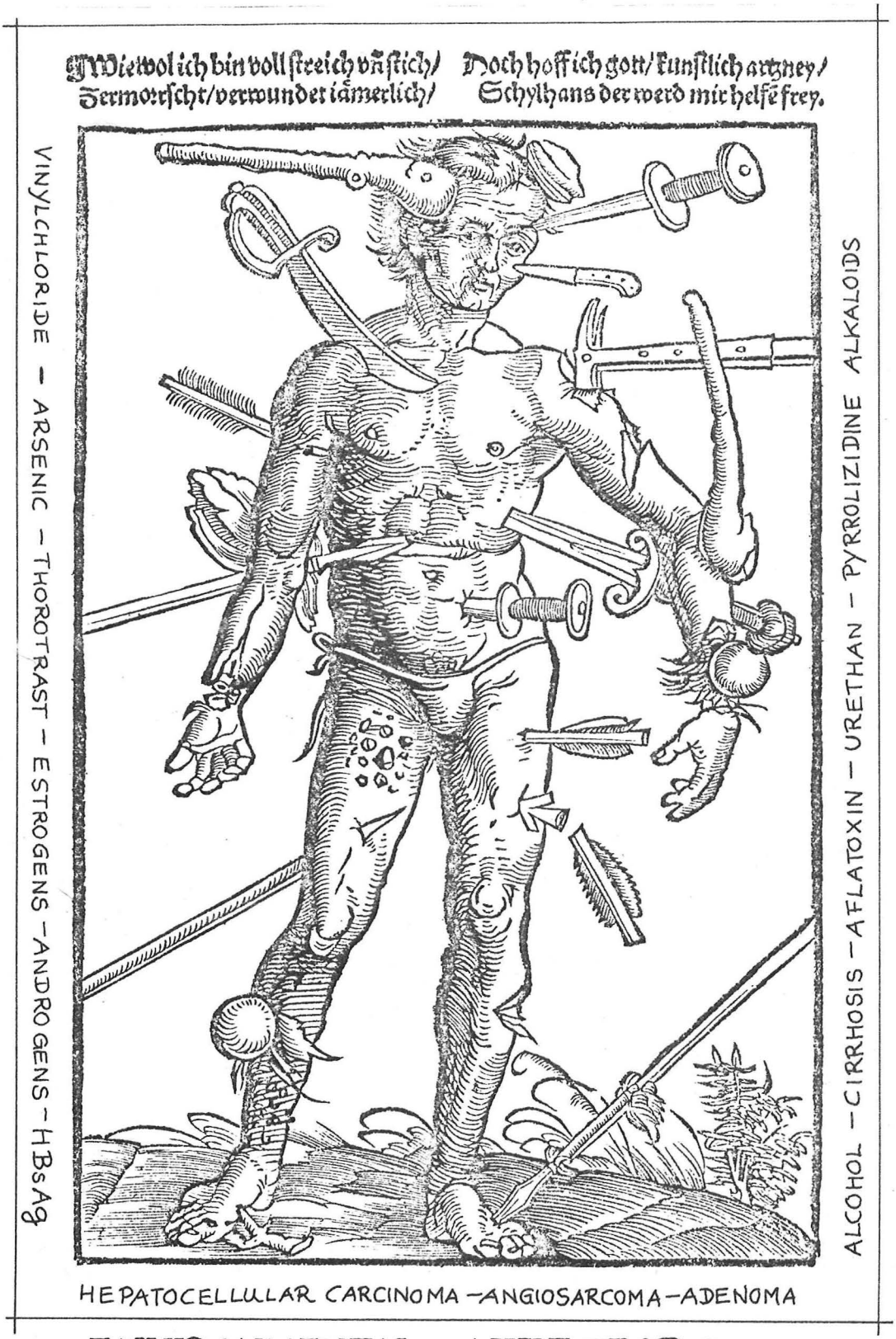


ENVIRONMENTAL AFFECTORS AND PRIMARY HEPATIC NEOPLASMS

WOODCUT FROM:

"Feldbuch Der Wundarznei"

by Hans Von Gersdorf (1517)

Strassburg

(Hans Von Gersdorf was a citizen of Strassburg, a physician and practicing surgeon for over 40 years.)

INTRODUCTION

Various health disasters of the recent past have increased awareness and anxiety about the possible future dangers and consequences brought upon by environmental chemicals, toxins and drugs for health in general and development of cancer in particular. A few examples will elucidate the scope of possible hazards which the environment has introduced in the recent past.

In 1957, the seed grain fungicide hexachlorobenzene induced more than 3000 cases of porphyria cutanea tarda in Turkey with a mortality rate of 10% (1). An outbreak of methylmercury poisoning in 1971/1972 in Iraq led to the hospitalization of 6530 patients with 459 dying as a consequence of eating homemade bread produced from wheat which was treated with this fungicide (2). Clustering of occupational cancers was observed in asbestos insulation manufacturing plants with high occurrence of lung cancer and mesotheliomas (3). An increased incidence of lung cancers in uranium miners with 62 deaths in 3414 white miners (4) and of bladder cancer in the electric cable industry were reported (5). 147 respiratory cancer deaths occurred among 8047 white male smelter workers exposed to arsenic fumes (6) and an increased formation of nasal cancer in woodworkers has been described (7).

The effect of the chemical industry on the environment is of great current interest. Approximately 500,000 to 600,000 different chemicals are produced and utilized in the U.S. alone with an increase of 500 new chemicals annually. For instance, from 1950-1970 an excess of 1.2 billion kilogram of DDT was produced in the U.S. while its "domestic disappearance" was about 50%. During 1950-1972 the production of aldrine-toxaphene pesticides reached a total of 865.6 million kg with a "domestic disappearance" of 706.6 million kg (8). The annual production of vinyl chloride monomer amounts to currently 2.3 billion kg (9) of which by EPA estimates 90 million kg are discharged into the atmosphere annually (10). One could proceed almost indefinitely with a presentation of such staggering figures which final impact on health and disease in the future can only barely be foreseen. Of course, the immediate and therefore limited group of humans generally exposed to environmental chemicals directly and to the highest possible degree include mostly industrial workers. Exposure occurs in the majority of the cases by skin contact, inhalation or orally. The skin, lung and liver are the major anatomic regions confronted by various "environmental affectors".

Today I should like to discuss the role of "environmental affectors" as etiologic agents for primary hepatic neoplasms. I will apply the phrase "environmental affectors" as a broad term to embrace all exogenously applied or attracted agents, either accidentally or by therapeutic intent, which are suspected to induce disease. The ones we will discuss today are summarized in Table I.

TABLE I

ENVIRONMENTAL AFFECTORS

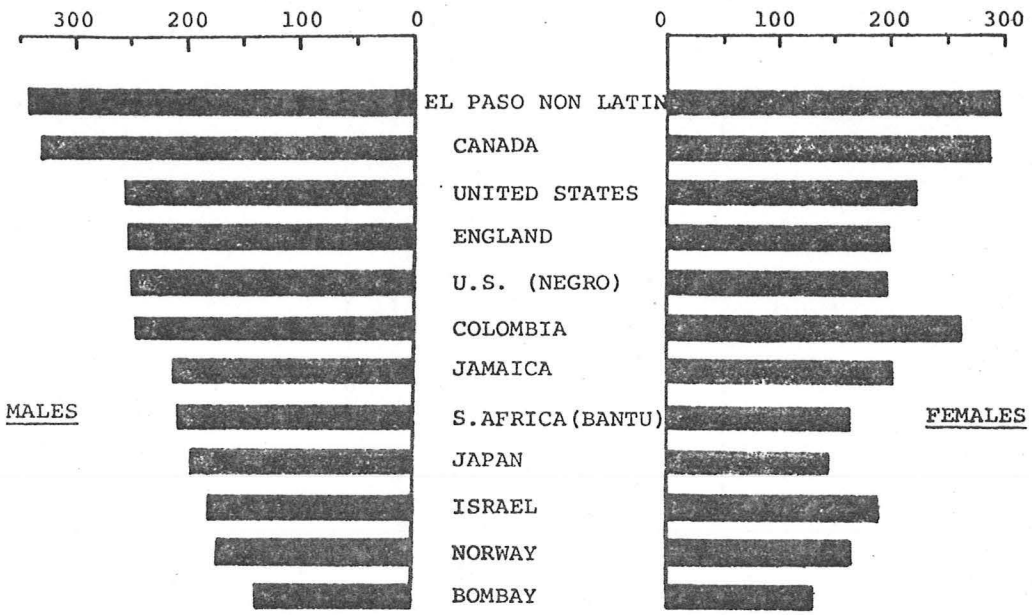
1. Mycotoxins (aflatoxin)
2. Viruses (HB-virus)
3. Pleasure inducers (alcohol)
4. Therapeutic chemicals (androgens, estrogens)
5. Diagnostic chemicals (thorotrast)
6. Industrial chemicals (vinyl chloride monomer, arsenic)

First, we will briefly review cancer epidemiology which has led to the worldwide discovery of striking differences in (a) the incidence of hepatocellular carcinoma (HCC), (b) the incidence in liver cirrhosis, and (c) the frequency of hepatitis B virus (HB-V) infection in humans of various geographic areas. Higginson has estimated that as much as 80% of occurring tumors may be conditioned by our present environment and thus are preventable (11). Ingelfinger (12), in an editorial in the New England Journal of Medicine, has warned that "cancerophobia has expanded into a demonism in which the evil spirit is ever present, but furtively viewed and spoken of obliquely." Thus, the intent of this grand rounds is not to increase cancerophobia but to rationalize the available data related to primary liver neoplasms and their etiology.

TUMOR EPIDEMIOLOGY

The drawback of any epidemiological consideration is that the epidemiologist has to measure the results and then determine what the experimental (or environmental) condition had been. The incidence of tumors reported on the basis of an actual clinical diagnosis or autopsy as well as the rate of death calculated from death certificates have significant inbuilt errors as a result of individual bias of the reporting physician. But the majority of data available come from this type of statistical reporting.

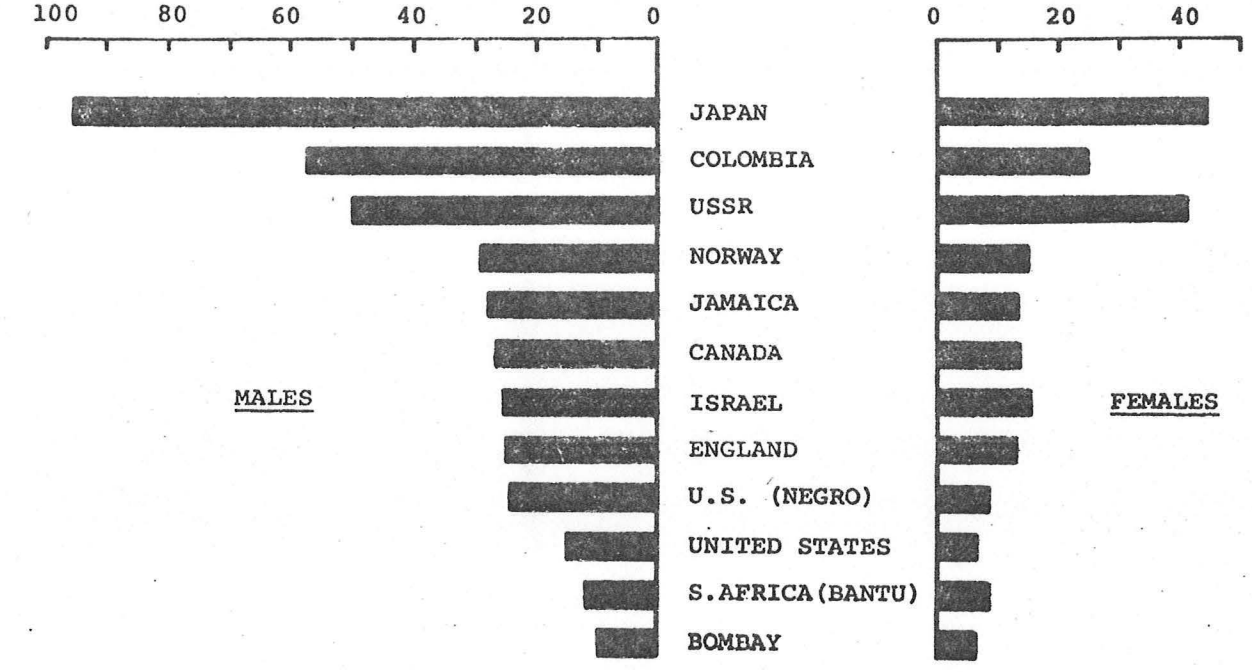
The worldwide incidence for cancer of all sites is shown in Figure 1 (13).



Histogram showing geographic variations in incidence for cancer of all sites (ICD 140-205). (All incidence data in this and subsequent figures are expressed in rates/100,000 per annum. Before using, consult text, pp. 242-251.)

Figure 1 (Ref. 13)

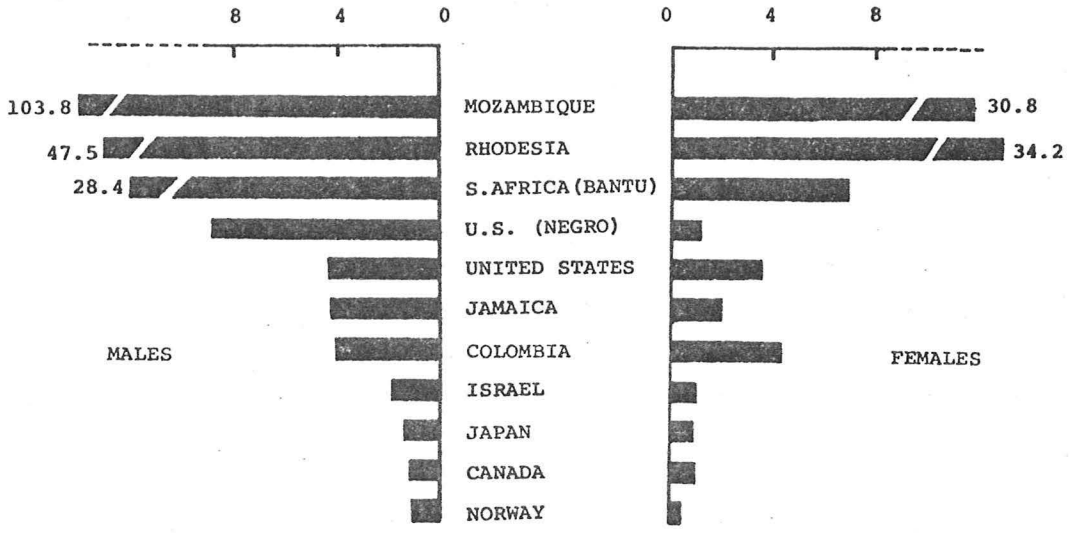
Remarkable is the high incidence for El Paso (Texas) which is significantly higher than the average value for the U.S. This is mostly due to the higher incidence of skin cancer. In comparison, the geographic variation of incidence for cancer of the stomach (Figure 2) is strongly in favor of Japan and much more predominant in males (13).



Histogram showing geographic variations in incidence for cancer of the stomach (ICD 151).

Figure 2 (Ref. 13)

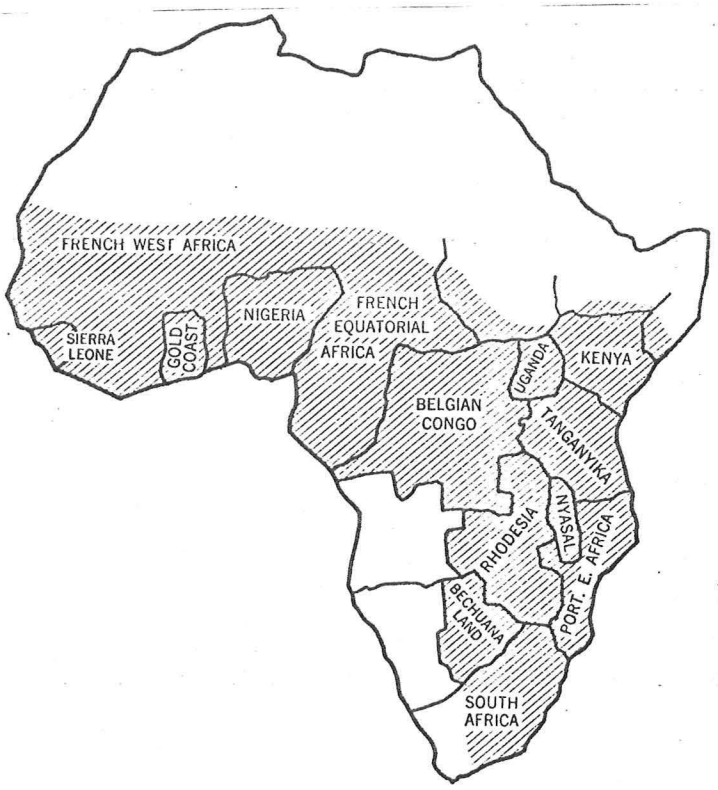
The incidence of primary liver cancer on a worldwide basis is shown in Figure 3 (13) which shows a frightening level in Mozambique (Africa) where liver cancer is more frequent than cancers of all other sites together.



Histogram showing geographic variations in incidence for cancer of the liver (ICD 155.0).

Figure 3 (Ref 13)

But even in Africa there is a distinct geographic variation of liver cancer incidence afflicting mostly sub-Saharan areas as shown in Figure 4.



Reported areas of high primary liver cancer frequency in Africa (after Berman, 1957).

Figure 4 (Ref. 14)

Among these geographic variations of the liver cancer incidence the U.S., with 4/100,000 population, lies rather on the lower end of the scale (Table II; 13).

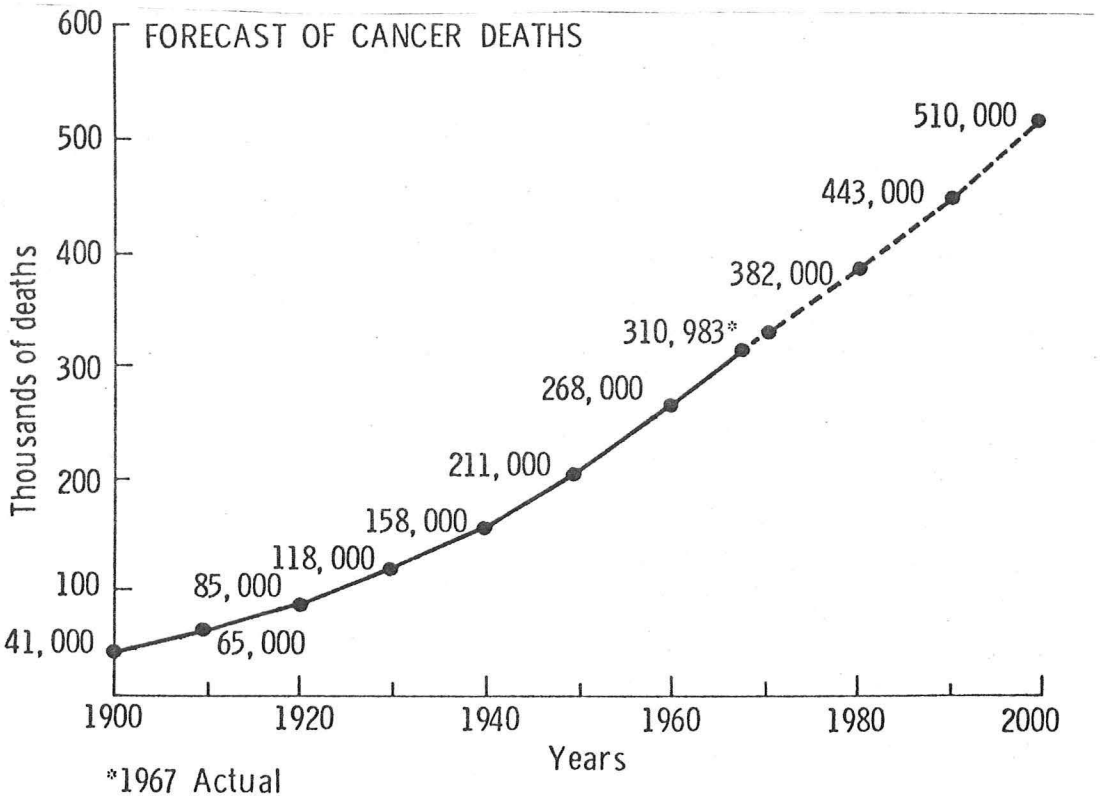
TABLE II

HIGHEST AND LOWEST CANCER MORBIDITY RATES FOR PRIMARY LIVER CANCER (AGE-ADJUSTED; NO./100,000/YEAR)

Male		Female	
Highest	Lowest	Highest	Lowest
103.8	0.3	34.2	0.1
(MOZAMBIQUE)	(JAPAN)	(RHODESIA)	(NEWFOUNDLAND)

To obtain a realistic impression of what cancer incidence rates mean when compared to the total number of people affected, the overall cancer occurrence of all sites and expected number of deaths will be compared with primary liver cancer.

The forecast of cancer deaths of all sites (Figure 5) in the U.S. predicts a steady increase. (15)



Forecast of cancer deaths, if present trends continue. Taken from the American Cancer Society, Inc., Epidemiology and Statistics Department.

Figure 5 (Ref. 15)

The estimate for cancer incidence and expected deaths for 1974 (expressed as percentage of all sites) is shown for the digestive system in both sexes in Figures 6 and 7. (16)

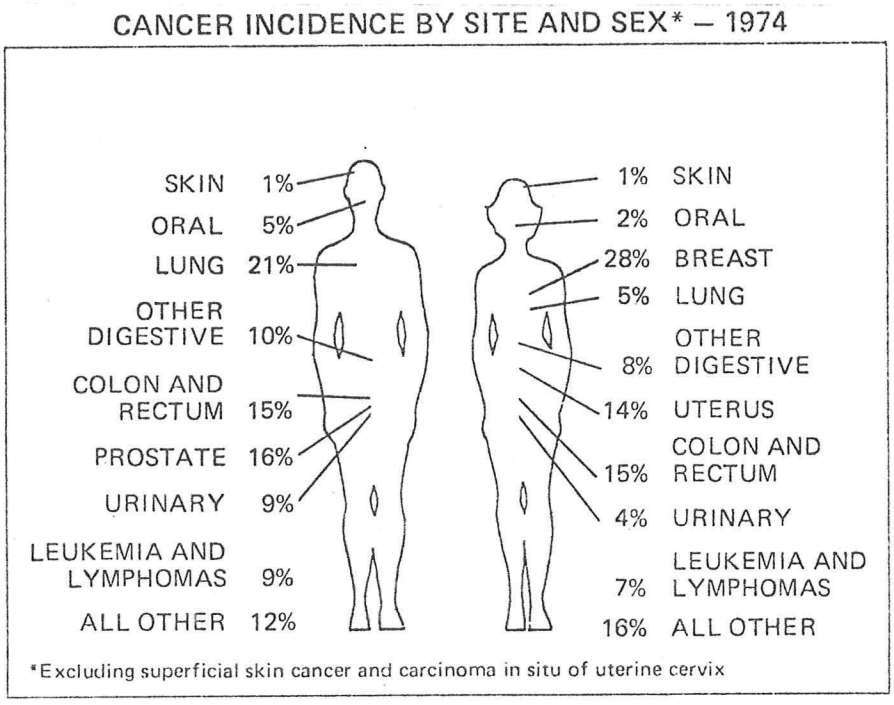


Figure 6 (Ref. 16)

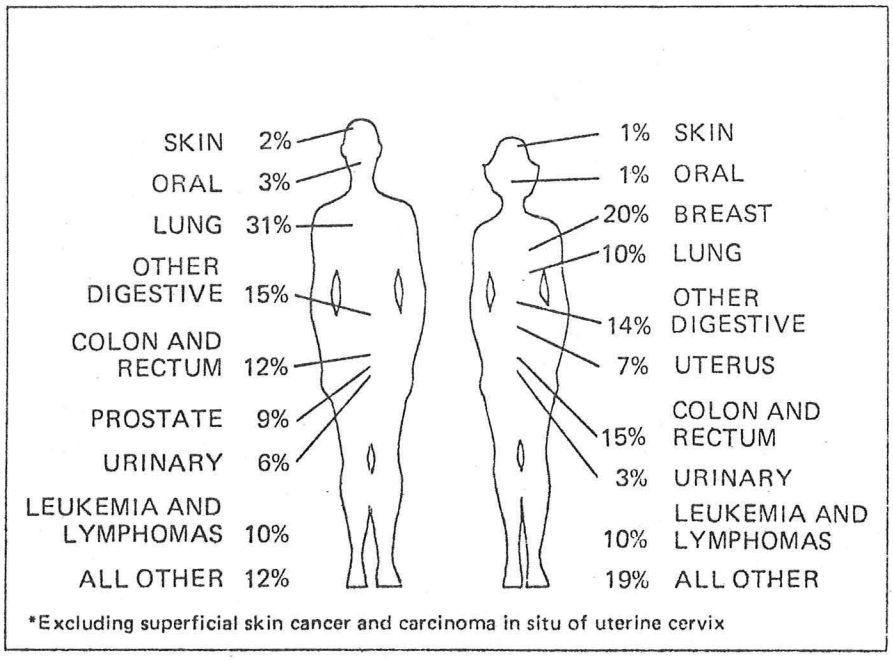


Figure 7 (Ref. 16)

The estimated total new cases (16) of primary liver cancers for the U.S. in 1974 were 11,400, with males and females almost equal (Table III).

TABLE III

U.S. 1974 ESTIMATED NEW CANCER CASES

	Total	Male	Female
All Sites:	655,000	326,000	329,000
Primary Liver Cancer:	11,400	5,600	5,800

The estimated deaths from all primary liver cancers for 1974 (16) were 9800 cases with females having a slightly higher incidence than males (Table IV).

TABLE IV

U.S. 1974 ESTIMATED CANCER DEATHS

	Total	Male	Female
All Sites:	355,000	193,000	162,000
Primary Liver Cancer:	9,800	4,800	5,000

The small difference in estimated new cases of liver cancer to expected deaths from this neoplasm clearly reflects the poor prognosis these tumors still have with regard to treatment.

Worldwide cancer epidemiology has also supplied some information about the influence of (a) racial and genetic factors, (b) sex, and (c) age on the variations in geographic distribution of liver cancers. (17).

(a) *Racial and Genetic Factors*

It has been noticed in the past that liver cancer incidence statistics of low incidence areas such as North America, Western Europe and Australia did not reveal any significant sex or racial differences. (13). Furthermore, people of African, Asian (high liver cancer incidence) or Japanese (high incidence of stomach cancer) descent who immigrated to countries of low cancer incidence acquired the cancer rate pattern of their adopted country in the first or second generation. (17) In contrast, Europeans who migrated from low to high cancer incidence areas, such as Africa, retained their low rates. Various ethnic groups in Uganda have the same high liver cancer incidence and therefore lessen the importance of genetic predisposition at least in this part of the world. (17) This emphasizes the significance of other environmental factors as being responsible for the occurrence rates of liver neoplasms.

(b) *Sex*

In the U.S. there is no significant difference in total liver tumor incidence between males and females. But these figures represent an average value for all primary liver cancers. If one considers specific types such as the hepatocellular carcinoma (HCC) then the male:female ratio is 2:1 which is similar in most parts of the world.

In areas of high liver cancer incidence such as Mozambique, Nigeria, Singapore and Hawaii, the ratio is over 3:1 (male:female). Women predominate the statistics in Chile, Iceland and Columbia where the male:female ratio is 0.5:1 to 0.9:1. The only country with true sex equality is Denmark with a 1:1 ratio for HCC occurrence.

(c) *Age*

In the high liver cancer incidence areas such as Mozambique there is a characteristic shift of the rising age-incidence curve for HCC towards the younger age group. In the 25-34 year age range the HCC incidence in this country is 500 times higher than in the U.S. where the highest incidence lies between 40-60 years of age. (13)

PATHOLOGY OF PRIMARY LIVER NEOPLASMS

Of all hepatic tumors in the Western world, as well as in Asia and Africa, the hepatocellular carcinoma (HCC) has the biggest share with 90%. (18) Cholangiocellular carcinoma occurs in 5-10% and mixed carcinoma in 2-5% of all primary liver neoplasms. All other primary tumors such as hemangiosarcoma and adenomas are extremely rare.

The most prominent hepatic tumors related to the "environmental affectors" which we will discuss later are the hepatocellular carcinoma (Aflatoxin, HB-Virus, alcohol), hemangiosarcoma (vinyl chloride monomer, arsenic, thorotrast) and the hepatocellular adenoma (anti-conceptiva). The pathological literature has introduced a great number of interchangeable terminologies which have been used preferentially by different authors. To eliminate confusion and facilitate interpretation of current literature I have compiled the various terminologies in Table V. The phrase "hepatoma" especially should be eliminated in the daily practice of medicine because of its inaccurate application.

TABLE V

SUMMARY OF LIVER TUMOR SYNONYMS

Hepatocellular Carcinoma (HCC)*	Adenoma*	Hemangiosarcoma*
Hepatoma, Carcinoma simplex, Carcinoma solidum, Hepatic cell carcinoma, Malignant hepatoma, Trabecular carcinoma	Benign hepatoma, Solitary adenoma, Hepatoma	Angiosarcoma, Angioblastic sarcoma, endothelial blastoma, Endothelioma, Kupffer cell sarcoma, Malignant hemangioendothelioma, Metastasizing hemangioma, Primary sarcoma reticuloendothelioma

I. HEPATOCELLULAR CARCINOMA (HCC)

1. *Incidence*

Moertel (18) estimated on the basis of the NCI Second National Cancer Survey (1964) an incidence of 2500 deaths from HCC in the U.S. which number was set as being equal to the incidence of occurrence because of negligible treatment success. A total occurrence of all primary liver cancers can be calculated for this time period (1964) as approximating 2780 cases (1.3/100,000). In comparison, using estimates from the NCI Third National Cancer Survey for 1974, the incidence of hepatocellular carcinoma has risen to 4.0/100,000 (or 8644 total HCC) over a period of 10 years in the U.S. These estimates agree well with those by Higginson (13) and have been shown previously in Figure 3.

The incidence of primary hepatic cancers (90% HCC) in large autopsy series varies with geography. Edmondson (19) found in 48,900 autopsies primary hepatic cancers in 0.2-0.25% of all cases. In contrast, a fairly high percentage of 3.0% and 9% for Chinese and Africans, respectively, has been reported for several autopsy series (20). The ratio of primary to secondary carcinomas of the liver has been estimated as 1:13 to 1:65 (21).

2. *Pathological morphology, histology of HCC* (22,23)

Liver weight is often increased to 2000-3000 g. The majority of the cancers are accompanied by cirrhosis. The tumor is massive (30% of all cases), nodular or diffuse. Hobnail surface of the liver is frequent but surface nodules are rarely umbilicated in contrast to metastases. The right liver lobe is preferentially affected (80-90%). The tumor itself is soft and friable.

Two-thirds of all HCC present as nodular masses and may occasionally replace the whole liver; no primary center is distinguishable.

The diffuse form of this neoplasm is present in 5% of the cases with the liver having a grayish-white appearance.

The major histological features may include (a) similarity of tumor cells to hepatic cell cords, (b) trabecular nature of growth, (c) intravascular growth of trabecular carcinoma, (d) formation of canaliculi or acini of variable size, (e) formation of bile, and (f) absence of collagen.

3. *Hepatocellular carcinoma (HCC) and metastases*

HCC, when diagnosed clinically or found at autopsy, shows a high degree of metastatic dissimination. Across the world literature frequency of metastatic disease from HCC has been stated to be between 40-50% (19,23).

Patients with cirrhosis and HCC have been found at autopsy to have a lesser incidence of metastases than the non-cirrhotic patients.The shorter life expectancy of the cirrhotic patient may be the determining factor for this phenomenon.

A typical pattern of metastatic dissemination from HCC is shown in Table VI (24) and the various pathways of tumor spread displayed in Table VII (22).

TABLE VI (Ref. 16)

Metastatic Patterns of HCC

	HCC Noncirrhotic (39 Cases)	HCC Cirrhotic (188 Cases)
No metastases	33%	54.8%
Single metastases	25.0	19.1
Lung	41.0	38.8
Lymph node (portal)	43.6	16.5
Portal vein	23.0	37.2
Hepatic vein	18.0	22.9
Skin	0	2.7
Serosa	23.1	7.4
Adrenal gland	3.0	6.9
Bone marrow	7.7	8.0
Heart	2.6	1.6
Spleen	7.7	2.1
Pancreas	0	1.1
CNS	2.6	1.1
Kidney	0	0
Diaphragm	2.6	3.7
Gallbladder	10.3	5.3
Other	5.1	3.2

TABLE VII (Ref. 22)

ROUTES AND SITES OF METASTASES OF LIVER CELL CARCINOMA

Via hepatic vein	Via portal vein	Via peritoneum	Via lymphatics
Lungs	Pancreas	Pelvic cavity	Periportal lymph nodes
Pleura	Spleen		Peripancreatic lymph nodes
Bone	Vertebrae thru vertebral veins		Retroperitoneal lymph nodes
Adrenals	Falciform ligament and umbilical area		Periaortic lymph nodes
Brain			Tracheobronchial lymph nodes
Myocardium			

4. *Hepatocellular carcinoma (HCC) and cirrhosis*

Pathologists, worldwide, have very early recognized the association between HCC and cirrhosis. The degree of association varies geographically from area to area and was remarkably different between the high and low HCC incidence regions.

It should be recognized that many past surveys in the United States comparing the incidence of HCC in "fatty nutritional cirrhosis " (FNC) (e.g., alcohol related) versus "postnecrotic" and "posthepatitic" cirrhosis actually represented comparisons of the early stages of alcoholic liver disease with well developed quiescent cirrhosis, both alcoholic and non-alcoholic (25,26). Thus, terminology that implies either pathogenesis (e.g., postnecrotic) or etiology ("posthepatitic, FNC) while defining those types of cirrhosis by purely morphologic means should be discontinued.

A survey of the international pathological literature shows that the incidence of HCC in cirrhotic livers is low in Europe and the U.S. but high in Africa and Southeast Asia (27,28,29,30,31,32). In reverse, the incidence of cirrhosis in livers with HCC is extremely high throughout the world and fairly uniform (14,17,19) as shown in Table VIII.

TABLE VIII

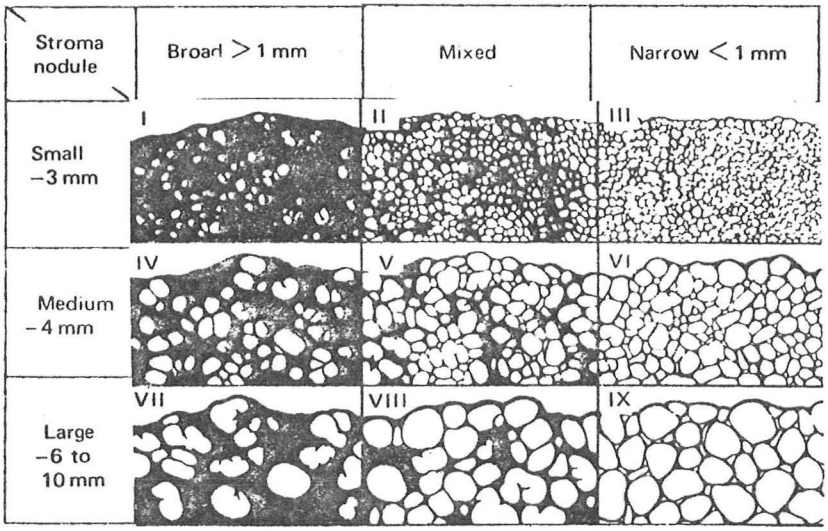
ASSOCIATION OF CIRRHOSIS AND HEPATOCELLULAR CARCINOMA (HCC)
(Data From Autopsies)

Geographic Area	% HCC in Cirrhosis	% Cirrhosis in HCC
Africa, Southeast Asia	40-50	80-90
Europe, USA	5-10	80-90

In Figure 8 Shikata (27) has classified and analyzed in a purely descriptive way the association of HCC with various stages of cirrhosis, from the broad septal ("postnecrotic", I,IV,VII) to the macronodular-thin septal ("posthepatitic", IX) appearance. It is apparent from these figures that hepatocellular carcinoma is most frequently associated with the macronodular group (VIII,IX).

5. *Alcohol, cirrhosis and HCC*

Alcohol which was listed in the introduction as an "environmental affector" has been implicated as an etiologic agent in the development of HCC. Since alcoholism was usually associated with the fatty nutritional micronodular type of cirrhosis which shows a rather low incidence for HCC, its significance for cancer development was questioned. But several authors had demonstrated by serial biopsies (25,33) that so-called "alcoholic nutritional" cirrhosis occasionally progressed to "post-necrotic" cirrhosis, hemochromatosis and HCC, making it indistinguishable from the so-called "post-hepatitic"



Macroscopic classification of liver cirrhosis.

Stroma nodule	Broad > 1 mm	Mixed	Narrow < 1 mm
Small –3 mm	I: o o o o o	II: o o o o o o	III: o o o o o / o o o o o / ● ● ● ● ●
Medium –4 mm	IV: o o o o o	V: o o o o o / o o o o o / ● ● ●	VI: o o o o o o o / o o o o o o o / o o o o o o / ● ● ● ● ● ● ●
Large –6 to 10 mm	VII: o o o o o	VIII: o o o o o / o o o o o / ● ● ● ● ● / ● ● ● ●	IX: o o o o o o / o o o o o o / ● ● ● ● ● ● / ● ● ● ● ●

o Cirrhosis without HCC
● Cirrhosis with HCC

Number of cases in various types of liver cirrhosis with or without HCC.

Figure 8 (Ref. 27)

type. Purtilo (31) compared large autopsy series at Boston City Hospital from the period 1917-1954 (23, 114 autopsies) with the period from 1955-1968 (14,000 autopsies). He concluded that cirrhosis and "hepatoma" at Boston City Hospital have progressively increased in frequency, especially

cirrhosis associated with alcoholism. This author suggested that chronic alcoholism and hepatitis B-virus could probably act synergistically to produce a type of cirrhosis which is associated with a higher incidence of HCC. An average of 8 years ensued from the onset of alcoholic cirrhosis to the appearance of HCC. Nevertheless, a cause-and-effect relationship for alcohol and HCC has not yet been proven.

6. *Hepatitis B-virus, cirrhosis and HCC*

French and American investigators postulated that the high incidence of HCC in Africa and Southeast Asia is related to the high prevalence of HB-V infection and macronodular ("posthepatitic") cirrhosis in those areas (34,35). After availability of serologic tests for HB_sAg, Anti-HB_s-AB and Anti-HB_c-AB this early speculation has now found well documented support.

Sera from 156 Chinese patients in Singapore were re-tested with the rather sensitive immune adherence hemagglutination assay (IAHA) for HB_sAg which was positive in 35% of sera in HCC patients as compared to 7% of controls (36).

The incidence of HCC-HB_sAg association was much higher in Africa (37) and Asia than in Europe and the U.S. but nevertheless the Western World showed still a significantly higher association of HB_sAg with HCC than with controls. These data are summarized in Table IX.

TABLE IX

INCIDENCE OF HB_sAg IN HEPATOCELLULAR CARCINOMA

Geographic Area	No. of Studies	HB_sAg	Matched Controls
Africa	3	63%	11.7%
Asia	5	47%	8.0%
USA and W. Europe	2	12%	0.5%

The significantly lower frequency of HB_sAg in HCC in Western Europe and the U.S. may also be partially reflected by the older age of HCC patients in these regions since frequency of HB_sAg declines with age both in the normal population and in patients with HCC (38). Prince and co-workers (38) tested 165 patients with HCC in Senegal against 154 controls with other cancers (closely matched with respect to age, sex, ethnic group and time of hospitalization) and 328 similarly matched controls without cancer. The radioimmunoassay (RIA) was used for HB_sAg detection. Essentially all of the HCC patients were chronic carriers. Data are shown in Table X.

TABLE X

INCIDENCE OF HB_sAg IN HCC, OTHER CANCERS AND CONTROLS IN SENEGAL (AFRICA)

	HCC	Other Non-Liver Cancers	Controls
HB_sAg	61.2%	11.7%	11.3%

Maupas (39) determined the anti-HB_c-antibody as a marker of active or recent infection with HB-V. The results are presented in Table XI.

TABLE XI

INCIDENCE OF ANTI-HB_c IN HCC PATIENTS VERSUS CONTROLS

Geographic Area	Anti-HB_c in HCC	Anti-HB_c in Controls
Senegal	87%	34%
Hong Kong	70%	36%
USA	24%	4%

Blumberg and co-workers (40) detected a high prevalence of HB_sAg in mothers of HCC patients in Senegal with 71.6% HB_sAg positive versus 16.6% in mothers of matched controls. He subsequently postulated a maternal-fetal or maternal-infant transmission.

A pathogenic mechanism for HB-V as a factor in HCC induction has not yet left the stage of pure speculation. It is of interest that the concentration of HB_sAg in serum of HCC patients is very low but abundant in liver tissue. This is in contrast to acute or chronic hepatitis (27). Liver cells containing HB_sAg are seen most numerously in the non-cancerous portion of the liver with HCC (27). Ohta (41) has estimated a 12.8 year interval (range 6-20 years) from onset of viral hepatitis to development of HCC. The interval from onset of liver cirrhosis to appearance of HCC was 8 years (range 5-15 years).

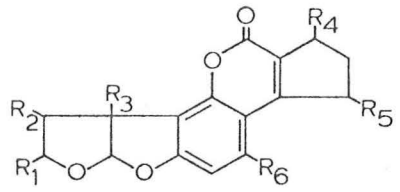
Another "environmental affector", namely aflatoxin, has been suspected for a long time to be involved in the etiology of HCC in the high liver cancer incidence regions of the world. The role of this mycotoxin as a possible co-carcinogen has recently gained more attention since the discovery

of the strong association of HCC incidence with degree of HB-V infection lessened its importance as a primary carcinogen. The risk of a chronic HB_sAg carrier in Mozambique to attract HCC has been estimated to be twice as great as compared to a chronic carrier in the U.S. (37). This strongly suggests additional environmental (or genetic) factors in Africa for the induction of HCC. However if HB-V could be indicted as the single most important carcinogen for HCC development in Africa an extensive future vaccination program could possibly eliminate one of the most important causes of death in African and Asian countries. Until final proof has been presented with regard to HB-V as an "ultimate carcinogen" the question still remains: is the virus the driver or the passenger?

7. *Aflatoxin and HCC*

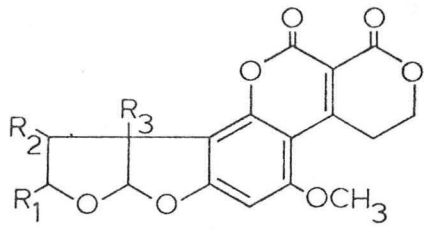
For a long time aflatoxin was held to be most likely responsible for the high incidence of HCC in Africa and Southeast Asia because the geographic distribution of tumor incidence matched fairly well the degree of food contamination with mycotoxins in these regions. When Dr. Siperstein 11 years ago (March 3, 1966) presented his Grand Rounds entitled "Aflatoxin", he reviewed some of the circumstantial evidence related to liver tumor induction in various animal species and reported some of the rather dubious data available with regard to food contamination. Since 1966 intense research has focused on two main aspects: (1) the metabolism and biochemical action of aflatoxin, and (2) the exact determination of actual aflatoxin intake/kg body weight/year of people living in high HCC incidence areas.

Aflatoxins are a whole group of mycotoxins produced mostly by the fungi Aspergillus flavus and Aspergillus parasiticus.



Aflatoxin	R_1	R_2	R_3	R_4	R_5	R_6
B_1	H	H	H	=O	H	OCH_3
B_2	H_2	H_2	H	=O	H	OCH_3
B_{2a}	HOH	H_2	H	=O	H	OCH_3
M_1	H	H	OH	=O	H	OCH_3
M_2	H_2	H_2	OH	=O	H	OCH_3
P_1	H	H	H	=O	H	OH
Q_1	H	H	H	=O	OH	OCH_3
R_0	H	H	H	OH	H	OCH_3

Aflatoxin B_1 and derivatives.



Aflatoxin	R_1	R_2	R_3
G_1	H	H	H
G_2	H_2	H_2	H
G_{2a}	OH	H_2	H
GM_1	H	H	OH

Aflatoxin G_1 and derivatives.

Figure 9 (Ref. 42)

They belong to the bis-furano-coumarins which colorless, pale yellow crystals have a characteristic UV-fluorescence of blue ("B"-aflatoxins) and yellow-green ("G"-aflatoxins). Their molecular weight is in the range of 298-330. Aflatoxin B_1 is not only the most potent toxin of its class but is also the most powerful natural occurring carcinogen known today.

At the present time there is a significant body of evidence that Aflatoxin B_1 is transformed by the microsomal oxidation system to an extremely reactive metabolite, aflatoxin B_1-2,3-epoxide (43,44). This metabolite is suspected to be the "ultimate" carcinogen which binds to various intracellular macromolecules such as DNA, t-RNA and r-RNA thus leading to mutagenesis and tumor induction.

Since Lancaster (45) and co-workers reported in 1961 the first liver carcinoma induced in rats by peanut meal feedings (aflatoxin contaminated), various animal species have been shown to be susceptible to this toxin, the most sensitive being the trout. 100% tumor induction can be achieved depending on level and time of application. Primates respond to repeated small doses by developing cirrhosis, with HCC in some survivors (46). Most of the hepatic tumors induced by aflatoxins are hepatocellular carcinomas and few are cholangiocellular cancers. The most obvious precancerous lesions observed in rat liver after aflatoxin administration are summarized in Table XII.

TABLE XII

LIVER LESIONS AFTER AFLATOXIN IN RATS

1. Periportal or centrilobular necrosis
2. Bile duct proliferation
3. Cirrhosis

In addition to the extensive progress of uncovering the metabolism and activation of aflatoxins to "ultimate carcinogens", several carefully controlled studies have now been completed which determined the food contamination with mycotoxins in areas of high and low HCC incidence in Africa and Asia. "Food-from-the-plate" has been analyzed in the homes of cancer victims as well as matched control populations for at least a one year period, and the total daily ingestion of aflatoxin has been calculated. The data are all summarized in the following tables (XII, Ref.47; XIV, Ref.48; XV, Ref.49; XVI, Ref.50; XVII, Ref.42).

TABLE XIII (Ref. 47)

Geographical Distribution of Malignant Hepatoma in Swaziland 1964 to 1968

	Highveld	Middleveld	Lowveld
Number of cases	11	34	44
Crude rate/10^5/year	2.2	4.0	9.7
Population ratios	1.0	1.7	0.9
Relative risk	1.0	1.8	4.5
Corresponding aflatoxin assays in groundnuts			
Positive samples (%)	20	57	60

Source. *Keen and Martin (41).*

TABLE XIV (Ref. 48)

Aflatoxin Contamination of Foods Versus Hepatoma Incidence in Ugandan Tribes

	Hepatoma Incidence (Cases/10^5/year)	Aflatoxin-containing Foods (%)	Number of Samples
Bwamba	No data	79	29
Karamojong	15.0	44	105
Baganda	2.0	29	149
West Nile	2.7	23	26
Acholi	2.7	15	26
Soga	2.4	10	39
Nakole	1.4	11	37

Source. *Alpert* et al *(42).*

TABLE XV (Ref. 49)

Daily Aflatoxin Intake and Liver Cancer Incidence in Kenya (Data for Males ≥ 16 Years Old)

	Altitude Subarea		
	High	Middle	Low
Frequency of diet contamination	39/808	54/808	78/816
Mean aflatoxin level (ppb)	0.121	0.205	0.351
Frequency of beer contamination	3/101	4/101	9/102
Mean aflatoxin level (ppb)	0.050	0.069	0.167
Mean aflatoxin ingested [a] ng/kg b.w./day	4.88	7.84	14.81
Liver cancer incidence	3.11	10.80	12.12

TABLE XVI (Ref. 50)

Aflatoxin Contamination of Selected Thai Foods (Market Samples 1967 to 1969)

Foodstuff	Contamination (%)	Aflatoxin Content (ppb) (mean)	(maximum)
Peanuts	49	1530	12,256
Corn	35	400	2,730
Chili peppers	11	125	966
Millet	11	67	248
Dried fish	5	166	772
Mung beans	5	16	112
Rice	2	20	98

TABLE XVII (Ref. 42)

Summary of Current Evidence on Aflatoxin Intake and Liver Cancer Incidence

Population	Aflatoxin Intake (ng/kg body wt/day)	Liver Cancer Incidence (cases/10^5/year)
Kenya—high altitude	4.88	3.11
Thailand—Songkhla	5.00	2.00
Kenya—middle altitude	7.84	10.80
Kenya—low altitude	14.81	12.12
Thailand—Ratburi	45.00	6.0
Mozambique—Inhambane	222.40	25.4

In conclusion, the present evidence, although very suggestive, still cannot be regarded as constituting unequivocal proof that aflatoxins are the most important single cause of HCC in these specific areas. But the data seem to warrant the conclusion that these mycotoxins could play a role at least as co-carcinogens in the etiology of HCC.

II. HEPATOCELLULAR ADENOMA

The second type of tumor discussed with regard to its inducing agents ("environmental affectors") is the "benign" hepatic adenoma. The accused agents supposedly inducing this tumor are synthetic steroids administered as birth control pills. The hepatic adenoma as an extremely rare tumor rather suddenly became the target of enthusiastic pathologists, clinicians and surgeons because of its enhanced appearance in young women. Several authors have already considered the adenoma as a precancerous lesion. Hepatic adenomas are benign tumors with regard to dissemination but may be clinically extremely hazardous as a result of sudden severe intraperitoneal hemorrhage.

1. *Pathology of adenomas*

The adenoma is usually a sharply demarcated, encapsulated tumor of tan to light brown color. It shows fairly homogenous appearance and right-lobe preference. Its size varies from 2-30 cm in diameter, is usually solitary but occasionally multiple. Degenerative changes may lead to necrosis, partial fibrosis and hemorrhage. True adenomas are rare in cirrhotic livers and possess abundant blood supply composed of small arteries and accompanying veins. A possible variant of this neoplasm is the "focal nodular hyperplasia" (FNH) which appearance has also been described in connection with birth control usage. The records of the Mayo Clinic between 1907-1954 reveal only 4 cases of hepatic adenoma (66). Only two cases were reported in 50,000 autopsies from 1918-1954 at the L.A. County General Hospital (22) and another four from the Memorial Sloan Kettering Cancer Center over a period from 1935-1965 (67).

Histologically the adenoma displays cell variation from normal to atypical forms, occasionally suggesting a precancerous lesion. No portal tracts, bile ducts or central veins are present. Cells are arranged in cords or tubules and appear often larger than normal and vacuolated (22,51,52).

2. *Tumor incidence and hormones*

After Baum and co-workers (53) published their first 7 cases of hepatic adenoma in women taking oral contraceptives a great number of additional case reports appeared claiming an association of birth control pills with benign hepatic adenomas (53-63).

Until January 1976 (64) 67 such cases were published in the international literature over a period of 3 years. 72% of these patients were under the age of 35 years. Oral contraceptives had been used between 6 months and 10 years. In 38% of these patients Progestin-dominant preparations (Ovral, Norlhyl, Ortho-novum, Norlestin) and in 25% of the women estrogen-dominant preparations (Enovid, Oracon, Ovulen) were used. The rest were not specified. Approximately 83% of 55 patients for whom duration of therapy was specified, had taken contraceptive steroids for a cumulative period of more than 4 years (64).

The synthetic estrogens and progesterones utilized in many of these oral contraceptive preparations are 17-α-alkyl-substituted steroids (65). Some of these chemical structures are depicted in Figure 10.

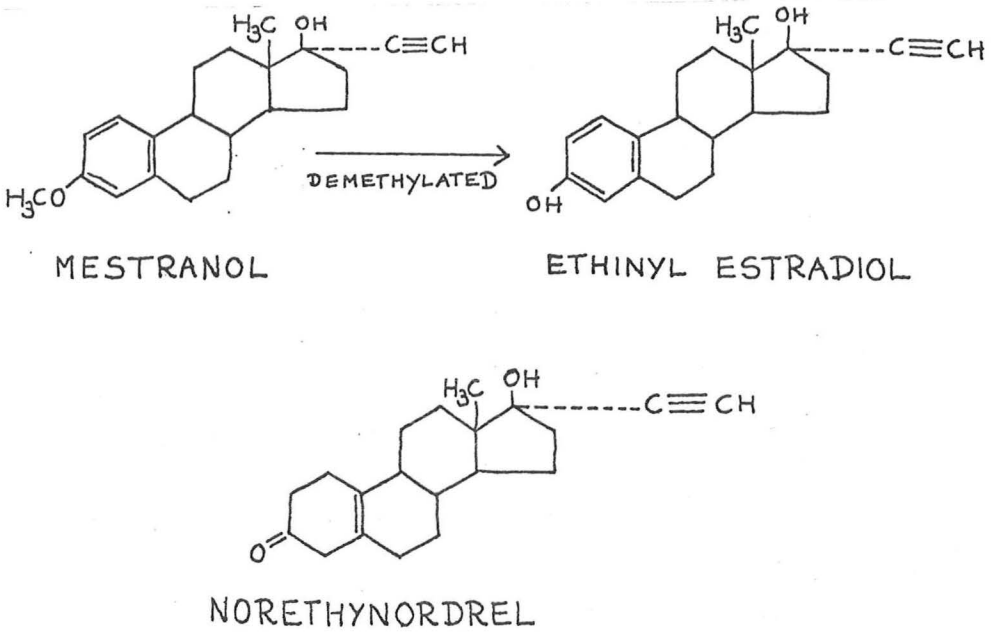


Figure 10

3. *Clinical presentation*

Over 50% of these 67 patients (64) noted acute or chronic right upper quadrant or epigastric pain. Syncope alone or followed by hemoperitoneum, hypotension and anemia was observed in 30% of the cases. These patients had either subcapsular or extracapsular rupture of their liver tumors. Approximately 40% experienced an upper abdominal mass and 10% were completely asymptomatic whose lesions were detected by coincidence during other surgery. Of the total 67 patients reported, 72% had partial hepatectomy and 74% of them revealed hepatic adenomas or focal nodular hyperplasia. The rest were hamartomas, one carcinoma, one Budd-Chiari and four undiagnosed lesions.

4. *Conclusions*

The sudden accumulation of case reports concerned with a formerly extremely rare tumor but which according to the Iowa State Cancer Registry shows a real increase in frequency is certainly an attention drawing event. However, despite the fact that in the majority of the cases the intake of oral contraceptives was the only known common "environmental affector" -- no absolute proof of a cause-and-effect-relationship has been established. But there have been scattered reports in the literature (60) including the case shown on our slide where an identical syndrome was presented in absence of contraceptives. One has to appreciate that the overall incidence of adenomas in 50 million women taking birth control pills is still extremely small. But nevertheless, until proven otherwise, synthetic steroids may

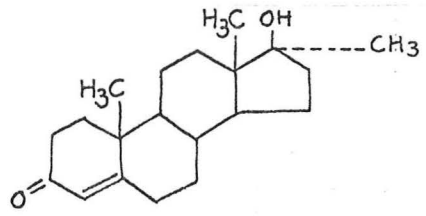
be considered as having a permissive role in individual cases for the development of such tumors as the hepatic adenoma. Possibly other environmental agents may be shown in the future as being the responsible chemical for the true increase of adenoma incidence at the present time.

III. ANABOLIC-ANDROGENS AND HEPATIC TUMORS

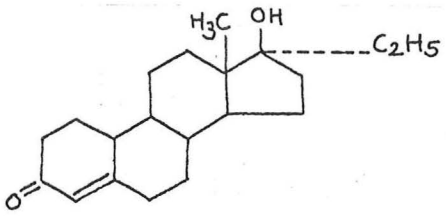
1. *Incidence and pathology*

For the sake of equal space for both sexes the anabolic-androgens and their association to hepatic tumors other than adenomas will be briefly discussed.

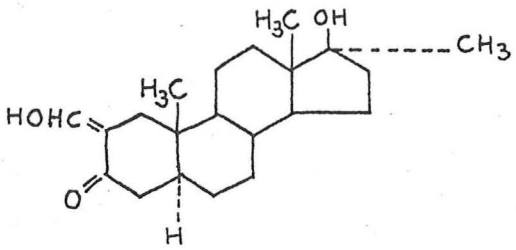
Androgenic-anabolic steroids such as oxymetholone, methyltestosterone and norethandrolone have been associated with the development of hepatocellular carcinomas with the peculiar property of absence of metastases (68,69). Some of their chemical structures are shown in Figure 11.



METHYLTESTOSTERONE



NORETHANDROLONE



OXYMETHOLONE

Figure 11

At least 12 patients taking anabolic steroids (70-73) have been reported in the literature with primary hepatocellular carcinoma. Some of these cases are summarized in Table XVIII.

TABLE XVIII (Ref. 74)

Summary of Reported Cases of Oral Adrenogenic-Anabolic Steroid-Associated with HCC

Patient	Age	Fanconi's Anemia	Transfusions Before Liver Disease	Agent	Dose (mg/day)	Duration (months)	Ref.
1	6	–	+	Oxymetholone	30–100	46	(9)
2	20	–	+	Oxymetholone	150–250	28	(9)
3	27	+	+	Methyltestosterone	20	40	(9)
4	21	+	–	Methandrostenolone	10–50	89	(9)
5	20	+	–	Oxymetholone	100	10	(7)
6	16[a]	–	+	Methyltestosterone	40–80	21	(16)
				Norethandrolone	10	3	
				Oxymetholone	100	35	
				Stanazalol	15	18	
7	68[b]	–	–	Methyltestosterone	?	360	(17)
8	6	–	+	Oxymetholone	40–60	41	(18)
9	6	–	+	Methyltestosterone	60	> 24	(19)

[a] Not histologically proved, alpha fetoprotein positive.
[b] History of "infectious jaundice" 40 years previously.

In addition to possible cancer induction Peliosis Hepatis (blood-filled cysts in the liver) with spontaneous rupture, hemorrhage and death has occurred in both men and occasionally in women (75-77). Even before the possible cancer-inducing properties of anabolic steroids had been speculated upon, the hepatic toxicity of oral androgenic-anabolic steroids was recognized and has been reviewed by Dr. Combes at Grand Rounds in 1967 (78). Further confirmatory reports have been published over the last several years (79,80). In humans the incidence of HCC is increased in males beyond puberty (81) and extensive animal experimentation support the contention that hepatocellular carcinoma favors an "androgenic environment". In agreement with this hypothesis is the increased incidence of spontaneous HCC in several rodent strains (C3H, CBA mice) which show a 3-6 times higher tumor occurrence in males (82). Castration of male mice reduces the incidence of spontaneous HCC from over 33% to less than 12% (82). Many more examples have been cited in the recent research literature.

2. *Application of anabolic steroids*

The U.S. Food and Drug Administration has approved the therapeutic use of anabolic steroids for aplastic anemia, disseminated breast cancer, pituitary dwarfism and other serious endocrine disturbances. But thousands of young women and men are taking anabolic steroids to improve their athletic performance like weight lifters, shot-putters, professional, college and even high school football players, sometimes in huge amounts for many years (83). The most peculiar but also most consistent abusers of anabolic steroids are the body-builders and Mr. Universe contestants.

3. *Summary and conclusion*

If a true association should exist between anabolic-androgenic steroids and hepatic neoplastic development, a great number of new cases should be discovered in the future among the above cited individuals. But the cautious assessment of carcinogenicity of hormones will require attention to the many variables including variation of inducibility of metabolizing enzymes and interference with or enhancement of their activity by endogenous hormones, other drugs, or chemical compounds in the environment (84).

IV. HEMANGIOSARCOMA

The last type of malignant neoplasms which we will discuss is the hemangiosarcoma, another extremely rare hepatic tumor. However, because of its rarity, sudden clustering of this malignant entity in association with arsenic, thorotrast and vinyl chloride monomer exposure has drawn great attention. It has been suggested that the rarer the types of tumors, the better and more sensitive markers they are for the sudden insult of an unknown "environmental affector", resulting in the enhanced appearance of malignant growth.

1. *Incidence*

The world literature discloses between 120-160 primary hemangiosarcomas of the liver in adults, not all of which are well documented (85,86). Based on available statistics, hemangiosarcoma accounts for 1.8% of all primary liver cancers and has an autopsy incidence of six per 100,000 (85). Based on data from the NCI Third National Cancer Survey (1969-1971) the expected annual incidence of this tumor is in the order of 0.0014 cases/100,000 population or 25-30 cases/year in the U.S. (87). There is no striking geographic variation in incidence of hemangiosarcoma. The male:female ratio of hemangiosarcoma is 2:1 and only 15% of the cases have occurred in persons below 40 years of age (85).

2. *Clinical signs and symptoms* are mostly abdominal discomfort and pain, swelling of the abdomen and ankles, weakness, anorexia, malaise, nausea and weight loss. Duration of symptoms vary from one week to 6 months (86). Hepatomegaly is almost always present and splenomegaly in some instances. Metastases are found in approximately 50%, mostly in lungs, lymph nodes, spleen, bones and other organs (87).

3. *Gross pathology* reveals tumors which can vary from solid, fleshy nodular masses to large, blood-filled cystic spaces with liver weights up to 6000 grams (85). In hemangiosarcomas associated with arsenic, thorotrast or vinyl chloride exposure, the non-neoplastic liver shows fibrosis or cirrhosis in almost all cases.

Histologically the tumors are composed of well defined blood channels lined with malignant epithelial cells. These, in the process of invasion, either line pre-existing channels or form new ones. Endothelial cells are larger than normal, have hyperchromatic nuclei and frequent mitoses. There are single or multiple layers of cells in blood vessels but no distortion of the liver cords. In the advanced stage, normal liver cells are surrounded by tumor cells and foci of extramedullary hematopoiesis are seen (22).

4. *Arsenic and hemangiosarcoma*

Arsenic was utilized in the past for many industrial and medical purposes. Abundant use was reported as arsenical insecticides in the form of lead arsenate dust in Germany (until 1942) and France, or as arsenic trioxide (As_3O_5) as liquid spray pesticide in vineyards containing 4.3% to 56% As_3O_5.

The best known medical preparation containing arsenic was "Fowler's solution" (1% potassium arsenite in aqueous ethanol) which was applied as treatment for chronic myelogenic leukemia and psoriasis. "Fowler's" solution was dropped from the National Formularies in 1965.

Roth (89-91) published in 1959 an autopsy series of 82 vineyard workers in Germany who had 12-17 years of heavy exposure to arsenic containing insecticides and an arsenic containing "wine" named "Haustrunk", a selfmade concoction from leftovers of pressed grapes (90). Eight cases of hemangiosarcoma were discovered among 28 of the 82 workers who also had cirrhosis. The estimated intake of arsenic was calculated as 53.7 grams over a 12 year period. Since this initial report 2 cases of angiosarcoma were discovered in patients treated with "Fowler's" solution for psoriasis over a period of 17 and 15 years, respectively (92,93).

Since those few cases in the literature represent probably the whole extent of arsenic association with hemangiosarcoma of the liver, a real cause-and-effect relationship is very doubtful. Arsenic is the only suspected chemical carcinogen where so far every attempt has failed to produce hepatic tumors in various animal species.

Even the worst arsenic exposure possible, namely that by the arsenic-eaters of Southern Austria and Styria, has never been shown to be associated with an increased incidence of hepatic neoplasms. Furthermore, these Austrian gourmets of high arsenic consumption felt (Quote, 1883) that "they improve in bodily condition, gain in breathing-power, and become stronger and more pugnacious, and also more salacious" (94). Thus, one has to conclude that the present evidence is too limited to allow acceptance of a true association of arsenic to hemangiosarcoma on etiological grounds. Whether arsenic has a coincidental relationship to tumors in vineyard workers or functioned as co-carcinogen remains to be explained. In a most recent paper in Gastroenterology (February 1977), Pimentel and Menezes presented evidence that a fungicide used in Portugal since 1885 for spraying in vineyards (so-called Bordaux mixture; copper sulfate plus lime) was associated with liver lesions similar to those described in arsenic exposure. One case of hemangiosarcoma was discovered among 30 rural workers (94a).

IV. THOROTRAST AND HEMANGIOSARCOMA

1. *Application and physical properties*

Compared to arsenic a direct association of thorotrast with the development of primary hepatic neoplasms seems well documented and occurs most likely on the basis of long standing radiation injury.

Thorotrast has been used between 1930-1953 as radiological contrast material for hepatolienography (60-80 ml I.V. in 3 doses), arteriography and opacification of body cavities (95).

It was supplied as a colloidal solution of 20% (w/v) thorium dioxide in 20% dextrin with 0.15% methyl-p-hydrobenzoate as a preservative. The physical halflife of thorium is 1.39×10^{10} years and its biological halflife approximates 400 years. Decay of thorium proceeds from ^{232}thorium to ^{208}Pb via six alpha and four beta disintegrations. There is overwhelming preponderance of alpha energy (90%) with beta-particle contribution of about 9% (96). Once injected thorotrast is fairly rapidly taken up by the reticuloendothelial system with a distribution of 70% in the liver, 20% in spleen and the rest in lymph nodes and bone marrow. 75 ml of injected thorotrast is equivalent to approximately 1.5-3.0 µg radium which relieves an average dose of 1.5 rads/week to the liver, 2.5 rads to the spleen and 0.3 rads to bone marrow. Because of its uneven distribution in the liver itself some areas of this organ may receive over a 25 year period 350 rads, others up to 7500 rads (97). In the United States a minumum of 4500 patients have been injected (98) and an estimated 50,000 to 100,000 worldwide (99).

2. *Incidence and clinical aspects*

Approximately 120 cases of thorotrast induced primary hepatic liver neoplasms have been reported worldwide (100) and a breakdown of the types of tumors induced is shown in Table XIX.

TABLE XIX

TUMORS IN LIVERS AFTER THOROTRAST

1.	Hemangiosarcoma	33%
2.	Cholangiocarcinoma	32%
3.	Hepatocellular carcinoma	20%
4.	Bile duct carcinoma	15%

The latent period between injection of the material and following clinical manifestations varied from three years, two months to 30 years (average 22 years). Since thorotrast usage had been discontinued in 1953 (24 years ago) we can hopefully expect to see in clinical praxis the last of these cases over the coming decade. This is certainly the most positive prognosis one can make about any of the known carcinogens. It should be emphasized that as early as 1932 the Council on Pharmacy and Chemistry of the American Medical Association (101) warned in an editorial in JAMA against possible hazards of thorotrast including oncogenicity. It was recommended to restrict the use to patients with malignant tumors, advanced age and shortened life expectancy. This early warning was not very successful since it took 21

more years until the medical community discontinued the use of this agent in 1953. This was still 6 years after the first case report of an angiosarcoma following thorotrast injection (102) had appeared. Over the last 5 years the Liver Unit has seen at least 3 cases of thorotrast injected patients at Parkland Memorial Hospital. Two of them have died from hepatic tumors and one is currently being followed by our outpatient clinic.

The history and course of one of the fatal cases is described as follows.

A 59 year old woman presented in January of 1972 with epigastric fullness, right upper quadrant aching pain, and jaundice.

Twentyfive years prior to admission she was hospitalized with right-sided abdominal pain, dark urine, and jaundice. An x-ray of the abdomen suggested hepatomegaly, confirmed by a thorotrast study (1 amp of thorotrast daily for 3 days followed by repeat x-ray studies). Metastatic malignancy was suspected.

Ten years prior to admission gynecologic surgery was done. The liver was noted to have whitish yellow plaques over its surface, but no mention was made of liver size. Liver chemistries were completely normal.

Two months prior to admission hepatomegaly was noted during evaluation for an episode of paroxysmal atrial tachycardia. Liver chemistries were again normal. The patient refused liver biopsy.

Physical examination on admission revealed a jaundiced woman with a firm, nodular liver palpable 5 cm below the right costal margin. There was no splenomegaly and stigmata of chronic liver disease were notably absent. Liver chemistries showed a bilirubin of 5.8, alkaline phosphatase of 135 King-Armstrong units, and an SGOT of 122. Albumin was 2.8, prothrombin time was normal and HB_sAg and α-fetoglobulin were negative. (X-rays confirmed the previous thorotrast administration.)

Liver biopsy at laparotomy showed residual thorotrast in the R.E. system, fibrosis, and cholangiocarcinoma. The subsequent course was marked by intractable ascites and a rising bilirubin. The patient died 3 weeks after the diagnosis was made.

The positive aspects about this episode of medical neglect of early warning signs is the fact that the number of patients subjected to thorotrast is rather limited and a complete phase-out of these cases should be expected over the near future.

V. VINYL CHLORIDE MONOMER and hemangiosarcoma

1. *Introduction*

The "environmental affector" vinyl chloride monomer (VCM) aroused significant anxiety around the world after the first reports from the United States (103,104) and Europe (105) appeared in 1974, describing the accumulation of angiosarcomas in the livers of workers employed in vinyl chloride polymerization plants. The great significance of these publications did not rest alone on the discovery of a sudden clustering of an extremely rare tumor in a specific population but in the subsequent uncovering of reports as far back as 1949 (106) and more recently in 1971 (107) describing hepatotoxicity in humans and oncogenicity in laboratory animals respectively. Vinyl chloride exposure resulted not only in tumor growth but in the appearance of a peculiar new set of signs and symptoms which is now referred to as "vinyl chloride disease".

2. *Chemistry of vinyl chloride monomer*

Vinyl chloride monomer (VCM) is a colorless, flammable gas of molecular weight of 62.5. It polymerizes in the presence of a catalyst to polyvinyl chloride (PVC) which still is probably the most important synthetic industrial product in the world. But vinyl chloride monomer has also been used directly as a propellant in spray paints, hairsprays and insecticide aerosols as well as coolant material in refrigerators. It also gained rapid recognition as an anesthetic gas which use was discontinued only after several cases of severe cardiac arrhythmias occurred.

The current hypothesis with regard to its carcinogenic properties considers a highly reactive metabolite (formed in liver and other tissues), namely chloroethylene oxide, which may be the "ultimate" carcinogen.

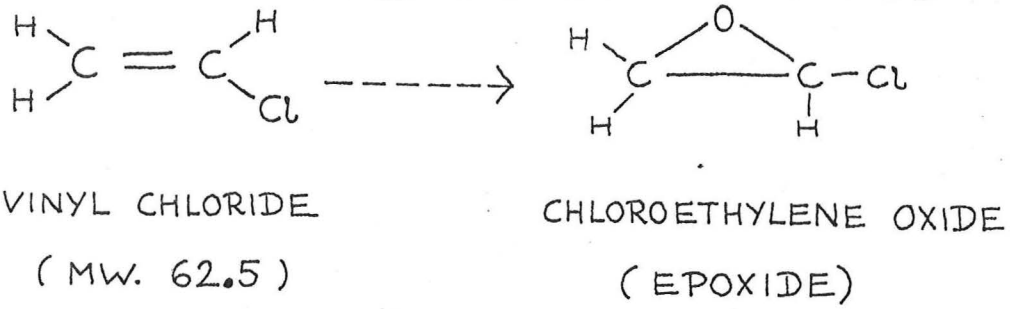


Figure 12

Current world production of VCM approximates 18 billion pounds annually (108) with the U.S. participating with 2.3 billion kg (9) of which 90 million kg are discharged into the atmosphere (10).

3. *Incidence*

Since January 1974 (103) a world wide total of 32 cases of hemangiosarcoma in vinyl chloride workers has been identified, 15 of them in the U.S. (109). Approximately 20,000 U.S. workers have been exposed to VCM in the past and currently 5400 people are employed in the production of this carcinogen. These workers as a special population have a 400 times higher calculated risk to attract hemangiosarcoma of the liver than the overall U.S. population (87). But since the end of 1974 strict safety precautions have been implemented requiring air concentrations of VCM not higher than 1 ppm at the working place. All aerosols containing VCM as propellant have been recalled by the manufacturers in late 1974. Workers had been exposed in the past to VCM concentrations up to 1000 ppm whereas Maltoni (110) could show that rats exposed to only 250 ppm of VCM developed over a period of 12 months a significant number of hemangiosarcomas in the liver.

Workers who developed hemangiosarcoma were exposed between 12-28 years with an average of roughly 20 years latency (111). The average age at diagnosis was 46.5 years.

Other disturbing findings were reported by several authors (112-114) showing an increased percentage of chromasomal abnormalities in workers following chronic VCM exposure. One report described the pregnancy outcome among wives of workers exposed to VCM which indicated an excess fetal loss compared to wives of non-exposed husbands (115).

4. *Clinical appearance and pathology*

The clinical manifestations and pathological findings of "vinyl chloride disease" are outlined in the following selected tables of various authors (116-119).

The phenomenon of acroosteolysis related to vinyl chloride exposure was noticed as early as 1957 (Table XX) and was subsequently described in detail by various clinicians. This peculiar lesion was only noticed in workers who cleaned the autoclave and polymerization tanks.

Evidence of hepatotoxicity of vinyl chloride monomer was first described by Russian investigators in 1949 (Table XXI) but their report went unnoticed for at least 16 years. Finally, the description of liver sarcomas in 1974 reminded the medical community all over the world that these overlooked publications probably were the first warning signs of more and worse to come.

The initial symptoms observed in 70 patients of a PVC factory are summarized in Table XXII and some of the more significant clinical laboratory findings are listed in Table XXIII. Reticulocytosis, splenomegaly, increased BSP retention and low platelets are the major disturbances observed. Other liver function tests are rather insignificant except that approximately half of the patients had an increased alkaline phsophatase (Table XXIV). Hepatosplenomegaly became more and more prominent as longer exposure to VCM had occurred (Table XXV).

5. *Pathology, histology*

Chronic vinyl chloride exposure leads in almost all patients to significant alteration of hepatic structures. Practically all patients with hemangiosarcoma have accompanying fibrosis of liver tissue. The major pathological alterations are summarized in Table XXVI and the course of pathogenesis is speculated upon in Table XXVII.

TABLE XX (Ref. 116)

ACROOSTEOLYSIS

Year	Author*	Finding
1957	Filatova and Gronsberg	"Angioneurosis of spastic character"
1963	Suciu *et al.*	Raynaud's syndrome (hands and feet), 6% of 168 exposed workers
		Scleroderma-like skin changes (hands, feet, face, neck, thorax), 3.6% of examined
1966	Cordier *et al.*	Raynaud's syndrome
		Scleroderma-like skin changes
		Lytic lesions of terminal phalanges in hands and feet
1967	Harris and Adams	The same changes and also pseudoclubbing of fingers
		Involvement of sacroiliac joints and patella
1967	Wilson *et al.*	Bone changes and Raynaud's syndrome
1971	Dinman *et al.*	Epidemiology of acroosteolysis
1972	Markowitz *et al.*	Skin biopsy and pathology data
1972	Jühe and Lange	Arteriography
		Occlusion of interosseous arteries
1973	Misgeld *et al.*	Arteriography → spastic arteries visualized only after Priscol

TABLE XXI (Ref. 116)

EVIDENCE OF LIVER DAMAGE IN PVC-EXPOSED WORKERS

Year	Finding	Author (Country)
1949	"Hepatitis-like liver changes"	Tribukh *et al.* (Russia)
1965	"Chronic epithelial hepatitis" in 15% of cases; hepatomegaly, increased bilirubin and prothrombin time, abnormal Takata-Ara test	Pushin (Russia)
1963	Hepatomegaly in 30% of 168 examined workers, splenomegaly (6%); liver biopsy in 2 cases: "chronic hepatitis"	Suciu *et al.* (Romania)
1967	Hepatomegaly; persistent raised bilirubin	Harris *et al.* (England)
1972	Increased BSP retention, raised icterus index—related to degree of exposure	Kramer and Mutchler (U.S.)
1972	Pain in RUQ and abnormal liver tests (in 2 out of 7 patients with scleroderma-like skin changes)	Jühe *et al.* (Germany)
1973	RUQ discomfort; abnormal liver changes.	Misgeld *et al.* (Germany)

TABLE XXII (Ref. 117)

SURVEY OF INITIAL SYMPTOMS OBSERVED IN 70 PATIENTS FROM A PVC FACTORY

Symptoms	No. of Patients	%
Upper abdominal complaints	42	60.0
Tiredness	27	38.6
Frequent dizziness	26	37.1
Paresthesia (numbness and tingling) in fingers and/or toes	22	31.4
Increased perspiration	19	27.1
Sensation of cold in individual fingers or hands	18	25.7
Arthralgia	17	24.3
Potency troubles	13	18.6
Pain in the head	9	12.9
Pain in the calves	9	12.9

TABLE XXIII (Ref. 117)

FREQUENCY OF CLINICAL, SCINTIGRAPHIC, RADIOLOGICAL AND PATHOLOGICAL LABORATORY FINDINGS IN 70 WORKERS FROM A PVC FACTORY

No. of Patients Examined	Finding	No. of Patients	%
70	Thrombocytopenia (17,000–143,000/μl)	57	81.0
67	Increased BSP retention (5.1–25.6 after 45 min)	45	67.2
68	Splenomegaly (scintigraphy)	39	57.4
58	Reticulocytosis (16–37%)	24	41.0
70	Increased serum enzymes (SGOT, SGPT, AP, SP)	10	14.3
70	Scleroderma-like skin changes	8	11.4
70	Varices in esophagus and/or fundus of stomach	8	11.4
70	Acroosteolysis	6	8.6
70	Raynaud's phenomenon	6	8.6
70	Leukopenia	5	7.1

TABLE XXIV (Ref. 116)

ABNORMAL LIVER FUNCTION TESTS AMONG 354 VC WORKERS CURRENTLY OR PREVIOUSLY EMPLOYED

Liver Function Test		Current Employment (267)	Prior Employment (87)	Hepatosplenomegaly, Hepatic Tenderness (66)
Bilirubin	>1.1	18 (6.7%)	3 (3.6%)	—
SGOT	>50	17 (6.4%)	3 (3.6%)	6/20 (30.0%)
SGPT	>36	26 (9.7%)	5 (5.7%)	8/31 (26.9%)
LDH	>225	6 (2.4%)	2 (2.3%)	—
Alkaline phosphatase	>86	43 (16.0%)	16 (18.0%)	27/59 (45.8%)

TABLE XXV (Ref. 116)

HEPATOSPLENOMEGALY AMONG 354 VC WORKERS

Duration of Exposure (y.)	Total No. Examined	Enlarged Liver*	Enlarged Spleen†
≤2	61	4 (6.5%)	1 (1.6%)
2.1–5	75	5 (6.7%)	2 (2.7%)
5.1–10	62	7 (11.3%)	2 (3.2%)
10.1–20	104	20 (19.0%)	3 (2.9%)
20+	52	17 (32.7%)	4 (7.7%)
Total	354	53 (15.0%)	12 (3.4%)

TABLE XXVI (Ref. 118)

LIVER DAMAGE AFTER EXPOSURE TO VINYL CHLORIDE

I. Degenerative lesions in hepatocytes:
  Cloudy swelling and hydropic degeneration
  Fatty change
  Focal cytoplasmic degeneration
  Single cell necroses
II. Adaptive responses in hepatocytes:
  Slight increase of smooth endoplasmic reticulum
III. Fibroses:
  Slight fibrosis in portal tracts and septal fibrosis
  Intralobular perisinusoidal "net-like" fibrosis
  Septal cirrhosis
IV. Hyperplasia, polyploidy, and proliferation of hepatocytes
  (in our material cancer did not develop)
V. Marked activation, hyperchromasia, and proliferation of sinusoidal cells
  Hemangioendothelial-, anaplastic-, reticulosarcoma

TABLE XXVII (Ref. 119)

PATHOGENESIS OF HEPATIC LESIONS IN VC-PVC WORKERS

1) Fibrosis
  Capsule
  Portal tracts
  Intralobular (perisinusoidal)
  → Portal hypertension → Splenomegaly, Varices
  Proliferation of bile ducts

2) Proliferation of sinusoidal lining cells with sinusoidal dilatation → Atypical hyperplasia → Multicentric (sinusoidal) angiosarcoma enveloping hyperplastic and atrophic hepatocytes and bile ductules

3) Stimulation of hepatocytes
  "megalocytosis"
  "little cell-big cell" change
  → Proliferation of hepatocytes → ? Regenerating nodules
  → ? Hepatoma

CONCLUSION AND ASSESSMENT

We have discussed a great number of "environmental affectors" all of which have been related to the induction of primary hepatic neoplasms. There is epidemiological evidence that aflatoxins and HB-V are involved in the etiology of HCC, frequently accompanied by macronodular cirrhosis.

Birth control pills have been implicated as being the cause of an increased appearance of hepatic adenoma but a cause-and-effect relationship cannot be proven at the present time. And there is even less direct evidence available for any carcinogenic properties of anabolic-androgenic hormones and the development of HCC.

Arsenic, thorotrast and vinyl chloride monomer have been implicated as the cause of mostly hemangiosarcomas in the liver. Whereas the role of arsenic as a hepatocarcinogen is still extremely doubtful, thorotrast and vinyl chloride seem to represent the best documentation of a cause-and-effect relationship. Especially these latter agents have taught the Medical community the lesson not to disregard even preliminary data which point towards the possibility of chronic injury and carcinogenicity. The battle between cancerophobia and simple disregard will almost certainly continue. Two final quotes should emphasize that (1) extreme caution should be applied in interpreting epidemiological data with regard to cause-and-effect relationships, and (2) that one should be receptive, at the same time, to the threat of unknown "environmental affectors" against our health:

> "Charles Darwin pointed out that only bumble-bees with their long tongues could adequately pollinate red clover and that their main enemies were field mice which devoured both larvae and honey combes. He ascribed the better crops of clover near villages to the control of mice by cats. Another scientist extended the train of events and suggested that since red clover was the staple diet of British cattle and bully beef the staple diet of the British sailor, a relationship might be shown between British naval victories and the habit of keeping cats." (Burkitt (1970), Ref. 120)

In contrast, Dr. I. Selikoff of the Mount Sinai School of Medicine emphasized to a rather perceptive audience of the Vinyl Chloride Conference of the New York Academy of Science in 1975 that

> "...it is sobering to realize that there may be other agents sitting in the wings, which we do not now suspect and which we still do not really know yet how to anticipate. We can't see them -- but we hear them moving about in the forest." (ref.121)

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