cinoma (75). A few cases of carcinoma have been reported in man following vinyl chloride exposure (76). Guided by the doses found to be effective in experimental animals, the vinyl chloride concentration permissible in the ambient air of factories has been reduced by regulatory action to levels which should avoid initiation of additional angiosarcomas or their precursor lesions. Because of the long period of promotion in carcinogenesis in general and particularly in factories where low-grade but still dangerous levels of vinyl chloride existed, it is still possible that additional cases of hepatic angiosarcoma will occur in the foreseeable future. To date, 64 angiosarcomas following vinyl chloride exposure in man are on record (77).

The same morphologic and clinical sequence has been observed in a small number of cases following exposure to *inorganic arsenic*, either in Fowler's solution (78, 79) used for the long-term treatment of psoriasis and asthma, or in pesticides applied in vineyards, particularly in Germany (80), where use of arsenic-containing pesticides has been discontinued. In the latter group, carcinoma has been reported. But an experimental counterpart of the arsenic-induced hepatic malignancy does not exist. Possibly, excess arsenic exposure in industrial settings or in drinking water may account for cases of human angiosarcoma without established etiology (81). Such cases may constitute approximately three-fourths of all cases of human angiosarcoma.

The same morphologic sequence, including carcinoma, mainly cholangiocarcinoma, has also been observed in some individuals years after the administration of *thorium dioxide* for radiologic visualization, especially of brain lesions (82, 83). Again, worldwide this sequence represents only a small fraction of all hepatic malignancies, with fewer than 100 known cases. Thorium dioxide administration produces angiosarcoma in animals (84). Other forms of radiation rarely seem to produce hepatic tumors in man (85).

The entire group of tumors induced by sex steroids and environmental agents (the latter causing the sequence terminating usually in angiosarcoma) appears characterized by a relatively small number of cases. However, the strong causal relationship between the etiologic factors and hepatic malignancy is reflected both in animal models and the absence of cirrhosis. In cases of angiosarcoma this relationship is further supported by the rarity of these tumors in the general population. Prevention of both medicinal and industrial exposure appears to be easy and seems, to a great extent, to have been accomplished.

In passing it should be mentioned that a quantitatively small group of hepatocellular carcinomas are associated with *metabolic alterations* (8). Within this group, the most frequent association is with iron overload disease of the type of hemochromatosis. A less common association occurs between hepatocellular carcinoma and porphyria, α_1-antitrypsin deficiency, Wilson's disease, and tyrosinemia (the latter in children).

PECULIARITIES OF HUMAN HEPATIC MALIGNANCIES

Ever since the 1930s, when Yoshida and Kinosita produced hepatocellular carcinoma in rats by chemical agents, an increasing number of such agents have been shown to produce the tumor, often preceded by a nodular lesion, in experimental

animals, including primates (86). The long list of chemical agents known to have hepatic carcinogenic potential in animals includes food additives (such as safrole and ponceau red), pesticides, industrial agents, such as polyhalogenated biphenyls, dioxan, phenobarbital in mice, and many others, which have been listed in many excellent reviews (87, 88). The carcinogenic potential of these agents in animals has led to the assumption that chemical factors cause also hepatocellular carcinoma in man. However, a review of the literature reveals a dearth of information about substantiated carcinomas in man by the large number of these agents (89). For instance, in one case of hepatocellular carcinoma recorded years after injury from carbon tetrachloride, alcoholism was also present (90). The same lack of substantiated information applies to production of human cirrhosis (as a precursor of carcinoma) by these agents and by other industrial compounds. One apparent exception to this are compounds like trinitrotoluene, which have been associated with hypersensitivity reactions (89). Table 1 correlates the rate of incidence, certainty of association, animal models, and approaches to the prevention of different human hepatic malignancies. A reliable estimate as to the total yearly number of cases of hepatocellular carcinoma in the world is impossible. A conservative assumption based on a 5/100,000/year incidence worldwide would account for at least 150,000 cases per year which are presumably induced by the three common factors discussed. This contrasts with at most 30 cases per year worldwide by the known industrial and therapeutic factors.

It should be emphasized that the two apparently most important carcinogens incriminated in human cancer in other organ sites have not been unequivocally associated with hepatocellular carcinoma in man, even though they are metabolized in the human liver. Specifically, polycyclic hydrocarbons do not produce hepatic tumors in any species, and there is no evidence that nitrosocompounds, potent hepatocarcinogens in many species, including primates (86), cause human

TABLE 1
ETIOLOGIC FACTORS IN HUMAN HEPATIC MALIGNANCIES

"Carcinogens"	Incidence	Animal model	Certainty of association	Prevention
Hepatitis B	Highest	0	+	Vaccine Immunoglobulin
Alcoholism	High	0	+	Life style change??
Aflatoxin	High	+	++	Technologic?
Anabolic steroids	Very low	+	+++	Possible
Contraceptive steroids	Very low	+	±	Possible
Vinyl chloride	Very low	++	+++	Possible
Inorganic arsenic	Very low	0	++	Possible
Thorotrast	Very low	+	+++	Possible
Common hepato carcinogens in experimental animals (87, 88)	?	+++	?	

hepatocellular carcinoma. This peculiar protection of the human liver, particularly in adults, can possibly be explained by its biochemical and biological characteristics (91). The liver is rich in hydratases, which can remove ultimate carcinogens; it has high activity of endonucleases, which excise altered DNA; and the turnover of hepatocytes favoring carcinogenic transformation is particularly low.

This does not exclude the possibility that these substances, many of which are stored for a long time in human fat tissue, have effects on hepatic metabolism which are detrimental. In animals, the vast majority of these substances enhance the enzymatic action of the microsomal biotransformation system, which potentially increases both the amount and the life span of the ultimate bioactive carcinogen, which binds to macromolecules, particularly to DNA. This "induction" of the biotransformation occurs in man, but its long-term effects in man are not known except in relation to adverse drug reactions (92). Induction in epileptics as a result of specific drug therapy has not resulted in an increased incidence of tumors which cannot otherwise be explained (93). However, both the establishment of induction in man and its epidemiologic consequences as far as carcinogenesis in the liver and in other organ sites is concerned require further study.

CONCLUSIONS

The geographic distribution of human hepatic malignancies strongly suggests a causative role of environmental factors. The vast majority of malignancies in all areas of the world are usually associated with cirrhosis and one of three factors: hepatitis B infection, alcoholism, or aflatoxin exposure. The greatest chance for the prevention lies in limiting hepatitis B infection. Although they constitute only a very small number of all hepatic malignancies, some tumors not associated with cirrhosis have been caused by industrial and therapeutic factors and prevention of these tumors is being accomplished. However, the correctable environmental, including industrial, burden is small. A large number of common carcinogens in experimental animals, many of them environmental and industrial agents, have so far not been proven to produce hepatic malignancies in man. Nevertheless, these substances may alter the hepatic metabolism with consequences for the liver and other organs which still require establishment. As long as the consequences of exposure to these agents remain unproven, there can be no justification for any relaxation of vigilance.

REFERENCES

1. Linsell, D. A., and Higginson, J. (1976). The geographic pathology of liver cell cancer. *In* "Liver Cell Cancer" (H. M. Cameron, D. A. Linsell, and G. P. Warwick, Eds.), pp. 1–16. Elsevier/North-Holland Biomedical Press, Amsterdam.
2. Kew, M. C. (1978). Hepatocellular cancer in southern Africa. *In* "Primary Liver Tumors" (H. Remmer, H. M. Bolt, P. Bannasch, and H. Popper, Eds.), pp. 179–183. MTP Press Limited, Lancaster.
3. Bradshaw, E., and Harington, J. S. (1977). Temporal changes in primary liver cancer in Black gold miners from Mozambique. *S. Afr. Med. J.* 50, 2022.
4. Weiss, W., and Hanak, H. (1977). Epidemiologie des primaeren Leberkarzinoms in Österreich. *Leber Magen Darm* 7, 283–288.
5. Tuyns, A. J., and Obradovic, M. (1975). Unexpected high incidence of primary liver cancer in Geneva, Switzerland. *J. Natl. Cancer. Inst.* 54, 61–64.
6. Szmuness, W., *et al.* (1978). Prevalence of hepatitis B virus infection and hepatocellular carcinoma in Chinese-Americans. *J. Infect. Dis.* 137, 822–829.

7. Mason, T. J., *et al.* (1976). Atlas of Cancer Mortality for U.S. Counties: 1950–1969. DHEW Publication No. (NIH) 75-780. U.S. Department of Health, Education, and Welfare.
8. Peters, R. L. (1976). Pathology of hepatocellular carcinoma. *In* "Hepatocellular Carcinoma" (K. Okuda and R. L. Peters, Eds.), pp. 107–168. John Wiley, New York.
9. Ishak, K. G., and Gluntz, P. R. (1967). Hepatoblastoma and hepatocarcinoma in infancy and childhood. Report of 47 cases. *Cancer* 20, 396–422.
10. Mori, W., and Nagasako, K. (1976). Cholangiocarcinoma and related lesions. *In* "Hepatocellular Carcinoma" (K. Okuda and R. L. Peters, Eds.), pp. 227–246. John Wiley, New York.
11. Hou, P. C., and Pang, L.S.C. (1964). *Clonorchis sinensis* infestation in man in Hong Kong. *J. Pathol. Bacteriol.* 87, 245–250.
12. Lowenfels, A. B., and Norman, J. (1978). Isoniazid and bile duct cancer. *J. Amer. Med. Assoc.* 240, 434–435.
13. Cain, H., and Kraus, B. (1977). Entwicklungsstoerungen der Leber und Leberkarzinom im Saeuglings- und Kindesalter. *Dtsch. Med. Wschr.* 102, 505–509.
14. Popper, H., *et al.* (1978). Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic. Comparison with cases of unknown etiology. *Amer. J. Pathol.* 92, 349–376.
15. Baxter, P. J., *et al.* (1977). Angiosarcoma of the liver in Great Britain, 1963–73. *Brit. Med. J.* 2, 919–921.
16. Kubo, Y., *et al.* (1978). Detection of hepatocellular carcinoma during a clinical follow-up of chronic liver disease. Observations in 31 patients. *Gastroenterology* 74, 578–582.
17. Anthony, P. P. (1976). The background to liver cell cancer. *In* "Liver Cell Cancer" (H. M. Cameron, D. A. Linsell, and G. P. Warwick, Eds.), pp. 107–115. Elsevier/North Holland Biomedical Press, Amsterdam.
18. Kew, M. C. (1978). Hepatoma and the hepatitis B virus. *In* "Viral Hepatitis" (G. N. Vyas, S. N. Cohen, and R. Schmid, Eds.), pp. 439–450. Franklin Institute Press, Philadelphia.
19. Nayak, N. C., *et al.* (1977). Association of human hepatocellular carcinoma and cirrhosis with hepatitis B virus surface and core antigens in the liver. *Int. J. Cancer* 20, 643–654.
20. Sherlock, S., *et al.* (1970). Chronic liver diseases and primary liver cancer with hepatitis associated (Australia) antigen in serum. *Lancet* 1, 1243–1247.
21. Sheldon, W. H., and James, D. E. (1948). Cirrhosis following infectious hepatitis. A report of five cases in two of which was superimposed primary liver cell carcinoma. *Arch. Int. Med.* 81, 666–689.
22. Kew, M. C., *et al.* (1974). Hepatitis-B antigen and cirrhosis in Bantu patients with primary liver cancer. *Cancer* 34, 539–541.
23. Ohta, Y. (1976). Viral hepatitis and hepatocellular carcinoma. *In* "Hepatocellular Carcinoma" (K. Okuda and R. L. Peters, Eds.), pp. 73–81. John Wiley, New York.
24. Tabor, E. R. J., *et al.* (1977). Hepatitis B virus infection and primary hepatocellular carcinoma. *J. Natl. Cancer Inst.* 58, 1197–1200.
25. Werner, B. G., Murphy, B. L., and Maynard, J. E. (1976). Anti-e in primary hepatic carcinoma. *Lancet* 1, 696.
26. Larouze, B., *et al.* (1976). Host responses to hepatitis-B infection in patients with primary hepatic carcinoma and their families. A case/combined study in Senegal, West Africa. *Lancet* 2, 534–538.
27. Hadziyannis, S. J., and Tricyopoulos, D. (1978). Hepatocellular carcinoma in Greece and its relationship to the hepatitis B virus. *In* "Primary Liver Tumors" (H. Remmer, H. M. Bolt, P. Bannasch, and H. Popper, Eds.), pp. 431–435. MTP Press Limted, Lancaster.
28. Blumberg, B. S. (1977). Australia antigen and the biology of hepatitis B. *Science* 197, 18–25.
29. Popper, H. (1978). Considerations as to an association between hepatocellular carcinoma and hepatitis B. *In* "Viral Hepatitis" (G. N. Vyas, S. N. Cohen, and R. Schmid, Eds.), pp. 451–454. Franklin Institute Press, Philadelphia.
30. Hadziyannis, S., *et al.* (1973). Cytoplasmic hepatitis B antigen in "ground-glass" hepatocytes of carriers. *Arch. Pathol.* 96, 327–330.
31. Hess, G., *et al.* (1977). Expression of hepatitis B virus-specific markers in asymptomatic hepatitis B surface antigen carriers. *Infect. Immunol.* 17, 550–554.

32. Gerber, M. A., *et al.* (1974). Electron microscopy and immunoelectronmicroscopy of cytoplasmic hepatitis B antigen in hepatocytes. *Amer. J. Pathol.* 75, 489–502.
33. Okita, K., *et al.* (1977). Early lesions and development of primary hepatocellular carcinoma in man—association with hepatitis B viral infection. *Gastroenterol. Japonica* 12, 51–57.
34. Huberman, E. (1977). Viral antigen induction and mutability of different genetic loci by metabolically activated carcinogenic polycyclic hydrocarbons in cultured mammalian cells. *In* "Origins of Human Cancer, Book C, Human Risk Assessment" (H. H. Hiatt, J. D. Watson, and J. A. Winsten, Eds.), Cold Spring Harbor Conferences on Cell Proliferation, Vol. 4, pp. 1521–1535. Cold Spring Harbor Laboratory, Cold Spring Harbor.
35. Lin, J. J., Liu, C., and Svoboda, D. J. (1974). Long term effects of aflatoxin B_1 and viral hepatitis on marmoset liver. A preliminary report. *Lab. Invest.* 30, 267–278.
36. Purcell, R. H., and Gerin, J. L. (1978). Hepatitis B vaccines. On the threshold. *Amer. J. Clin. Pathol.* 70 (Suppl), 159–169.
37. Dosik, H., and Jhaveri, R. (1978). Prevention of neonatal hepatitis B immunoglobulin. *N. Engl. J. Med.* 298, 602–603.
38. Beasley, R. P., and Stevens, C. E. (1978). Vertical transmission of HBV and interruption with globulin. *In* "Viral Hepatitis" (G. N. Vyas, S. N. Cohen, and R. Schmid, Eds.), pp. 333–346. Franklin Institute Press, Philadelphia.
39. Alter, H. J., Holland P. V., Purcell, R. H., and Popper, H. (1978). Transmissible agent in non-A, non-B hepatitis. *Lancet* 1, 459–463.
40. Okuda, K., and Nakashima, T. Hepatocellular carcinoma: A review of the recent studies and developments. *In* "Progress in Liver Diseases" (H. Popper and F. Schaffner, Eds.), Vol. VI. Grune & Stratton, New York, pp. 639–650, 1979.
41. Worner, T., and Lieber, C. S. Hepatic carcinoma in alcoholics without cirrhosis. In preparation.
42. Lee, F. (1966). Cirrhosis and hepatoma in alcoholics. *Gut* 7, 77–85.
43. Gall, E. A. (1960). Primary and metastatic carcinoma of the liver. Relationship to hepatic cirrhosis. *Arch. Pathol.* 70, 226–232.
44. MacDonald, R. A., and Mallory, G. K. (1958). The natural history of postnecrotic cirrhosis. A study of 221 autopsy cases. *Amer. J. Med.* 24, 334–357.
45. Schmidt, W., and de Lint, J. (1972). Causes of death of alcoholics. *Quart. J. Stud. Alc.* 33, 171–185.
46. Monson, R. R., and Lyons, J. L. (1975). Proportional mortality among alcoholics. *Cancer* 36, 1077–1079.
47. Martini, G. A. The role of alcohol in the etiology of cancer of the liver. *Dtsch. Med. Wschr.*, in press.
48. Hällén, J., and Linné, I. (1970). Cirrhosis of the liver in one community. A study of 768 cases of liver cirrhosis from a city with one hospital: Incidence, etiology and prognosis. *In* "Skandia International Symposia. Alcoholic Cirrhosis and Other Toxic Hepatopathias" (A. Engel and T. Larsson, Eds.), pp. 336–352. Nordiska Bokhandelns Förlag, Stockholm.
48a. Ugarte, G., and Donoso, S. (1978). Primary hepatic tumors in Chile. *In* "Primary Liver Tumors" (H. Remmer, H. M. Bolt, P. Bannasch, and H. Popper, Eds.), pp. 165–169. MTP Press Limited, Lancaster.
49. Popper, H. (1977). Pathologic aspects of cirrhosis. A review. *Amer. J. Pathol.* 87, 228–264.
50. Hasumura, Y., Teschke, R., and Lieber, C. S. (1974). Increased carbon tetrachloride hepatotoxicity, and its mechanism, after chronic ethanol consumption. *Gastroenterology* 66, 415–422.
51. Obe, G., and Herha, J. (1975). Chromosomal damage in chronic alcohol users. *Humangenetik* 29, 191–200.
52. Wogan, G. N. (1976). The induction of liver cell cancer by chemicals. *In* "Liver Cell Cancer" (H. M. Cameron, D. A. Linsell, and G. P. Warwick, Eds.), pp. 123–136. Elsevier/North-Holland Biomedical Press, Amsterdam.
53. Buening, M. K., *et al.* (1978). 7,8-Benzoflavone stimulates the metabolic activation of aflatoxin B_1 to mutagens by human liver. *Biochem. Biophys. Res. Commun.* 82, 348–355.
54. Van Rensburg, S. J., *et al.* (1974). Primary liver cancer rate and aflatoxin intake in a high cancer area. *S. Afr. Med. J.* 48, 2508a–2508d.
55. Shank, R. C. (1977). Epidemiology of aflatoxin carcinogenesis. *In* "Advances in Modern Toxicol-

ogy, Vol. 3. Environmental Cancer" (H. F. Kraybill and M. A. Mehlman, Eds.), pp. 291–318. Hemisphere Publishing Corporation, Washington.
56. Tandon, B. N., *et al.* (1977). Study of an epidemic of jaundice, presumably due to toxic hepatitis, in Northwest India. *Gastroenterology* **72**, 488–494.
57. Purchase, I. F., and van der Watt, J. J. (1970). Acute toxicity of sterigmatocystin to rats. *Food Cosmet. Toxicol.* **8**, 289–295.
58. Uraguchi, K., *et al.* (1972). Chronic toxicity and carcinogenicity in mice of the purified mycotoxins, luteoskyrin and cyclochlorotine. *Food Cosmet. Toxicol.* **10**, 193–207.
59. Svoboda, D. J., and Reddy, J. K. (1972). Malignant tumors in rats given lasiocarpine. *Cancer Res.* **32**, 908–912.
60. Johnson, F. L., *et al.* (1972). Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* **2**, 1273–1276.
61. Farrell, G. C., *et al.* (1975). Androgen-induced hepatoma. *Lancet* **1**, 430–431.
62. Maedows, A. T., Naiman, J. L., and Valdes-Dapene, M. (1974). Hepatoma associated with androgen therapy for aplastic anemia. *J. Pediat.* **84**, 109–110.
63. Popper, H., *et al.* (1977). Comparison of neoplastic hepatic lesions in man and experimental animals. *In* "Origins of Human Cancer, Book C, Human Risk Assessment" (H. H. Hiatt, J. D. Watson, and J. A. Winsten, Eds.), Cold Spring Harbor Conferences on Cell Proliferation, Vol. 4, pp. 1359–1382. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.
64. Klatskin, G. (1977). Hepatic tumors: Possible relation to use of oral contraceptives. *Gastroenterology* **73**, 386–394.
65. Jick, H., and Herman, R. (1978). Oral-contraceptive-induced benign liver tumors—The magnitude of the problem. *J. Amer. Med. Assoc.* **240**, 828–829.
66. Knowles, D. M., II, *et al.* (1978). The clinical, radiologic, and pathologic characterization of benign hepatic neoplasms. Alleged association with oral contraceptives. *Medicine* **57**, 223–237.
67. Gold, J. H., Guzman, I. J., and Rosai, J. (1978). Benign tumors of the liver. Pathologic examination of 45 cases. *Amer. J. Clin. Pathol.* **70**, 6–17.
68. Altmann, H.-W. (1978). Pathology of human liver tumors. *In* "Primary Liver Tumors" (H. Remmer, H. M. Bolt, P. Bannasch, and H. Popper, Eds.), pp. 53–71. MTP Press Limited, Lancaster.
69. Edmondson, H. A., *et al.* (1977). Regression of liver cell adenomas associated with oral contraceptives. *Ann. Int. Med.* **86**, 180–182.
70. Davis, M., *et al.* (1975). Histological evidence of carcinoma in a hepatic tumour associated with oral contraceptives. *Brit. Med. J.* **4**, 496–498.
71. Christophersen, W. M., and Mays, E. T. (1977). Liver tumors and contraceptive steroids: Experience with the first one hundred registry patients. *J. Natl. Cancer. Inst.* **58**, 167–171.
72. Carcinogenicity Tests of Oral Contraceptives. (1972). A Report by the Committee on Safety of Medicines. London, Her Majesty's Stationery Office.
73. Maltoni, C., and Lefemine, G. (1974). Carcinogenicity bioassays of vinyl chloride. 1. Research plan and early results. *Environ. Res.* **7**, 387–405.
74. Creech, J. L., Jr., and Johnson, M. N. (1974). Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J. Occup. Med.* **16**, 150–151.
75. Maltoni C: (1976). Predictive value of carcinogenesis bioassays. *Ann. N.Y. Acad. Sci.* **271**, 431–447.
76. Gokel, J. M., Liebezeit, E., and Eder, M. (1976). Hemangiosarcoma and hepatocellular carcinoma of the liver following vinyl chloride exposure: A report of two cases. *Virchows Arch. Pathol. Anat.* **372**, 195–203.
77. Spirtas, R., and Kaminski, R. (1978). Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. *JOM* **20**, 427–429.
78. Morris, J. S., *et al.* (1974). Arsenic and noncirrhotic portal hypertension. *Gastroenterology* **66**, 86–94.
79. Lander, J. J., *et al.* (1975). Angiosarcoma of the liver associated with Fowler's solution (potassium arsenite). *Gastroenterology* **68**, 1582–1586.
80. Roth, F. (1957). Arsen-Leber-Tumoren (Haemangioendotheliom). *Zschr. Krebsforsch* **61**, 468–503. 1957

81. Falk, H. In preparation.
82. da Silva Horta, J., and Cayolla da Motta, L. (1967). Follow-up study of thorium dioxide patients in Portugal. *Ann. N.Y. Acad. Sci.* **145**, 830–842.
83. Selinger, M., and Koff, R. S. (1975). Thorotrast and the liver: A reminder. *Gastroenterology* **68**, 799–803.
84. Swarm, R. L., Miller, E., and Michelitch, H. J. (1962). Malignant vascular tumors in rabbits injected intravenously with colloidal thorium dioxide. *Pathol. Microbiol. (Basel)* **25**, 27–44.
85. Moore, T. A., Ferrante, W. A., and Crawson, T. D. (1976). Hepatoma occurring two decades after hepatic irradiation. *Gastroenterology* **71**, 128–132.
86. Adamson, R. H. (1972). Long-term administration of carcinogenic agents to primates. *In* "Medical Primatology" (J. Moor-Jankowski, Ed.), pp. 216–255. S. Karger AG, Basel.
87. Farber, E. (1976). On the pathogenesis of experimental hepatocellular carcinoma. *In* "Hepatocellular Carcinoma" (K. Okuda and R. L. Peters, Eds.), pp. 3–22. John Wiley, New York.
88. Higginson, J. (1977). The role of the pathologist in environmental medicine and public health. *Amer. J. Pathol.* **86**, 459–484.
89. Popper, H., *et al.* Environmental hepatic injury in man. *In* "Progress in Liver Diseases" (H. Popper and F. Schaffner, Eds.), Vol. VI. Grune & Stratton, New York, pp. 605–638, 1979.
90. Tracey, J. P., and Sherlock, P. (1968). Hepatoma following carbon tetrachloride poisoning. *N.Y. State J. Med.* **68**, 2202–2204.
91. Popper, H. Hepatocellular carcinoma—Old and new problems. *In* "Problems in Liver Diseases" (C. S. Davidson, Ed.). Stratton Intercontinental Medical Book Corporation, New York, pp. 14–24, 1979.
92. Pessayre, D., *et al.* (1977). Isoniazid-rifampizin fulminant hepatitis. A possible consequence of the enhancement of isoniazid hepatotoxicity by enzyme induction. *Gastroenterology* **72**, 284–289.
93. Clemmesen, J., and Hjalgrim-Jensen, S. (1978). Is phenobarbital carcinogenic? A follow-up of 8078 epileptics. *Ecotoxicol. Environ. Safety* **1**, 457–470.