

ANGIOSARCOMA OF THE HUMAN LIVER

by

Howard L. Richardson, M.D.
Environmental Protection Agency

FILE COPY
DO NOT REMOVE

Similar terminology or synonyms or semantics used for the same tumor are to be found in the literature.

1. Hemangio-endothelial Sarcoma
2. Malignant vascular tumor of the liver
3. Kupffer Cell Sarcoma
4. Hemangioendothelioma
5. Hemangioblastoma
6. Endothelioblastoma
7. Reticuloendothelioma (Purdy Stout)
8. Angioplasic Sarcoma
9. Primary Hepatic Sarcoma
10. Angioblastic Sarcoma
11. Endothelioma, grades - undifferentiated, well-differentiated, and anaplastic
12. Hemangiosarcoma
13. Malignant Hemangiosarcoma
14. Malignant Hemangioendothelioma
15. Metastasizing Hemangioma

Historically, there are many reasons for the above fence-sitting type of terminology.

In 1940, James Ewing reports in his textbook, *Neoplastic Disease*, "I do not believe, therefore, that the existence of a true angiosarcoma arising from blood vessels of the liver has been satisfactorily demonstrated."

As late as 1948, Rupert A. Willis in his textbook on *Pathology of Tumors* states, "We come now to a difficult question: Do truly neoplastic angiomatous growths occur? They are very

rare and most supposed examples are either multifocal hamartomas or vascular tumors of other kinds."

Thorotrast and Angiosarcoma of the Human Liver

1925----Egas Moniz of France first demonstrated that a radioactive material in the form of colloidal Thorium dioxide could be used in cerebral vessel visualization.

1930----Heyden Products manufactured Thorotrast for wide distribution in Europe and the United States for use in vascular visualization-arteriography-hepatosplenography- and cerebral graphy.

1932----The Council of Pharmacy of the American Medical Association took a stand against its use.

1940----Thorotrast was still in use, although animal experimentation had demonstrated the formation of cancers and in the liver, angiosarcomas.

1947----Finally discontinued when the human cases of angiosarcomas were reported.

It was K.H. Bauer of Germany who compared the time of appearance of neoplasms after the injection of thorotrast, experimentally produced in animals, with their average life expectancy and the average span of life in man. He came to the conclusion that such tumors should appear between the 12th and the 18th year after the injection into the vascular system of man (textbook).

- 1947----MacMahan, H.E., Murphy, A.S., and Bates, M.I.,
Endothelial Cell sarcoma of the liver following
thorotrast injection, Am J Path, 23, 585-611.
The first case of angiosarcoma from thorotrast
was reported in the U.S. The latency period was
17 years.
- 1961----Nettleship, A. and Fink, W.J., Neoplasms of the
liver following injection of thorotrast,
Am J Clin Path, 35, 422-426.
This was the 8th reported case of angiosarcoma
of the liver due to thorotrast. The latency period
was 16 years.
- 1961----Suckow, E.G., Henegar, G.G., and Baserza, R.,
Tumors of the liver following administrations of
thorotrast, Am J Path, 38, 663-677.
10 cases of angiosarcoma of the liver were reported
due to thorotrast used intravascularly. The
latency periods were 3 to 24 years, with the
average being 15 years.
- 1965----Da Silva Horta, J, et al, Malignancy and other
late effects following the administration of thoro-
trast, Lancet, 2, 201-205.
22 additional cases of angiosarcoma of the liver
were reported in this article.

By this time, hundreds of cases of angiosarcoma of the liver have been produced from this radioactive substance. It was first claimed there was no danger because thorotrast was an alpha emitter. However, the standard dose of 75 ml ordinarily used gives a gamma radiation equivalent of 1.37 micrograms of radium. The half-life of thorium is 1.39×10 years, and the radioactivity of thorium dioxide rises after 5 years; the breakdown products are active and reach a peak after 15 years. With the Kupffer cells being a storage point in the liver, one can easily see the damaging effect of radiation.

Arsenic and Angiosarcoma of the Human Liver

More than any other element of metal carcinogenesis, arsenic remains one of the enigmas. It is commonly referred to as one of the implicating factors in human cancer formations. One group in Chicago claims it is a producer of angiosarcoma of the human liver. It is for this reason that a short literature review is made.

Complicating the interpretations of studies dealing with arsenic is the fact that no satisfactory animal models have been found.

1947----Neubauer, O., Arsenical cancers-a review, Brit J Cancer, 1, 192-251.

The author estimated the latency of arsenical cancer to be 18 - 20 years.

1953----Sommers, S.C. and McManus, R.G., Multiple
arsenical cancers of the skin and internal organs,
Cancer, 6, 347-359.

The estimated latency of arsenical cancer was
13 to 50 years.

1956----Roth, F., Zeit Krebsforsch, 61, 287-319.

1957----Roth, F., Zeitschrift Krebs Forschung, Bd., 61(s),
468-503.B.

3 hemangioendothelial sarcomas of the liver were
described from 27 autopsies in vintner. Latency
in the German Vineyard workers was 12 to 17 years.
Estimated intake of arsenic was 53.7 gms over a
12 year period.

1959----Roth, F., Zentrelblatt Alleg Pathol, 100, 529-530.

8 hemangiosarcomas of the liver were reported in a
study from 82 autopsies. These were vineyard
workers exposed to chronic arsenic intoxication in
the form of oral ingestion via insecticides, sprays,
and dust.

1968----Regelson, W., Kim, V., Ospina, J., and Holland, J.F.,

One case of hemangioendothelial sarcoma of liver
from Chronic Arsenic Intoxication by Fowler's
Solution, Cancer, 21, 514-521.

Latency period of 17 years plus 7. The amount of
arsenic ingested was estimated to be about 50 grams.

An Environmental and Industrial Chemical Registry is needed to face our daily environmental chemical exposure. Most recently, another case of angiosarcoma has been reported with no history of thorium dioxide or arsenic. The case was from the New York Hospital, Cornell Medical Center, and was in a 46 year old white male.

1974----Sussman, E.B., Nydick, L., and Gray, G.F.,

One case report of hemangioendothelial sarcoma of liver, AMA Arch of Pathol, 97, 39-42.

In summary, we have histologically angiosarcomas from thorotrast, arsenic and vinyl chloride, which have the same morphological appearances.

Spontaneous Angiosarcomas of the Liver in Animals

Rats - In the rat, this is an unknown entity. Dr. K.C. Snell at the National Cancer Institute, in thousands of animals, has never seen this lesion. I have in my files records of over 10,000 rats with many different strains and have never seen this lesion.

Mice - In mice, angiosarcomas do spontaneously occur. This is in the Haired and Hairless strain H.R. mouse. Hemangio-endotheliomas (angiosarcomas) were observed in 45 out of 251 in the control groups.

(Deringer, M.K., J of the Nat Cancer Inst, 12, 437-445, Oct 1951).

As would be expected, when O-aminoazotoluene was subcutaneously inoculated, the incidence of angiosarcomas increased.

(Ibid., 17, 533-539, 1956). Swiss Albino mice have a spontaneous 5% occurrence of angiosarcoma of the liver.

Experimental Angiosarcomas in Animals due to Thorotrast

1936----Capillary angiosarcomas were produced in mice by F. Selbie. Selbie, F., Experimental production of sarcoma with thorotrast, Lancet, 2, 847.

1938----Reticulosarcomas (angiosarcomas) of the liver were produced by intravenous injections. Onufrio, O., Su di un caso di reticulosarcoma sperimentale do thorotrast, Folia Med, 24, 1245 (probably used a different species).

Arsenic Experimentation in Animals and Its Effect on Man

An excellent monograph on Arsenicals has been written by A. Furst and will be published in the future by the World Health Organization Working Group on the Evaluation of Carcinogenic Risks of Chemicals to Man.

Chemicals Which Produce Angiosarcomas of the Liver in Animals

Nitrosodimethylamine - (Magee, P.N., Barnes, J.M., Brit J Cancer, 10, 114, 1956) Orally administered the chemical to rats.

Hirold, K.M., J of th Nat Cancer Inst, 39, 1009, 1967. Subcutaneous administration to Syrian Hamsters. Otsuka, H. and Kuwahara, A., Gann, 62, 147-156, 1971. By oral administration and subcutaneous injection to DDD and BAL b/c strain mice.

Urethane - Deringer, M.K., J of the Nat Cancer Inst, 34, 841-847, 1965. Gave intraperitoneal injections to DBA/2eBDe strains of mice.

1,2-Dimethylhydrazine Dihydrochloride - Syrian Golden Hamsters were given, in water daily, 0.156 mg to the female and 0.161 mg to the male. Angiosarcomas occurred in 89% of the females and 82% in the males. The tumors were in the liver lung muscle, heart, and pancreas. No such tumor is seen in the control. (Toth, B., Cancer Res, 32, 2818-2827, 1972)

Ethylhydrazine hydrochloride - 0.0125% was given in drinking water and 38% vascular tumors were produced in Swiss Albino strain mice. (Toth, B., Scientific Proceedings, AAPB, San Francisco, Ca., 1974) N-Butyl-hydrazine HCL - only lung cancer. 1-carbamyl-2-phenylhydrazine - only lung cancer. Control incidence of angiosarcoma in the Swiss Albino mouse is 5%.

Methylhydrazine - (a rocket fuel component) Syrian Golden Hamsters received 0.01% in drinking water. Angiosarcoma of the liver (malignant histiocytoma, Kupffer cell sarcoma) was produced in 32% of the females and 54% of the males. Latency period was 70 and 78 weeks. No such tumor was seen in the controls. (Toth, B. and Shimizu, H., Cancer Res, 33, 2744-2753, 1973)

1-carbamyl-2-phenylhydrazine - A 0.25% solution in drinking water was given throughout the life span of Swiss mice. Angiosarcomas of the liver occurred in 8 out of 72, and in the controls, 4 out of 44. (Toth, B. and Shimizu, H., J of the Nat Cancer Inst, 52, 241-251, 1974)

Are Environmental Hazards in This Group?

Hydrazines are used in industry as a rocket propellant. Monomethylhydrazines are used as corrosive agents. Maleic hydrazide used as a herbicide is hydrolysed to hydrazines. 2-Hydroxyethylhydrazine is used to ripen pineapples and is sprayed on. Phenylhydrazine is used in medicine for polycythemia vera.

Nephroblastoma

Since Professor C. Maltoni mentioned the high incidence of nephroblastoma in rats treated with vinyl chloride, a brief statement is included for the Interagency Group and the Environmental Protection Agency Task Force.

Renal Adenocarcinoma in our population has shown a rapidly increasing incidence with age in both sexes. This is well-documented by the State of California, Alameda County, Department of Public Health, California Tumor Registry (1960-1969). A review on Cancer of the Kidney - Etiology, Epidemiology, and Pathology has been recently published by J.L. Bennington in Cancer Research, 32, 1017-1029, November 1973. In view of Dr. Maltoni's

experiments, should not the vinyl chloride workers and families be studied with this lesion in mind, as well as the liver?

Howard L. Richardson, M.D.

Medical Officer Pathologist
Pesticide Office Program
Environmental Protection Agency

April 17, 1974

ADDENDUM TO "ANGIOSARCOMA OF THE HUMAN LIVER"

by

Howard L. Richardson, M.D.

Thorotrast

1972----Thorotrast induced hepatoma, Smoron, C.L. and Battifora, H.A., Cancer, 30, 1252-1259. A case of thorotrast hepatoma is presented in a 60 year old female with a latency period of 28 years. This article is an excellent review and states that an increase has taken place in Japan and Scandinavian countries. No increase in American U.S. citizens.

1973----Thorotrast induced hepatoma presented as hyperthyroidism, Kiely, J.M., Titus, J.L., and Orvis, A.L., Cancer, 31, 1312-1314, 1973. Since 1947, approximately 115 additional cases of malignant tumors of the liver have been noted. It is estimated there are still 50,000 to 100,000 carriers of this radioactive contrast media. Ref: Minn Med, 53, 1137-1139, 1970. Primary liver sarcomas 22 years after the administration. This contrast media is still the best for visualization of the cerebral vessels and is used for this purpose. Benefit versus risk ratio.

Arsenic and Human Cancer Formation

Tseng, W.P., et al, Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan, J Natl Cancer Institute, 40, 453-- , 1968. The arsenic level in some drinking water is above 0.6 ppm. In areas of high concentration skin cancer are 21.4 per 1,000 of population. In areas of low concentration - 2.6 per 1,000 of population.

In view of the reported cases of human arsenic angiosarcomas, a review of the histopathological material present in the Taiwan pathological laboratories is warranted because of the following report in the literature:

Ti n-Wu Lin, et al, Serum alpha-fetoglobulin and primary cancer of the liver in Taiwan, Cancer, 30, 435-443, 1972, From the Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan, Republic of China (Taiwan also has a large vinyl chloride manufacturing plant). Primary cancer of the liver is as high as that of Africa and other Asian countries. 5.5% of all autopsies. 19.5% of all male cancer patients at the above hospital in the last 10 years. No histological classifications were given.

A Review of Malignant Hemangioendotheliomas in Infants and Children (Angiosarcoma)

1961----Kauffman, S., and Stout, A., Malignant hemangioendothelioma in infants and children, Cancer, 14, 1189--1961. Malignant vascular tumors are rare at all ages, but almost curiosities in children. 129 cases are recorded in the Laboratories of Columbia University College of Physicians and Surgeons, New York, New York, during the past 54 years. 9 cases were in children less than 16 years of age or 7%. In a review of the literature only 9 other acceptable cases could be located in the neck, jaw & mouth, arm, femur, gluteal muscle, and leg. The 9 cases of Kauffman and Stout were distributed as follows:

- (1) Age 9, male, lymph node of the neck with metastasis to the lung.
- (2) Age 8, female, scapula tumor.
- (3) Age 14, male, right erector spinal muscles.
- (4) Age 23 months, female, liver angiosarcoma.
- (5) Age 13, female, distal phalanx of the right toe.
- (6) Age 12, male, scalp.
- (7) Age 17, female, right upper eyelid.
- (8) Age 15, male, middle right finger (fifth).
- (9) Age 7, female, thigh.

1969----Blumenfeld, T., Flemming, I., and Johnson, W., Juvenile hemangioendothelioma of the liver: Report of a case and review of the literature, Cancer, 24, 853--1969. Prior to 1961, these authors had four cases that survived surgery and two cases after. It is not clear what their yearly distributions were in their review, but they are as follows:

- (1) Case of hemangioendothelioma in a 2½ year old female. The solitary nodule was removed and the patient still survived.
- (2) 4 cases of solitary nodules successfully removed in children 2½ months and above in age.
- (3) 36 cases with multiple liver tumors - all died within 6 months.

1973----Hansen, R.C., et al, Cancer, 32, 136-141, 1973.
Describes a case in a 7 month old female of mesenteric hemangioendothelioma with thrombocytopenia which received radiation therapy and had a resolution after 1000 rads.

Statistical Occurrence of Hepatoblastoma in Children from Autopsy

1971----El-Domeiri, A.A., Huvos, A.G., Goldsmith, H.S., and Foote, F.W., Jr., Primary malignant tumors of the liver, Cancer, 27, 7-11, 1971. This study represents a twenty year review at the Memorial Hospital, New York City, between 1947-1966.

- (1) 137 primary malignant tumors of the liver cells.
- (2) 23 found in children (16%) under the age of 14 years with the youngest one 8 months of age. All had been diagnosed by the pathologists as hepatocellular carcinoma of the adult or embryonal type.

Adenocarcinoma

Synonyms and related terms: alveolar carcinoma, clear cell adenocarcinoma, dark cell adenocarcinoma, granular cell carcinoma, Grawitz tumor, hypernephroid carcinoma, hypernephroma, papillary cystadenocarcinoma, parenchymal carcinoma.

Nephroblastoma

This was the term used by Professor Maltoni, and in view of the vinyl chloride problem, needs histopathological clarification at the earliest possible date.

Synonyms and related terms: adenomyosarcoma, adenosarcoma, alveolar carcinoma, blastoma tumor, blastoma mesoblastica polyvalentia, carcinosarcoma, chondrosarcoma, developmental tumor, dysembryoma, dysembryoplasia, embryoma, embryonal adenocarcinoma, embryonal adenomyosarcoma, embryonal adenosarcoma, embryonal carcinoma, embryonal mixed tumor, embryonal nephroma, embronal

sarcoma, embryonary nephroma, fibro-lipo-osteoad nom atypique, fibrosarcoma, hypernephroid sarcoma, leiomyoadenosarcoma, leiomyosarcoma, malignant embryoma, malignant leiomyoma, malignant nephroma, malignant teratoma, mesenchymal tumor, mesoblastic nephroma, mesoblastic sarcoma, mesothelioma, mixed teratoid tumor, myoblastic sarcoma, myochondroadenosarcoma, myochondrosarcoma, myofibrosarcoma, myoma sarcomatodes, myosarcoma striocellulare, nephrogenous dysembryoma, osteoblastoma, rhabdomyosarcoma, round cell sarcoma, sarcoma fusocellulare, sarcoma musculaire, spindle cell sarcoma, teratoma, unclassified embryonal tumor, Wilm's tumor.

In view of the above bewildering nomenclature, I have written to Professor Maltoni on behalf of the Environmental Protection Agency to bring representative slides to New York on May 8-11, 1974 for the National Academy of Sciences' vinyl chloride meeting. I have also requested slides and block for the National Cancer Institute's Small Animal Tumor Registry.

Carcinoma of the Kidney in a 15 Year Male

1973----Pratt-Thomas, H.R., Spicer, S.S., Upshur, J.K., and Greene, W.B., Cancer, 31, 719-725, 1973.
Until 1934, renal cell carcinoma in children was controversial and in doubt. However, by 1973, we now have a total number of 59 cases reported in the English literature.