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ANGIOSARCOMA OF THE HUMAN LIVER

Similar Terminology or ^{Synonyms} ~~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. Angioplasmic 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
- double
space*

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

In 1940 James Ewing reports in his textbook on "Neoplastic
Disease" quote: "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.

1961—— Tumors of the Liver following Administrations of
Thoratrast. Suckow, E.G., Henegar, G.E., and Baserza, R.
Am. Journal of Pathology. Vol. 38: 663--677.

due to thoratrast used intravascularly.

The latency periods were 3 to 24 years with the average 15 years.

1965—— Malignancy AND other Late Effects Following the
Administration of Thorotrast. Da Silva Horta, J. et al.:
Lancet 2: 201--205.

22 Additional cases of Angiosarcoma ~~in~~ 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
~~the~~ 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 micro-gram of
radium. The half life of thorium is 1.39×10^4 years, and the
radioactivity of thorium dioxide rises after 3 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.

*Double
Space*

THORATRAST AND ANGIOSARCOMA OF THE HUMAN LIVER

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

distribution in Europe and the United States for use vascular visualization-arteriography-hepatosplenography- and cerebral graphy.

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

1940——Thoratrast was still in use although animal experimentation had demonstrated the formation of ^{CANCERS} carcinomas 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 ^{of} should appear between the 12th and the 18th year after the injection into the vascular system of man. (TEXT BOOK)

double space

1947——Endothelial Cell Sarcoma of the Liver following the Thoratrast Injection. MacMahan, H.E., Murphy, A.S., and Bates, M. I. American Journal of Pathology

23: 585--611.

The first case of angiosarcoma from thoratrast was reported in the U.S.A. The latent period was 17 years.

1961——Neoplasms of the Liver following Injection of Thoratrast. Nettleship, A., and Fink, W. J. Am. Journal of Clinical Pathology Vol 35: 422--426.

This was the 8th reported case of angiosarcoma of the liver ~~due to thoratrast~~ due to thoratrast. The latency period was 16 years.

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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 the "Silent Killer" and is one of the important factors in human ~~carcinogenesis~~ cancer formations. One group in Chicago claims it is a producer of angiosarcoma of the human liver. It is for this reason a short brief literature review is made.

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

1947—Arsenical Cancers—a Review, Neubauer, O.: British Journal of Cancer 1: 192—251.

The authors estimated the latency of arsenical cancer to be 18—20 years.

1953—Multiple Arsenical Cancers of the Skin and Internal Organs. Sommers, S. C., and McManus, R. G.. 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.

Three hemangioendothelial Sarcomas of the liver were described from 27 autopsies in vinters.

Latency in the German Vineyard workers was 12 to 17 years.

Estimated intake of Arsenic was 53.7 Gms over a 12 yr. period.

1959—Roth, F.: Zentrelblatt Alleg. Pathol. 100: 529—530.

Eight 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— One case of Hemangioendothelial Sarcoma of Liver

Fowler's Solution. Regelson, W., Kim, V., Ospina, J.,
and Holland, J.F. 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 ~~everyday~~ ^{daily} environmental chemical exposure. Most recently
another case of Angiosarcoma has been reported with no history
of thorium dioxide or arsenic. ~~However~~ The case was from the
New York Hospital, Cornell Medical Center and was in a 46 year
old white male.

1974— One Case Report of Hemangioendothelial Sarcoma of

Liver and Hemochromatosis. (With widespread metastasis)
Sussman, E. B., Nydick, L., and Gray, G. F.,
A.M.A. Archives of Pathology 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
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 Angiosarcoma does spontaneously occur. This is
~~in mice~~ in the Haired and Hairless strain H.R. mouse. Hemangio-
endotheliomas (Angiosarcomas) were observed in 45 out of
251 in the control groups. w 1870

Deringer, M. K., J. of the National Cancer Institute.
Vol: 12: 437-445, Oct. 1951.

As would ~~xxx~~ be expected when (C-aminazotoluene) was
subcutaneously inoculated the incidence of angiosarcomas
increased. -----Ibid; 17: 533-538, 1956

Swiss Albino mice have a spontaneous 3% occurrence of
angiosarcoma of the liver.

EXPERIMENTAL ANGIOSARCOMAS IN ANIMALS DUE TO THOROTRAST

1936-----Capillary angiosarcomas were produced in mice by
RATS Selbie, F., Experimental Production of Sarcoma with
~~xxx~~ Thorotrast. Lancet 2: 847.

1938-----Reticulosarcomas(angiosarcomas) of the Liver was produced
by intravenous injections. Onufrio, G., Su di un caso di
Reticulosarcoma sperimentale do Thorotrast. Folia med.
24: 1245. (probably used different species)

ARSENIC EXPERIMENTAL 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 Organisation
working group on Evaluation of Carcinogenic Risks of Chemicals to
Man.

Chemicals which produce angiosarcomas of the liver in animals

Nitrosodimethylamine---Hagee, F. K., Barnes, J.M., British
Journal of Cancer 10: 114, 1956.

Herrold, K. M., Journal of the National Cancer
Institute. 39: 1008, 1967. Subcut. administration
to Syrian Hamsters.

Otsuka, H. and Kuwahara, A., Gann 62:147-156, 1971.
By oral administration and subcutaneous injection
to DDD & BAL b/c strain mice.

Urethane-----~~Experiments with mice~~ DERINGER, M. K.,
Journal of the National Cancer Institute
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 livers, lungs, muscle, heart, and pancreas.
No such tumor is seen in the control.
Toth, B., Cancer Research, 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, A.A.P.B. San Fran 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. Angio-
Sarcoma of the liver (Malignant Histiocytoma)
(Kupffer Cell Sarcoma) was produced in 32 %
of the females and 54 % of the males.
Latency period 70 and 78 weeks,.
No such tumor was seen in the controls,

Toth, B., and Shimizu, H. Cancer Research
33: 2744-2753, 1973.

1-Carbonyl-2-phenylhydrazine is a 0.25% solution in drinking

Swiss mice. Angiosarcomas of the liver
occurred in 8 out of 44, and in the controls
4 out of 44. Toth, B. and Shimizu, H.
Journal of the National Cancer Institute.
52: 241-251, 1974.

100 mg 0.5% in
2 ml
100 mg 0.5% in
8 ml
37 mg 0.5% in
100 mg 0.5% in

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 hydrolyzed to hydrazines.

2-Hydroxyethylhydrazine is used to ripen pineapples and is sprayed.

Phenylhydrazine is used in medicine for polycythemia vera.

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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 is recently published by J.L. Bennington in Cancer
Vol 32: 1017--1029, Nov. 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 J. Richardson, M.D.
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San Jose Office Program,
April 17, 1974