

MALIGNANCIES IN DANISH THOROTRAST PATIENTS*

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Abstract—The Danish Thorotrast follow-up has been running since 1949. As of 1973, 1012 cases were known with 391 still living. The malignancies are classified as Thorotrast inducible and other tumors. Thorotrast inducible were 11 hemangioendotheliomas, 9 cholangiocarcinomas, 12 hepatomas and 11 leucaemias. In addition, 52 other cancers were observed. The 3 types of liver tumors (hemangioendotheliomas, cholangiocarcinomas, and hepatomas) showed a similar number of cases, latency periods, rises in cumulative incidence with time, and radiation doses to the liver. No bone tumors were observed. The 11 cases of respiratory cancer were all in males with 4 having latency periods under 15 yr, which does not support a radiation induction. However, the high ratio of anaplastic lung tumors/epidermoid lung tumors, agrees with findings in the uranium miners, and could indicate some influence from radiation. It is uncertain whether the two cases of pleural mesothelioma may have been induced by Thorotrast because there is no evidence for significant irradiation of the pleura. It is concluded that a larger population or a longer follow-up is necessary to exclude or include bone sarcomas and lung tumors as being due to Thorotrast.

INTRODUCTION

THE DANISH Thorotrast patients have been under observation since 1949 and surveys of the status of the study has been made at intervals (Faber 1962; 1967; 1973a). The patients were injected intravascularly between 1935 and 1946 for arteriography of urological disorders, except for one case injected for a haemangioma on the foot.

MATERIAL

Apart from an increased incidence of brain tumors, for which the Thorotrast was sometimes injected, the population was considered as being equivalent to the general Danish population, so that the figures from the Danish cancer registry (C164; 1965; 1969) could be used when expected tumor incidences were calculated. This was, furthermore, an absolute requirement as it was impossible to collect a control group which

would match exactly in sex ratio, age distribution, and date of entrance into the study. It is important in a study, which now covers close to 40 yr of observation, that the shift in cancer incidence with time is taken into consideration in the calculations. A reasonable equivalent of the possible carcinogenic factors connected with the disease for which the Thorotrast was given is also of importance. These two points practically exclude the possibility for collecting a control group in Denmark because all cases with the same diseases had their normal diagnostic studies at the hospital where the Thorotrast was used.

Thorotrast injected persons could be expected to deviate from the normal population by an increased risk of exposure to carcinogenic drugs. The group contains a number of patients with lifelong headaches and concomitant use of many different drugs. Smoking may be predominant, and we know that the suicide rate is high. About 10-20% of the patients had epilepsy. Finally, it has to be remembered that a few of the patients were

*Dr. Faber was unable to attend, but advance copies of his manuscript were distributed at the symposium.

given X-ray therapy for some of the diseases for which Thorotrast was injected.

The follow-up as of 1973, is summarized in Table 1. The observation time of the patients in relation to injected dose is presented for males and females in Tables 2 and 3.

Table 4 registers the malignant tumors. The estimates of expected malignancies have been calculated from the size and age distribution of the remaining population, year by year.

The number of cancers and leucaemias had now grown to 95. They can, from previous experiences, be split into two groups. Those where the dependency on Thorotrast is recognized and the others.

THOROTRAST INDUCIBLE TUMORS

The dependent malignancies are liver tumors and leucaemias.

Table 1. Danish Thorotrast injected patients

	Dead	Living	Total
Male	MI	210	571
Female	260	181	441
Total	621	391	1012

Three main groups of liver tumors were found; the haemangioendotheliomas, the cholangiocarcinomas, and the hepatocellular (hepatic cell carcinomas).

The hemangioendothelioma has repeatedly been shown, both in human experience (Fa62), and in animal experiments (Joss), to be a type of tumor intimately connected with Thorotrast deposits. The primary tumor is mostly located in the liver in man, but usually in the spleen in the rabbit.

A knowledge of the pattern of appearance in relation to the time after Thorotrast injection is useful when the Thorotrast inducible tumors are compared with the other tumors found in the Thorotrast patients. A difference in behaviour can be seen in Fig. 1.

The cumulative incidence of those tumors where, so far, no causal relation to Thorotrast has been demonstrated, rises by a straight line starting immediately after the injection.

The Thorotrast inducible tumors, however, show a latency period without the appearance of any tumor. This latency period varies

Table 2. Danish Thorotrast patients according to dose and time of observation—males

Yr	0-9 ml	10-19 ml	20-29 ml	30-39 ml	40-49 ml	50+ ml	unknown	all cases
0-1	4	45	43	13	7	0	22	134
2	2	3	7		1		4	17
3		3	1			1	2	7
4		1	4				2	8
5		6	3			1	2	11
6		2	2	1			2	7
7		5	2				0	5
8	1	3	1				1	6
9		3	3	1		1	1	9
10		3	5	1	2		2	14
11	1	4	3	3	2		1	11
12		2	3	2				7
13		4	2	2				8
14		6	2		1			9
15		5	1					6
16		2			2			4
17		3	1	1				5
18		4	1			1	1	7
19	1	1	1	1	1		1	6
20		4	2			1		7
21		3	2		1		2	8
22		1	3					4
23		2	2	1		1		6
24		2	3		1		2	8
25			1				3	4
26		3	3	1			1	8
27		10	14	1	4	3	5	37
28	1	15	12	4		2		34
29	4	21	13	2		1	2	43
30	3	15	5	4	2		1	30
31	4	12	5	1	1		1	24
32	2	12	6	3	1	1	5	30
33		5	7	3	1		4	20
34		5	4	1			1	11
35		5	3			1	1	11
36		3	0				1	4
37								
38		1						1
All cases								571

Table 3. Danish Thorotrast patients according to dose and time of observation—Females

Yr	0-9 ml	10-19 ml	20-29 ml	30-39 ml	40-49 ml	50+ ml	unknown	all cases
0-1	1	33	31	9	4	3	16	97
2			1			1		2
3		6	1				1	8
4		1	1		2		2	6
5		3	1	1			1	6
6		1	1	1	2		1	7
7		2	3	1	1		2	10
8		4	3				1	8
9		3		1			1	5
10			2					2
11		3	1		1			5
12		2	3			1		6
13			3				1	4
14		1	1	1				3
15			1			1		2
16		2	1			1		4
17		1	3	2	1	1	2	10
18								1
19		1	1	1	1		1	4
20					1			1
21		2	1	1				4
22		2	2					4
23		3	2				2	7
24		1	1	3			1	6
25		1	4	2	1		7	16
26		11	16	3	4	3	3	45
27		15	13	2	1	2		36
28		13	9	1	2			25
29		12	7	1		1		22
30	1							2
31	3	11	6	1			7	26
32	1	15	5	5				26
33	1	4	4	1		1	2	13
34	1	2	1		1			4
35	1	8	4		1		2	16
36		1		1				2
37							1	1
38							2	2
All cases								441

Table 4. Malignancies in Danish Thorotrast patients registered by injected dose

	found expected	10-19 ml	20-29 ml	Latency periods in years 30-39 ml	40-49 ml	50 ml +	unknown
Digest	14/27	6†-8-16-23	5-22-23-24	1-28	27		19
Liver	32/0.60	27*-28*-34*	19-23-22-24	18-23-24-26*-27	21*-31	18*-19	26-27
Resp.	11/4.1	34-28	26-31-27	28-29-28*-33-33	24	20*-29	28*-31
Breast	3/6	13-31-35‡	13-26-27‡	26			10-11-21
Male genit.	1/3.5	26		11		7	19
Female genit. + uterus	5/7.6	4-22-24	15			3	
Urinary	1						25
Other organs	9	4-18-31	5-28-28	25		23	25
Lymph. and blood	13/4.7	23-23	10-21-22-26	20-25		-14-17	9-22-33
Metast.	6	7-7-13	3	5			4
All Male	57/36.5	14	14	9	4	5	11
All Female	38/34.5	10	11	9	0	4	4
Total	95/71	24	25	18	4	9	15

*Haemangioendotheliomas.

†Females underlined.

‡Mesothelioma.

tween the different malignancies. As was to be expected, the leucaemias had the shortest minimum latency period of about 8 yr. The curve for the rise in cumulative number follows reasonably close to a straight line.

The curve for the primary liver carcinomas and the one for the haemangioendotheliomas have a minimum latency period close to 17 yr. Both rise reasonably rectilinearly with time, and it is doubtful, when the data in Table 5 are taken into consideration, whether these

Table 5. The three histologically different liver tumors

	No.	Mean latency period (yr)	Mean age at injection (yr)	Mean dose to liver (Rad)
Hepatoma	12	25.5	33.2	609
Cholangio carcinoma	9	26.6	32.6	636
Haemangio	11	26.1	30.4	609

two curves are different. They are, therefore, combined as a single curve in Fig. 1.

The primary liver cell tumors are generally described as being either primary hepatomas

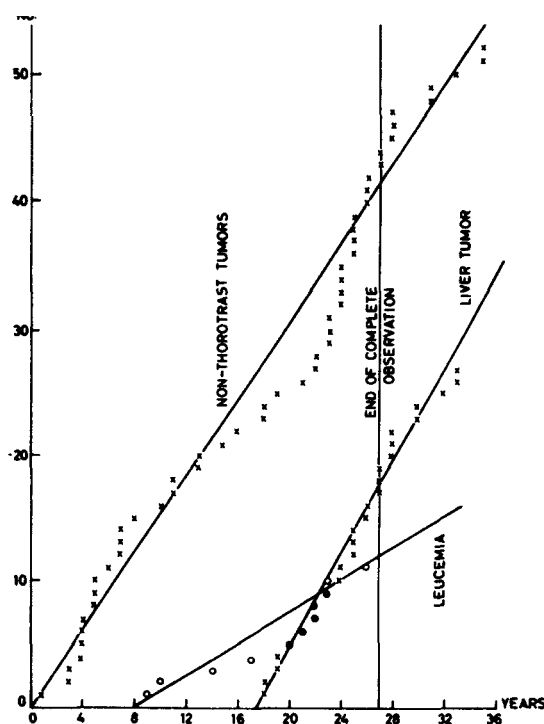


FIG. 1. Cumulative number of liver tumors, leucemias, and combined other tumors in the Danish Thorotrast patients by year after Thorotrast injection.

or cholangiocarcinomas on the basis of differences in histology. It is doubtful whether the difference is meaningful, but if this should be the case, it is of interest to know whether the histologic findings reflect a difference in carcinogenic action of the Thorotrast during the prolonged stay in the liver. Both in humans and in rabbit experiments it is evident that the Thorotrast with time is collected in connective tissue scars where most of the granules are localized in macrophages or in multinuclear cells. This connective tissue is the result of repeated episodes of liver cell death with a proliferation of new liver cells in nodules without Thorotrast. In the connective tissue bands we find a large number of surviving bile ducts, apparently unchanged, and surrounded by cells that contain Thorotrast. If during the evolution to this stage there should be a

difference in the radiation exposure to the two cell systems, hepatic cells and bile duct cells, this could be reflected in the type of liver tumor found. However, an analysis of the 12 hepatomas, 9 cholangiocarcinomas, and 11 hemangioendotheliomas (Table 5) does not give any support for such a separate behaviour with respect to the number of cases, latency period, rise in cumulative incidence with time, and α -dose to the liver calculated from the estimates of Kaul (1969) and Faber (1973b).

In the evaluation of these curves a certain unreliability has to be recognized. As of January 1973, it was 38yr since the first patient was injected with Thorotrast. It was, however, only 27yr since this happened to the last patient. This means that only that part of the curves in Fig. 1 which covers the first 27yr after the injection represents a completed observation. During the next years more cases will probably appear, and they may change the last part of the curves.

It is interesting that no cases of leucaemia have appeared later than 23yr after the injection, and that the same is the case with the nonleucaemic haematological diseases. This may be a sign that the spatial distribution of the irradiation to the bone marrow has become such that little radiation is received by the sensitive cells. This is the case in rabbit experiments with Thorotrast enriched with ^{230}Th , but is not very probable in man. The significance of this observation for the Thorotrast patients can not be resolved from this material alone.

OTHER TUMORS

Bone tumors

Due to the translocation of thorium daughters from the liver and spleen deposits to the bone, the bone surfaces receive protracted irradiation (Rowland and Rundo, 1973), and it should be possible to induce bone sarcomas in this ways.

The incidence of bone sarcomas in Denmark from 1943-1967 has been unchanged and close to one case per 100,000 persons/yr, with only small variations according to sex, and without any marked change in incidence with rising age. The expected number of

naturally-occurring bone sarcomas can, therefore, be calculated from the 18,000 person-yr of observation (9973 male-yr plus 8,172 female-yr). This predicts 0.2 naturally-occurring cases expected over the entire present Danish Thorotrast follow-up. For the person-yr at risk beyond a reasonable latent period, less than 0.1 naturally-occurring bone sarcoma is expected.

The lack of observed cases may be due to a number of factors of which insufficient dose and insufficient dose rate are of importance. The estimated expectancy for cancer induction after incorporation of ^{224}Ra in relation to dose is based on observations of German patients where all of the dose was received during a short period of time after the last ^{224}Ra injection, in contrast to the Thorotrast cases where the bone dose is being built up with time. This contrasting mode of dose delivery could give a difference both in the dose-effect relationship and in the duration of an effective latency period. The conclusion must be that a longer observation time is necessary to be able to observe the existence of a significant number of bone sarcomas in a population of this size.

Finally, a complicated pathophysiological question. The incidence of bone sarcomas in man has been of the same order of magnitude in the Danish cancer registry since 1945. The evaluation of this figure in the elderly can, however, be criticized. In the clinic, bone sarcoma is a disease of youth and young adults—not of the elderly. Unless a complete histological study has been performed, the risk of a misdiagnosis in relation to unspecified metastases within bone must exist.

Respiratory tumors

The tumors which at present are of great interest are the 9 in the lung proper and the 2 mesotheliomas in the pleura (Table 4). The combined expectation is approximately four cases. This could suggest an increase which might be due to the Thorotrast.

When evaluating these cases as a result of radiation from thorium daughters, a number of points have to be taken into account. The amount injected does not support dose effect relation as most cases were

injected with low doses. The age at appearance corresponds to the one observed in the general population. The latency periods could indicate that the high incidence was purely fortuitous when it is considered that four out of eleven cases had a latency period shorter than the 15 yr to be expected for a radiation induced solid tumor.

A support for a radiation genesis is to be found in the histological typing of the lung tumors with 5 cases of anaplastic tumors and 2 epidermoid tumors. Saccomanno *et al.* (1971) have analysed the type of tumor found in uranium miners and found an increase of the anaplastic against the epidermoid tumors. The pulmonary tumors from the Danish Thorotrast patients show the same skewness in the histological typing. For both of the populations it must be remembered that such a division may be erroneous due to the fact that the histological typing may not be homogenous throughout the tumor (Clemmensen, 1965).

Our material contains two cases of histologically verified mesothelioma of the pleura, and one additional case is suspected as being of this type. When taking into consideration that the expected incidence is virtually zero, this is too large a number. If pleural tumors should be due to Thorotrast this might require a subpleural deposit of thorium in lymphatic vessels. Histological evidence from both human and injected animals does not support such a deposition.

Finally, those patients who present more than one malignancy should be searched for evidence of other Thorotrast induced tumors. A survey of the three patients with this behaviour show that two have died from classical Thorotrast tumors. The other tumors could not be suspected of being directly induced by Thorotrast.

CONCLUSION

As a result of this analysis of the cancers in the Danish Thorotrast patients, the conclusion is clear that liver cancers and leucaemias can be induced by Thorotrast. A larger population or a longer follow up time is needed to resolve the question of whether other tumors, such as those of bone or lung,

are induced by intravascularly injected Thorotrast.

REFERENCES

- Clemmesen J., 1965, *Statistical Studies in Malignant Neoplasms*, Vol. I, Kobenhavn: Munksgaard.
- Clemmesen J., 1964, *Statistical Studies in Malignant Neoplasms*, Vol. II, p. 194 Kobenhavn; Munksgaard.
- Clemmesen J., 1969, *Statistical Studies in Malignant Neoplasms*, Vol. III, Kobenhavn: Munksgaard.
- Clemmesen J., Fuglsang-Frederiksen V. and Plum C. M., 1974, *Lancet*, **1**, 705.
- Faber M., 1962, in: *Some Aspects of Internal Irradiation*, p. 473 (Edited by Dougherty T. F., Jee W. S. S., Mays C. W. and Stover B. J.), Oxford: Pergamon Press.
- Faber M., 1967, *Ann. N.Y. Acad. Sci.* **145**, 843.
- Faber M., 1973a, "Follow-up of Danish Thorotrast cases" in: *Proceedings of The Third International Meeting on The Toxicity of Thorotrast*, Riso Report No. 294, p. 137.
- Faber M., 1973b, "Dose effect relations in hepatic carcinogenesis" in: *Proceedings of The Third International Meeting on The Toxicity of thorotrast*, Riso Report No. 294, p. 308.
- Johansen C., 1955, *Acta path. microbiol. scand.* suppl. 105.92.
- Kaul A., 1969, *Zsotopenpraxis* **5**, 85.
- Rowland R. E. and Rundo J., 1973, "The Skeletal Dose from ^{224}Ra Following Intravascular Administration of Thorotrast" in: *Proceedings of The Third International Meeting on The Toxicity of Thorotrast*, Riso Report No. 294, p. 95.
- Sacomanno G., Archer V. E., Kuschner M., Saunders R. P. and Klein M. G., 1971, *Cancer* **27**, 515.