A FOLLOW-UP OF 1000 THOROTRAST CASES IN DENMARK

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Abstract—A series of Thorotrast injected patients has been followed in Denmark since 1949. The series now numbers 1000 patients of which 510 are still alive. The follow-up is performed through hospital contacts and is activated by notice of death. Some patients have been seen but only as a neurosurgical follow-up. All patients have had a neurosurgical carotid arteriography. Record of death is verified from the physicians, hospital records and autopsy records.

The most common cause of death is of course the neurosurgical diseases of which some 300 have died. Non-malignant diseases of other organs have been the cause of death in 150 cases, and 40 cases of malignant diseases have been observed. Among the non-malignant diseases there has been observed a number of bone-marrow discrasias of non-leukaemic type but amazingly few signs of serious hepatic disorder.

The total number of malignant diseases is very close to the one expected from cancer statistics in Denmark. However, 4 haemangioendotheliomas and 8 leukaemias have been met with, both a definite increase above expectation. The number of primary hepatic tumors are also slightly above expectation. The significance of these results will be discussed in relation to other comparable materials.

SINCE Thorotrast was introduced into clinical medicine in 1930 a very large but unknown number of patients have been injected with this radioactive contrast medium. It is still being produced and publications on the use of Thorotrast appear every year. In Denmark it was used from 1935 until 1946, when it was discontinued with the reappearance of iodine containing contrast media after the war. Thorotrast was used practically only for arteriography in neurosurgical departments and accordingly the series will only consist of patients with the classical deposits in liver and spleen as it is seen after intravenous injections. After a thorough search of hospital records we have now collected 1000 injected patients and of these some 500 are still alive. The doses used were relatively small. 75% of the injected patients had doses below 20 ml.

The status of the series is illustrated in Fig. 1 where the living patients are registered according to time of observation and the dead according to the time of death after injection. The very large number of deaths just after the injection is of course due to the neurosurgical disease for which the contrast medium was injected.

This group of patients has now been followed for more than 15 years. The follow-up has in general been performed without contact with the patients, through hospital records when known, through folk registries, etc. Although a system has been set up which should detect all dead patients it has been necessary to check at intervals on the status of the patients surviving at that time. In the following discussion I shall concentrate on some of the diseases which might be considered as being due to the presence of Thorotrast.

The presence of a radioactive substance will immediately give rise to the question whether this group of patients shows an increase in the incidence of malignant tumors, and if so where the tumors are to be found. Figure 2 shows the expected cumulative incidence of cancer in a population of the size of the Danish Thorotrast series calculated on the basis of tables published from the Danish Cancer Registry in relation to the known number of cancers occurring up till

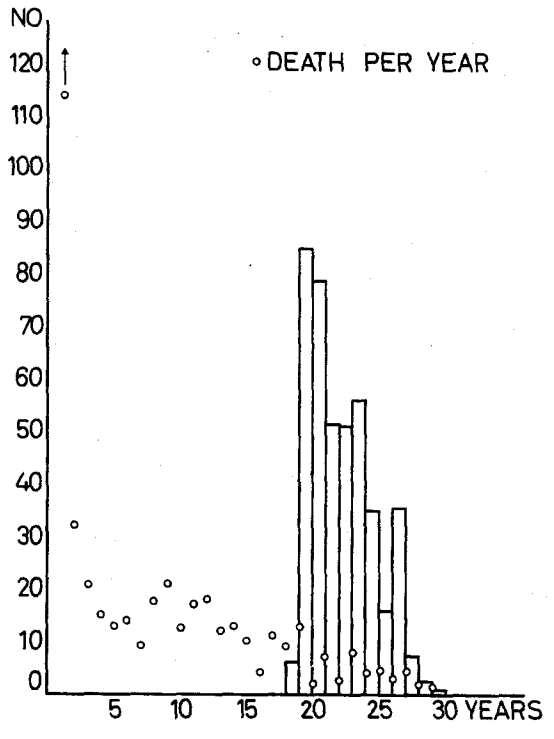

FIG. 1. The dead and the surviving Danish Thorotrast patients in relation to time of injection.

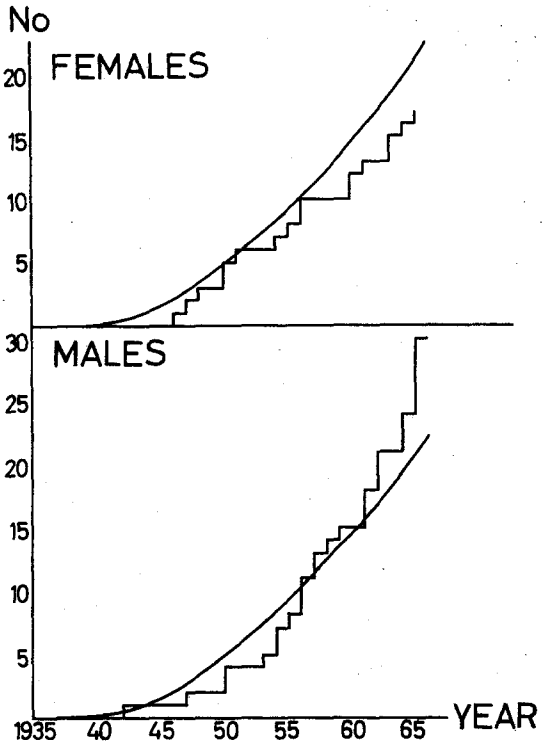

FIG. 2. The observed cumulative cancer mortality in relation to the expected, calculated on cancer registry data.

January 1, 1966. It can be seen that the two curves follow each other fairly closely during most of the follow-up period. Not until the last year or two has any sign of an increase in the general cancer incidence been observed, and so far this increase is of no statistical significance.

If we, however, leave the total incidence of cancer and look for tumors which might be due to Thorotrast, it has to be noted that the number of haemangioendotheliomas of the liver is now increasing. During the last years four cases of haemangioendothelioma, the classical Thorotrast tumor, have appeared among the Danish Thorotrast patients. This increase which occurred after many years of observation of an apparently symptomless group is of very great interest, and can with present knowledge be discussed from two points of view.

The first question is whether the occurrence of haemangioendothelioma in man can be shown in any way to be dependent on the dose of Thorotrast injected. Unfortunately only in very few of the published cases are both dose and latency period known. Only two large series can be used for this purpose, our own group of four cases among 1000 injected persons and the fourteen histologically verified Portugese cases published by da Silva Horta[1] from a group of 1800 cases. To these can be added seven isolated cases from the literature. As can be seen from the figure it is very difficult to claim that there is a relationship between the dose injected in ml Thorotrast and the time at which the tumor appears.

The next question is whether it is possible to evaluate now the risk of the future appearance of haemangioendotheliomas in a series of Thorotrast injected persons. At present 41 cases of haemangioendothelioma of the liver have been published, where time of injection and time of

Table 1. *Cancer in Thorotrast Group*

	No.			Latency period month
	Males	Females	All	
Stomach	2	1	3	237–286–291
Small intestine	1	—	1	19
Colon A. Rectum	2	2	4	103–196–263–290
Pancreas	1	—	1	277
Liver	6	3	9	221*–225–226–250–257* –266–312–321*–331*
Lung	8	—	8	121–123–156–158–162 –247–254–319
Uterus	—	3	3	55–79–176
Leukaemia	5	3	8	106–122–170–205–234 –258–261–302
Others	6	5	11	30–59–63–67–87–88– 123–137–157–211–233

death from the tumor is known. We have tabulated these cases and the result can be seen in Fig. 4. In this connection it must be remembered that the longest observation period of these patients under all circumstances must be below the 35 years that have elapsed since Moniz[3] in 1930 started injecting Thorotrast into patients. The first 4–5 years after the introduction of the procedure it was mainly used in Portugal, and other countries did not join the Thorotrast users until somewhat later. It is quite evident from the figure that the maximum incidence of haemangioendotheliomas in relation to the time after injection of Thorotrast has not yet been reached. This perhaps can not be considered to be unexpected if we compare with the observation of Goolden and collaborators[3] on the latency period for pharynx malignancies after therapeutic irradiation of the thyroid where the maximum incidence of radiation cancer appears after 30 years. This, however, is a short time irradiation with no exposure to ionizing radiation afterwards. It is difficult to compare these conditions with the chronic irradiation in the Thorotrast patients, when furthermore the dose delivered is smallest in the initial period after injection. The minimum figures for the incidence of haemangioendothelioma in Thorotrast cases must so far be taken from the Portugese series where evidence for haemangioendothelioma is present in 26 cases among 1800 intravenously injected patients.

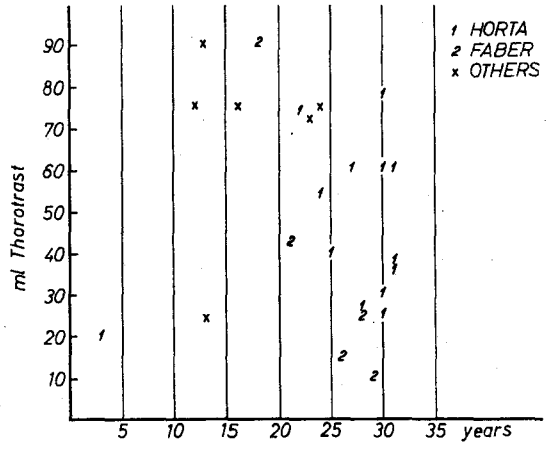

FIG. 3. The relationship between time of death of verified haemangioendotheliomas and dose of Thorotrast injected. Own and other published data.

The two series are, however, not quite comparable because some of the Portugese patients were injected up to 5 years before the first Danish patients, while a large group was injected simultaneously or later. It is, however, known (Silva

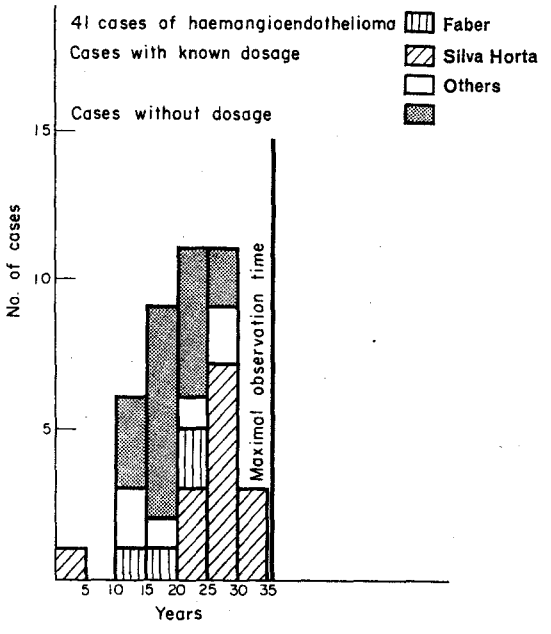

FIG. 4. Latency period in Thorotrast induced haemangioendotheliomas. Own and other published data.

Horta) that approximately one-third of the Portugese patients were injected before the Danish neurosurgeons started using large amounts of Thorotrast and when the latency period of the haemangioendotheliomas from Fig. 4 is taken into consideration, then it must be from this group that most of the tumor cases stem.

The evaluation of a minimum figure should then be possible. A direct calculation would suggest 10–14 new cases in the Danish group during the next 10 years. If this result has to be corrected for the difference in date of injection it may be too low by a factor of 2–3. The influence of a difference in injected doses resulting in a difference in radiation dose is so far unknown, but it may decrease the expected incidence due to the larger doses injected in Portugal.

It is evident that this calculation would gain considerably if the two series could be treated as one, and attempts are being made at present to realize such a pooling. With the increase in knowledge of dosimetry and other necessary parameters it appears possible that the Thorotrast injected person may supplement our knowledge on the effect of chronic irradiation in man and one must hope that a sufficiently large number of well-planned epidemiological studies can be initiated to collect this valuable material before it is too late.

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