Chronic Myelosis Following the Use of Thorotrast

By M. Netoušek, J. Boreš and K. Dvořák

REPORTS have recently been appearing in the world literature, pointing out the late deleterious effects of thorotrast, which has been used since 1930, especially for hepatoheliography. The majority of these communications lay stress on the toxic effect of the radioactive material emitted by thorotrast and warn against its further use; many authors emphasize in particular the carcinogenic effect of thorotrast which is only displayed after a long period of latency.

In the literature available we found only four reports1-3 on the occurrence of leukemia following the use of thorotrast for diagnostic purposes and we therefore submit a short report on a case observed by us.

CASE REPORT

In April 1931, in the Second Clinic of Internal Medicine of the Charles University, Prague, a tumor was found in the right mesogastrium of a woman born in 1879; hepatoheliography was carried out using 50 ml. of thorotrast, together with intravenous urography, and a diagnosis was made of a tumor of the right kidney. At operation on May 30, 1931, a tumor of the right kidney was found weighing 2,015 Gm.; histologic examination showed a rare melanotic adenoma of the suprarenal gland. On April 29, 1931, the blood picture was normal, as regards both the red and white components (see table 1).

The patient felt well up to May 1953, when an infection of the urinary tract was diagnosed in the District Hospital in Pisek and was treated with penicillin. At this time, abdominal x-rays demonstrated deposits of thorotrast in the liver and spleen but these were assumed to be calcified tuberculous foci. The blood picture was normal.

In June 1954, because of general weakness, dyspnea and paraesthesias in the lower limbs, an examination was made, as a result of which chronic myelosis was diagnosed. At the beginning of 1955, because of deterioration of the patient’s condition and an increase in the number of leukocytes, x-ray irradiation of the spleen was carried out in eight doses, from January 26, to February 18, 1955, the total dose being 920 r. In spite of this, the number of leukocytes rose from 421,000 to 644,000. Because of this paradoxical effect it was recommended that the patient be admitted to hospital. The liver was found to be enlarged two to three fingers below the costal margin; the spleen descended to the costal margin and was therefore not discernibly enlarged. The lymphatic glands were not enlarged. The blood picture is given in table 1.

In an x-ray examination carried out on March 21, 1955, there was increased density of the shadows of the liver and spleen and numerous denser shadows of the size of a pea and larger extending in linear formation from the hilum of the spleen along the pancreas into the vicinity of the hilum of the liver. These were evidently deposits of thorotrast in the liver, spleen and glands. The glucose tolerance curve was of an hepatic type, the galactose test was positive and cholesterol was normal (190 mg.%). Flocculation reactions: Takata ++++. Weltman 9, thymol reaction 1.4 units; bilirubinemia 0.53 mg.%.

A sternal puncture made on March 21, 1955 showed discernible hyperplasia of the granulocyte series, giving evidence of chronic myelosis (table 2). Examination of smears from the marrow puncture showed isolated reticular cells containing minute particles and crystals of...
CHRONIC MYELOSIS FOLLOWING THOROTRAST

Table 1—Hematologic Data of the Patient

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<thead>
<tr>
<th>DATE</th>
<th>RBC (mil-</th>
<th>Hb °c</th>
<th>WBC (Thou-</th>
<th>S</th>
<th>St</th>
<th>mM</th>
<th>pM</th>
<th>Mbl</th>
<th>Eo</th>
<th>Ba</th>
<th>M L</th>
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X-RAY THERAPY JANUARY 26-FEBRUARY 18

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X-RAY THERAPY JULY 4-JULY 21

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</table>

a substance, evidently phagocytosed particles of thorotrast (fig. 1). In a panoptically stained smear these cells measured 30–40 μ and showed a green fluorescence.

In June 1955, the spleen was again irradiated and again there was a paradoxic increase in the leukocytes, after a total dose of 920 r (see table 1). The original number of leukocytes was 67,888; after 14 doses of irradiation there were 120,000 leukocytes per cml. and six weeks after completing irradiation the number fell to 94,400.

Splenic punctures made on July 5, 1955 at three different sites gave no results.

Since the patient's discharge from the hospital on July 21, 1955, the number of leukocytes has remained low on the continued use of Myleran.

Discussion

The thorotrast produced by Messrs. Heyden is a thorium dioxide sol stabilized with a 25 per cent watery solution of glucose. It is a dense, milky, oleaginous fluid which is radioactive and mixes in any proportion with the body fluids. An ampoule contains 12 ml. of fluid with approximately 2.5 Gm. of thorium.

Thorotrast was introduced into medical practice as a diagnostic medium almost simultaneously by the authors Oka4, 5 and Radt6 following animal experiments. Preliminary observations made by these authors showed that thorotrast injected intravenously is deposited chiefly in the reticulo-endothelial system of the spleen...
TABLE 2.—Relative Number of Cells in the Bone Marrow of the Patient

<table>
<thead>
<tr>
<th></th>
<th>Per Cent</th>
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<td><strong>White series</strong></td>
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<tr>
<td>Promyelocytes</td>
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<td>Myelocytes:</td>
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<tr>
<td>neutrophilic</td>
<td>20.5</td>
</tr>
<tr>
<td>eosinophilic</td>
<td>1.5</td>
</tr>
<tr>
<td>basophilic</td>
<td>0.5</td>
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<tr>
<td>Metamyelocytes:</td>
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<tr>
<td>neutrophilic</td>
<td>13.0</td>
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<tr>
<td>eosinophilic</td>
<td>0.5</td>
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<tr>
<td>Stab cells:</td>
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<tr>
<td>neutrophilic</td>
<td>7.0</td>
</tr>
<tr>
<td>eosinophilic</td>
<td>0.5</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>42.0</td>
</tr>
<tr>
<td>Segmented eosinophils</td>
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<tr>
<td><strong>Total</strong></td>
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<tr>
<td><strong>Red series</strong></td>
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<tr>
<td>Proerythroblasts</td>
<td>0.5</td>
</tr>
<tr>
<td>Normoblasts</td>
<td>7.0</td>
</tr>
<tr>
<td>Mitoses</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Lymphoreticular series</strong></td>
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<td>Lymphocytes</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
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and liver, but also in the bone marrow and lymphatic glands. In the very first communications on the diagnostic use of thorotrast, mainly in hepatoliemography, it was generally agreed that thorotrast injected into the body cannot be excreted from the organism. The American Medical Association Council of Pharmacy and Chemistry, therefore, closed its inquiry on thorotrast in 1937 with the note that this substance should be excluded from general use because of the danger of later damage to the organism.

Yater and Coe\(^8\) followed-up the subsequent history of 274 patients who had been subjected to hepatoliemography ten years previously. Their series did not include patients with signs of damage to the individual organs but we are obliged to conclude that an observation period of ten years is too short and we cannot from this reach an optimistic conclusion, in contrast to the point of view expressed in the American inquiry of 1932.\(^7\)

Thomas, Henry and Kaplan\(^9\) published a very valuable study on the late effects of thorotrast. On the basis of a series of 4,325 cases, in about half of which hepatoliemography had been carried out, these authors concluded that the main danger of thorotrast is late fibrosis and cicatrization, particularly in the liver and spleen. Figure 4 in this communication demonstrates very clearly the fibrosing effect of deposits of thorotrast in the spleen; this organ, which on an x-ray made in 1936 measured 13.7 cm. had by 1950, i.e., 14 years later, decreased to 6.9 cm. Looney and Colodzin\(^3\) also pointed out that, after the use of thorotrast the architecture of the spleen was gradually destroyed, the pulp was replaced by
connective tissue and the entire organ decreased in size. These authors also examined liver function in 35 patients, but found retention with the bromsulphalein test in only three.

In addition to its fibroplastic effect, thorotrast also has a carcinogenic action. Although in Thomas's series of 4,325 patients to whom thorotrast had been administered years previously, only two tumors were found, the carcinogenic significance of thorotrast must not be underestimated. Many authors have demonstrated the development of tumors in experimental animals following the administration of thorotrast. Observations in human pathology also provide evidence of a causal relationship between thorotrast and the development of tumors. Twelve years after the injection of thorotrast for the purpose of hepatorenography, McMahon et al. observed an endothelial sarcoma of the liver, which was demonstrated histologically. Zollinger found a spino cellular renal sarcoma 16 years after retrograde pyelography, Da Silva Horta a sarcoma of the liver three years after cerebral arteriography and Grossiord et al. an adenocarcinoma of the liver, with cirrhosis, 21 years after arteriography.

Thorotrast has a noteworthy effect on hematopoiesis. Leukocytosis, together with monocytosis, and in the red blood picture anemia, with normoblasts in the periphery, have been observed as early signs following the use of thorotrast. As far as the late effects of thorium and thorotrast on blood formation are concerned, mention should be made of some observations of panmyelopathy following the use of thorotrast. Squize described chronic lymphadenopathy following the use of thorotrast, Meessen described two cases of myelosis following the use of thorium. A girl aged 19 was given 15,000 c.u. of thorium X and ten months later
TABLE 3.—Half-life and Quality of Radiation Transmutation Products of the Thorium Series

<table>
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<th>Element</th>
<th>Chemical symbol</th>
<th>Half-life</th>
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<td>Thorium</td>
<td>Th</td>
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<td>$\alpha$</td>
</tr>
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<td>Mesothorium I</td>
<td>MsTh I</td>
<td>6.7 yr.</td>
<td>$\beta^-$</td>
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<td>$\beta^-$</td>
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<td>Radiothorium</td>
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<td>1.9 yr.</td>
<td>$\alpha$</td>
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<tr>
<td>Thorium X</td>
<td>Th X</td>
<td>3.64 days</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Thoron</td>
<td>Tn</td>
<td>54.5 sec.</td>
<td>$\alpha$</td>
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<td>Th A</td>
<td>$1.58 \times 10^{-1}$ sec.</td>
<td>$\alpha$</td>
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<tr>
<td>Thorium B</td>
<td>Th B</td>
<td>10.6 hr.</td>
<td>$\beta^-$</td>
</tr>
<tr>
<td>Thorium C</td>
<td>Th C</td>
<td>60.5 min.</td>
<td>$\beta^-$</td>
</tr>
<tr>
<td>Thorium C'</td>
<td>Th C'</td>
<td>$3 \times 10^{-2}$ sec.</td>
<td>$\sigma$</td>
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</table>

Chronic myelosis was diagnosed; a man aged 53 suffering from Bechterew disease was given 5,700 e.u. of thorium X and soon after signs of paramyeloblastic leukemia appeared. Looney and Colodzin observed chronic lymphadenosis nine years after the administration of thorotrast.

In the present case, the possibility of a causal relationship between chronic myelosis and the injection of thorotrast made 25 years ago, cannot be excluded. On that occasion the patient was given 50 ml. of thorotrast, i.e., about 10 Gm. of thorium. It should be borne in mind that the half-life of thorium Th is $1.8 \times 10^{10}$ years and that it emits all three types of radiation, just as the uranium and actinium series, while at the same time, by the emission of corpuscular alpha and beta radiation it is converted into known transmutation products, of which the half-life and quality of the radiating energy are given in table 3.

In thorium, alpha radiation takes effect in the most marked manner. Although the penetration of alpha radiation is small, since it penetrates the tissue to a depth of only 50 micro, so that about 90 per cent of the radiation is absorbed by the substance of the thorotrast itself, about 1 per cent of the alpha radiation penetrates the tissue, i.e., about 890 r/year from 1 Gm. thorium. To this should be added further radiation from the beta and gamma rays produced by the transmutation products, which according to the calculations of Prof. Béhounek also amount to 890 r/1 Gm. thorium per year. Since the annual dose from a deposit of 1 Gm. thorium in the organism is twice 890 r (i.e., 1780 r), and the patient was given 10 Gm. thorium, it follows that the internal organs, particularly the spleen, liver, bone marrow and the lymphatic glands were for 25 years exposed to the highly carcinogenic dose of 1,780 r per year. According to Prof. Béhounek the admissible dose of thorium in insoluble form is about 0.028 µg. of thorium. The dose to which our patient has been exposed for more than 25 years is many times greater.

Unfortunately, we had no accurate counter available for expressing the activity of the radiation emitted by the thorium deposits in our patient, in actual figures. Many research workers have done this successfully in their patients.

A remarkable phenomenon was observed in our patient on x-ray irradiation, i.e., the paradoxical increase in leukocytes following irradiation of the spleen, instead of the expected decrease. As stated in the case history, the patient responded to a dose of 920 r with an increase in the leukocytes from 421,000 to
644,000 and to a second dose of 920 r with an increase from 46,000 to 120,000. Biologically, the phenomenon is incomprehensible. In reply to a query as to whether it might be possible for x-ray radiation to lead to activation of the thorotrast deposits and to an increase in their radioactivity, Prof. Běhounek stated⁷ that the electronic radiation which was added to the thorotrast on deep x-ray irradiation, was negligible as compared with the permanent dose from the thorotrast in the patient's body. Although no quantitative significance can be attached to ionizing radiation, the fact cannot be denied that the irradiation of the spleen resulted in an inversion of the usual reaction seen in chronic granulocytic leukemia.

The leukemia which developed in our patient 23 years after hepatolienography differed from the usual picture of chronic myelosis by the relative mildness of its course and by the absence of splenomegaly; this could possibly be explained by the fibrosing effect of the thorotrast on the spleen pulp. From the biological aspect, an unusual aspect of the case was the paradoxic reaction to irradiation of the spleen with ionizing x-ray radiation.

**Summary**

Following hepatolienography which was carried out in a woman aged 52 in 1931, for a tumor of the right kidney which was removed at operation, chronic myelosis developed in 1954. This was remarkable for the absence of splenomegaly, a relatively mild course and a paradoxic reaction to x-ray irradiation of the spleen, when instead of the expected decrease there was a doubling in the number of leukocytes. A causal relationship of myeloid leukemia to the thorotrast administered 23 years previously cannot be excluded.

**Summario in Interlingua**

Post hepatolienographia, executate in 1931 in un patiент feminin de 52 annos de etate ante le ablatiomi chirurgic de un tumore del ren dextere, chronic myelosis se declarava in 1954. Isto esseva remarcabile per le absentia de splenomegalia, su curxo de character relativemente leve, e un reaction paradoxe al roentgeno-irradiatiom del splen, consistente in le duplication del numero de leucocytos in loco del expectate reduction. Il non es possibile rejicer le possibilitate de un relation causal inter le leucemia myeloide e le administration de thorotrast 23 annos retro.

**References**

1. SQUIZE, F. H.: cit. according to.⁹


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M. NETOUSSEK, J. BORESS and K. DVORRAÁK