Environment International, Vol. 19, pp. 467-473, 1993
Printed in the U.S.A. All rights reserved.

0160-4120/93 $6.00 +.00

HISTORY AND CURRENT USES OF ^{224}Ra IN ANKYLOSING SPONDYLITIS AND OTHER DISEASES

R. R. Wick

Institut für Strahlenbiologie, GSF—Forschungszentrum für Umwelt und Gesundheit, Neuherberg, D-85764 Oberschleißheim, F. R. Germany

W. Gössner

Institut für Pathologie, GSF—Forschungszentrum für Umwelt und Gesundheit, Neuherberg, D-85764 Oberschleißheim, F. R. Germany

EI 9203-138 M (Received 28 January 1992; accepted 15 March 1993)

During and briefly after World War II, ^{224}Ra was used in a German hospital in combination with platinum and eosin (*Peteosthor*) for the treatment of tuberculosis and ankylosing spondylitis. The patients, primarily children and juveniles, received repeated intravenous injections of up to 2 MBq ^{224}Ra per injection twice a week for months, sometimes even for years. Injected amounts totalled up to 140 MBq. Following this therapy, an enormous increase in the incidence of bone tumors (56 cases among 900 patients), as well as other lesions was observed. The surviving patients are still under follow-up. Treatment of ankylosing spondylitis with drastically reduced doses of ^{224}Ra, however, was continued up to the recent present and over 1500 patients were so treated in West-German hospitals. This second cohort, exclusively adults, received much lower amounts applied in most cases as one series of 10 weekly injections of about 1 MBq of ^{224}Ra each. This would result in a cumulative alpha-dose of about 0.56 Gy to the marrow-free skeleton of a 70 kg man. These patients have been followed for several years, together with a control group of ankylosing spondylitis patients not treated with radioactive drugs or x-rays. By August 1991, three cases of malignant bone tumors have been observed among the exposed (0.7 - 2.4 cases expected) vs. one case among the controls. Diseases of hematopoietic tissue included leukemias (9 in the exposure group vs. 6 in the control group) and bone marrow failure (12 cases vs. 9). The increase of total leukemias among the exposed, compared to a standard population, is highly significant (9 cases observed vs. 2.8 expected, $p < 0.003$). Chronic myeloid leukemia, specifically, was elevated in the exposed group (3 cases observed vs. 0.8 expected, $p = 0.047$) but not in the control group.

INTRODUCTION

Radium-224 is one of the decay products of the natural thorium series, formally known under its historical name "thorium X" (Fig. 1). It was first separated in the supernatant remaining after precipitation of a thorium salt solution with aqueous ammonia by Rutherford and Soddy(1902). Radium 224 decays by alpha-disintegration, with a half-life of 3.66 d to ^{220}Rn (thoron) and then by three further alpha- and two beta-decays to the stable ^{208}Pb (Fig. 2). The daughters of ^{224}Ra are all short-lived; the longest half-life is that of ^{212}Pb (thorium B, 10.6 h), and altogether six different radionuclides are represented.

Radium 224 is an alkaline earth element which deposits preferentially in the bone when introduced into an organism. Due to its short half-life, most of the nuclide decays at the bone surface, thus, showing a similar distribution pattern and radiobiological

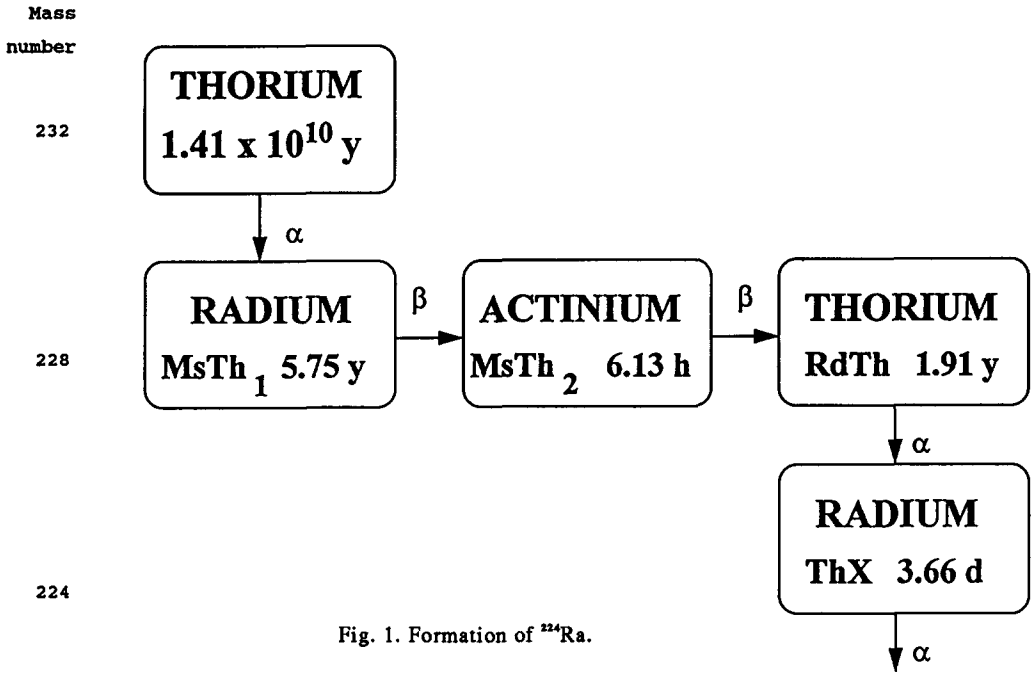

Fig. 1. Formation of ^{224}Ra.

behaviour to ^{239}Pu, which also is predominantly deposited on the bone surface. Internally applied, ^{224}Ra is mainly effective by its alpha-irradiation; the beta- and gamma-radiation is of minor importance. The decay products are partially accumulated in liver, kidney, spleen, and also in the eye. Investigations in humans on the distribution and excretion of ^{224}Ra have shown (Schales 1966), that about 50% of the

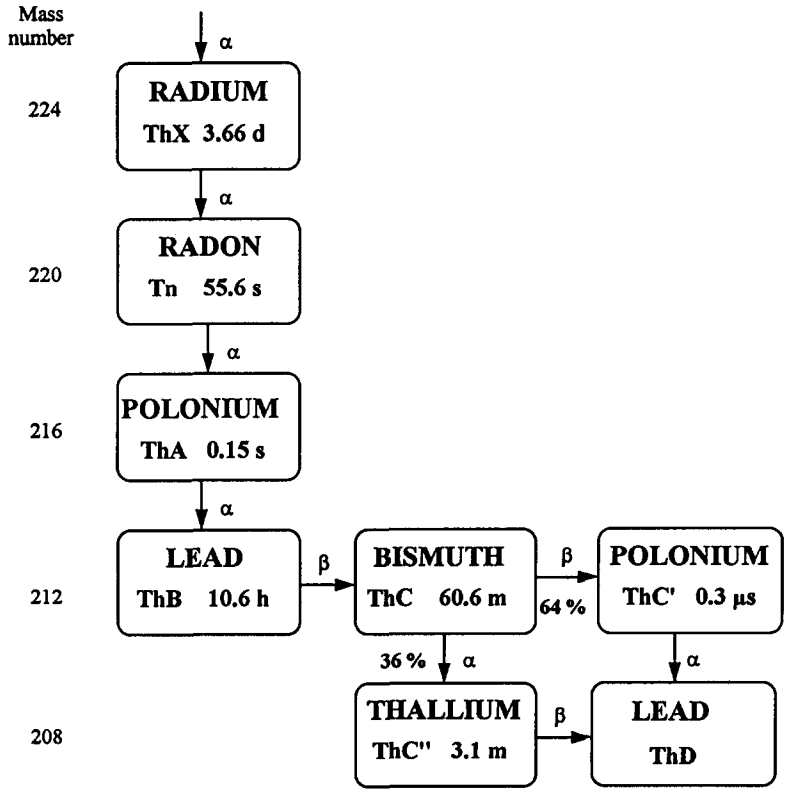

Fig. 2. Decay scheme of ^{224}Ra and daughters.

applied amount is excreted within the first week via feces and urine with a ratio of about 30:1. The biological half-life in the human body, excluding bone is 6 d, 10^4 d for kidney and liver, and 1.64 × 104 d for bone; giving effective half-lives of 2.3 d for total body, 2.7 d for kidney and liver, and 3.6 d for the bone (Seelentag and Schmier 1962). The resulting alpha-dose per 1 MBq of injected ^{224}Ra to the marrow-free skeleton of a 70-kg adult male is 0.56 Gy, or 0.67 Gy for a 63-kg adult female.

Soon after the first separation of ^{224}Ra in 1902, there was great interest in its potential therapeutic uses due to its radiochemical and biological properties. Numerous publications can be found in the medical literature before World War I, but there was no systematic search for medical uses and no animal experiments were reported from that period. Bickel (1913) was the first to report the treatment of ankylosing spondylitis with the new radionuclide.

Ankylosing spondylitis is a chronic inflammatory disease of the vertebral column which affects about 0.1% of the population. Onset is around the age of 20 y and is followed by a progressive stiffening of the whole spine caused by new bone formation. The disease was described at the end of last century independently by Bechterew in Russia, by Strumpell in Germany, and by Marie in France (Moll 1980).

Intravenous injection of ^{224}Ra (ThX), however, fell into disuse after several untoward incidents following internal application of large amounts of ^{224}Ra solution. Two patients actually died with acute radiation syndrome. After this experience, only external dermatological use in the form of ointments or lacquers continued. In France, intravenous injection of ^{224}Ra in patients with rheumatic diseases was reintroduced by Léri (1922), and was continued from around 1930 by Forestier (1951) with allegedly good success. In England, Hernaman-Johnson (1946) started with ^{224}Ra therapy of ankylosing spondylitis. In Germany, Troch (1943; 1949), relying on a historical hypothesis by von Wassermann (von Wassermann and von Hansemann 1912) about a reversed electrical polarity of diseased cells, developed a compound preparation of ^{224}Ra and traces of platinum stabilised by eosin which he called Peteosthor. When, after World War II, Troch became the head of a tuberculosis sanatorium, he introduced the Peteosthor treatment, mainly for the different forms of tuberculosis, into his hospital and later adopted it for ankylosing spondylitis also.

In the years between 1946 and 1950, about 2000 people, most of them children and juveniles, received repeated intravenous injections of Peteosthor, up to 2 MBq ^{224}Ra per injection twice a week for months or even for years, resulting in total injected quantities of up to about 140 MBq ^{224}Ra. This Peteosthor was used for the treatment of various diseases, such as tuberculosis of bone and soft tissue, ankylosing spondylitis, and others. The pretended improvement in tuberculosis treatment could not be verified by other clinicians, and use of the treatment did not spread to other institutions. Moreover, beginning in the early 1950's, objections to the treatment were raised—the primary one being that ^{224}Ra deposited in the growing skeleton of the children and juveniles would cause severe damage.

DAMAGE IN THE EARLY HIGH-DOSE PATIENTS

Rathke (1954) was the first to publish on the appearance of a bone tumor in a Peteosthor-treated juvenile coxitis patient; in 1955, he reported two osteosarcomas in juvenile TB patients. Spiess (1956) observed an alarming increase of bone tumors in the patients, among them mostly children and juveniles, treated with the high doses of Peteosthor by Troch. Thereafter, he made extensive efforts to relocate as many of those patients as possible, and to include them in a still ongoing follow-up study, with the late C. W. Mays as co-investigator from about 1970 until his untimely death in 1989. Their study generated numerous important contributions on the dosimetry and the biological effects of incorporated radionuclides.

Spiess and Mays (Spiess 1969; Spiess and Mays 1970; Mays et al. 1978; Mays et al. 1989) were the first to extensively investigate the epidemiologic consequences of exposure to the short-lived bone seeker ^{224}Ra in humans. Since the beginning of that study, they have reported 56 cases of bone tumors, mostly osteosarcomas among patients aged 2 - 56 y at beginning of injection. Among the children and juveniles studied, 38 cases (38/218, 17%) have been reported, whereas among the adults only 18 cases (18/682, 2.6%) have occurred. All, or virtually all, of these bone tumors can be ascribed to radiation, since only 0.3 cases would have been expected naturally, based on the general population rate of 2 bone sarcoma/y·100 000 persons. The distribution of tumor appearance times ranged from 3.5 to 33 y, averaging about 10 - 12 y. The last bone tumor appeared in 1985 after a latency time of 33 y. Based on present trends, few, if any, additional bone sarcomas are expected among the surviving ^{224}Ra patients (Chmelevsky et al. 1988; Chmelevsky et al. 1990).

Most data previously obtained on the induction of bone tumors by incorporated radioactivity have been

related to long-lived radionuclides (Vaughan 1973). The long duration of irradiation was believed to be necessary in order to produce those effects. A well-known example in human experience is the increased incidence of osteosarcomas following the intake of long-lived ^{226}Ra by luminous dial painters.

It is interesting to compare the distribution of appearance times of bone sarcomas induced by short-lived ^{224}Ra vs. those from the long-lived ^{226}Ra and ^{228}Ra (Fig. 3). The earliest appearance times are similar: 4 y in the ^{224}Ra patients and 5 y in the U. S. dial painter group. The important difference is that whereas the risk from short-lived ^{224}Ra seems to be exhausted after 33 y, tumors induced by the long-lived radium continue to appear throughout the remaining lifespan. This effect can be attributed to the continued production of new tumors by radiation received a long time after the initial deposition of the long-lived radium. For example, the bone sarcoma appearing after 63 y might have been induced by alpha-particles emitted 10 y earlier, some 53 y after the initial skeletal deposition of ^{226}Ra.

Bone tumors, however, were not the only lesion observed after injection of high amounts of Peteosthor or ^{224}Ra into mostly juvenile patients. Spiess and his co-investigators, as well as other study groups, have reported increased incidences of cataracts (Chmelevsky et al. 1988; Stefani et al. 1989; Honegger 1969; Taylor and Thorne 1988), tooth damages (Spiess 1969; Sonnabend et al. 1986; Haunfelder et al. 1977; Reichart 1979), exostoses (Spiess and Mays 1979), and growth retardation (Spiess et al. 1986; Koch 1957) after incorporation of high amounts of ^{224}Ra. Also, diseases of the liver (Spiess and Mays 1979) and kidney (Spiess and Mays 1979; Mays et al. 1989) have been described. In none of these treatments could a beneficial effect on the primary tubercular disease be verified.

RECENT TREATMENT OF ANKYLOSING SPONDYLITIS

Contrary to those uniformly negative observations for the various forms of TB and the other diseases, beneficial and long lasting results, mostly relief of pain, have been obtained in the treatment of ankylosing spondylitis. Treatment with ^{224}Ra was adopted by Pitzen (1949) for ankylosing spondylitis and subsequently therapeutic guidelines were established by Koch (Koch and Reske 1952; Koch 1978). Eosin and platinum, first omitted from the mixture for purely financial reasons, were soon shown in animal experiments to be completely without influence on distribution and effect.

Since the 1950's, the total amount of ^{224}Ra administered during a course of treatment has been drastically reduced to about 10 - 12 MBq. The treatment with ^{224}Ra, mostly at this dose level, has been performed by a great number of orthopedic hospitals in Germany which, unanimously, have reported beneficial analgesic effects, ranging from pain-free to at least moderate reduction of pain in the vast majority of cases (Schneller 1950; Mahlo 1952; Wilde 1952; Lentz 1952; Titze 1952; Rütt 1952; Kaiser 1953; Herdt 1956; Kutz 1957; Weber-Böllhoff 1959; Best 1959; Härtling 1962; Diederich 1965; Kellermann 1968; Rudolph et al. 1980). Radium 224 has been

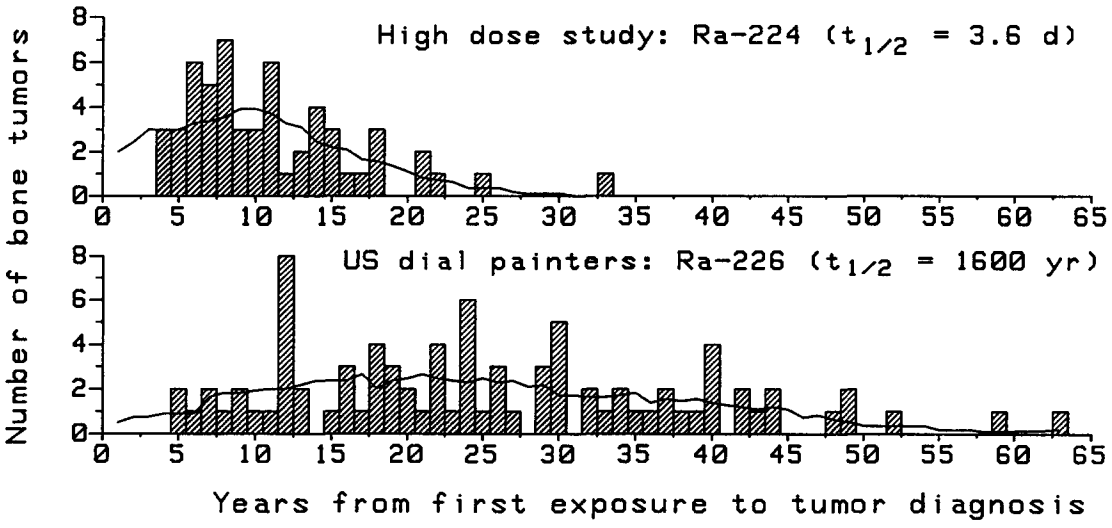

Fig. 3. Bone tumor latency.

used sporadically in neighbouring countries too (Erlacher 1953; Louyot et al. 1970; Bertrand et al. 1978; Roux et al. 1978; Roux and Mattei 1988). In France, it was injected also intra-articulary, as an alternative to other radionuclides, for the treatment of rheumatoid synovitis.

Dosages in prior times were usually calculated in electrostatic units (elektrostatische Einheiten, esE), an obsolete unit of radioactivity which was used until 1969 for the medical dosage of ^{224}Ra. This unit was based on an early experimental technique for the measurement of alpha-ray ionisation. Here, the geometry of the apparatus and the rapidity with which the measurements followed the separation of the ^{224}Ra sample from its parents both play an important role, and it is not possible to specify an universal conversion factor. For the preparations used in Germany for the treatment of ankylosing spondylitis, an equivalent of 28 μCi (1.036 MBq) for 200 esE of ^{224}Ra is generally accepted.

EPIDEMIOLOGICAL INVESTIGATIONS OF RECENT ^{224}Ra TREATMENT

One of the most severe late effects detected in the high-dose study of Spiess and Mays was the induction of bone tumors. The lowest dose associated with a bone tumor was found to be 0.9 Gy. Patients having received lower doses, however, were not sufficiently represented in that study. In order to extend the conclusions, a new study was started in 1971 (Schales 1978; Wick and Gössner 1983; Wick et al. 1986; Wick and Gössner 1989). The objective was the evaluation of the late effects risk to humans for bone tumors and other lesions potentially related to injected alpha-emitters below that lowest dose of 0.9 Gy.

This lower dose study includes most patients treated in West Germany for ankylosing spondylitis with low amounts of ^{224}Ra (Table 1). As of August 1991, the study includes around 1500 ankylosing spondylitis patients from nine hospitals. The majority of these patients, most of them treated in the years 1948-75, received one series of ten weekly injections, each of about 1 MBq of ^{224}Ra. In addition, there exists a control group of ankylosing spondylitis patients not treated with radioactive drugs or x-rays.

Up till now, causes of death have been ascertained in 542 patients of the exposure group and in 650 patients of the control group. Table 2 shows a summary of the cancers of bone and soft tissue observed so far in this study. In this table, we have considered only those diseases which are known or implied from the higher dose study to be associated with administration of

Table 1. Exposure and follow-up parameters.

	Exposure Group	Control Group
Observed patients	1471	1336
cause of death certified	542	650
av. inj. ^{224}Ra (MBq/kg)	0.17	–
av. skeletal dose (Gy)	0.67	–
av. inj. span (weeks)	10.2	–
av. follow-up time (yr)	19.0	20.4

Table 2. Cancers of bone and soft tissue.

	Exposure Group		Control Group	
	obs	*exp*	*obs*	*exp*
Total cancers	117	118–144	146	154–188
Liver	1	2.5–3.7	7	3.4–4.8
Urinary System	9	8.1–10.6	9	10.7–13.9
Female Breast	1	2.6–4.3	1	2.2–3.6
Skeleton	3	0.7–2.4	1	0.8–2.8
Leukemia	9	2.7–2.8	6	3.3–3.5
Chron. myeloid Leuk.	3	0.8	1	1.1

^{224}Ra. There is no significant difference between observed and expected cases for cancers of the liver, urinary system, or the female breast. Malignant primary bone tumors (according to the histological typing of bone tumours of WHO) have been observed in three cases in the exposure group: one fibrosarcoma of bone; one reticulum cell sarcoma (malignant lymphoma) of bone; and one medullary plasmocytoma (multiple myeloma) originally observed in the bone marrow of sternum and pelvis. The expected number of spontaneous bone tumors for the present follow-up time is estimated to be 0.7 - 2.4 cases, determined from the age-dependent spontaneous rates for bone tumors from the three cancer registries of the Federal Republic of Germany. Thus, an increased incidence for bone tumors in the exposure group of this lower dose study cannot be verified statistically.

Diseases of hematopoietic tissue among the study population included leukemias (9 in the exposure group vs. 6 in the control group) and bone marrow failure (12 cases vs. 9). The increase of total leukemias is, compared to a standard population, highly significant for the exposure group (9 cases observed vs. 2.7 - 2.8 expected, $p < 0.003$) and striking also for the controls (6 cases observed vs. 3.3 - 3.5 expected, $p = 0.14$). Possibly, the increase of leukemias in the control group may indicate an effect of the generally considerable intake of painkilling or other drugs for the treatment of the basic disease. Subclassification of the leukemias shows a clear preference for chronic myeloid leukemia in the exposure group (3 cases observed vs. 0.8 expected, $p = 0.047$), whereas in the control group (1 case observed vs. 1.1 expected) the observed cases are within the range of expectancy. Disorders of the hematopoietic system following treatment with ^{224}Ra have been reported earlier by other authors (Kutz 1963; Stieglitz et al. 1973) even at the same low dose level. Animal experiments with varying amounts of ^{224}Ra have also shown that mice given amounts of ^{224}Ra lower than those found to cause osteosarcomas may be at risk instead from myeloid leukemia (Humphreys et al. 1985).

EPILOGUE

Due to technical and commercial reasons, the production of ^{224}Ra for injection purposes was discontinued in spring 1990. It is uncertain whether it will ever be re-established.

Acknowledgment — This research has been supported by the Radiation Protection Programme of the Commission of the European Communities (CEC), Contract No. BI6-D-0083 D.

REFERENCES

Bertrand, A.; Legras, B.; Martin, J. Use of radium-224 in the treatment of ankylosing spondylitis and rheumatoid synovitis. Health Phys. 35: 57-60; 1985.

Best, G. Über die funktionelle Therapie bei der Spondylitis ancylopoetica in Verbindung mit Thorium X-Gaben. Arch. Orthop. Unfall-Chir. 50: 368-399; 1959.

Bickel, A. Weitere Beiträge zur ThX-Therapie bei Anämie, Leukämie und rheumatischen Erkrankungen. Berliner Klin. Wochenschr. 50: 346-348; 1913.

Chmelevsky, D.; Kellerer, A.M.; Land, C.E.; Mays, C.W.; Spiess, H. Time and dose dependency of bone sarcomas in patients injected with radium-224. Radiat. Environ. Biophys. 27: 103-114; 1988.

Chmelevsky, D.; Mays, C.W.; Spiess, H.; Stefani, F. H.; Kellerer, A.M. An epidemiological assessment of lens opafications with impaired vision in patients injected with radium-224. Radiat. Res. 115: 238-257; 1988.

Chmelevsky, D.; Spiess, H.; Mays, C.W.; Kellerer, A.M. The reverse protraction factor in the induction of bone sarcomas in radium-224 patients. Radiat. Res. 124: 69-79; 1990.

Diederich, O.; Klinik und Therapie der Spondylarthritis ankylopoetica -Behandlungsergebnisse mit Thorium X und Corticoiden. Bonn: Thesis, University, 1965.

Erlacher, P. Zur Behandlung des Morbus Bechterew mit Thorium X. Wien. Klin. Wochenschr. 65: 825-826; 1953.

Forestier, J.; Jacqueline, F.; Rotes-Querol, J. La Spondylarthrite ankylosante. Paris: Masson; 1951.

Härtling, S. Ein Beitrag zur Thorium-X-Therapie bei der Spondylitis ankylosans. Dresden: Thesis, Academy of Medicine; 1962.

Haunfelder, D.; Gessner, B.; Barckhaus, R.H.; Niemann, R.; Themann, H. Spätschäden am Odonton nach Behandlung mit Thorium X. Dtsch. J. Mund-Kiefer-Gesichts-Chir. 1: 191-201; 1977.

Herdt, L. Nachuntersuchungen an mit Peteosthor bzw. Thorium X behandelten M. Bechterew-Kranken des "Annastifts" Hannover. Hamburg: Thesis, University; 1956.

Hernaman-Johnson, F. Thorium X in spondylitis and chronic rheumatism. Rheumatism 3: 21-24; 1946.

Honegger, H. Strahlenkatarakt nach Peteosthorbehandlung (Thorium X). Monatsbl. Augenheilk. 155: 890-893; 1969.

Humphreys, E. R.; Loutit, J. F.; Major, I. R.; Stones, V. A. The induction by ^{224}Ra of myeloid leukemia and osteosarcoma in male CBA mice. Inter. J. Radiat. Biol. 47: 239-247; 1985.

Kaiser, G. Über die Behandlung des Morbus Bechterew, insbesondere mit Thorium X. Dtsch. Gesundheitswes. 8: 474-479; 1953.

Kellermann, P. Erfolge und Gefahren bei der Behandlung des Morbus Bechterew mit Thorium X. Berlin: Thesis, Karl-Marx-University; 1968.

Koch, W.; Reske, W. Die Ergebnisse der intravenösen Thorium X-Behandlung bei der Spondylarthritis ankylopoetica (M. Bechterew). Strahlentherapie 87: 439-457; 1952.

Koch, W. Strahlenbedingte Wachstumsstörungen der Gliedmassen. In: Proc. Septième Congrès de la Société Internationale de Chirurgie Orthopédique et de Traumatologie, Barcelona 16-27 septembre 1957. Brussels: Soc. Internat. de Chirurgie Orthopédique et de Traumatologie:1957: 457-466.

Koch, W. Indication for ^{224}Ra-therapy in ankylosing spondylitis (Morbus Strumpell-Bechterew-Marie). In: Müller, W. A.; Ebert, H. G., eds. Biological effects of ^{224}Ra-benefit and risk of therapeutical application. The Hague: Martinus Nijhoff Medical Division; 1978: 21-29.

Kutz, G. Zur Behandlung des Morbus Bechterew mit Thorium-X., Thesis, University Frankfurt; 1957.

Kutz, G. Zur Frage von Spätschäden nach der Behandlung mit Thorium-X. Z. Orthop. Traumat. 97: 474-482; 1963.

Lentz, W. Die Behandlung der Bechterew'schen Erkrankung mit Peteosthor. Med. Wochenschr. 7: 78-84; 1952.

Léri, A.; Thomas, M. Traitement des Rhumatismes Chroniques par le Thorium. Bulletins et mémoires de la Société Médicale des Hôpitaux de Paris 44: 10-13; 1922.

Louyot, P.; Mougin, G.; Legras, B.; Montet, Y.; Combebias, J.-F.; Pourel, J.; Simon, J.-M.; Diebold, P. La thérapeutique médicamenteuse de la spondylarthrite ankylosante. Rev. Rhum. 37: 281-309; 1970.

Mahlo, K.L. Orales Thorium X als Mittel der Wahl beim Morbus Bechterew. Dtsch. Med. J. 3: 472-474; 1952.

Mays, C.W.; Spiess, H.; Gerspach, A. Skeletal effects following ^{224}Ra injections into humans. Health Phys. 35: 83-90; 1978.

Mays, C. W.; Spiess, H.; Chmelevsky, D. Malignancies in patients injected with Radium-224. In: Taylor, D. M.; Mays, C. W.; Gerber, G. B.; Thomas, R. G., eds. BIR Report No. 21, Risks from Radium and Thorotrast. London: British Institute of Radiology: 7 - 12; 1989.

Moll, J.M.H. Ankylosing spondylitis. Edinburgh: Churchill Livingstone; 1980.

Pitzen, P. Über die Behandlung des Morbus Bechterew mit Peteosthor (Troch). Med. Klin. 44: 1111-1115; 1949.

Rathke, F.W. Schädigungen und Spätschäden nach Peteosthorbehandlung. Münch. Med. Wochenschr. 96: 884-886; 1954.

Rathke, F. W. Kritische Stellungnahme zur Frage der Schädigung nach ThX-Behandlung. Münch. Med. Wochenschr. 97: 952-953; 1955.

Reichart, P. A. Radiographic finding in ^{224}Ra-caused dental resorptions. Int. J. Oral Surg. 8: 467-473; 1979.

Roux, H.; Schiano, A.; Liprandi, D.; Serratrice, G.; Paulin, R.; Roux, F. Notre expérience du 224-Ra dans le traitement de la spondylarthrite ankylosante. In: Müller, W. A.; Ebert, H. G., eds. Biological effects of ^{224}Ra-benefit and risk of thera-peutic application. The Hague: Martinus Nijhoff Medical Division; 1978: 212-214.

Roux, H.; Mattei, J.-P. Traitement de la Spondylarthrite ankylosante par les radiations ionisantes. In: Simon, L.; Herisson, Ch., eds. La Spondylarthrite ankylosante, actualités nosolagiques et thérapeutiques. Paris: Masson; 1988: 142-147.

Rütt, A. Zur Therapie des Morbus Bechterew. Dtsch. Med. Wochenschr. 77: 649-652; 1952.

Rudolph, F.; Salewski, H.; Franke, J. Spätergebnisse nach Thorium-X-Behandlung des Morbus Bechterew (eine 15-Jahres-Studie). Beitr. Orthop. Traumat. 27: 29-37; 1980.

Rutherford, E; Soddy, F. The radioactivity of thorium compounds. Part I. An investigation of the radioactive emanation.Trans. Chem. Soc. London 81: 321-350; 1902a.

Rutherford, E; Soddy, F. The radioactivity of thorium compounds. Part II. The cause and nature of radioactivity. Trans. Chem. Soc. London 81: 837-860; 1902b.

Schales, F. Strahlenbelastung bei der therapeutischen Anwendung von Thorium X (Radium 224). Strahlentherapie 130: 420-425; 1966.

Schales, F. Brief history of ^{224}Ra usage in radiotherapy and radiobiology. Health Phys. 35: 25-32; 1978.

Schneller, H. Erfahrungen mit Peteosthor-Behandlung bei Morbus Bechterew. Med. Klin. 46: 142-144; 1950.

Seelentag, W.; Schmier, H. Inquiry into the treatment with Thorium-X, delivered by request of the Senator for Public Health of Berlin. 2. Auflage vom 7.5.1962. Berlin: Bundesgesundheitsamt; 1962 (in German).

Sonnabend, E.; Spiess, H.; Mays, C.W. Tooth breakage in patients injected with ^{224}Ra. Strahlenther. Suppl. 80: 60-64; 1986.

Spiess, H. Schwere Strahlenschäden nach der Peteosthorbehandlung von Kindern. Dtsch. Med. Wochenschr. 81: 1053-154; 1956.

Spiess, H. Radium-224-induced tumors in children and adults. In: Mays, C.W.; Jee, W. S.S.; Lloyd, R.D.; Stover, B.J.; Dougherty, Jean H.; Taylor, G.N., eds. Delayed effects of bone-seeking radionuclides. Salt Lake City, UT: University of Utah Press; 1969: 227-248.

Spiess, H.; Mays, C.W. Bone cancers induced by ^{224}Ra (Th X) in children and adults. Health Phys. 19: 713-729; 1970. + addendum Health Phys. 20: 543-545; 1971.

Spiess, H.; Mays, C.W. Liver disease in patients injected with ^{224}Ra. Environ. Res. 18: 55-60; 1979.

Spiess, H.; Mays, C.W. Exostoses induced by ^{224}Ra (ThX) in children. Eur. J. Pediatr. 132: 271-276; 1979.

Spiess, H.; Mays, C.W.; Spiess-Paulus, E. Growth retardation in children injected with ^{224}Ra. In: Gössner, W.; Gerber, G.B.; Hagen, U.; Luz, A., eds. Suppl. to Strahlentherapie Vol. 80. The radiobiology of radium and thorotrast. München-Wien-Baltimore, MD: Urban & Schwarzenberg; 1986: 45-50.

Stefani, F.H.; Spiess, H.; Mays, C.W. Cataracts in patients injected with a solution of radium-224, colloidal platinum, and the red dye eosin (Peteosthor). In: Taylor, D.M.; Mays, C.W.; Gerber, G.B.; Thomas, R.G., eds. BIR Report No. 21, Risks from radium and thorotrast. London: British Institute of Radiology; 1989: 12-21.

Stieglitz, R.; Thiele, M.; Stobbe, H.; Wegner, G. Schädigungen der Hämatopoese durch Thorium-X-Therapie. Folia Hämatol. (Leipzig) 100: 95-103; 1973.

Taylor, D.M.; Thorne, M.C. The potential for irradiation of the lens and cataract induction by incorporated alpha-emitting radionuclides. Health Phys. 54: 171-179; 1988.

Titze, H. Ergebnisse der Peteosthorbehandlung bei Bechterewscher Erkrankung. Die Medizinische (Stuttgart) 22: 763-765; 1952.

Troch, P. Über Peteosthor und seinen Einfluß auf bösartige Geschwülste des Menschen. Monatsschr. Krebsbekämpf. 11: 77-91; 1943.

Troch, P. Neue Wege des Heilens. Braunschweig: Vieweg; 1949.

Vaughan, J. M. The effects of irradiation on the skeleton. Oxford: Clarenton Press; 1973.

von Wassermann, A.; von Hansemann, D. Chemotherapeutische Versuche an tumorkranken Tieren. Berliner Klin. Wochenschr. 49: 4-10; 1912.

Weber-Böllhoff, H. Die Behandlung des Morbus Bechterew mit Peteosthor und Thorium X unter Berücksichtigung möglicher Spätschäden. Düsseldorf: Thesis, University; 1959.

Wilde, R. Peteosthor und Thorium X als Therapeuticum des Morbus Bechterew. Arch. Orthop. Unfall-Chir. 45: 329-333; 1952.

Wick, R.R.; Gössner, W. Follow-up study of late effects in ^{224}Ra-treated ankylosing spondylitis patients. Health Phys. 44 (Suppl.1): 187-195; 1983.

Wick, R.R., Chmelevsky, D.; Gössner, W. ^{224}Ra: Risk to bone and haematopoietic tissue in ankylosing spondylitis patients. In: Gössner, W.; Gerber, G.B.; Hagen, U.; Luz, A., eds. Suppl. to Strahlentherapie Vol. 80, The Radiobiology of radium and thorotrast. München-Wien-Baltimore, MD: Urban & Schwarzenberg; 1986: 38-44.

Wick, R.R.; Gössner, W. Recent results of the follow-up of radium-224 treated ankylosing spondylitis patients. In: Taylor, D.M.; Mays, C.W.; Gerber, G.B.; Thomas, R.G., eds. BIR-Report No. 21, Risks from radium and thorotrast. London: British Institute of Radiology; 1989: 25-28.