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Late Effects of Internally Deposited Radioactive Materials

by

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Radium salts were given orally and intravenously for hypertension, arthritis, syphilis, anemia, leukemias and mental disorders from about 1915 to 1930. The painting of watch dials with luminous material containing radium, mesothorium, and radiothorium started in this country in about 1915. The present determinations of the amounts of heavy radioelements that can be safely retained by the body are based in a large measure on the radiobiological data obtained from these patients. However, additional information is necessary to establish more accurately maximum permissible levels of exposure.

Seventy eight people were recently evaluated at the Harvard Medical School, the Argonne National Laboratory, and the Massachusetts Institute of Technology who had radioactive materials present in their bodies for protracted periods of time. Twenty eight of these people were formerly employed as luminous dial workers, and fifty were given radium salts.

More than 90% of the radium is rapidly eliminated. The average amount of radium present in 19 mental patients at 6 months was 4%, at 12 months 2%, and at twenty years .8%. Practically all of the retained radium is deposited in the skeleton in small highly concentrated areas.

SLIDE 1

This is a gross autoradiograph of a tibia. The dark areas show the irregular deposition throughout the entire section.

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SLIDE 2

This is a detailed autoradiograph showing the alpha tracts coming from radium concentrated in 2 haversian syetems.

One of the most important histopathological findings of these investigations has been the presence of an atypical osseous tissue in the trabecular spaces. Similar changes have been found in animals following the administration of plutonium, strontium, and other bone seeking radio-elements.

SLIDE 3

This is a photomicrograph showing bone, the darker staining atypical osseus tissue, and acellular fibrous tissue.

SLIDE 4

This is a roentgenogram of a vertical and horizontal section of the fibula showing the small areas of destruction that occurred in the cortex of the long bones of these patients.

SLIDE 5

This is a roentgenogram of the humerus showing areas of increased density in the head produced by atypical osseus tissue and areas of decreased density in the cortex produced by bone destruction.

The long bones of patients having over one microgram of radium were involved about three times as often as those patients having under one microgram, thus showing that some correlation can be made between the roentgenographic changes and increasing amounts of radium in the body.

Destructive changes were found as often in the absence as in the presence of radium. It is obvious that the mechanism of production of skeletal change from deposited radioactive materials is complex. When the repairative

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processes can no longer be maintained at a rate equal to the destructive processes, permanent changes occur.

Symptoms which could reasonably be attributed to radium deposition, usually resulted from aseptic necrosis of the bones. Symptoms began to develop about 15 years after radioelement deposition. About one half of the patients had symptoms referable to the presence of radioactive materials. Significant hematological changes did not occur until the disease process was well advanced and terminally they usually had about 10 grams of hemoglobin and 3 million erthrocytes per cubic millimeter.

There is a rather general agreement the malignancies originate in or around the proliferation of fibrous connective tissue and atypical osseus tissue. Since radioactivity is usually absent in these areas, the initial conclusion of Martland that sarcomas develop as a direct result of irradiation is unlikely.

Thirteen tumors developed in the 89 patients of the 1951 series. 8 of these tumors developed in luminous dial workers and 5 in the radium patients.

SLIDE 6

This slide shows the distribution and type of tumor found in the 1951 investigations. The tumors that developed in the radium patients are shown on the right, and the tumors that developed in the luminous dial workers are shown on the left side of the skeleton. Note that tumor origin was almost always in cancellous bone, the site of atypical osseus tissue formation.

SLIDE 7

The clinical course of 5 patients of Martland's 1931 series was compared with the 1951 series. The average age at the time of deposition of the radio-

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active materials was 17 years for the luminous dial workers and 39 years for the radium patients. The tempo of the entire clinical course seems to be accelerated with increasing amounts of radioactive materials. It took about three times as long for the first symptom to develop and death to occur in the 1951 series compared to the 1931 series. However, Martland's cases had about 8 times as much radium as the patients investigated in 1951. These data are inconclusive but they suggest that some relation exists between the amount of radium present and the time malignancy develops.

There is a marked acceleration of the disease process when malignant changes occur. The patient follows a rather rapid down-hill course, he becomes emaciated, anemia develops, and pain increases and becomes generalized. Death usually occurs about one year after symptoms began at the site of the tumor origin. Patients who do not die from malignancy usually die from emaciation, anemia and secondary infection.

There has been considerable interest recently in the potential use of thorium as a breeder material in the production of atomic energy. Thorotrast containing thorium began to be used for the visualization of the liver, spleen and blood vessels in about 1930.

Two investigations of the late effects of thorium are now being carried out, one at the Naval Medical Center, Bethesda, Maryland in conjunction with the Universities of Utah and Rochester, and the Atomic Energy Commission and the other at the Finsen Institute, Copenhagen, Denmark in conjunction with the British Medical Research Council. Approximately 250 people who received thorotrast have been recently evaluated.

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When thorotrast is given almost all of the thorium is taken up by the reticulo-endothelial system and retained indefinitely. Only one half of one percent of the thorium was eliminated from a patient who died 17 days after thorotrast administration. More than 90% was eliminated the first week.

SLIDE 8

This is a slide showing the distribution of thorium in this patient. The thorium concentration in the adrenal gland was one third the concentration in the liver. Concentration in the heart was forty times greater than in muscle. Dense cortical bone had a very small amount of thorium.

SLIDE 9

This is a slide showing the concentration of thorium in the patient who received thorotrast 17 days prior to death compared with another who received thorotrast 20 years prior to death. There is an apparent redistribution to the spleen and lungs and sternum. The concentration in the liver, bone marrow and skeleton ~~was~~ about the same in the two patients.

Radiochemical analysis of the organs was made for the radium isotopes, mesothorium I and thorium X, the first and fourth daughter products of thorium. It was considered that mesothorium formed in the liver and spleen might be transferred to the skeleton in significant amounts, The results from these two patients does not indicate that transfer occurred.

SLIDE 10

This is a photomicrograph of a histological section of the liver showing the large thorium deposits. Note the destruction of normal liver architecture and replacement fibrosis. The material for this slide and the slides to follow was taken from a patient who had thorium 20 years prior to death.

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SLIDE 11

This is a photomicrograph of an autoradiograph of the liver showing alpha tracts coming from thorium deposits.

SLIDE 12

This is a photograph of longitudinal undecalcified section of the femur. The endosteum has a trabeculated appearance.

SLIDE 13

This is a photomicrograph of the endosteal surface of the bone. Note the small particles of thorium in relation to the cells.

SLIDE 14

This is a roentgenogram of the midsection of the tibia. Note the longitudinal striations and the thickened shaft.

We have evaluated seventeen patients who were given thorotrast on an average of 16 years prior to this study. Over fifty percent of these patients had minor skeletal changes which were present most often in the humerii, ulnae, and tibiae.

The inherent difficulty in critically evaluating these changes and their relation to thorium administration is the wide variation in the normal skeletal roentgenographic pattern. The demonstration of thorium, and radioactivity from the radium isotopes, mesothorium I and radiothorium, in bone is highly suggestive that a definite relation between these skeletal changes and thorium administration exists. Further study is in progress to clarify this relationship.

Three large follow-up studies were made in 1935, 1943, and 1950 on the clinical status of patients in this country who received thorotrast. It was concluded from these investigations that no significant clinical changes had occurred in over 4000 patients.

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In 1953 a confidential report was made on the 243 cases studied in ~~Denmark~~ EUROPE. Equivocal complaints have been related to throium in some of these patients. Spleenectomy was performed on five patients with some reported symptomatic relief of pain in the region of the spleen. The hemoglobin, erythrocyte, and lymphocyte values were slightly decreased in a majority of these patients.

SLIDE 15

This slide gives the number of patients who developed either malignancies or hematological disorders in the United States and Denmark. This very small number of cases is not significant, and the findings may be coincidental. Since radium began to be used 10-15 years before thorotrast was introduced as a diagnostic procedure, a longer time will be necessary for adequate evaluation.

It is evident from these recent investigations that small amounts of radioactive materials may remain in the body for long periods of time before significant clinical changes are produced. The foundation for the safe industrial, military and medical use of radioactive materials is based in a large measure on the radiobiological data obtained from these patients. From these tragic results of the first medical and industrial use of radioactive materials elaborate safety precautions have been taken. The results from the recent investigations indicate, however, that subtle changes , such as reduction in the reserve function of an organ, may be produced and be undetected by present clinical tests. Until the foundation upon which the safe use of radioactive ~~materials~~ materials is completed, we must exercise caution and constant vigilence in their medical, military and industrial use. May I urge you to refer these patients to laboratories equipped to evaluate their status and determine the radioactivity present. It is only through proper evaluation and continued follow up studies that we may more adequately protect the increasing numbers of our population who will be exposed to radioactive materials.

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