Osteogenic Sarcoma in Dial Painters Using Luminous Paint

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Of some fifteen girls whose deaths were attributed to radium-mesothorium poisoning incurred while they were employed at painting watch dials with luminous paint, two were found to have osteogenic sarcoma of the bone.

The etiology, the general and the special symptomatology, the pathologic anatomy, the prognosis and the treatment in this new industrial hazard were first described by Martland and his associates in 1925 and 1926.1

Only a brief résumé of the observations on this disease is necessary in this paper.

The paint used consisted of crystalline phosphorescent zinc sulphide, ZnS (Sidot's blend), rendered luminous by the addition of extremely small amounts of radium, mesothorium and radiothorium. These radioactive substances were in the form of insoluble sulphates in the paint when it was used.

The mode of poisoning in these cases was by ingestion. Owing to a general habit among these workers of pointing their brushes in their mouths while painting the dials, they swallowed small amounts of the radioactive paint day after day. They were also exposed to radioactivity by absorption of the substance through the skin and by inhalation, especially of the dust of the luminous paint, but these portals of entry were not considered significant. The girls affected had swallowed the paint for periods of from one to four years or more.

Most of the paint swallowed passed rapidly through the gastrointestinal tract and was eliminated. A small amount, however, was continually absorbed and eventually stored as insoluble sulphates of particulate or colloidal size in the main organs of the reticulo-endothelial system and, above all, in the bones. The exact mode of intestinal absorption is not clear. Whether the insoluble radioactive substance was picked up by wandering histiocytes of the intestine and taken into the thoracic duct, then to the blood and then to the storage organs, in which it was phagocytosed by the fixed histiocytes of the blood sinusoids, the Kupffer stellate cells of the liver and the splenic phagocytes, whether small quantities passed through the intestinal tract in a manner not understood, or whether the radioactive substances had some fixed position in the zinc sulphide molecule which allowed it to be absorbed with the zinc is unsettled at present. Perhaps the conceptions of absorption from the intestinal tract must be augmented and modified considerably. It should be recalled that the entrance into the body of insoluble matter of particulate size is thought to be easier by inhalation than by ingestion. For instance, in anthracosis, the foreign matter is

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readily picked up from the alveoli of the lungs by the phagocytic cells or histiocytes of the reticulo-endothelial system, and then by lymphatic drainage it is distributed over the entire lung and taken to the hilum nodes in enormous quantities. Anthracosis of the intestinal tract and its lymphatics is, on the other hand, unusual. The same anatomic pathways are seen in exogenous infection of the lung with human tubercle bacilli.

The deposits in the bones were generalized over the entire skeleton. One bone did not contain more radioactivity than another. A study of its minute distribution in the individual bones (which, on account of the extremely small amounts present, could be determined only by photographic methods) showed an irregular distribution in the bone and often a concentration in certain portions. The outer layers of the cortex seemed to be the final position of storage. Here, it was frequently stored in large amounts and probably replaced calcium in these areas.

After final deposition in the bones, these deposits emitted their characteristic radiations day after day (every minute of the twenty-four hours), month after month, and year after year. As about 95 per cent of the radiation coming from these deposits was alpha and only 5 per cent beta and gamma, the blood-forming centers, owing to their proximity, were constantly bombarded by the alpha particle, exposing vital centers to a type of radiation never before known to have occurred in human beings.

The alpha particles are probably the most potent and destructive agent known to science. They consist of nuclei of helium atoms containing two positive charges (He⁺⁺) ejected from the radioactive substances with great force, attaining an initial velocity equal to from one twentieth to one twelfth that of light. Aside from the beta rays, which are negative electrons and much smaller, they represent the fastest space-occupying objects yet known. They collide with other atoms with terrific impact, usually jerking off a negative electron. The chemical changes resulting from this ionization are of the ordinary molecular character. Occasionally, the alpha particle may strike the atomic nucleus of lighter atoms, causing disruption with the liberation of a high velocity atom of hydrogen (H rays). Biologically, the alpha rays are much more destructive than either the beta or the gamma rays, the relation being 10,000 to 100 to 1, respectively. Therefore, radioactive elements in such small amounts that the beta and the gamma radiations are almost negligible still produce, through their alpha radiations, intense physiologic effects, if given by mouth or vein.

In addition, the preponderance of mesothorium in this paint is of great toxicologic importance for the reason that mesothorium in equilibrium with its radioactive emits five alpha particles, whereas radium emits only four, also, the alpha particles of mesothorium and the products of its decay have a greater velocity and penetration than those of radium, and, therefore, are, chemophysically and physiologically, more active.

As a result of the continuous and constant radiation from the deposits on the blood-forming centers, especially of the deadly alpha rays, these centers in time became exhausted, and a leukopenic anemia, in most cases of the regenerative type, but occasionally of the aplastic or aregenerative type, developed. This anemia often proved fatal. Anemias previously recorded, due to external radiation, were all described as aplastic. This judgment was based almost entirely on clinical observations, unsupported by autopsy and histologic evidence, these being unfortunately lacking in almost every case. The alpha particle never entered into the etiology to any extent, as the radiation was almost entirely penetrative and chiefly due to gamma rays.

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Due to a continuous radiation from the deposits, a radiation osteitis often developed in these cases, similar to that seen in bones as a result of large doses of external irradiation. Because of the proximity of the mouth—the dirtiest part of the body—to the mandible and the maxilla, a superadded bacterial infection, usually by way of the teeth, resulted in extensive, intractable necrosis of the jaw, which, together with the anemia, formed the outstanding clinical features of the early fatal cases.

In the later cases (at the time of writing the patients are still alive), a sufficient period of time had elapsed after the exposure (from six to seven years) to allow the mesothorium, which formed some 70 per cent of the radioactivity, to diminish in quantity by its own natural, uninfluenceable decay to below one-half its strength (6.7 years, half period). In the later cases, therefore, the patients seemed to be escaping the extensive necrosis of the jaw and the fatal leukopenic anemias of the regenerative type. They showed, however, chronic crippling lesions of the bones the result of radiation osteitis, most marked in the bones that were subject to weight, pressure and trauma, such as the head of the femur and the acetabula, the spine, the scaphoid bone of the foot, etc. The anemias were milder, and, if progressive, were more apt to be of the aplastic or regenerative type, and to be characterized at autopsy by a bone marrow similar to that seen in chronic benzol poisoning.

As regards the occurrence of sarcoma of the bone in these cases, unfortunately in the first case, the clinical data are meager, and pathologic material is not now available. In this case, the girl died in 1924. A clinical diagnosis of osteogenic sarcoma of the femur was made from the symptoms and the roentgenograms. She was treated by deep roentgen therapy. The presence of sarcoma, however, was never proved by operation or autopsy.

In the second case, a diagnosis of osteogenic sarcoma of the scapula was made during life and proved at autopsy. After a fall, in which the patient hurt her right shoulder, a sarcoma of the scapula developed to which, in addition to severe anemia, she succumbed. She never had severe necrosis of the jaw, but during life showed evidence of a radiation osteitis in the scaphoid bone of the right foot, in the heads of both humeri and in the glenoid cavities. Her bones after death were radioactive, and it appears plausible that the sarcoma originated in a bone that previously had been the seat of a radiation osteitis.

The incidence of two sarcomas of bone in fifteen cases of radium mesothorium poisoning is too large to be passed over as due to coincidence. Since this is the first time to our knowledge that sarcoma of the bone has been attributed to radiation, the case is of sufficient interest to be reported.

Report of a Case

History.—A woman, aged 33, worked as a painter of dials eight years before her death. When applying luminous material to watch dials, she was in the habit of pointing the brushes with her lips. She had little trouble with her teeth and never had any extensive necrosis of the jaw. Roentgenograms taken by a dentist in 1926 showed lesions, which we have interpreted as typical radiation osteitis, involving chiefly the alveolar portions of the mandible.

In September, 1926, fourteen months before her death, she fell while working in a department store, injuring her right shoulder. There was pain with limited motion, and she was later referred to the compensation department. Roentgenograms showed a slight downward displacement of the head of the humerus. She was operated on, but disease was not found in her shoulder. The wound healed promptly without complications.

In July, 1927, six months before her death, she still complained of pain in her right shoulder. She also had pain and lo-
calized tenderness over the scaphoid bone of her right foot. At this time, she was seen by one of us (H.). An examination of the original roentgenograms demonstrated peculiar changes in the right humerus, the scapula and the scaphoid bone of the right foot. He concluded that the condition resembled a radiation osteitis similar to that seen in other painters of dials. It was then ascertained that she formerly had been a dial painter.

In September, 1927, three months before her death roentgenograms for the first time showed a sarcoma of the right scapula, springing from its anterior and upper portion and an osteitis of the scaphoid bone of the right foot with fragmentation.

In December, 1927, she returned to the hospital with her right upper extremity markedly swollen down to the hand. She had pain, which was constant and unrelied by morphine. To lessen the pain, an operation was performed to relieve pressure on the main nerve trunks. Large masses of tumor tissue were removed. She died a few hours later. During life, tests were not made to prove the presence of radioactivity in her body such as the examination of the exhalatory air for the presence of emanation or an examination for the alpha particle by scintillation methods, or the use of the gamma electrometer for the demonstration of penetrative radiations coming from the body. The latter method, however, is of little use in these cases, on account of the extremely small amounts deposited in the bones.

Autopsy. — A large osteogenic sarcoma of the right scapula was found, invading the whole anterior and upper part of the bone, with infiltration into the supraspinous and infraspinous muscles. Visceral metastases were not found. A profound anemia was present. The yellow marrow of the femurs was entirely replaced by dark red apparently regenerating marrow.

Histologic Examination. — An osteogenic sarcoma was seen, in which there was considerable cartilage. In places, the growth was cellular, with mitotic figures and hyperchromatism; in other places, it was sclerotic. New formation of bone was common.

The bone marrow showed a regenerative leukopenic anemia of the megaloblastic type, similar to that described as having occurred in three other fatal cases.

Sections from the scaphoid bone of the right foot showed a radiation osteitis, the marrow being replaced by loose, gelatinous, myxomatous, fibroblastic tissue, in which there was considerable fat.

Demonstration of Radioactivity in the Bones by Photographic Methods. — Dental films in their original packets, when strapped to the bones, showed photographic impressions in from fourteen to thirty days. The outlines of metal clips, coins and the like placed between the bone and the surface of the film were clearly visible. These shadowgrams were produced by beta and gamma rays coming from deposits in the bones, the alpha rays being screened and filtered out by the paper of the dental pack.

The bones, when placed directly on photographic plates or films, produced photographic impressions in as short a period as three days. After seven days' exposure, the irregular distribution of the radioactive deposits could be plainly ascertained with typical alpha penciling.

Bones incinerated to a white ash and given thirty days in which to regain their equilibrium, when placed on photographic films, produced photographic impressions in from two to three days' exposure. The sarcoma when ashed and treated similarly showed only faint radioactivity. This was undoubtedly due to the impossibility of separating portions of the scapula from the new bone formed in the osteogenic sarcoma.

Demonstration of Radioactivity in the Bones by Scintillation Methods. — When portions of dried bone from various parts of the skeleton were held near a screen of phosphorescent zinc sulphide uncontaminated by radioactive substances and the screen was examined under a large magnifying glass, the latter showed typical scintillations. This was absolute proof of radioactivity, for each scintillation represented the light produced by the collision of an alpha particle (a double-charged nucleus of helium) against aggre-
gates of zinc sulphide molecules. The bombardment of the alpha particle could undoubtedly have been heard if proper radio amplifiers had been used.

Demonstration of Radioactivity in the Bones by Means of an Alpha Electroscope.—Samples of bones, after being dried in an electric oven, showed positive evidence of radioactivity when placed in the lower chamber of an alpha electroscop of the Lind type.

After the bones had been incinerated to white ash and had been given thirty days in which to regain their equilibrium, the increased leak due to radioactivity was easily demonstrable with the alpha electroscope.

Chemical Extraction with Determination of the Amount of Radioactivity.—After samples of bone had been incinerated in the electric oven to a white ash with an excess of carbon, a paste of the ash was made with barium chloride and hydrochloric acid. This was boiled with hydrochloric acid and distilled water and filtered while hot. The precipitate was dried, incinerated and after thirty days measured for radiothorium. Sulphuric acid was added to the filtrate, and, after being left to stand for precipitate, the mixture was boiled and then filtered while hot so that the calcium sulphate might be held in solution. The precipitate was again dried, incinerated and after thirty days measured for radium and mesothorium. By this method, a calculation was made, after receiving with the gamma electrometer against known standards, which showed that the entire skeleton in this case contained about 50 micrograms of radioactive substances, in which mesothorium predominated.

Concerning the amount of radioactive substance recoverable at autopsy in these cases, it is of interest to consider my previous experience. The amounts recovered were small. In the first case seen by one of us (M), that of a chemist who died from a rapidly progressing anemia of the regenerative type, the amount of radioactive substances present in the entire skeleton was estimated by the company's physicist to be about 14 micrograms, of which 45 percent was radium and the remainder mesothorium. At that time we were not aware of the importance of the cases and because of the restrictions placed on the performance of the autopsy, we were able to submit only a few of the lumbar vertebrae to the physicist for examination. In the next case, we had a better opportunity. By chemical methods, the radioactive substances were extracted, and it was estimated that the skeleton contained about 180 micrograms, of which 70 percent was mesothorium and the products of its decay. In the third case, 150 micrograms of radioactive substances were found. In a case described by Flinn, in which the gamma electrometer was used during life, he estimated that about 100 micrograms was present in the body. In another case examined by St. George and Gettler, 48,282 micrograms were recovered from the bones, liver and lungs. It may be seen, therefore, that the lethal amount; if there is such a quantity in these cases, is extremely small. Judged by former experience, the amounts deposited in the body as insoluble sulphates sufficient to cause death by production of anemia of the regenerative or aregenerative type, or of necrosis of the jaw from an infection superimposed on a radiation osteitis ranged from 14 to 180 micrograms. Our contention has always been that if there is enough radioactive substance deposited in the bones to secure photographic impressions in from five days' to two weeks' time, then during life there must have been sufficient radiation from these deposits to cause, in time exhaustion of the blood-forming centers.

Comment

Several features in this case, combined with facts ascertained in a previous study of cases of occupational radium-mesothorium poisoning, have led us to believe that the preexisting deposits of radioactive substances in the bones in this case played an important etiologic role in the subsequent development of the sarcoma. Of course, this is an alluring theory; which at present is not provable. The arguments for and against it may be summed up, as follows:

1. There was clinical evidence during life, supported by roentgenograms, that
peculiar changes existed in the bones long before the appearance of the sarcoma. These were noted chiefly in the head of the right humerus, the acromion and the body of the right scapula and in the scaphoid bone of the right foot. They were of the nature of a radiation osteitis.

2. Microscopic sections of the scaphoid bone, removed at autopsy, showed a lesion that was indistinguishable from the irradiation osteitis produced by heavy external irradiation, as described by Ewing.3

3. Anything approaching a sarcomatous transformation in irradiation osteitis due to heavy external irradiation, as seen by radiotherapeutists, has never been recorded. In fact, the general observation is that the process is more apt to become sclerotic, inactive and acellular.

The effects of single or repeated doses of external irradiation; however, must be quite different from those due to a never ceasing radiation coming from fixed deposits of radium and mesothorium in the bones. Furthermore, in all previously reported injuries of body or tissues as due to radiation and irradiation, the alpha rays never played the important role that they did in these cases. Here 95 per cent of the radiation was alpha, which biologically and chemophysically is much more destructive to body tissues than either beta or gamma radiation. In no previous experience have the internal vital organs been constantly exposed to their deadly effect for periods of years, for, in the case of all forms of external therapeutic irradiation, the alpha particle is usually screened or cannot penetrate more than 1 mm. of skin.

4. There was clinical evidence during life, supported by roentgenograms, that the sarcoma started in an area that previously was the seat of a radiation osteitis, while surrounding areas, also the seat of an osteitis, were not affected.

5. It should also be noted that while internal metastases and metastases to the bones were not observed in this case, there was a profound anemia, which at autopsy was shown to be a regenerative, leukopenic anemia, the femurs being filled with dark red marrow. This same type of anemia was found in three other fatal cases among watch dial painters, and was described as due to the effects of constant bombardment of the adjacent blood-forming centers especially by alpha particles.1 Of course, the same type of marrow has been seen in other diseases, notably addisonian anemia, and by Ewing4 in large areas of bone the seat of spontaneous osteogenic sarcoma having nothing to do with radium.

6. The part played by trauma in this case is difficult to determine. Many surgeons would find an adequate cause for the sarcoma in the fall followed by limited motion and pain in the shoulder and the insult of an exploratory operation that did not disclose any pathologic change. We have always been of the opinion that single falls and external violence in the production of osteogenic sarcoma have been greatly exaggerated. They do not offer a satisfactory explanation. Trauma, however, cannot be entirely ignored. In this connection, the remarks of Ewing5 are of interest. "The idea that trauma, or any other factor, may lead to the development of sarcoma at the ends of long bones which are previously normal, is, I think, without satisfactory foundation. I have examined many cases of supposed traumatic origin and nearly always found that the tumor preceded the trauma. The high proportion of traumatic bone sarcomas reported by some observers seems to be obtained by very uncritical study. The previous integrity of the part can rarely be determined with reasonable certainty, and cannot be assumed on the statement of the biased patient." Kessler,6 medical director of the New Jersey Workmen's Compensation Bureau, informed us that in 56,000
injuries examined by him, the result of industrial accidents, he observed only nineteen alleged malignant conditions attributed to trauma. Of the nineteen cases, but six were fairly well proved (the compensation law giving the employee the benefit of the doubt). Sarcoma of the bone was found in only one instance.

7. Since the cause of osteogenic sarcoma is unknown, the great majority of cases must be classed as spontaneous in origin. Why is not this case, therefore, of the same origin? Against this assumption is the incidence. Ophuls, in an analysis of 3,000 autopsies, encountered sarcoma of the bone in only two cases, or 0.06 per cent. During the years from 1918 to 1927 inclusive, of 134,500 admissions to the Newark City Hospital (850 beds), only 14 (0.001 per cent) were for osteogenic sarcoma of a long bone. Primary bone tumors, then, are of unusual occurrence. The incidence of two osteogenic sarcomas in fifteen persons dying as the result of an occupational poisoning by radioactive substances is too high to be mere coincidence.

8. It is of great importance to radiotherapeutists that they should recognize the possibility of the production of a malignant growth by undue or excessive irradiation. The radiation in these dial painters was unique, in that it was constant over every second of the day for years. In addition, the alpha particle played an important part, never played by it before, according to previous records of the deleterious effects of irradiation. What evidence is there that single or repeated interrupted exposures to X-rays or radium produce malignant changes in the tissues? With the exclusion of many reports of epitheliomas that have been engrafted on irradiation dermatitis, which are now becoming rare owing to better protective technic, there still remains evidence in the literature that malignant changes, especially sarcomatous changes, have followed irradiation. Only a few of these instances need be mentioned: A sarcoma following roentgen treatment for joint tuberculosis was reported by Baumann. A sarcoma of the uterus and ovaries following irradiation was reported by Vogt. A sarcoma of a cicatrix after an irradiation dermatitis was reported by Complani, and instances of roentgen sarcoma were recorded by Pfarringer.

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