THE OCCURRENCE OF MALIGNANCY IN RADIO-ACTIVE PERSONS

A General Review of Data Gathered in the Study of the Radium Dial Painters, with Special Reference to the Occurrence of Osteogenic Sarcoma and the Inter-Relationship of Certain Blood Diseases

HARRISON S. MARTLAND, M.D.

(From the Department of Pathology of the Newark City Hospital and the Office of the Chief Medical Examiner of Essex County, Newark, N. J.)

It is the purpose of this paper to call attention to certain data which the writer has accumulated in the study of the radium dial painters which may have an important bearing on future research in the etiology of cancer and of certain obscure blood diseases.

Occupational Poisoning in Manufacture of Luminous Watch Dials

The etiology, the general and special symptomatology, the pathology, toxicology, and prognosis of this new occupational disease were described by Martland and his associates in 1925 and 1926 (1), and the whole subject of the New Jersey cases was later reviewed by him in 1929 (2).

In addition, important papers by Hoffman (3), Castle and the Drinkers (4), Flinn (5), St. George, Gettler and Muller (6), Schlundt, Flinn and Barker (7), and Barker and Schlundt (8), covering the nature of the exposure, factory inspections, methods of detection of radio-activity during life, and treatment have about completed the description of this new industrial hazard.

The report of the U. S. Department of Labor (9) and the special
survey of the U. S. Public Health Service (10), both of which cover not only the New Jersey cases but those occurring in other states, give an excellent resumé of the industrial hazard and complete the disease as an occupational one.

Little has been said, however, of the many scientific problems bearing no relation to the industrial aspect which have arisen in the study of this fascinating disease. As the Lancet (22) has stated, "knowledge of causation is naturally followed by abolition of risk, and so this occupational disease must disappear. But it will continue to live for the light it has shed upon the occurrence of anemias." It may continue to live, also, through the light it sheds on the etiology of malignancy and the close interrelationship of certain blood diseases.

The radium cases should be looked upon as an unfortunate but valuable experiment in which, through ignorance and lack of proper governmental supervision, human beings have been allowed to swallow, over long periods of time, radio-active substances.

_Resumé of the New Jersey Cases_

It will be necessary to review briefly the essentials of this occupational disease, as observed in the New Jersey cases. During the years 1917 to 1924, an accumulative total of about 800 girls were employed in a factory in New Jersey painting the dials of watches and clocks with luminous paint. There were never more than 250 girls working at one time. Many of the girls did this work for only a short period. It is important to note that all the known cases of radium poisoning affected girls who had worked steadily in the plant for from one to two years or longer.

The paint used consisted of crystalline, phosphorescent zinc sulphide, rendered luminous by the addition of small amounts of radium, mesothorium, and radiothorium. These radio-active substances were in the form of insoluble sulfates in the paint.

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 radio-active paint day after day. They were also exposed to radio-activity by absorption of the substance through the skin and by inhalation, especially of the dust of 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 gastro-intestinal tract and was eliminated. A small amount, however, was continually absorbed and eventually stored as an insoluble sulfate, in particulate or colloidal form, 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 radio-active substances were 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 they were phagocytized by the fixed histiocytes of the blood sinusoids, the Kupffer cells of the liver, and the splenic phagocytes; whether small quantities passed through the intestinal tract in a manner not understood; whether small amounts of the insoluble salts were converted in the stomach into soluble ones and thus absorbed (this in my opinion is extremely doubtful, as radium sulfate is over 200 times more insoluble than barium sulfate); or whether the radio-active substance had some fixed position in the zinc molecule which allowed it to be absorbed with the zinc still remains unsettled.

The deposits in the bones were generalized over the entire skeleton. A minute study of the individual bone, however, showed an irregular distribution and often a concentration in certain portions, especially a final deposition in the dense outer cortex. Here the substance 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, month after month, and year after year, diminishing in amount only by their uninfluenceable natural decay.

Autopsy has shown that the lethal amount of radio-active substances ranged from 10 to 180 micrograms, estimated as radium element, distributed over the entire skeleton. Because of the fact that patients frequently lived three to eight years or more after they left their work as dial painters, the radio-active substances at time of death were confined entirely to the bones, the other storage and filtering organs having eliminated almost all of their deposits. Even the liver and spleen have been free from any appreciable radio-activity.

In patients who are still alive but suffering from characteristic symptoms of so-called radium poisoning the amounts have been estimated as from 2 to 15 to 20 micrograms in the body during life.
Of course these small amounts can be detected only by electrical methods, that is by use of electrometers.

As about 92 per cent of the radiation coming from the deposits in the bones is alpha and only 8 per cent beta and gamma, and as the total amount necessary to produce fatal results is so very small (10 to 180 micrograms), it will be seen that in these cases the small amount of beta and gamma radiation is practically negligible. The damage in the radium dial painters is due almost entirely to an internal bombardment by the alpha particle, a type of radiation never before known to have occurred in human beings.

Alpha particles are probably the most potent and destructive agent known to science. They consist of nuclei of helium atoms containing two positive charges ejected from the nuclei of the parent radio-active atoms with great force, attaining an initial velocity equal to 12,000 to 18,000 miles per second (one twentieth to one twelfth that of light). Aside from the beta rays, which are negative electrons shot out from the nuclei of the parent radio-active atoms at a velocity of 60,000 to 180,000 miles per second, they represent the fastest space-occupying objects yet known. Gamma rays are high-frequency ether vibrations similar to light, traveling at the rate of 186,000 miles per second.

Lind (11) says: "The great kinetic energy possessed by an alpha particle compared with that of even the swiftest beta particle (roughly 100 times as great) is due to the large mass of the former, approximately 7,000 times that of an electron. The alpha particle collides with a large number of molecules in a short path, thus limiting its total penetrating power in spite of its great momentum."

Alpha particles collide with other atoms with terrific impact, usually jerking off a negative electron as they pass through the electron system surrounding the nucleus. The chemical changes resulting from this ionization are of the ordinary molecular character. The effect of alpha radiation is primarily disruptive. It disrupts molecules of any inorganic or organic salt. For example, it decomposes water into hydrogen, oxygen, and hydrogen dioxide, and hydrochloric acid into chlorin and hydrogen. Occasionally, the alpha particles may strike the atomic nucleus of lighter atoms, causing disruption with the liberation of a high-velocity atom of hydrogen (H rays). It has been estimated that the number of alpha particles emitted from radium is very large (3.72 \times 10^{10} per gram per second), reaching as high as thirty seven billion helium atoms per second from one gram of radium.
Biologically, the alpha rays are more destructive than either beta or gamma rays, the relation being 10,000 to 100 to 1. Therefore, radio-active elements in such small quantities that the beta and 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 luminous paint is of great toxicologic importance since the mesothorium in equilibrium with its radiothorium 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.

In order to indicate the infinitesimal amount of radio-active substance necessary to destroy life, the following illustration may be cited: A milligram of radium bromide is not much larger than a small grain of sand. One microgram is only one thousandth as large, is invisible, and cannot be detected by any known chemical method. It is necessary to have only ten micrograms, or one hundred thousandth of a gram, distributed over the entire skeleton to produce a horrible death years after it has been ingested. This is interesting when it is recalled that the fatal dose to man of the toxin produced by *Bacillus tetani*, one of the most powerful soluble poisons known, is 0.22 mg., or about 1/300 grain.

Gettler (12), after examining the bones of a dial painter, exhumed five years after death for litigation purposes, in whom he found 50 micrograms or 1/20 of a milligram of radium distributed over the entire skeleton, made some interesting calculations. He estimated that one quarter of an ounce of bone from this painter contained about 1/50,000 of a milligram of radium. The number of atoms of radium present in this amount of bone was $5.0 \times 10^{13}$ or 50,000 billion. For every atom of radium there were 600 million molecules of bone tissue.

This one quarter of an ounce of bone ejected 1,000 alpha particles per second. As radium emits 5 helium nuclei and 4 electrons at a time, such a bone would give off 800 electrons per second. When the bone was held before a Geiger counter, an instrument that contains a complicated set-up, somewhat like that of a radio, the electrons which entered the ionization chamber of the counter, the alpha particles being screened by the target of the counter, could be amplified and converted into audible waves by means of a loud speaker. A Neon bulb flashed as each electron passed through
the diaphragm of the counter. The electric charge of each electron was estimated as being $4.77 \times 10^{10}$, or 47,700,000,000 of an electrostatic unit, and the size of the electron as $9 \times 10^{28}$, or 90,000,000,000,000,000,000,000,000,000 of a gram. As in the case of radium $1.25 \times 10^{13}$ atoms would decay in 1,700 years, so in this bone 200 atoms of radium would decay every second.

As a result of the continuous and constant radiation from the deposits in the bones, the blood-forming organs and the bone marrow are exposed to continuous bombardment by the alpha particle. The symptoms, therefore, are dependent upon the terrible disruptive effect of alpha bombardment and the consequent ionization.

Number of Known Deaths: To the best of my knowledge there have been, up to the present time (May 1931), 18 deaths among former employees of the New Jersey plant, in which so-called radium poisoning is strongly suspected. In 8 of the cases, it was proved by autopsy. In addition, there are perhaps some 30 persons alive who are either suffering from typical symptoms of radium poisoning at the present time or are potential candidates for the development of crippling and perhaps fatal lesions at any time, due to their radio-activity.

How many of the girls have scattered over different parts of the country and have died as the result of this poisoning is unknown, as the symptoms are insidious and so confusing that even at the present time cases might readily pass through even so-called Medical Centers undiagnosed.

The Early Cases: From 1922 to 1928, 13 deaths occurred which I have designated as early cases. These cases showed during life a clinical picture quite different from that in cases which developed later. They were characterized by the presence of jaw necroses and the development of anemias. Most of these cases occurred four and six years after the girls had left their employment as dial painters.

As a result of the continuous and constant radiation from the alpha particles on the blood-forming centers, periods of irritative stimulation and over-stimulation were soon followed by a period of exhaustion. A leukopenic anemia of the regenerative type (red marrow) developed. This anemia, when once established, resisted all modern forms of treatment and usually proved rapidly fatal.

Due to a continuous radiation from the deposits, an intense
radiation osteitis often developed in various areas over the skeleton. 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 feature of the early fatal cases.

The Late Cases: In the late cases, most of these patients being still alive, a sufficient period has elapsed after exposure (from six to seven years) to allow the mesothorium which was responsible for some 70 per cent of the radio-activity, to diminish in quantity by its own natural, uninfluencable decay to below one half its strength (6.7 years, half period). These patients, therefore, seem to be escaping the extensive necroses of the jaw and the fatal leukopenic anemias of the regenerative type. They show, instead, chronic crippling bone lesions, developing years after they have left their work as dial painters, and often after several years of good health.

The bone lesions are in the nature of a radiation osteitis and are most marked in bones that are subject to weight, pressure, and trauma, such as the head of the femur, the acetabulum, the spine, the pelvis, and the tarsal scaphoid.

The anemias are milder, and when progressive are still of the regenerative type.

From our electroscopic studies on radio-active dial painters during life and after death it would appear that this difference in the symptomatology of the early and late cases is due to the preponderance of mesothorium or of radium. In the early cases mesothorium, which is chemophysically and physiologically more active than radium, predominates. Hence the severe anemias and the extensive jaw necroses in the early cases.

In the late cases in which death has occurred, only radium has been detected post mortem. This is of interest since, when I first described this disease, there was a strong tendency among some of those interested in the production and therapeutic use of radium to place the entire blame on mesothorium.

The Occurrence of Bone Sarcomas: In 1924 and 1927, two dial painters died from osteogenic sarcomas. These cases were reported by Martland and Humphries (13).

Towards the end of 1928, I was beginning to hope that we had passed over the worst period, as far as the New Jersey cases were concerned, and that, except for an occasional borderline case
appearing mainly for litigation purposes, no more girls who had been employed as dial painters in this plant would develop symptoms of radium poisoning. Dial painting had stopped here over five years ago.

There was an insidious lull, to be followed at the end of 1929 by the death from sarcoma of the femur and pelvis of one of the original five girls (known to the public as "the five women doomed to death") in whose cases a settlement out of court had been made. In September 1930, I had the opportunity of examining another girl dying from extensive sarcoma of the hollow of the pelvis and sarcoma of the orbital cavity. Until a few weeks before death no connection between the disease and her previous work as a dial painter was suspected.

Still later another dial painter, whom I had described in 1925 as a healthy case, sustained a spontaneous fracture of the femur, roentgenograms showing osteogenic sarcoma at the site of the fracture. In my earlier report I had stated that any insurance company would pass this girl as being in perfect health, yet positive electroscopic tests for radio-activity in her expired air led me to ask even then: "Who can tell when crippling bone lesions may occur?"

A few weeks after this I examined the roentgenograms of a girl who had twice sustained a pathologic fracture of the femur, at the same site, and was told that she had been a dial painter. The last fracture was not uniting. This patient has considerable callus, and sarcoma is suspected. Tests for radio-activity with the gamma electrometer and emanation tests of the expired air yielded positive results.

Shortly after this I received a roentgenogram showing the pelvis of another former dial painter. An osteogenic sarcoma of the descending ramus was observed. The name of this girl I found among a list of 50 which I had placed in a note-book in 1925. These girls had been employed in the New Jersey plant and were selected from a total of 800 because of the long time they had worked as dial painters. I believed that most of the future cases would develop in this group. With terrible, almost mathematical regularity, I have been crossing off these names as the girls have died or developed symptoms of radium poisoning. More recently my attention has been called to four more possible cases of sarcoma in dial painters.

Regarding the New Jersey cases, it would now appear that we
Table I

Deaths from So-called Radium Poisoning Occurring among 800 Employees of a New Jersey Plant Manufacturing Luminous Watch Dials

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Age</th>
<th>Work*</th>
<th>Date of Death</th>
<th>Death Certificate Signed</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A.M.</td>
<td>25</td>
<td>DP</td>
<td>Sept. 12, 1922</td>
<td>Ulcerative stomatitis, syphilis</td>
<td>St. George, Gettler (exhumed five years later)</td>
</tr>
<tr>
<td>2</td>
<td>M.W.</td>
<td>54</td>
<td>Ch</td>
<td>Nov. 18, 1922</td>
<td>Pernicious anemia</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>H.Q.</td>
<td>23</td>
<td>DP</td>
<td>Jan. 3, 1923</td>
<td>Necrosis of jaw, anemia</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>I.R.</td>
<td>20</td>
<td>DP</td>
<td>May 20, 1924</td>
<td>Necrosis of jaw, phosphorus poisoning</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>H.K.</td>
<td>24</td>
<td>DP</td>
<td>Dec. 9, 1924</td>
<td>Necrosis of jaw and maxilla, anemia</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>J.S.</td>
<td>20</td>
<td>DP</td>
<td>Dec. 15, 1924</td>
<td>Sarcoma of femur</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>M.H.</td>
<td>36</td>
<td>DP</td>
<td>Mar. 3, 1925</td>
<td>Anemia</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Dr.L.</td>
<td>36</td>
<td>Ch</td>
<td>June 7, 1925</td>
<td>Regenerative anemia. Occupational poisoning by radio-active substances</td>
<td>Martland</td>
</tr>
<tr>
<td>9</td>
<td>S.M.</td>
<td>33</td>
<td>DP</td>
<td>June 18, 1925</td>
<td>Necrosis of jaw, regenerative anemia. Occupational poisoning by radio-active substances</td>
<td>Martland</td>
</tr>
<tr>
<td>10</td>
<td>F.S.</td>
<td>22</td>
<td>DP</td>
<td>June 23, 1925</td>
<td>Necrosis of jaw</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>M.C.</td>
<td>24</td>
<td>DP</td>
<td>Dec. 26, 1925</td>
<td>Necrosis of jaw, regenerative anemia. Occupational poisoning by radio-active substances</td>
<td>Martland</td>
</tr>
<tr>
<td>12</td>
<td>L.D.</td>
<td>24</td>
<td>DP</td>
<td>Jan. 8, 1927</td>
<td>Necrosis, anemia</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>V.R.</td>
<td>44</td>
<td>Ch</td>
<td>Dec. 20, 1927</td>
<td>Pernicious anemia</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Dr.S.</td>
<td>46</td>
<td>Ch</td>
<td>Nov. 14, 1928</td>
<td>Regenerative anemia</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Q.M.</td>
<td>34</td>
<td>DP</td>
<td>Dec. 7, 1929</td>
<td>Sarcoma of pelvis and femur. Occupational poisoning by radio-active substances</td>
<td>Norris, Martland</td>
</tr>
<tr>
<td>17</td>
<td>A.S.</td>
<td>27</td>
<td>DP</td>
<td>Sept. 13, 1930</td>
<td>Sarcoma of pelvis and orbit. Occupational poisoning by radio-active substances</td>
<td>Martland</td>
</tr>
<tr>
<td>18</td>
<td>L.P.</td>
<td>30</td>
<td>DP</td>
<td>June 16, 1931</td>
<td>Sarcoma of pelvis</td>
<td>Martland</td>
</tr>
</tbody>
</table>

* DP signifies dial painters. Ch signifies chemists and physicists.

have reached a point when we will no longer encounter the anemias and jaw necroses seen in the earlier cases, but instead the girls will appear with terrible, usually rapidly growing embryonal or anaplastic osteogenic sarcomas, the result of radio-activity.

In Table I are given the details of the 18 fatal cases so far observed.
FIG. 1. CASE 1. SHOWING LOCATION OF SARCOMA.
Osteogenic Sarcoma Occurring in Radio-active Dial Painters

Report of Fatal Cases from New Jersey Plant

Case 1: Pain in right knee while a dial painter. Two years later osteogenic sarcoma of right femur. No necropsy.

J. S., a white female, aged twenty, was employed as a dial painter for about four years. During the last year she developed a swelling of the right knee with pain, which necessitated stopping work in 1922.

The swelling increased and the knee pained greatly at night. In July 1923 a surgeon was consulted, and fluid was found in the joint, with sharp pain on motion. Tuberculosis was suspected. Aspiration showed no organisms in the fluid and guinea-pig inoculations were negative. Roentgenograms showed marked changes in the soft tissues, but the bone was apparently normal. Some of the patient's teeth were in very bad condition, and seven were extracted. A blood count was practically normal and the blood Wassermann test was negative.

In December 1923 the patient was admitted to a hospital and roentgenograms showed an osteogenic sarcoma of the lower end of the femur. She was discharged for deep ray therapy, receiving several treatments between Dec. 23, 1923, and March 4, 1924. She suffered severe pain.
and died on April 15, 1924. The death certificate gives the cause of
death as sarcoma of the right knee.

Comment: This case was reported by Martland and Humphries
(13) in 1929 and is the first recorded case of sarcoma among dial
painters. Unfortunately in this case the clinical data are meager
and pathological material is not now available. A clinical diag-
nosis of osteogenic sarcoma was made from the symptoms and the
roentgenograms. A study of the roentgenogram shows no appar-
ent involvement of the femur, and the large fusiform mass sur-
rounding the bone suggests a periosteal fibrosarcoma, a growth
which is usually quite mature in its histologic appearance. The
patient was treated with deep x-rays by a competent man (Dr.
Ernst A. May), to whom I am indebted for the roentgenograms.
The sarcoma, however, was never proved by operation or autopsy.

CASE 2.: Injury to right shoulder six years after stopping work as a
dial painter. Typical radiation osteitis. One year later, osteogenic sarcoma
of scapula. Necropsy.

E. E., a white female, aged thirty-two, was employed as a dial painter
for about three years. When applying luminous material to watch
dials, she was in the habit of pointing the brushes with her lips. She
stopped work as a dial painter in 1919. She had little trouble with her
teeth and never had any extensive jaw necrosis. Roentgenograms taken
by a dentist in 1926 showed lesions, which we interpreted later as typical
radiation osteitis, involving chiefly the alveolar portions of the mandible.

In September 1926, fourteen months before her death, this patient
fell while working in a department store, injuring her right shoulder.
There was pain, and motion was limited, and the case was later referred
to the compensation department. Roentgenograms showed slight down-
ward displacement of the head of the humerus. The patient was operated
upon and no disease found in her shoulder. The wound healed promptly
without complications.

In July 1927, six months before death, the patient still complained
of pain in the right shoulder. She also had pain and localized tenderness
over the scaphoid bone of her right foot. An examination of the original
roentgenograms demonstrated peculiar changes in the right humerus,
right scapula, and tarsal scaphoid of the right foot. The changes were
similar to those seen in other dial painters, which we had interpreted as
areas of radiation osteitis. It was then ascertained that the patient had
been a dial painter over seven years before.

In September 1927, three months before death, roentgenograms for
the first time showed a sarcoma of the right scapula, springing from its
anterior and upper portions.

In December 1927 the patient returned to the hospital with the right
upper extremity markedly swollen down to the hand. She suffered
Fig. 3. Case 2. Showing location of sarcoma.
Fig. 4. Case 2. Roentgenogram of the Right Shoulder Taken Two Months Before Death.

An extensive, rapidly growing, osteogenic chondrosarcoma springing from the anterior surface of the scapula and the glenoid process may be noted.

Fig. 5. Case 2. Roentgenogram of the Right Foot Taken Five Months Before Death.

The dense periphery and fragmentation of the tarsal scaphoid may be noted. The patient suffered exquisite tenderness over this bone.
constant pain, which was unrelieved by morphine. On December 13, 1927, an operation was performed to relieve pressure on the main nerve trunks. Large masses of tumor tissue were removed. Death occurred a few hours later. During life no tests were made to detect radioactivity.

Necropsy (CME 4192), performed by Martland: A large osteogenic sarcoma of the right scapula was found, invading the whole anterior

![Image](image.png)

**Fig. 6. Case 2. Periosteal, Osteogenic Sarcoma of Right Scapula.**

**Osteochondrosarcoma.**

The differentiation in mature cartilage may be noted. This is unusual in the sarcomas occurring among the dial painters, most of the tumors being of the embryonal or anaplastic type. × 150.

and upper part of the bone, with infiltration into the supra- and infraspinous muscles. Visceral metastases were not found. A profound anemia was present. The yellow marrow of the femurs was entirely replaced by a dark red, apparently regenerating marrow.

**Histologic Examination:** Examination of the tumor showed a rapidly growing osteogenic sarcoma. In places the growth was cellular, with mitotic figures and hyperchromatism; in other places it was sclerotic. New formation of bone was common. The tumor contained considerable
cartilage and had the general appearance of a rather mature type of sarcoma.

The sections from the bone marrow showed a regenerative, hyperplastic marrow similar to that described in other cases of radium poisoning.

Sections from the tarsal scaphoid showed a typical healing radiation osteitis, the marrow being replaced by loose, gelatinous, myxomatous, fibroblastic tissue, in which there was considerable fat.

Demonstration of Radio-activity: The presence of radio-active substances in the skeleton of this case was proved by photographic methods,

![Image of sections from bone marrow and tarsal scaphoid](image)

**Fig. 7. Case 2. Periosteal, Osteogenic Sarcoma of Right Scapula.**

Tumor mitosis, hyperchromatism and differentiation into adult cartilage may be noted. \( \times 140. \)

by laying dried bones directly on photographic plates and by strapping dental films on dried bones with interposed metal clips. It was further proved by means of alpha radiations from the incinerated bones, by scintillation tests, and by detection of gamma radiations from the bone ash. Further chemical extraction and measurement with the gamma electrometer showed an estimated amount of 50 micrograms in the entire skeleton, estimated as radium element. Radium predominated.

Comment: Reporting this case in 1929, Martland and Humphries (13) stated: "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 radio-active substances in the bones of this case played an important rôle in the subsequent development of the sarcoma. Of course, this is an alluring theory, which at present is not provable. . . . 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 right tarsal scaphoid. They were of the nature of a radiation osteitis. . . . 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."

At the time we reported this case we were somewhat loath to attribute the occurrence of two sarcomas in dial painters directly to the deposits of radio-active substances in the bones. The incidence of two sarcomas of bone, however, in 15 fatal cases of radium-mesothorium poisoning, was too large to be passed over as a mere coincidence. As this was the first time that sarcoma of the bone was ever thought to be attributable to radiation, the cases were of sufficient interest to be placed in literature.

Since that time the occurrence of two more fatal cases of bone sarcoma in radio-active dial painters, and of at least five suspected cases, the latter patients being still alive, greatly strengthens our original opinion. We can now say beyond any doubt that the sarcomas in the dial painters have a direct relationship to the osteitis caused by alpha bombardment from minute amounts of radio-active deposits in the bones.

It is interesting to note that in this case we have a more mature or adult form of osteogenic sarcoma in which osteoid tissue, fairly good bone, and cartilage are produced. This is unusual, as most of the radium sarcomas are more rapidly growing, anaplastic, and almost embryonal in type.

**CASE 3:** Left work as dial painter in good health. No anemia. No necrosis of jaw. Five years later pain in hips, limp. Late lesions of radiation osteitis, progressive. Positive tests for radio-activity during life. Death ten years later of rapidly growing osteogenic sarcoma of pelvis and femur. Extensive metastasis. Necropsy.

Q. M., a white female, aged thirty, started to work as a dial painter in 1917, when seventeen years of age. She worked for fifteen months and then married, quitting her work as a dial painter. According to
FIG. 8. CASE 3. SHOWING LOCATION OF SARCOMA.
one of her co-workers, she fairly "ate the paint" and frequently spoke of the gritty sensation in her mouth while working.

After the birth of a child in 1923, she developed pain in both hips and lower extremities. Roentgenograms in 1924 were normal.

In 1925 the patient was beginning to limp, and roentgenograms showed areas of radiation osteitis in the heads of both femurs. When

![Figure 9. Case 3. Periosteal, Osteogenic Sarcoma of Right Femur.](image)

Showing tumor mass, 15 cm. in diameter, surrounding the acetabulum, with invasion of the pelvis. The tumor was soft, anaplastic in type, and showed very little osteoid or osseous new bone formation.

she was examined by me in June 1925, her expiratory air was radio-active, containing a small amount of emanation from mesothorium and a larger amount of radon. Her blood at this time was nearly normal: hemoglobin 80 per cent, erythrocytes 4,200,000, and leukocytes 8,200. The blood Wassermann reaction was negative.

This patient was one of five girls said to be suffering from radium poison who, in May 1927, started suit in the Supreme Court of New
Jersey, a suit which became well known, through the press, as “the case of the five women doomed to die.” In 1928, these cases were settled out of court, the girls being awarded pensions for life. At that time, the present patient was in fair physical condition and, except for a limp in walking, little evidence of her condition could be detected on superficial examination. She never had any severe necrosis of the jaw.

After the settlement these girls were under the care of a committee composed of Doctors Lloyd F. Craver, James Ewing, and Edward B. Krumbhaar. The crippling bone lesions in the present case became progressively worse, and the patient was admitted to the Memorial Hospital in New York, where she developed a large sarcoma of the right pelvis, infiltrating the buttock, with extensive pulmonary metastasis, emaciation, and anemia. She died Dec. 8, 1929.
right lateral wall of the pelvis. It was so firmly attached to these structures that it could be removed only by sawing through the pelvis. The mass apparently sprang from around the neck and great trochanter of the femur, where the periosteum is roughened in places. It then grew anteriorly and encased the hip-joint. The tumor was well circumscribed, hard, often reflected high lights on section, but showed no gross bone spicules or sand-like grating.

The tumor mass bulged through the right lateral wall of the pelvis, pushing the bladder upward and to the left. There were a few small lymph nodes over the brim of the pelvis on the right side and about the abdominal aorta, which were inflammatory and did not show metastasis. The thoracic duct was normal. There was marked coxa vara.

The liver contained innumerable round and oval, grayish masses, none of which was umbilicated, ranging in size from those just visible to an occasional mass 4 cm. in diameter. They were soft, encephaloid, and well circumscribed. An occasional tumor mass appeared cystic, with its center filled with fluid and clotted blood. There were two small periportal nodes, the larger being 1 cm. in diameter. Both lungs showed innumerable metastatic nodules similar to those found in the liver.

The spine showed numerous areas of radiation osteitis, the bodies of the lumbar vertebrae sawing soft and woody. The cancellous bone

---

**Fig. 11. Case 3. Periosteal, Osteogenic Sarcoma of Right Femur.**

Showing embryonal, anaplastic type of sarcoma. \( \times 112. \)
towards the center of the body of the vertebra showed pale, white, hard bony areas or islands, some of them 1 to 2 cm. in diameter.

The marrow of the right femur was a dark mottled red color and showed many grayish white areas of radiation osteitis measuring 1 to 2 cm. There was no metastasis.

**Histologic Examination:** Sections from the tumor of the pelvis and hip showed a very cellular, rapidly growing osteogenic sarcoma in which many of the cells were of the embryonal type. Many tumor giant cells were present. Mitosis and hyperchromatism were extensive. In a few places there were evidences of slight attempts to form new bone of the osteoid type. The metastatic nodules in the lungs and liver were very cellular and there was no attempt at new bone formation.

Sections made from the femur and vertebra showed a regenerating marrow of the megaloblastic type, with many primitive cells. Mature cells of the granulocytic series were scant, except for the presence of innumerable eosinophil myelocytes. Megakaryocytes appeared to be abundant. In many of the marrow cavities this hyperplastic marrow was beginning to be replaced by a very cellular fibroblastic growth containing many eosinophil myelocytes, plasma cells, and lymphocytes. Mitotic figures in these areas were common, and such areas were distinguished only with great difficulty from sarcoma. In other areas, especially those which grossly appeared as hard, grayish areas of radiation
osteitis, this fibroblastic replacement of the original hyperplastic marrow was distinctly acellular. Here the marrow had been replaced by more or less dense fibroblastic acellular tissue.

Estimation of Radio-activity: The incinerated bones were examined by means of the gamma electrometer, and it was calculated that the entire skeleton contained about 14 micrograms of radio-active substances, estimated as radium element. No mesothorium was found. A celebrated physicist estimated that this girl's body had contained about 13 micrograms of radio-active substances during life. On examining samples of her bones after death he found about 12 micrograms in the entire skeleton.

Comment: It will be noted in this case that the sarcoma, after it appeared, grew very rapidly and caused extensive metastasis to the viscera, chiefly the liver and lungs, by way of the venous blood stream. There was no evidence of lymphatic extension.

The histologic character of the growth denotes a wild growing, embryonal type of tumor very different from those encountered in cases 1 and 2. The majority of the radium dial painters' sarcomas are of this anaplastic type.

In the ordinary periosteal osteogenic sarcoma metastasis to the bones is rarely encountered, and there were no metastases to the bones in this case. Any areas in the bones, therefore, which histologically resembled sarcoma, must be interpreted as having no connection with the original tumor, but as being a reaction in loco to the irritating effects of alpha bombardment. This was the first case in which I was able to interpret properly the logical order of the various stages of the radiation osteitis of dial painters. My interpretation of these changes will be described later.

It will be seen from this case that there can occur in this disease multiple areas, scattered over various bones, which histologically are so cellular that they defy differentiation from sarcoma. It is possible, therefore, to predict that in some cases sarcomas may arise in these areas as multiple primary tumors. This is what actually took place in the next case.

Case 4: Left work as dial painter in good health. No anemia. No necrosis of jaw. Married and had a child. Eight years later developed two primary osteogenic sarcomas: one of the left orbit with metastasis by way of ophthalmic vein to lungs; the other of the pelvis without metastasis. Necropsy.

A. S., a white female, twenty-seven years of age, worked as a dial painter from 1919 to 1922. She married in 1925 and had a child two years later. She never had any necrosis of the jaw. Although she
Fig. 13. Case 4. Showing Location of Two Primary Sarcomas.
never was strong and always complained of vague pains, she had had no serious illness until her present complaint.

In July 1930 she had a fainting attack, with pain in the region of the heart, and was admitted to the Orange Memorial Hospital. It was noticed in the examination that her left eye bulged and that she complained of pain in the right lower abdominal quadrant and over the right hip. Roentgenograms showed what was interpreted as a sarcoma of the floor of the left orbit invading the ethmoid. In a few weeks she was sent home as inoperable.

---

FIG. 14. CASE 4. ROENTGENOGRAM SHOWING PRIMARY SARCOMA OF LEFT ORBIT AND ETHMOIDAL CELLS.

Shortly after the patient's discharge from the hospital her family physician, Dr. Henry DeVincentis, felt a mass in the hollow of the ilium on the right side. He ascertained for the first time that she had been a radium dial painter years before, and being familiar with the original radium cases, was well aware of the clinical possibilities. Re-examination of the original roentgenograms showed a beginning osteogenic sarcoma of the ilium on the right side, a sarcoma of the left orbit, and areas of radiation osteitis in the flat bones of the skull. A diagnosis of sarcoma in a radium dial painter was made. It was impossible to state which was the primary growth, that in the orbit or the pelvic mass, or whether both were primary, arising in areas of previous radiation
osteitis. The patient began to run a septic type of temperature, with severe pains in the chest, cough, and bloody sputum. She died Sept. 13, 1930, two months after she complained of her original symptoms.

Necropsy (CME 9128), performed by Martland: Necropsy showed a large retroperitoneal mass on the right side, about 15 cm. in diameter. This started near the symphysis and passed upward into the hollow of the ilium. On section, it was well circumscribed, grayish white, and reflected high lights. Numerous pinkish and reddish areas and an occasional spicule of bone deep in the tumor mass could be seen. The mass passed beneath Poupart's ligament, eroded the anterior superior spine and the crest of the ilium, and infiltrated the right femoral and inguinal regions. It was firmly adherent to the pelvis and passed outward over the region of the hip. There was no involvement of the retroperitoneal glands, nor of the pelvic or thoracic lymph nodes. The acetabulum and head of the femur were normal.

Fig. 15. Case 4. Roentgenogram showing primary osteogenic sarcoma of the right innominate bone.
On removing the brain another sarcoma was seen involving the left lateral plate of the ethmoid bone and appearing as a nodular, hard growth covered by dura. This growth extended down in the left orbit, where it became softer and compressed the left ophthalmic vein, which ran through the tumor mass. The vein was eroded and filled with tumor tissue in a small area 2 mm. in diameter. The sphenoidal cells were filled with tumor masses and the left lateral wall of the orbit was extensively involved.

Both lungs showed innumerable small and large masses of encephaloid reddish gray metastases, ranging in size from 5 mm. to 5 cm. in diameter and reflecting high lights on cut section. Many of the masses showed yellowish areas of necrosis and occasional large hemorrhagic areas. The mediastinal nodes were uninvolved. There was beginning infiltration of the visceral pleura over both lungs.

The calvarium was hard and ivory-like and showed hardly any cancellous bone. An occasional oval, expansive area on the inner table of the skull in the parietal regions was seen. On section a small amount of red cancellous bone was observed in these areas, with thinning and erosion of the inner table (radiation osteitis).

The bodies of the vertebrae showed occasional grayish white areas of radiation osteitis in the cancellous bone. The marrow in the middle of the femur was red and hyperplastic.

Histologic Examination: Sections from the tumor of the left orbit showed a very cellular, rapidly growing osteogenic sarcoma in which many of the cells were of the embryonal type. In many areas numerous bizarre tumor giant cells were seen. Mitosis and hyperchromatism were extensive. In other areas the growth was more sclerotic and showed a
considerable laying down of osteoid tissue. The metastatic nodules in
the lungs were highly cellular, with no bone formation. They were
entirely embolic by way of the pulmonary artery, and tumor masses
could be seen protruding into the alveolar air spaces from their site of
growth in the intra-alveolar capillaries. Sections from the tumor of
the pelvis were of the same nature. Bony spicules were occasionally
formed.

Sections from the femur and vertebra showed a regenerating marrow
of the megaloblastic type with many primitive cells resembling hemo-

cytoblasts. In many of the marrow cavities this hyperplastic marrow
was beginning to be replaced by a very cellular fibroblastic growth
containing many eosinophil myelocytes, plasma cells, and lymphocytes.
Mitotic figures were frequently seen. So cellular were some of these
areas that they could not be distinguished from sarcoma. In other
areas the marrow spaces were filled with acellular fibroblastic tissue
(healed lesion).

Sections made from the rarefied lesions in the flat bones of the skull
showed that the marrow spaces in the inner half of the calvarium were

FIG. 17. CASE 4. METASTASIS TO LUNGS BY WAY OF OPHTHALMIC VEIN FROM PRIM-
ARY OSTEOGENIC SARCOMA OF ORBIT.

The tumor growth in the interalveolar capillaries filling the alveoli may be noted.
× 150.
FIG. 18. CASE 4. PRIMARY OSTEOGENIC SARCOMA OF PELVIS SHOWING PRODUCTION OF OSTEOID TISSUE. × 112.

FIG. 19. CASE 4. PRIMARY OSTEOGENIC SARCOMA OF PELVIS. The embryonal and anaplastic type of the tumor may be noted. × 112.
filled with the same hyperplastic marrow containing many eosinophil myelocytes with large numbers of osteoclasts causing erosion of bone.

The ovaries were sclerotic and showed almost an entire disappearance of graafian follicles.

*Estimation of Radio-activity:* Incinerated bones showed positive alpha radiations. Estimation with the gamma electrometer showed over 6 micrograms, estimated as radium element, in the entire skeleton. No mesothorium was found.

*Comment:* The rapid growth of the sarcomas in this case should be noted, the patient dying within three months after the first symptoms were observed. Histologically the sarcomas were very embryonic, with little differentiation into adult types of tissue.

Metastasis by way of the blood stream is beautifully illustrated in this case, the tumor breaking into the ophthalmic vein and being filtered out by the pulmonary capillaries, with the production of extensive pulmonary metastases but no systemic ones. The same logical sequence of the lesion, radiation osteitis due to alpha bombardment, may be observed: first, a hyperplastic marrow; second, a replacement by very cellular fibroplastic tissues; and finally the last stage showing subsiding inflammation, the marrow being entirely replaced by acellular fibrous tissue (healed lesion).

This is the only case so far that has shown a multiple primary origin of the sarcomas. In addition, the roentgenograms taken during life showed rarefied areas in the flat bones of the skull which on histologic examination were shown to be due to the same irritative hyperplastic marrow. These skull lesions had been previously observed by Flinn in some of the Connecticut cases, but this was the first New Jersey dial painter in whom this lesion was encountered.


L. P., a white female, thirty years of age, was employed as a radium dial painter from 1917 to 1921. She had some necrosis of the jaw and lost a few teeth. The jaw healed after dental care. Reexamination of dental roentgenograms made in 1925 showed typical areas of radiation osteitis. Previously the patient had been in good health and had dismissed from her mind recollection of her earlier work as a dial painter. She married and had three miscarriages.

In the summer of 1930 this patient felt a swelling inside the vagina,
Fig. 20. Case 5. Showing Location of Bone Sarcoma.
which gradually became larger and interfered with intercourse. In October 1930 she also had considerable pain in the left knee. At that time a vaginal examination could hardly be made on account of the tumor blocking the entrance. Roentgenograms showed an osteogenic sarcoma arising from the superior and inferior rami of the left os pubis.

Thinking that there might be some connection between the present trouble and the patient's work as a dial painter nine years before, Drs. W. G. Herrman and M. Silverstein of Asbury Park brought the x-rays to me with the history of the case. The patient was placed under the care of Dr. R. E. Humphries. Treatment by Dr. Ernst A. May with deep x-ray therapy held the growth in check for a few months, but the sarcoma gradually grew larger and the patient became bedridden.

![Image](https://example.com/image.jpg)

**Fig. 21. Case 5. Roentgenogram Showing Primary, Periosteal, Osteogenic Sarcoma of Pelvis Arising from the Superior and Inferior Rami of the Left Os Pubis.**

The extensive production of new bone may be noted.

(I am indebted to her family physician, Dr. D. N. Shack, for the opportunity of seeing and reporting the case.) She rapidly became emaciated. The tumor extended into the soft parts about the left hip and into the abdomen. Dyspnea developed, and intense pain, which could be relieved only by large doses of morphine. Death occurred June 16, 1931, about nine months after the first complaint of a tumor mass in the vagina.

**Necropsy (CME 10447),** performed by Martland: The left thigh was semiflexed and rotated externally by extensive sarcoma of the pelvis infiltrating the soft tissues of the thigh. The entire pelvic cavity was occupied by an osteogenic sarcoma springing from the periosteum of the ascending and descending rami of the left os pubis. Numerous large and small spicules of bone could be felt in the sarcoma at a considerable
distance from the pelvic bone. The bladder and vagina were pushed over to the right lateral wall of the pelvis. The growth overhung the pelvic bones and invaded the obturator foramen, the soft parts of the thigh, and the abdomen. The left broad ligament was markedly infiltrated, with invasion of the posterior wall of the uterus. The uterine endometrium and the vaginal vault contained no new growth. The veins in the left broad ligament were infiltrated by metastatic tumor which extended into the left common iliac vein and into the inferior vena cava as high as the diaphragm. The left ovarian vein was not invaded. The upper end of the tumor thrombus in the vena cava was firm and smooth, affording little opportunity for emboli to break off and be washed to the right heart. The vena cava had an average diameter of 4 cm., being distended with the tumor thrombus. There was a small metastatic nodule in each lung. There were no metastases to liver or other organs. The left renal vein was blocked by retrograde tumor thrombus. The main visera showed marked anemia. There was no involvement of the retroperitoneal or mediastinal nodes. The bone marrow in the middle of the femurs was a deep, intense red color. The marrow in the vertebrae was deep red in color and showed many lighter areas of radiation osteitis.

**Histologic Examination:** Sections from the tumor mass in the pelvis showed a typical osteogenic sarcoma of rapid growth in which there was a great deal of new bone formation.

Sections from the bone marrow showed the typical hyperplastic marrow seen in the other cases, with many areas of radiation osteitis scattered throughout the marrow.

**Estimation of Radio-activity:** This has not been completed in this case. Qualitatively the bones are radio-active.

**Comment:** While the growth in this case is histologically distinctly embryonal in type, yet bone formation is quite marked, more pronounced in fact than in any of the other sarcomas in the dial painters. The strong tendency of osteogenic sarcoma to metastasize by the blood stream rather than lymph nodes is again emphasized in this case.

**Report of Living Cases (July 1, 1931) from New Jersey Plant**

**Case 6:** Dial painter and instructress. Eight years after leaving work was in good physical condition, but radio-active. Nine years after, limped. Spontaneous fracture of femur. Osteogenic sarcoma at site of pathological fracture. Condition, progressive, critical.

K. S., a white female, aged thirty, was a dial painter and instructress in the studio for about four and one-half years during a total period of five and one-quarter years. She also painted samples. She always operated with good brushes and did not pass the brush over the lips and into the mouth as often as other painters. She would lick the brush perhaps once or twice for every two watches. She was one of the famous five girls whose cases were settled out of court in 1927.
Fig. 22. Case 6. Showing location of sarcoma with pathologic fracture.
While this patient had been ill two years after starting work as a dial painter and once or twice later, serious difficulty did not appear until November 1926, more than nine years after she began to work with radio-active material. She suffered neuralgia-like pains, lost two teeth, and had a small amount of necrosis of the mandible, which healed under dental care.

In 1926 she began to limp and to complain of pain in her left knee. Roentgenograms showed beginning radiation osteitis in the lower end of the femur. The limp became progressively worse, so that the patient had to hobble around with the aid of a cane. Her blood remained nearly normal.

In August 1930 she came to see me, complaining of considerable pain in the knee. Roentgenograms at this time showed extensive radiation osteitis in the lower end of the left femur. The patient quit the laboratory and left for the country to find a boarding house. About four hours after I had seen her a physician telephoned that she had sustained a spontaneous fracture just above the right knee. Reexamination of the x-rays showed definite evidence of osteogenic sarcoma.

The patient was immediately placed under the care of Dr. R. E. Humphries. Under deep x-ray therapy by Dr. Ernst A. May, the

---

**Fig. 23. Case 6. Roentgenogram, Taken Two Hours Before Pathologic Fracture, Showing Primary Periosteal, Osteogenic Sarcoma of Femur.**

**Fig. 24. Case 6. Roentgenogram, Taken Several Weeks Following Pathologic Fracture, Showing Primary Periosteal, Osteogenic Sarcoma of Femur.**

Union finally took place, which is not uncommon in bone sarcoma.
tumor mass became smaller and union took place in about four months time. She then started walking, using a brace. Lately, however, she has begun to lose weight and is now (July 1, 1931) in a more or less critical condition.

Comment: This case is extremely interesting, having been reported in 1925 (1) as a healthy case (viz.: exposure with storage of radio-active substances, without apparent effect on health). At that time the patient's expiratory air showed the presence of both mesothorium and radium. Her blood was practically normal. I stated: “This girl, like many others, had a history of exposure to radio-active paint. She ingested radio-active elements during her occupation, enough in fact to cause her blood to throw off emanation by way of the expired air and in measurable quantities, long after she ceased to work. Her general physical condition is good and she could at the present time pass a strict medical examination and obtain almost any amount of insurance. Yet she has active deposits of insoluble products of radium and mesothorium in her bones, which are constantly bombarding her blood-forming centers. Who can tell when she may develop an acute fatal anemia, or a more chronic anemia, with or without crippling bone lesions?”

We did not know then that the final lesion was to be a sarcoma.

Case 7: Dial painter. Quit work in good health. Married and has children. Two spontaneous fractures of the femur with slow healing occurring eight and nine years after she stopped work as dial painter. Suspicious osteogenic sarcoma arising in callus.

Mrs. B., a white female, thirty-two years of age, was employed as a radium dial painter in 1921. She left work and married, had children, and was in good health. On May 21, 1928, on stepping from a stool, she sustained a spontaneous fracture of the middle third of the right femur, which required twelve weeks for firm callus formation.

On November 28, 1929, again while stepping from a stool, she sustained a second spontaneous fracture of the right femur, the fracture line being about three inches above the previous fracture site. Union was again delayed, with a resultant malposition of the fragments and two inches of shortening. In July 1930 an open reduction to overcome malposition was done. The patient is still in a plaster cast, under the care of Dr. L. G. Beisler at the Elizabeth General Hospital, and no signs of firm callus formation are evident since the open operation.

After the open operation, it was learned that the patient had been a radium dial painter. The history was typical, and examination of the roentgenograms showed suggestive areas of radiation osteitis in the skull and femurs.

In November 1930 she was examined by Dr. F. B. Flinn, who found her to be radio-active, and estimated that her body contained about 15 micrograms of radium. She is now receiving viosterol.
Fig. 25. Case 7. Showing location of pathologic fractures.
Comment: While we cannot make a positive diagnosis of sarcoma in this case at the present time, its occurrence is strongly suspected from what we already know of the other cases. I am indebted to Dr. Beisler for the opportunity of reporting this case.


G. F., a white female, aged twenty-seven, worked as a dial painter for nearly four years (1918–1921). About two years after she left the studio, rheumatic pains developed in one foot, later extending to the back. The condition became progressively worse, the teeth became affected, several were extracted, and necrosis of the jaw developed. The patient was hospitalized, and the jaw operated upon. According to the hospital records, an x-ray diagnosis of “chronic osteomyelitis of the jaw, possibly due to phosphorus poisoning,” was made.

The patient is still alive, a number of operations having been performed on the jaw at intervals of a few months, about twenty in all, some slight and some painful.
Fig. 27. Case 8. Showing location of radiation osteitis in left hip. There is strong presumptive evidence that sarcoma is developing in this case.
This girl, one of the famous five women "doomed to death," became progressively worse. She kept her position as a clerk in a bank for some time, stopping work only recently. She was examined by me in 1925 and found to be radio-active, and several subsequent examinations made by experts confirmed the radio-activity. During the last two years she has had considerable trouble with the lumbar spine, but this has cleared up and she has been able to discard a brace, which she required for a time. She has also had considerable pain in the tarsal scaphoid of the right foot, and roentgenograms have showed radiation osteitis.

About two months ago the patient had considerable pain in her left hip and limped more than usual. A swelling in the soft parts over the hip could be felt, but roentgenograms showed no positive evidence of sarcoma. She is now under treatment with parathormone (Eli Lilly & Co's preparation of Collip's parathyroid extract), a low calcium diet, and viosterol.

Comment: From my experience with past cases, I feel quite certain that this girl is developing a sarcoma of the left femur.

Report of Fatal Case from New York and Connecticut Plants


L. P., a white female, aged twenty-three, worked as a dial painter in a Long Island clock factory for a period of two years, from 1923 to 1925, and in a Connecticut clock factory from 1925 to 1926, a total of a little over three years. She states that it was the custom of the other girls doing this work to paint until the radium dried on their brushes, and then to moisten the brushes with the lips and tongue. She, however, used a small bottle of water to keep her brush moist. Most of the radium was washed out and sank to the bottom of the bottle. She then shaped the brush with her lips. She stated that several of the girls in the Long Island plant suffered from necrosis of the jaw.

About two months before admission to the Brooklyn Hospital this patient had pain in the right axilla and felt a lump about the size of a plum, hard but not very painful. Thinking it would disappear, she at first paid little attention to it, but as it continued to grow, she consulted a physician.

She was admitted to the Brooklyn Hospital on Jan. 22, 1931. Examination showed a pale, poorly nourished, round-shouldered girl. On the right ninth rib was a large, hard swelling about the size of an orange. It was not tender. Towards the back was a second swelling, much smaller and more painful, with the overlying skin movable. The large mass moved with the ribs.

Roentgenograms showed a fracture of the ninth rib in the mid-axillary line and some irregularity in the dorsal portion of the rib. The
Fig. 28. Case 9. Showing location of sarcoma.

Primary periosteal osteogenic sarcoma

Early invasion of pleura
skull showed several discrete areas of rarefaction in the frontal and parietal regions. The mandible showed unusually clear bone markings. The head of each humerus was somewhat spotty, with areas of increased density. To a lesser degree the same lesion was noticed in the heads of both femurs and in both tibia and fibula.

At operation the rib with the attached tumor was separated from the surrounding structures and removed. A new growth had penetrated through the pleura in two places and had become adherent to the lung. On its removal the lung collapsed.

The specimen, when examined by the pathologist, showed a segment of rib about 14 cm. long. There was an ovoid tumor 5 x 7 cm. in diameter and three smaller masses 2 cm. in diameter. The tumors were grayish white, edematous, and contained no recognizable bone. The rib had largely been destroyed by the tumor. Sections showed a cellular malignant tumor of bone which generally bore some resemblance to periosteum but which in places produced osteoid tissue and cartilage of varying degrees of perfection. A diagnosis of osteogenic sarcoma was made.

About three weeks later a second operation was performed for implantation of radium for recurrent sarcoma. Most of the wound where the rib was resected was healing. The anterior part showed definite recurrence. One hundred milligrams of radium in capsules were implanted over the malignant area.

An extension of the recurrence rapidly developed and the patient became emaciated and died in June 1931. No autopsy was obtained.

Comment: I am indebted to Dr. Walter S. Sherwood, Attending Surgeon, Brooklyn Hospital, and to his associate, Dr. E. K. Tanner, for the foregoing report and the privilege of including it in this paper; to Dr. James Denton for the pathological report, and to Dr. Edwin J. Grace, who succeeded in growing the sarcoma removed at operation in tissue culture. Dr. Grace classified the tissue culture as a grade IV fibroblastic sarcoma of rapid growth.

This case is of interest as the first case of sarcoma observed in a radium dial painter not employed in the New Jersey plant. It shows that the disease exists among the dial painters of New York and Connecticut. This was to be expected, as the same paint was used and was applied to the dials in the same manner as in the New Jersey plant.

Discussion of Osteogenic Sarcomas Occurring in Radium Dial Painters

Following the original interpretation of Ewing the term "osteogenic sarcoma" is used in this paper to denote a tumor arising from cells whose function it is to form bone, but which may not always do so.
Since the causes of primary sarcoma of bone are unknown, the great majority of cases must be classified as spontaneous in origin. In the sarcomas arising in the radium dial painters, however, for the first time a definite etiologic factor—the alpha particle—is established as the cause of some bone sarcomas.

**Incidence of Primary Bone Sarcoma**

In the discussion of the origin of osteogenic sarcomas in radium dial painters the argument that they may be explained by mere coincidence must first be met. Why are not the sarcomas in these cases of the same unknown origin as the ordinary variety of bone sarcoma and why is not their occurrence pure coincidence?

Against this assumption is the incidence of primary bone sarcoma. Speiser (14) states that Milieki in 7,186 autopsies in the Hansemann Institute found 560 malignant tumors, a percentage of 7.5. Of these, 516 were carcinomas and 31 sarcomas, and of the latter only 5 were osteosarcomas. Primary bone sarcomas, therefore, represented only 0.07 per cent of the entire number of autopsies. Ophüls (15), in an analysis of 3,000 autopsies, encountered sarcoma of the bone in only two cases, or 0.06 per cent. During the years 1918 to 1927 inclusive, of 134,500 admissions to the Newark City Hospital (850 beds), only 14 or 0.0001 per cent were for osteogenic sarcoma of the long bones.

While it has been stated that almost one case out of every three of sarcoma of the human body is a bone sarcoma, primary sarcoma of bone is actually of unusual occurrence, although it may seem more common in special institutions devoted to the treatment of malignancy.

The incidence of 4 deaths from osteogenic sarcoma in 17 deaths as the result of an occupational poisoning by radio-active substances, or about 23 per cent, should be conclusive evidence that more than a mere coincidence exists. In addition, the occurrence in some 30 former dial painters who are still alive but radio-active, of 4 other sarcomas, and the occurrence of osteogenic sarcoma in other plants where the same paint and the same manner of application were used, are overwhelming evidence of a direct cause in the etiology of these tumors.

**Trauma**

The next objection to be met is the part played by trauma in the production of osteogenic sarcoma. In only two of the radium dial painters' sarcomas was there a history of injury. In Case 2,
the growth would, no doubt, be considered by many surgeons to have followed the injury to the shoulder in the patient's fall in a department store. Roentgenograms, however, showed extensive radiation osteitis in this location, which had existed long before the trauma. Others might interpret the open operation for the relief of pain as additional insult.

In Case 7, there occurred a fracture of the femur after stepping from a stool. Here again we are dealing with a pathological fracture which took place, after slight injury, through an area already the seat of a radiation osteitis.

The part played by trauma in the production of bone sarcoma is always difficult to determine. I have always believed that single falls and external violence have been greatly exaggerated as causes. They do not offer a satisfactory explanation. Trauma, however, cannot be ignored. The remarks of Ewing (16) are pertinent: "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 percentage of traumatic bone sarcomas reported by some observers seems to be obtained by very uncrirical 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."

Matz (17), in a study of 45 cases of bone tumors among ex-service men, of which over 80 per cent were osteogenic sarcomas, found that 13, or 28.9 per cent, gave positive histories of trauma and 31, or 68.9 per cent, gave no evidence one way or the other. He states that trauma with the consequent repair, leads to temporary elimination of "growth restraint," with resultant acceleration of regenerative processes and a multiplication of the mesoblastic cellular elements. Very few cases of bone sarcoma are preceded by trauma, and very few traumas of bone are followed by the development of sarcoma. The small percentage of cases of bone fracture followed by malignancy is strong evidence against the importance of trauma in the etiology of bone sarcomas.

Recently it has been the fad, when positive evidence of trauma is slight or doubtful, to assume that malignancy develops because of hereditary susceptibility in the individual. Has not extensive breeding for generations of tumor-bearing mice shown this to be
true? I am afraid that those who believe strongly in a general constitutional susceptibility as an important factor in malignancy in human beings, will receive little comfort from the cases of the dial painters. The sarcomas seem to be attacking those who have the greatest amounts of radio-activity with almost demoniacal certainty, and without the slightest regard for their hereditary chromosome set-up.

It would seem, therefore, that the question of trauma may be easily dismissed as not playing any rôle in the development of the sarcomas in dial painters.

The Theory of Chronic Irritation

In the cases reported, there was usually clinical evidence during life, supported by roentgenograms, that the sarcoma started in an area that was previously the seat of a radiation osteitis. It would seem reasonable, therefore, to assume that the malignant process started on a focus of chronic irritation.

Do the sarcomas in the radium dial painters arise in areas of chronic inflammation? Is the intense and peculiar inflammation set up by alpha bombardment responsible for the occurrence of these sarcomas?

In osteitis due to heavy external irradiation, as seen by radiotherapeutists, anything approaching a sarcomatous transformation has never been recorded. In fact, the general observation is that the process is more apt to become sclerotic, inactive, and acellular. It must be recalled, however, that the internal radiation seen in the radium cases is quite different from any form of external radiation and that the two cannot be compared.

In my opinion the secret of the radium sarcomas lies in the intense destructive effect of alpha bombardment and in this alone. It will be necessary, therefore, to summarize my interpretation of the radiation osteitis occurring in these cases.

Radiation Osteitis

Due to the deposits of radio-active substances in the bones in these cases and because the radiation is chiefly alpha radiation, and the amount is extremely small, the marrow spaces of the entire skeleton are continuously bombarded by the alpha particle over a period of years.

The first reaction to the disruptive effect of ionization produced by the alpha particle is a stimulation of the hematopoietic centers
in the bone marrow. During this period, which may last for years, it is entirely possible to have a very good state of general health, with increased red cell production and possibly stimulation of even the leukocytes. This primary stimulation is not normal. It is what I prefer to call an irritative stimulation, which is compensatory to tissue destruction produced by alpha bombardment. The result is stimulative, also, because of the very small amount of radio-activity present in these cases. As a result, the marrow

becomes hyperplastic or regenerative in type. In time the compensatory stimulation becomes over-stimulation, and, finally, at a time which cannot be foretold in the individual case, exhaustion occurs.

In the early fatal cases, in which death was due to anemia and jaw necrosis, I described the blood condition as a profound leukopenic anemia of the regenerative or megaloblastic type. Attention was called to the fact that this was unlike any anemia previously described in the literature as caused by undue exposure to external penetrative radiation and irradiation from the gamma rays of radium and x-rays. Heretofore anemias due to radio-activity and x-rays, as reported by Mottram, Weil, Lacassagne, Brule, et al., had been described as of the aplastic type, showing little or no evidence of regeneration. As in practically none of these cases was necropsy performed and a study of the bone marrow made, this conception is purely a clinical one, and, in my opinion, may not always be substantiated by the facts as we know them.

---

**Fig. 29. Case 3. Radiation Osteitis. Midsection through Bodies of Lower Dorsal Vertebrae.**

The cancellous part of the bones is the seat of an extensive osteosclerosis (radiation osteitis) causing the vertebrae to assume a marbled appearance. These areas are not metastatic sarcoma.
In spite of the lack of anatomical proof, I am of the opinion that undue exposure to external radiation or irradiation from radium or x-rays sufficient to cause an anemia, usually produces a leukopenic, aplastic, or aregenerative anemia. The circulating red cells are regular in size and shape, show no evidence of regeneration, and toward the end a thrombocytopenia usually develops, the fatal outcome being characterized by the hemorrhagic diathesis, sepsis, etc.

Fig. 30. Case 3. Radiation Osteitis. Microscopic Appearance of Gross, Lesions Shown in Fig. 29.

All three successive stages of radiation osteitis occurring in the dial painters may be noted in the same section. The first stage of hyperplastic, irritative marrow (A); the second stage of cellular fibroblastic replacement in which areas the sarcomas are likely to develop (B); and the final or healing stage of acellular fibrosis with decalcification (C). × 42.

In the radium dial painters who develop anemias with fatal outcome, the blood picture towards the end is a profound leukopenic regenerative one. The hemoglobin had often reached as low as 20 per cent, with a red cell reduction of less than one million per cubic millimeter. The color index is often one plus, and a large cell anisocytosis with many macrocytes has not been infrequent. Occasionally a megaloblast has been found. The leukocytes are always diminished in number, a definite leukopenia existing, reaching as low as 1000 and 2000 cells per cubic millimeter
in some cases. There is a tendency towards an agranulocytosis, the normal lymphocyte of the blood being the predominating leukocyte. In some cases, the polymorphonuclears have been practically absent from the peripheral blood. In only one of six fatal cases was there extensive bleeding from the mucous membranes and into the skin, and in this case the megakaryocytes were undoubtedly affected, as the blood platelets were markedly decreased. Petechiae which sometimes occur in the terminal stages are due chiefly to the superimposed sepsis. In spite of the resemblance to pernicious anemia, of the early cases in which death was due to the anemia and the jaw necrosis and not to sarcoma, there was little or no evidence of so-called increased hemolysis. The icterus index was normal or low, and the van den Bergh tests were negative. In the cases in which autopsies were performed there was no pronounced increase in hemosiderin deposits in the liver, spleen, and kidneys, such as is seen in addisonian anemia.

I have stated in other papers that if radio-active substances are ingested or administered by way of the vein, in large enough amounts and over a period of time long enough to allow deposition in the bones sufficient to cause an anemia, an aplastic anemia rarely develops. The anemia is usually of the leukopenic, regenerative, megaloblastic, or pernicious type. The hemorrhagic tendency is usually not marked, as the megakaryocytes are not especially affected. The blood picture before death shows anisocytosis, macrocytes and other evidence of regeneration.

In spite of this clearly stated position, I have been quoted by Rolleston (18), Rosenthal (19), and others, as saying that the anemias in the dial painters were aplastic in type. This was not my experience. None of the radium dial painters whose cases I have reported have died of an aplastic anemia. von Soehocky, the physicist, did, and had during life extensive bleeding from the mucous membranes and kidneys. He was not, however, a dial painter. Although he had carelessly swallowed luminous paint, his anemia was due mainly to exposure to enormous amounts of external penetrative radiation in the extraction of radium. In this respect the work of Maisin (20) is interesting. In studying the inhibitory effects of various heavy metals on experimental tar cancer, he found that he could give his animals large doses of ionium (an alpha rayer) over long periods of time without causing an aplastic anemia; while external radiation produced aplastic anemia.
Figs. 31 and 32. First Stage of Radiation Osteitis. Hyperplastic, Irritative Compensatory Bone Marrow. × 96.
In every one of the radio-active dial painters whom I autopsied, six in all, the remarkable lesion was an intense replacement of the normal adult fatty marrow by a red regenerating bone marrow. The marrow of the femurs was dark red throughout, and the lesion more pronounced than that seen in the most characteristic case of pernicious anemia.

Histologically the marrow showed an astonishing picture, quite unlike that seen in any other disease. The general architecture, structure, and landmarks were entirely obscured by the extreme hyperplasia, with a packing of immature and primitive cells. The marrow spaces were so filled that in the smaller a distinct widening and increase took place. In the cancellous portions of the calvarium this sometimes was so marked as to produce localized areas of apparent rarefaction in the roentgenograms, causing the so-called skull lesions seen in some cases.

Some 60 per cent of the cells in well packed areas were very large, 12 to 15 to 20 microns in diameter, with large vesicular nuclei containing one to three or more nucleoli. There was a distinct nuclear limiting membrane with condensation of nuclear chromatin along its edges. The cytoplasm was dull, bluish gray (hematoxylin-eosin), smooth, and glassy, and contained no granules. The cells contained no hemoglobin. What these
cells should be called depends entirely on what theory the observer favors for the origin of the blood cells. I am an adherent of Maximow, and I will, therefore, call them hemocytoblasts, proerythroblasts, and promyelocytes. These premature stem cells may form megaloblasts, normoblasts, and eventually mature erythrocytes, or they may form cells of the granulocyte series, or both.

Mixed with these predominating primitive cells were many megaloblasts, some polychromatophilic, many containing various amounts of hemoglobin and many in mitosis. Normoblasts of all varieties were present. Mature erythrocytes were scant and occurred in groups, most of them being normal in size.

**Fig. 34. First Stage of Radiation Osteitis. Hyperplastic, Irritative, Compensatory Bone Marrow.**

The abundance of primitive cells of myeloid and erythroblastic series may be noted. Megakaryocytes are not usually affected, hence the absence of the hemorrhagic diathesis in most cases. $\times 250$.

The only cells of the granulocyte series were innumerable eosinophil myelocytes, which occurred more or less in group formation. A few eosinophil leukocytes were present. Practically no neutrophilic myelocytes or their mature derivatives were seen.

Lymphocytes were not present, nor were other cells of the lymphoblastic series. Megakaryocytes were usually abundant.

If we attempt to correlate the findings of the marrow in the dial painters with the clinical and morphological study of the anemias during life, we find some rather interesting and important observations. The marrow was packed with premature stem cells
which failed to differentiate into leukocytes of the granulocyte series with the exception of eosinophil myelocytes and polymorphonuclear eosinophiles. The polymorphonuclear neutrophil was practically absent, as were its precursors back to the promyelocyte, and even the hemocytoblast. This accounts for the leukopenia during life, with a tendency toward agranulocytosis.

In addition, the marrow contained an enormous number of eosinophil myelocytes with occasional maturation into polymor-
other cells which approach maturation are the red cells. Many of the primitive cells still have the power to form megaloblasts. Non-hemoglobiniferous and hemoglobin-containing nucleated red cells may be seen in all stages from megaloblast to normoblast. Again the blood pictures during life have shown that these cells gained entrance into the circulating blood. Anisocytosis, macrocytes, polychromatophilic red cells, and occasional normoblasts and megaloblasts were seen in blood smears. The red cell production, however, was greatly reduced because of the marked

failure of the hyperplastic marrow to reach maturity. This accounts for the anemia, which is formative in type, and not destructive, as studies of the blood and organs show no evidence of increased hemolysis.

All these observations would tend to support the modified monophyletic views of Maximow, that the primitive blood cell is a hemocytoblast, from which, in the bone marrow, either red cells or cells of the granulocyte series may develop.
I have been unable to determine with any degree of certainty whether the primitive cells form the red cell series intravascularly or extravascularly, because of the packing of the cells. They are probably formed intravascularly, as some immature cells have gained entrance into the peripheral blood during life. In later stages of radiation osteitis, where the intense cellular marrow has been replaced by fibrous tissue, megaloblasts and normoblasts were formed in the intersinusoidal capillaries of Sabin.

It also appears that most of the predominating primitive stem

![Image](https://example.com/image.png)

**Fig. 37. First Stage of Radiation Osteitis. Hyperplastic, Irritative, Compensatory Bone Marrow.**

The great number of eosinophil myelocytes may be noted. The primitive stem cells have lost their ability to form other cells of the granulocyte series. Hence the tendency toward an agranulocytosis. × 750.

cells in this marrow are extravascular in location, and so have not reached the peripheral blood during life. This accounts for the resemblance, during life, of the anemias to those of the aplastic type, as the immature cells have never entered the circulating blood. This is, perhaps, what Schilling would call a pseudo-aplastic anemia, the bone marrow being hyperplastic without showing hematological evidence of this condition.

I have also been unable to confirm the views of Piney, that
megaloblasts and their offspring are separate cell types derived from entoderm, and that their appearance in pernicious anemia is due to hereditary persistence of vestiges of their entodermal "anlage," while the ordinary nucleated red cells of the marrow are derived from reticulo-endothelial cells originating from their intravascular side. I am quite unable to distinguish the megaloblastic series from what he calls the macronormoblastic series.

**Hyperplastic Irritative Marrow:** I have interpreted and designated the marrow changes described above as the first stage of radiation osteitis in these cases, namely, a hyperplastic, irritative marrow due to compensatory stimulation caused by the alpha particle.

**Replacement Fibrosis:** After this hyperplastic irritative marrow has developed over various parts of the skeleton, the lesion starts to subside or heal in patchy areas. This is essentially a replacement fibrosis, and I speak of it as the second stage of radiation osteitis. In the beginning the reaction is a very cellular one. Young fibroblasts grow across and into the hyperplastic marrow.
FIGS. 39 AND 40. SECOND STAGE OF RADIATION OSTEITIS. CELLULAR, REPLACEMENT FIBROSIS. The sarcomas develop in these areas. \( \times 90 \).
Such areas can be seen grossly as distinct, grayish white areas, usually reflecting high lights, and ranging in size from those scarcely visible to those 1 to 2 cm. in diameter. The very cellular fibroblastic growth contains many eosinophil myelocytes, plasma cells, and lymphocytes. Mitotic figures are common in these areas, with hyperchromatism. Many of these areas can be differentiated from sarcoma only with a great deal of difficulty. In some no differentiation is possible. It is important to note that all stages of this radiation osteitis may be seen in a single bone.

![Second Stage of Radiation Osteitis](image)

This very cellular stage of radiation osteitis is responsible for the development of sarcoma. The multiplicity of the lesion over the skeleton also explains the multiple primary origin of sarcomas in some cases.

The only other known lesion of bone which resembles this stage of radiation osteitis is the sclerosing type of Garré's non-suppurative osteomyelitis, with this difference: that the intense inflammatory reaction in the radium cases is far more severe than that of any previously described bone lesion. In Garré's disease,
also, observers have found areas which could only be distinguished with great difficulty from sarcoma. I have never heard, however, of a malignancy developing from the non-suppurative osteomyelitis of Garré.

Due also to considerable decalcification, the bones become soft, and deforming lesions result. I. Tarsal scaphoid, × 10. II. Area A, higher magnification, × 75.

**Fibrosis, Healed Lesion:** The third or final stage in radiation osteitis in these cases is one of healing, with almost entire subsidence of all inflammatory lesions. Here the marrow is entirely replaced in patchy areas, and in some cases over extensive areas, by a non-cellular fibroblastic tissue. There have been bone absorption and considerable decalcification.

The bones at autopsy at this stage saw with a soft, woody feel and show grayish white sclerotic areas in the marrow. They are soft and elastic. The marrow spaces are converted into loose, fibroblastic tissue, with consequent softening of bone, production of coxa vara, spontaneous fractures, and other deforming lesions.

**Sarcoma in Paget's Osteitis Deformans**

The correctness of the interpretation of the sarcomas in the radium dial painters as beginning in bones which were the seat of previous chronic inflammation is supported by an interesting analogy, namely the occurrence of bone sarcomas in Paget's osteitis deformans, and occasionally in osteitis fibrosa localisata and osteitis fibrosa cystica generalis of von Recklinghausen.
Paget, in his original paper, noted the association of bone malignancy with osteitis deformans. Ochsner and Gage (21) state: "It is almost universally agreed at the present time that sarcoma occurring in bones affected with osteitis deformans is the result of a previous osseous lesion and is not merely incidental."

Speiser (14) states that sarcoma occurs as a complication of Paget's disease in about 2 per cent of all cases, and he does not believe that its occurrence is incidental. He believes that the occurrence in Paget's disease is thirty times more frequent than
one would anticipate in the development of sarcoma in the osseous system under ordinary circumstances.

Segale (23) believes that antecedent osteitis deformans plays a definite etiological rôle in the development of osteogenic sarcoma. In support of this he cites the well known fact that malignant disease may follow chronic irritation. He also relates a case in which a sarcoma developed at the site of a fracture with non-union.

Bird (24) calls attention to the fact that sarcoma of the long bones usually occurs in younger individuals. He quotes Gross as finding, in a study of 165 cases of sarcoma of the long bones, 39 cases of periosteal sarcoma, the average age at onset being twenty-three years. In Bird's series of sarcomas associated with Paget's disease the average age at onset was fifty-seven years. This would indicate that the sarcomas have a direct bearing on the presence of a chronic bone lesion in Paget's disease.
Gruner, Scrimger, and Foster (25) state: "The essential difference between the sarcomatous portions and the adjoining osteosclerotic portions lies in the unrestrained multiplication of tumor cells, which here fail to exhibit the slightest tendency to deposit bony matter around them." They believe that the tumor is superadded to the osseous tissue, which has been altered by the osteitis deformans.

The first stage of radiation osteitis, the hyperplastic, irritative marrow may be noted. On account of the preponderance of primitive cells and the resemblance to a panmyelosis, these lesions mimic multiple myeloma × 375.

Cone (26) states that both osteitis deformans and sarcoma develop principally at those points of greatest pressure and traction. It will be noted that the same seems to hold for the sarcomas in the radium dial painters.

Ochsner and Gage (21) collected 31 cases of sarcoma in the literature developing in lesions of osteitis deformans. In addition, eight other cases were found in which the diagnosis was questionable. They found that the humerus predominated as the site of election, the skull came next, then the femur, tibia, ilium, etc. Sarcoma in the scapula, clavicle, and maxilla was rare.

Smith (27) states that Codman, in his recent investigation of
bone tumors, found that 14 per cent of all persons with Paget's disease die of osteogenic sarcoma. A still more recent report from the Bone Registry of the American College of Surgeons says that 5 per cent of osseous sarcomas begin in bones involved in deforming osteitis. If we are to believe these statistical reports, the occurrence of bone sarcomas in cases of osteitis deformans is more than coincidence.

**Fig. 46. Osteogenic Sarcoma in Radium Dial Painters of Embryonal or Anaplastic Type. \( \times 390. \)**

*Direct Effect of Radio-activity in Production of Malignancy*

While in the sarcomas of the radium dial painters, and in those developing in osteitis deformans, a previous chronic irritative bone lesion exists and seem to play the important rôle in the production of the neoplasm, there is the possibility that in the radium dial painters a more direct effect of the intense atomic disruption produced by ionization, due to the bombardment of the alpha particle, may be an important causative factor.

In this connection it is of interest to note that McCombs and McCombs (28) have recently advanced the hypothesis that cancer
FIG. 47. OSTEOGENIC SARCOMA IN RADION DIAL PAINTERS OF EMBRYONAL OR ANAPLASTIC TYPE. $\times 312$.

FIG. 48. OSTEOGENIC SARCOMA IN RADION DIAL PAINTERS OF EMBRYONAL OR ANAPLASTIC TYPE. $\times 600$. 
is due primarily to mutation in a somatic cell, caused, possibly, in some instances by ionization. They state that it is a well known fact, genetically, that experimentally mutations can be speeded up tremendously by exposure to stimulating amounts of radiation, where greater doses are destructive. Is it possible that some such agency is active in the greatly increased prevalence of cancer?

Babcock and Collins (29) performed an experiment with Drosophila, comparing the rates of occurrence of sex-linked lethal mutations in a street-car tunnel in San Francisco and in their laboratory. A location was discovered in the tunnel where the natural ionization radiation was fully twice as great as the radia-

Fig. 49. Osteogenic Sarcoma in Radium Dial Painters of Embryonal or Anaplastic Type. × 450.

...tion in their laboratory in Berkeley. The difference in rate was 2.5 times the probable error for the flies which had been exposed in the tunnel. In other words, the rate of lethal sex-linked mutation was more than doubled when the flies were transferred to a more highly ionized location.

Hanson and Hays (30) performed, independently, similar experiments in a carnotite mine in Colorado, where the air was strongly ionized. Their results check closely with those of Babcock and Collins. Some think that the forms of certain prehistoric animals, especially those of the more bizarre types, were due to active volcanic disturbances with the liberation of large amounts of emanation from radio-active ores, causing mutations in the germ cells.
It is not the purpose of this paper to advance any absurd and fantastic theory for the cause of cancer. The author does not wish to be classed with those who, for instance, claim that a diminution in the strength of the cosmic rays may have something to do with the matter, a theory which Wood (31) has aptly described as "an arrant bit of moonshine," which may be "gently and cheerfully consigned to the limbo of pure phantasy."

We have, however, in the study of the radium dial painters, proof that radiation can produce malignancy by causing chronic irritative bone lesions, which become sarcomatous, and a suggestion that more direct action of the radiation may cause, or speed up, somatic cell division, also causing malignant changes as a final result. A combination of both processes may occur.

**The Schneeberg Lung Cancer**

It may be said by some that the radium cases here discussed are the only known instances of malignancy directly attributable to radio-activity, except for those cases of malignancy of the skin following x-ray and radium burns, and that such an occurrence, now that the industrial dangers are fully recognized, is of little practical importance.

In a discussion of a recent paper by Martland (32), Blumer called attention to the high incidence of cancer of the lung in cobalt miners, and asked if the ore were radio-active. Years ago Osler (33), quoting Ancke, stated that the cobalt miners of Schneeberg were very liable to have a primary carcinoma of the lung which might run an acute or fulminating course.

Recently Weller (34), in a general review of the pathology of primary carcinoma of the lung, went into considerable detail concerning the Schneeberg cases. He says: "Pulmonary carcinoma affords in the Schneeberg 'lung cancer' what is probably the most extraordinary and at the same time least understood of all the associations which have been discovered to exist between occupation and the incidence of neoplasm." For centuries (since 1500) it has been known that a considerable portion of the underground workers in the cobalt mines of the Schneeberg district, in Saxony, had in each generation died, in middle life, from some pulmonary disease. The picture of the disease seems not to have varied through the centuries, being characterized by cough; mucoid, mucopurulent or bloody sputum; progressively increasing dyspnea; loss of weight and strength; tendency to sweating; boring
pain in chest and back, and death after a varying period of incapacity.

An official investigation over a period of three and a quarter years was made by Thiele, Rostoski, Saupe, and Schmorl, (35). One hundred and fifty-four miners were studied by methods of modern clinical diagnosis, including roentgenoscopy. During this same period 21 of these died, and in 13 (62 per cent) a diagnosis of carcinoma of the lung was established at autopsy. At the same time, 362 persons from the same district, but not employed in the mines, were examined without yielding a single example of carcinoma of the lung.

For many years the Schneeberg lung tumor was incorrectly interpreted. Early workers believed it to be a sarcoma, a lymphosarcoma, or a lymphosarcoma fibromatoides. The above investigators, however, concluded that the condition is one of epithelial neoplasia, and that mistakes in diagnosis have been due to the misinterpretation of undifferentiated carcinomas of the lung. The small-cell, primary carcinomas of the lung are of special importance, because it is this undifferentiated or anaplastic form which has quite naturally been mistaken in the past for sarcoma of the lung. The carcinoma occurred only in miners, or those in most intimate contact with the products of the mines.

The rapid clinical course of these carcinomas, and their very anaplastic type on histologic examination, should be noted and compared to the sarcomas in the radium dial painters.

Many theories have been advanced to explain the etiology of these carcinomas. The mines are damp, and show abundant growth of microscopic and larger fungi. The men are compelled to climb up and down ladders for considerable distances, even as much as 1,000 feet. In the harder rock, where drilling is necessary, the fine stone dust is an industrial hazard. The ore contains iron, bismuth, tin, zinc, lead, manganese, uranium (which is radio-active), cobalt, and nickel, chiefly in combination with sulphur and arsenic. The ore is radio-active, and the air of the mines has a radio-active emanation content of from a few to 50 Maché units. Schmorl felt that the chalicosis in the lungs of these miners must be of significance (it should be recalled, however, that in silicosis it must be rare for malignancy to develop, the final outcome being usually tuberculosis). He was uncertain as to what to blame, but considered the possibility of mechanically irritating stone dust; chemically active dust, particularly arsenic; inhalation of arsine,
di-ethyl arsine, or other volatile arsenical compounds; the flora of the damp mines, and the inhalation of radio-active substances.

So far as I am able to ascertain, no examination after death has been made for the presence of radio-activity. It is possible that none would be found, as the effect may be due entirely to the inhalation of emanation, the active deposit from which would be entirely too small to be measured.

THE JOACHIMSTHAL LUNG CANCER

Another example of the high incidence of malignancy of the lung in workers exposed to radio-active substances is making its appearance in the pitchblende mines of Joachimsthal. So far as I am able to learn there is no literature at the present time on these cases.

In 1930, Teleky (36), expressing his interest in the osteosarcoma investigation in the radium dial painters, said: I think it to be analogous to the pulmonary cancer of the workmen at Joachimsthal in Böhmen and perhaps at Freiberg in Saxony (Schneeberg)."

Swarz (37) has recently told me that the incidence of lung cancer among these miners is so high that it was the subject of discussion at a recent meeting of the Medical Section of the League of Nations.

EFFECT OF ALPHA RADIATION IN EXPERIMENTAL TAR CANCER

Maisin (20), in an experimental study of tar cancer, has shown that certain mineral salts, especially copper and magnesium, when used in sufficient doses, delay the appearance of experimental tar cancers and greatly lower the percentage of positive takes. On the other hand, the salts of radio-active substances have the opposite effect. A great number of Maisin’s rabbits injected intravenously with ionium (an alpha ray) showed progressive metastasizing tar tumors, while the controls never showed progressive tumors. In addition, after the injection of ionium, Maisin and Dupuis produced large and malignant embryomas in chickens.

THE MULTIPLICITY OF LESIONS PRODUCED BY IRRADIATION AND RADIATION

In the study of the radium dial painters and a review of the harmful effects of irradiation from x-rays and radium applied
externally one cannot but be struck by the multiplicity of lesions and diseases produced by the same etiologic agent (radiation).

Occupational poisoning in radium dial painters must go down in medical history as the outstanding example of a disease produced entirely by a physical agent, namely, the alpha particle. An attempt has been made, for the first time, to bring out the difference in the reactions of the bone marrow in man to internal bombardment by the alpha particle, and to external irradiation from roentgen rays and the gamma rays of radium. Otherwise x-rays or radium and its allied products produce essentially the same biologic effects, and are so closely related that, for simplicity's sake, we may speak of them as a single etiologic agent.

With this in mind, I will summarize these effects, with the idea of especially calling attention to the close interrelationship of certain blood diseases. If a variety of lesions or disease entities can be produced by a single etiologic agent, such diseases must bear a close relationship, and be no more than manifestations of various degrees of stimulation, destruction, irritation, or exhaustion of normal tissues.

The human body may be exposed to x-rays and the radiation from radio-active substances with deleterious effects, in one or more of four main ways.

1. *Penetrative or External Radiation*

We have abundant clinical evidence, supported by animal experimentation, of the harmful effects of over-exposure, or long continued exposure, to external irradiation or radiation by means of roentgen rays, radium, mesothorium, etc. The numerous reports of roentgen-ray dermatitis, x-ray and radium burns, skin cancers, the temporary and fatal anemias in radioologists and radium workers, intestinal injuries, and sterility, all demonstrate the occupational and therapeutic hazards likely to be encountered.

Authorities mostly agree that contact with radio-active substances and x-rays frequently produces, aside from lesions in the external organs, such as the skin, deep and often profound alterations, of which the principal objective symptoms are usually a leukopenia, more rarely a leukemia, an anemia usually of the aplastic type, a fall in systolic blood pressure, and sterility. Some of these alterations may occur soon after the first contact, and be mild in character and curable, or, when once established after undue exposure, they may persist even after cessation of exposure.
An excellent summary of the harmful effects of irradiation is given in Rolleston's recent critical review (18). It is necessary here to state only a few observations.

Lavedan (38), in a review of the literature on the condition of the blood in radiologists, including the results of the questionnaire by Pfahler in 1922 to a thousand radiologists, states that the consensus of opinion in regard to the white cell count points to a leukopenia with a diminution in the polymorphonuclear leukocytes. A moderate increase in the number of red cells was not uncommon and was ascribed to stimulation of the red bone marrow by irradiation. In some cases there was an eosinophilia.

Gudzent and Halberstaedter (39) found among radium workers a relative and absolute lymphocytosis averaging 46 per cent, with a diminution of the polymorphonuclears averaging 50 per cent and a slight fall in the total leukocyte count and the hemoglobin, but no change in the erythrocytes. The leukopenia immediately following the irradiation has been ascribed to the direct action of irradiation on the leukocytes, on the ground that their remains can be seen in blood films, whereas the prolonged leukopenia has been regarded as due to damage to the hemopoietic tissues.

Rolleston states that the number of x-ray and radium workers who have become leukemic is small. Of the recorded cases, acute or subacute in character, six occurred in x-ray workers, one in a radium worker, and one in a worker in radium and thorium. Rolleston believes, therefore, that the occurrence of leukemia is a pure coincidence. There are others, however, who claim that both myeloid and lymphatic leukemia may be caused by undue radiation or irradiation. In view of the marked hyperplastic marrow in radium dial painters, which assumes the appearance of a panmyelosis, but with premature stem cells, it would seem very likely that a myeloid leukemia could easily develop; and if we believe that Maximow's hemocytoblast can also form cells of the lymphoblastic series, the occurrence of a lymphatic leukemia would not be impossible.

As regards the occurrence of aplastic anemias in persons exposed to undue irradiation, Rolleston states that out of twelve collected cases following long-continued exposure to irradiation, seven were among radium workers, one was in a thorium worker, and three were due to x-rays. In view, therefore, of the relatively much larger number of x-ray than of radium workers, it would appear
that the gamma rays of radium have a much greater tendency to cause aplastic anemia than have x-rays.

Although only a few cases of aplastic anemia due to radium and x-rays can be found in the literature, this severe disease is, without doubt, more frequent than published reports indicate. Aubertin states that there is a whole group of professional anemias due to roentgen rays, radium, and mesothorium, and that they are of the aplastic type and can be produced experimentally. I have already called attention to the paucity of anatomical proof in these cases among human beings.

De Laet (40), in 1928, reviewed the deleterious effects of the professional handling of radio-active substances and x-rays. Permanent changes in other viscera than the blood-forming organs may result from irradiation, whether given in large doses on one or a few occasions, or in small doses spread over a long period. Such changes have been observed clinically and experimentally. The most important and outstanding has been the production of sterility in both sexes. In addition, the production of chronic nephritis, extensive lime deposits in viscera due to bone decalcification, hepatic cirrhosis, and even changes in the myocardium, have been described.

Another recorded lesion is the acute damage done to the intestinal tract following irradiation, resulting in necrosis and intestinal ulceration. Norris (41) autopsied a case in which radium given for malignancy of the esophagus had been accidentally swallowed and found peritonitis due to an ulcer of the intestine.

To summarize, we may state that the harmful effects of external irradiation, or radiation, are chiefly acute constitutional symptoms, such as radio-toxemia and roentgen-ray intoxication; chronic constitutional changes such as leukopenias; mild leukopenic anemias; fatal aplastic anemias, usually with hemorrhagic tendencies; possible myeloid and even lymphatic leukemias; hypotension, sterility, intestinal ulceration, and various fibrotic changes in certain viscera.

2. Inhalation of Dust Containing Radio-active Substances and Inhalation of Emanation

There are certain manipulations required in the radium industry, such as the purification and fractional crystallization of radio-active substances; the tubing and retubing of partly aged radium material; repairing needles, placques and containers; the preparation of radium and mesothorium and their decaying prod-
ucts for the manufacture of luminous paint; the retubing of needles and the brushing of dishes, etc., in which the chemist and worker cannot always be properly screened or protected from radio-active dust or from the inhalation of emanation.

In the refining of radium and mesothorium, Schlundt and his associates (42) have shown that the intensity of radiations from all sources may be reduced to a practical minimum by proper technic. Only two radiations remain which may be regarded as potentially harmful, viz.: the gamma rays not removed by shields and other screening devices, and the alpha rays from emanations present in the air breathed by the worker. These authorities say: "Active particles of dust in the air are ordinarily not of importance since throughout the process of refining the salts may always be kept in solution. It is only when the finished products are finally tubed and sealed preparatory to shipment that great precautions are necessary to prevent small particles of the dried and finely divided salt from finding its way into the air, being inhaled and deposited as radio-active centers in the lungs." The air in the refining laboratory always contained radon and thoron. These two isotopic radio-active gases after escape into the atmosphere decay with the emission of alpha particles and the formation of solid active deposits on all exposed surfaces. If this deposit is formed on the lining of the lungs, active materials may find their way into the blood stream and to various parts of the body, there to decay with emission of all types of radiation.

The inhalation or swallowing of thoron is practically harmless, as its active deposits are short-lived, none lasting more than a few minutes. Radon, however, has long-lived active deposits, the half period of radium D being 16.5 years and that of radium F 136 days. Radon is, therefore, cumulative in its effect, and its inhalation or ingestion is distinctly dangerous.

I personally know of deaths from anemia in which this mode of entry played the important etiologic rôle. The case reported by Reitter and Martland (1) of the physicist Lehman is one. He died from an anemia of the regenerative type, similar to that seen in the dial painters, due to both inhalation and ingestion of radio-active substances. After death radio-activity was demonstrated in the lungs and bones. His is the first recorded case in which at autopsy the anemia was proved to be of the regenerative type.

It is quite possible that the lung carcinomas in the miners of Joachimsthal and Schneeberg are chiefly due to the inhalation of emanation and radio-active dust.
3. Ingestion of Radio-active Substances

The outstanding examples of this mode of poisoning are the radium dial painters. Here, for the first time, we have in the human body the record of the effects of internal bombardment by the alpha particle. In the study of these cases we have encountered the following lesions: irritative hyperplasia and compensatory stimulation of the bone marrow of a very primitive type; leukopenias; mild anemias of the pseudo aplastic type; fatal anemias of the regenerative or megaloblastic type with leukopenias approaching agranulocytosis, but with no evidence of hemolysis and rarely marked hemorrhagic tendencies; replacement fibrosis with production of a radiation osteitis; necrosis of the jaw due to superimposed infection upon a radiation osteitis; crippling and deforming bone lesions due to healing radiation osteitis, with coxa vara, deformities of the spine, spontaneous fractures, etc.; a packing of the bone marrow with primitive stem cells resembling a leukemoid state; the possibility of the development of myeloid leukemias and even multiple myelomas, and finally osteogenic sarcomas.

Prior to the study of the radium dial painters no anemias of the regenerative type had ever been recorded as a result of undue exposure to radiation or irradiation.

A source of danger which must be seriously considered in the light of our knowledge of the dial painters' history is the sale, usually by quacks, of radio-active waters for the cure of everything from ingrowing toe-nail and alopecia areata to the sexual impotence of senescence, high blood pressure, chronic arthritis, and arteriosclerosis. There are two main types of radio-active waters: those containing radio-active substances in solution and those containing only emanation.

In 1925 I made the statement: "Should the waters contain radium or mesothorium in solution, their use would be distinctly dangerous on account of their cumulative effect." This was a logical assumption based on my experience with the radium dial painters. It was ridiculed by many, and I never had the opportunity actually to prove the correctness of my views until recently. A few months ago I was called to testify against the interstate sale of vials of mesothorium and radium, to be ingested, after dissolving in water, for the cure of most of the ailments of mankind. The directions called for the consumption of one vial or more every day for at least two to three months or longer. The amount of radio-
active substances to be swallowed per day equaled that taken by some of the dial painters. Though these substances are in soluble form, they are changed, in the blood, into the more insoluble carbonates, phosphates, and even sulphates of radium and mesothorium, and eventually reach the bones. Recently I had the opportunity of examining two patients who had taken this water for a period of one to two years. Both showed radio-activity when tested by electrometers, one having as much as 30 micrograms in his body. Both have extensive necrosis of the superior maxillae. In one there is almost entire sloughing of the bones.

Should the waters contain only radon or thoron it would seem that a great amount would be lost in the air before any could be swallowed, and gallons of the water would have to be drunk quickly, a palpable absurdity, to introduce even minute amounts of radio-active substance in the body. It would appear, therefore, that while the so-called emanators or activators on the market furnish emanation as stated in their advertisements, it would be a physical impossibility, on account of the rapid escape of the gas, to swallow enough to produce supposed beneficial results. They are frauds. Treatment by such means can have only a psychic effect on the patient—perhaps, unfortunately, on a few physicians—and is mere charlatanism.

Recently, however, I have begun to doubt the harmlessness of these emanators, chiefly because of the occurrence of malignancy in radio-active persons. It is important to know whether such apparatus is dangerous on account of its widespread use. In 1926 over one hundred and fifty thousand emanators were sold on the Pacific coast. Many users of the water are enthusiastic over the results obtained (psychic).

I am now of the opinion that the normal radio-activity of the human body should not be increased, strongly presuming that increased amounts of radio-activity may produce, over a number of years, malignancy. In this respect it should be noted that the normal atmosphere is radio-active, as is the human body in its normal environment.

The drinking, over long periods of time, of radio-active waters containing radon may allow a small amount of active, long-lived deposit to enter the body, part of which may finally be deposited in the bones and other organs as more or less insoluble salts. Thoron, on account of its very short-lived active deposits, is probably not dangerous.
The above arguments are applicable, also, to the natural radio-active springs. The beneficial results of treatment in such spas is due more to the regular habits and hygiene of the patients, and to the tremendous psychic effect, than to any actual absorption of radio-activity. If large amounts of radio-active substances were swallowed, the results would be distinctly dangerous rather than beneficial.

Illustrating further the popular idea that radium puts \textit{le désir de vivre} in individuals, there has recently appeared on the market a German chocolate candy containing radium, to be used for most of the ailments of mankind.

4. \textit{Intravenous Injection of Radio-active Substances}

For intravenous therapeutic injections, the soluble bromides and chlorides of radium, mesothorium, and radiothorium are most used. They behave in the same manner as barium salts or lead. They are, in spite of their original solubility, converted in the blood into possible carbonates and phosphates and, as I stated in 1925, are even more apt to be changed by the normal sulphuric acid ions into very insoluble sulphates of radium and mesothorium. They then become fixed deposits, especially in the bones.

It would appear that the intravenous injection of long-lived radio-active elements, or the internal administration of radium, mesothorium, or radiothorium, is highly dangerous on account of the late harmful effects. It is not warranted in any medical condition, as none of the known radio-active substances produces any specific or curative result. The supposed beneficial effects from the early irritative stages may be countenanced only in the treatment of leukemias, Hodgkin's granuloma, and other malignant conditions in which a fatal outcome is to be expected. The intravenous use of polonium (an alpha rayer) in the treatment of syphilis may be objected to on the same grounds.

It is interesting to consider the possibility of the radio-active dial painters transmitting radio-activity to their children. A competent authority has told me that he saw one child who was radio-active to an extremely slight degree, whose mother was pregnant while she was working as a dial painter. This could occur only through the absorption of emanation from the mother's blood through the placenta, with a final deposit of minute amounts of long-lived active deposits in the bones of the fetus.
Summary

1. Martland and Humphries in 1929 reported two osteogenic sarcomas among 15 deaths in dial painters from a New Jersey plant using luminous paint. They attributed the development of the sarcomas to chronic irritation caused by a radiation osteitis, produced by internal bombardment from deposits of radio-active substances in the bones, thus establishing a definite cause for sarcoma of the bone for the first time. On account of the small number of cases covered, this was regarded at the time by some as "an alluring theory, not yet subject to proof."

2. This paper reports an additional number of bone sarcomas occurring among dial painters. There have been five deaths from osteogenic sarcoma in a total of 18 originating in occupational poisoning by radio-active substances in former dial painters from the New Jersey plant, an incidence of 27 per cent.

As the incidence of the ordinary variety of primary osteogenic sarcoma is only about 0.07 per cent, this is overwhelming evidence that the radio-activity of these dial painters is the true cause of the sarcomas.

3. In addition, three cases of former dial painters from the same plant still living are reported. In one of these there is undisputable evidence of osteogenic sarcoma of the femur. In the remaining two there is strong presumptive evidence that such a lesion is developing.

The report of a death from osteogenic sarcoma of the rib, occurring in a dial painter employed in New York and Connecticut clock factories, is also included, to show that radium poisoning is not indigenous to New Jersey, but has occurred in other states where luminous watch dials have been manufactured. The number of dial painters dying in other states has never been determined, as radium poisoning was never heard of, or recognized, until the New Jersey cases were described.

4. A short sketch, or résumé of the author's interpretation of so-called radium poisoning in the watch dial industry has been given to facilitate an understanding of the occurrence of the bone sarcomas. The extensive literature should be consulted for more detailed description of this disease.

5. The osteogenic sarcomas in the radium dial painters undoubtedly develop in areas which have previously been the seat of a radiation osteitis. We have also to consider the possibility that the alpha particle may have a more direct action in producing
malignancy by speeding up somatic cell division as a result of its destructive ionization.

The term "radiation osteitis" was first used by Ewing to describe changes taking place in bones which received large external doses of irradiation for therapeutic purposes, usually adjacent to a malignancy. He found that the marrow had been replaced by a loose, non-cellular, fibroblastic tissue in which there was considerable fat. His lesion never showed, however, the intense inflammatory character seen in the dial painters, the process always being of a sclerotic nature.

6. The author's interpretation of the radiation osteitis seen in dial painters may be summed up as follows: In a radio-active dial painter who has, for example, 10 micrograms of radio-active substances deposited as insoluble sulphates in the entire skeleton, there are constantly being ejected about 370,000 space-occupying alpha particles a second, with a speed approximating 18,000 miles per second. This bombardment, which I have designated as an internal bombardment, is continuous, and will last for an indefinite period. For instance in the year 3491 A.D., the skeleton will still be giving off 185,000 alpha particles per second.

The tremendously disruptive effect of ionization produced by this bombardment causes atomic and molecular disintegration. In time, a hyperplastic, red marrow results, due to compensatory stimulation. Such a marrow is characterized by a packing of the marrow spaces with primitive stem cells, which I have interpreted as promyelocytes, proerythroblasts, and hemocytoblasts.

The ability to form cells of the granulocyte series, with the exception of the eosinophil myelocyte, is practically lost. As these cells are chiefly extravascular in location, very few immature cells escape into the circulating blood; hence the leukopenia with a tendency toward an agranulocytic blood picture.

The power to form red cells is retained, but greatly reduced, and reverts to an embryonal, megaloblastic type of production. As the formation of the red cells is chiefly intravascular, many immature cells are washed into the blood stream, especially macrocytes. Hence the resemblance of the blood picture to that of addisonian anemia. This hyperplastic, irritative, embryonal marrow I have designated as the first stage of radiation osteitis.

The process now subsides in patchy areas over the skeleton. A very cellular replacement fibrosis, of an intense, inflammatory character, develops, with numerous eosinophil myelocytes, lympho-
cytes, and plasma cells. Many of the fibroblasts show mitotic figures and hyperchromatism, and these areas can be distinguished from sarcoma only with great difficulty. It is in these areas that sarcoma arises. On account of their wide distribution over the skeleton, it is easily seen how multiple primary sarcomas may occur in the same individual. I have called this the second stage of radiation osteitis.

In the final stage of the process of radiation osteitis the marrow is entirely replaced by an old, non-cellular fibroblastic tissue. The bones become soft, partially decalcified, and deforming lesions occur, particularly in areas subject to a great deal of weight or trauma. Coxa vara, deformities of the spine, spontaneous fractures, etc., are likely to occur.

7. Attention is called for the first time to the difference in biologic effects on the human bone marrow of external penetrative irradiation and internal alpha radiation as seen in these cases. In this respect attention is called to the fact that the anemias developing from undue exposure to external radiation (gamma rays of radium and x-rays) are considered by most authorities as of the aplastic type, although anatomical proof of this is woefully lacking. On the contrary, the anemias caused by internal alpha bombardment, as first described in the radium dial cases, are of the regenerative, hyperplastic, or megaloblastic type.

8. Attention has also been called to the occurrence of bone sarcoma in Paget’s deforming osteitis and its rare occurrence in the osteitis fibrosa cystica of von Recklinghausen, showing that the literature already records instances of malignancy developing in bones which were the seat of chronic inflammatory lesions which were not nearly as severe and intense in character as the radiation osteitis in the dial painters.

9. That radio-activity in the human body may play an important part in the production of other forms of malignancy in no way connected with radium dial painting is suggested, the high incidence of primary carcinoma of the lungs in the cobalt miners of Schneeberg and in the pitchblende mines of Joachimsthal being noted.

10. The multiplicity of lesions and diseases produced by irradiation from external exposure to radium and x-rays, and radiation from internal bombardment by the alpha particle, such as occurred in the dial painters, is noted.

We may encounter: leukopenias; mild anemias; local skin
lesions such as x-ray dermatitis, radium burns, epidermoid cancers, etc.; fatal anemias of the aplastic or aregenerative type; fatal anemias of the regenerative or pernicious type; panmyelosis and leukemoid bone marrows; myelogenous leukemias, in acute and subacute forms; lymphatic leukemias, in acute and subacute forms; radiation osteitis with jaw necrosis; radiation osteitis with crippling bone lesions, such as coxa vara, deformities of the spine, and spontaneous fractures; radiation osteitis with skull lesions; radiation osteitis with the development of osteogenic sarcomas, and primary carcinomas of the lung. All are produced by practically the same etiologic agent, either by light waves (gamma rays of radium and x-rays) or by bombardment of space-occupying masses (alpha particles and negative electrons).

Such a variety of lesions produced by a single agent might indicate that many of these lesions are closely interrelated and are only manifestations of various degrees of injury to, or stimulation or exhaustion of, certain normal body tissues.

CONCLUSIONS

1. These studies indicate that it is important to have proper medical supervision over the use of radium and x-rays for therapeutic purposes, and governmental control over industries and occupations in which exposure to radio-active substances takes place.

It would seem that the use of radiations for therapeutic purposes should be confined to hospitals and institutions specializing in and competent to handle such treatments, and that the indiscriminate use of radium and x-rays should be in some way controlled.

All occupations in which the handling of radio-active substances occur should be under strict governmental control and supervision. Rules and regulations covering the dangers of exposure should be outlined. Technical methods should be devised in specific industries so that exposure is reduced to a minimum. In the refining of radio-active substances, for instance, Schlundt is of the opinion that this can be accomplished.

If in a certain industry the exposure cannot be reduced to a safety minimum, the procedure in use should be given up for some other method; if this is not possible, the industry should be discontinued. In this respect it is interesting to note that the U. S. Public Health Survey, which shows that the habit of licking brushes
in the watch dial industry has been stopped and that various mechanical methods have been devised to apply luminous paint, states that, in spite of the utmost care and precautions against undue exposure, girls who work under the new methods still become radio-active and show an average of one half a microgram of radio-active substance in their bodies. It is a question whether under these conditions we should be satisfied to regard the industry as a safe one.

The above arguments apply also to the sale of radio-active waters, emanators, activators, etc. The sale of all such commodities should be stopped until it is definitely established that they are harmless. The indiscriminate sale of these waters and apparatus by laymen and quacks is criminal. Their therapeutic effects are nil if we exclude the psychic effects produced on the patient. The human race would not suffer by eliminating them.

2. These studies, aside from drawing attention to the occurrence of malignancy in radio-active persons and giving another cause for osteogenic sarcoma, may be of importance in the experimental study of cancer. It may be possible to show new methods by which malignant tumors may be produced in animals. Recently, in Germany, bone sarcoma has been produced in the rabbit by means of irradiation from implanted radium.

3. The question arises, may not other forms of malignancy depend upon the presence in the human body of increased amounts of radio-activity too small, perhaps, to detect by our present methods?

This question will be harder to answer than appears at first thought. While the amounts of radio-active substances in the dial painters are extremely small, being measured only with great difficulty, they must be very much greater than one would ever expect the normal individual to acquire. Unfortunately, at the present time, we are unable to estimate much smaller quantities. A great deal less might produce malignant changes over a longer period of time. Some have thought that 10 micrograms of radium deposited in the tissues of the body is probably just within the limits of tolerance of the average person. From my experience, it is impossible to state what is the greatest amount of radio-activity the body can safely carry. My idea is that less than one half of a microgram is dangerous. Theoretically the exposure to, or the use of any radio-active substance that will increase the normal radio-activity of the body is dangerous. At the present
time I can only suggest that some other types of malignancy may be caused by minute amounts of radio-active substances to which the human body, in its normal environment, is exposed.

REFERENCES


15. U. S. Public Health Service Survey: About to be released.
36. TELEYKY, L.: Personal communication, March 26, 1930.
37. SWARZ, LOUIS: Personal communication, January 5, 1931.
40. DE LAET, MAURICE: La pathologie professionelle due aux corps radioactifs, Ann. de med. lég. 8: 443, 1928.
41. NORRIS, CHARLES: Personal communication, May 1926.