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THE FATE OF INDIVIDUALS CONTAINING RADIUM

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In 1898, Pierre and Marie Curie separated two new elements from pitchblende. Like uranium, the main constituent of the mineral, they gave off Becquerel rays. There were two of these: one that was carried with bismuth, they named "polonium", and the other, named radium, followed barium in the separation. They set about obtaining more substantive evidence of these elements. In 1902, four years after working over several tons of ore in a shed near the Sorbonne, they had separated about 100 milligrams of radium to a degree of purity that permitted an almost exact determination of its atomic weight.

It was not long before attempts were made to exploit the new material. By 1903 it was known that alpha particles induce scintillations in certain materials such as zinc sulfide, and in 1905 George F. Kunz, a gem expert, obtained a United States patent covering the whole process of producing "cold light", including a general statement of sources of alpha radiation and crystals that may be activated, one of which he renamed "Kunzite".

This process was put to use in Central Europe in about 1908, and some watch dials were painted with radium-zinc sulfide preparations; but these were rather expensive and not many were produced. Between 1913 and 1915 the use of trace elements to enhance luminosity resulted in a rapid development of the dial-painting industry. By 1917, about 300 workers, mostly girls, were employed at a factory in Orange, New Jersey.

Between 1922 and 1924, nine young employees from this factory died after developing severe oral lesions and anemias. Their deaths were certified by different local physicians, with a variety of diagnoses including Vincent's angina, syphilis, phosphorus poisoning, primary anemia, and osteomyelitis. The company became quietly aware of this situation and requested a medical investigation; this was carried out by Cecil K.

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Drinker and William B. Castle; a report was prepared which was not released until later,[1] apparently because of pending litigations. In January 1924 a dentist, Theodor Blum, who had seen one of these girls, made the suggestion in a footnote to a publication[2] that the condition be called "radium jaw". Two publications appeared in the next few months: one by Dr. F. L. Hoffman,[3] who had been engaged by the New Jersey Consumers' League to look into the matter and another by the county medical examiner, Dr. Harrison Martland, whose curiosity had been aroused by Blum's footnote. Martland had, in the interim, interviewed some of the workers, performed an autopsy on the chief chemist of the plant, demonstrated radioactivity in this man and in the exhalations of two living patients. In his paper[4] he included a warning of the danger of delayed lethal effects of internal administration of radioactive materials.

After a two or three year period of litigation, a settlement was reached in 1928, in which awards of $10,000 each and medical expenses were made to the plaintiffs, whose deterioration of health had been reported regularly in the newspapers, accompanied by appropriate rhetoric and photographs. During this period, two or three cases of bone sarcoma had occurred and the factory had been shut down. In 1929 and 1931, Martland wrote his two definitive papers on radium poisoning;[5, 6] the following two decades yielded few clinical publications.

The use of radium-226 as a luminizer has continued under increasingly stringent precautions to avoid internal exposure. Hardly any cases of serious contamination have appeared in individuals who became employed in dial painting after 1925.

It is not surprising that attempts were made to explore the possibilities of such a unique agent for use against intractable ills. Just when the first such attempts took place will never be clear, but injections may have been made as early as 1910. At about that time Standard Chemical Company was organized to extract radium from the carnotite ore of the western states, which had been worked as a source of vanadium. Soon Standard Chemical engaged a physiologist and a pathologist to study effects of injected radium by a series of animal experiments, and in 1913 a report[7] appeared on the injection of four human cases, given between 60 and 500 microcuries (200 microcuries was considered below the amount that would cause anemia). Following this report, several practitioners undertook this form of therapy, and observed that radium injections reduced hypertension, relieved the pain of arthritis and gout, and was useful in the treatment of venereal disease. The confidence with which physicians used this treatment is shown by the fact that several of them administered it as a tonic to themselves and their families. Even in recent years, persons (for example, with an old history of rheumatoid arthritis) have been discovered to contai apparently administered as nameless inje decade of this century.

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arthritis) have been discovered to contain large burdens of radium, apparently administered as nameless injections in the third or fourth decade of this century.

Another widespread mode of administration of radium was by mouth. A former employee of the plant in Orange, New Jersey, and a confidence man of considerable ability, began in 1925 to market a solution of radium and mesothorium salts under the name of Radithor.[8] There seems no way of estimating how much of this material was distributed, but the daily recommended dose (one bottle) cost a dollar a day and was guaranteed to be harmless. In 1927 a well-known industrialist and sportsman suffered a painful fracture by falling out of an upper berth after a Harvard-Yale game, and began taking Radithor. After the fracture healed he continued this treatment because he liked the effects of it, and in 1932 died with necrosis of the jaws and a brain abscess.[9]

This case gained a great deal of publicity and thus had a deleterious effect on the therapeutic use of radium, although the element continued in some favor for a while, and there was a good deal of controversy concerning its harmfulness. Various radium preparations had been listed in the A.M.A. annual *New and Non-official Remedies* during the 1920's and were withdrawn in 1929 by the Council on Pharmacy and Chemistry through an editorial in the A.M.A. Journal,[10] on the basis that their effectiveness in various conditions had not been proven; a subsequent letter to the editor[11] pointed out, as Martland had done four years before, that it is dangerous as well.

A few dozen patients were recorded and studied prior to 1950. In 1952 a publication appeared by Aub *et al.*[12] dealing with 30 radium cases, and in 1955 one by Looney *et al.*[13] including 42 from the Chicago area. Among the total, 14 malignant tumors of bone and air sinuses had appeared at the respective dates of publication. At that time bone tumors were known to occur in rats given radium injections.[14] An examination of available human data had led to the adoption of the one-tenth microcurie maximum permissible burden for persons subject to occupational exposure to radium, which has been used as the basis for other bone-seeking radioelements.

Since the cases described up to that point were obtained in a random way, usually through personal communication channels, there was a high proportion of individuals suffering from gross pathologic changes. It was clear that this might give a false impression of the probability that a given burden would lead to malignancy, so that collection of cases unbiased by clinical selection was needed. The most favorable for such study were dial painters, who were numerous and subject to search as groups from existing records. Cases treated by physicians were for obvious reasons less likely to be found in available records, and in most

cases would not be acquainted with one another.

Three broad studies were instituted in this period: one at Argonne National Laboratory, another at the Massachusetts Institute of Technology, and a third centered at Orange, under the New Jersey Department of Health. Since 1971 these studies have been combined under the direction of the Center for Human Radiobiology at Argonne. The records of the Center include about 5000 individuals believed to have been exposed to internal radium contamination; there is clinical information on most of these and measurements of body radium content on almost 2000.

Clearly, radium-related pathology is most likely to occur in those who carry the largest radium burdens; these are (1) dial painters and other radium workers who were first exposed prior to 1927 (or at latest 1930), and (2) persons receiving radium for therapeutic purposes, i.e. prior to the mid-1930's. However, workers of later periods are also sought and kept under surveillance to avoid missing any more subtle or improbable effects of exposure. Those in the former "at risk" groups are therefore over sixty at the present time, but a majority are still living.

The earliest exposed cases included those exposed to the heaviest contamination, who had died with aplastic anemia and necrosis of the jaws, probably having burdens close to 10 microcuries or higher and having originally absorbed a total in the order of 500 or more. Subsequent to the elimination of these unfortunates, our records show 82 verified cases of osteosarcoma or other sarcomas arising at or near bone surfaces, and 33 cases of nasopharyngeal, nasal accessory sinus, and mastoid carcinoma, as well as a few additional probable or suspected cases.

At present there is an apparent shifting of the ratio: since 1969 the population has yielded one case of osteosarcoma but seven verified mastoid carcinomas. The leukemias that have appeared in the population under observation do not exceed the expected incidence except for a few early chemical workers who were exposed to high doses of external radiation and in most cases are recorded as having skin burns.

Reports from the Center are at present necessarily preliminary because of the high proportion of living persons. This can be illustrated by data on two well-defined groups. In Table I is shown the fate of 94 female dial painters who are in a group photograph, obtained in 1955, of the personnel of a plant in early September, 1924. In the course of extensive interviewing of these individuals and of their contemporaries, all but two of them have been identified; 43 have died and 49 are living, of whom 39 are considered to be in good health at a median age of 71. Sixteen of the dead and four of the living have had "radiogenic" lesions.

The other group includes 28 inmates of a state hospital who were

unsuccessfully treated for schizophrenia by radium injections in 1930. Six of the 28 are living and two are still being sought: the dead are summarized in Table II. This group was measured for radium retention for a few months after injection[15] and repeatedly since 1950,[16] and has been of great value in establishing the long-term retention curve (about 0.5 per cent of the injected dose remains at 45 years). The records indicate that they received radium chloride intravenously, 10 microcurie doses weekly, to totals ranging from 70 to over 400.

It has not been possible to estimate the number of persons who received radium injections during the heyday of this therapy. Radium chloride was usually given intravenously using ampoules containing 10

TABLE I

Status, 1976, of 94 Female Employees Identified in 1924 Group Photograph

(Median age, 22)

43 Dead	49 Living
5 Osteosarcoma	2 Fractures
2 Sarcoma	1 Inop. mastoid
5 Mastoid or sinus ca	1 Cured mastoid and sarcoma
2 Possible mastoid ca	
2 Osteitis	
5 Ca breast	2 Emphysema
4 Ca bowel	2 Stroke
1 Leukemia	2 Arthritis
17 Cardiovascular, etc.	1 Cured breast ca
	(10 infirm)
(2 not identified)	

TABLE II

Present Status of 28 Schizophrenic Patients Given Radium Injections in 1930

(Median age at injection, 22)

	6 Living
Dead:	4 Ca mastoid or sphenoid
	1 Osteosarcoma
	10 Cardiovascular or senility
	2 Tuberculosis
	1 Cirrhosis
	1 Ca bladder
	1 Suicide
Lost:	2

micrograms (microcuries) and injected periodically as in the state hospital study; all of these patients received amounts that resulted in radiologically visible lesions. This practice was widespread and two physicians in private practice have estimated that each injected several hundred patients. It seems likely, in view of the way in which the known cases were found, that there are several times as many, who have not been discovered: (1) There are many persons who are aware that they received radium but for one reason or another fail to mention it in a medical history; (2) it appears that the treatment was such a usual one that patients were often not apprised of the nature of the medications; and (3) many radiologists confronted by the more or less characteristic skeletal effects of radium retention, but without the history, are likely to pass them off as atypical instances of metastatic carcinoma, multiple myeloma, osteoporosis or Paget's disease.

Figures 1 and 2 illustrate characteristic skeletal changes in moderately severe cases, who are at some degree of risk for malignancy. More severe cases may suffer fractures and other complications, of which

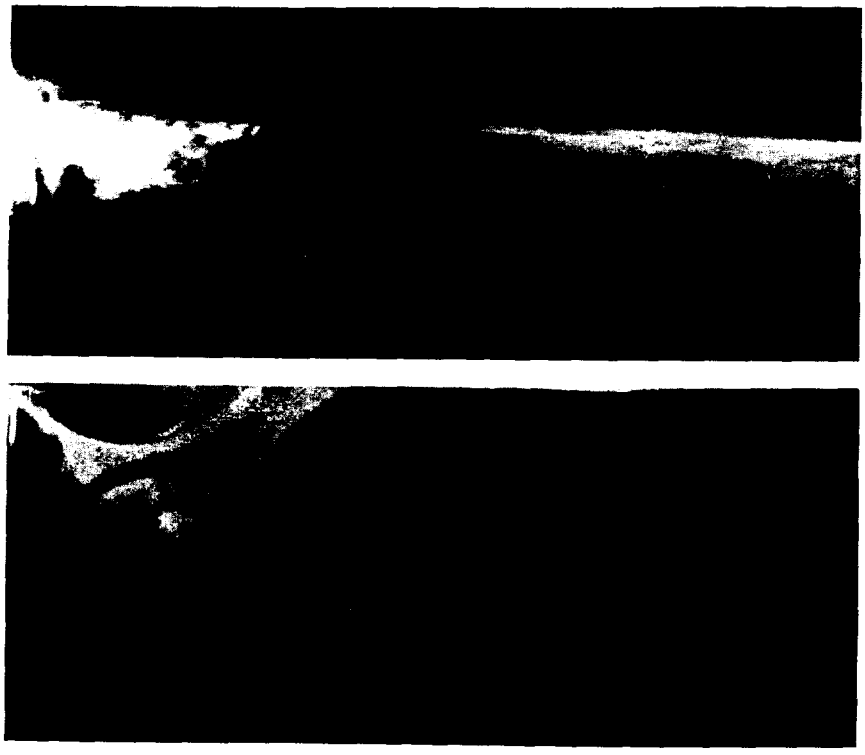

FIG. 1. Radium effects in long bones. (Above) Sclerosis in distal end of tibia. (Below) Lytic lesions in shaft of humerus.

FIG. 2. Multiple lytic lesions in skull. A large area of destruction in the region of the temporal bone is caused by a mastoid carcinoma.

necrosis of the femoral heads is a frequent one. Sclerotic changes in the long bones may generally be distinguished from those occurring in chronic pancreatitis by their symmetrical distribution. The apparently random nature of the lytic lesions is probably due to the distribution of radium in "hot spots" of its initial deposition in osteon formations within resorbed haversian systems.[17]

Although most cases of radium poisoning originated in occupational or "therapeutic" exposures in the period before 1930, the sequelae continue to appear and seem to be changing somewhat in character, with an increasing incidence of mastoid carcinoma. Continuing studies are in order for the light that may be shed on the pathologic effects of transuranic and other bone-seeking radioactive contaminants, and on the quantitative relation between doses and effects.

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