Carcinogenesis by Radioactive Substances*

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Knowledge of the potential dangers of exposure to radioactive substances and the institution of proper safety precautions have helped to reduce accidental exposures to radioactive substances. However, the carcinogenic hazard from them has by no means been eliminated, and, in spite of the exercise of reasonable care and the use of improved techniques, accidents in the laboratory and industry may still occur. Because of the vastly increased scientific usage and the projected expansion of atomic power in industry, the potential hazard will increase in the future.

In the following we shall review briefly carcinogenesis in man by naturally occurring and artificially produced radioactive substances, the lung cancer problem in miners, the development of bone tumors in luminous dial painters and in patients treated with radium-containing nostrums, and the development of cancers in patients who received thorotrast (ThO₂) as a diagnostic procedure several decades ago. We shall also review some of the experimental work which indicates the extensiveness, the limitations, the problems, and the prospects associated with the use of radioisotopes as carcinogenic agents. Finally, brief consideration will be given to the external use of radioisotopes and to the "fall out" problem.

GENERALITIES

Tumor induction by ionizing irradiation can be brought about (a) by direct action (as in skin, bone), (b) by indirect action (as ovarian and mammary tumors, and leukemias), and (c) by co-carcinogenic action. In the last instance isotopes are presumed to condition another force or be conditioned by one (as aseptic or microbial inflammation, fractures, carcinogenic hydrocarbons).

Radioisotopes may induce neoplasms by a predominantly local action without exerting a systemic effect. This may be explained in part by the tendency of certain isotopes to concentrate in specific loci in the body, and in part by the general protection afforded by relatively undamaged tissues. On the other hand, some isotopes, such as P³⁰⁰, that are widely distributed in the body can produce leukemia in susceptible animals. Also, destruction or depression of one organ may initiate changes in another organ. For example, radiothyroidectomy in mice leads to the development of pituitary tumors. This is the consequence of sustained stimulation of thyrotropes which continue to proliferate in the absence of the thyroid. Likewise, ovarian depression by irradiation leads to stimulation of gonadotropes which in turn cause tumorous changes in the irradiated ovaries. The precise role of ionizing irradiation in this type of carcinogenesis is controversial. It is now widely accepted that, in the induction of tumors of endocrine glands, a direct mutagenic radiation effect plays little if any role, and that an indirect specific hormonal imbalance is essential for their development.

Tumor induction is influenced by mitotic activity only in a limited sense. A rapid rate of replacement of injured cells does not necessarily indicate likelihood of tumor formation. For instance, the replacement rate of epithelial cells of the cornea and of the small intestine is high, yet they do not give rise to tumors. On the other hand, growing human bone is more radiosensitive than resting bone. If the cell in mitosis is an end-cell, injury to it will not cause a cancer; if it is a reserve cell, it may.

Some other basic factors determining the induction of cancer are: (a) the half-life of the isotope, (b) the amount retained in the body, (c) the character and dose of irradiation emitted, (d) the char-
acter of decay products, (e) the individual sensitivities of cells and tissues, (f) degree of protection afforded by nonirradiated cells in the irradiated host, and (g) a variety of other known and unknown co-carcinogenic factors.

The belief that long-continued and repeated application of radiation is essential for carcinogenicity is fallacious, as the effects of instantaneous exposures to atomic bombs indicate. When exposures are repeated, the dose rate, the interval between doses, and the total dose all are important, and the response will vary with different types of cells. There can be additivity or synergism, or apparent antagonism. Evidence is accumulating in favor of the theory that carcinogenesis is a multistage process. Small doses of a carcinogen may cause hidden changes which become manifest when the cells are exposed to a second stimulus.

The carcinogenic response varies so widely with species and strains that the liability of man to develop certain neoplasms will be learned only from observations on man. Animal experiments help in the understanding of the underlying basic mechanisms and in obtaining leads on possible events in man, but direct extrapolation of data among species is not permissible.

**Uranium Mining and Milling and the Lung Tumor Problem**

Mining and processing uranium ores in the United States is a recent, rapidly expanding venture. The median Rn concentration found in the unventilated mines of Colorado Plateau is higher than the median concentration reported in the U ore mines of Bohemia and Saxony (20), where pitchblende has been mined for centuries. Sufficient time has not elapsed to allow lung cancer to become a problem in the American mines, but it has long been a controversial problem in the European pitchblende mines (73, 74, 83). This controversy is due in part to inadequacy of the available records. According to one of the last available reports, 180 miners in Jáchymov (Joachimsthal), Bohemia, received compensation for lung cancer during the 4 years between 1939-43 (83). That is more than half the number of miners employed there 10 years earlier. Of thirteen Jáchymov miners examined at autopsy in 1939-39, nine had pulmonary cancers and only four were cancer-free (73). The time spent in mines by patients with cancer range from 13 to 23 years. Two were working until shortly before death, and seven had been out of work for periods of from 1 to 27 years. Evidence of anthracosis and silicosis were minimal. Later, Šíkl (83) stated that, of 52 deaths, twenty were caused by carcinoma of the lung.

One explanation offered for the extraordinary frequency of lung tumors in the uranium miners of Schneeberg and Jáchymov was that of Lorenz (61), who believed that the Rn concentration in the air was not great enough to be carcinogenic and postulated the essentiality of some contributory factors, such as chronic respiratory disease, inhaled ore dust, or heredity. Evans maintained that the Rn concentration in the air of the mines (averaged 3 x 10^-12 curies/cc; tumor dose about 3000 rem [roentgen equivalent mammal]) was the chief factor in the production of lung cancers in these miners (22-24).

While the greatest potential radiation hazard comes from Rn and two of its alpha-emitting daughters, dust particles also may contain and collect radioactive material, be inhaled, and become fixed in the lungs. Solid daughters of Rn become attached to the bronchial epithelium as well as to dust, and thus ventilation and dust control are basic safeguards.

In a consideration of carcinogenesis by particular matter, there is the problem of lack of uniformity in distribution. For bone-seeking metals, a tenfold difference in concentration is used in calculations. From the distribution of anthracotic material in the lungs, it is apparent that minute foreign particles have a tendency to pile up in certain loci. It is highly probable that the pulmonary cancers produced by radioisotopes result from a local action of radioisotopes fixed in such loci. The lung cancers in the miners, like lung cancers in man in general, arise mainly in the bronchi. According to Evans “the tissue dose of alpha-radiation delivered to the bronchial epithelium is greatest in the larger bronchi” (33). It should now be possible to quantitate, by autoradiographs of lungs of uranium miners, the amount of radioactivity in different loci of the respiratory tract, as was done with bone tumors induced by Ra (60). Experimentally, this problem has not been studied adequately. This is owing in part to lack of an experimental animal susceptible to lung tumors similar to those of man.

Although the reported isolated instances of lung tumor among workers in radium laboratories in Europe (Neizel, see Lorenz [61]) are of little statistical significance, the four cases of squamous-cell carcinoma of paranasal sinuses among the dial painters are probably due to Rn and are somewhat analogous to the lung tumors of the miners. The dose of Rn is small but inflammation of the sinuses may have facilitated fixation of Rn or acted as a co-carcinogen. This relationship, first indicated by Lacassagne and associates, has been discussed elsewhere (30).
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NEOPLASMS CAUSED BY RADII AND MESOTHORIUM IN MAN

Martland's description of osteogenic sarcoma in the radium dial painters (1925) served as a warning to curtail the industrial and therapeutic use of radium (66). The technic of dial painting was changed, and the use of radium water orally and injection of radium chloride for treatment of various diseases were discontinued. However, in all of those who had been exposed previously, the hazards of late effects persist.

Aub et al. (5) reviewed 30 cases of radium poisoning in which they estimated the radium content. There had been ten deaths in this group at the time of this report; eight were caused by malignant tumors. Data on these cases are shown in Table 1.

The radium paints for luminous watch dials and the medicinal radium waters contain variable amounts of mesothorium (MsTh), an isotope of radium with the same chemical but different decay characteristics. The decay products of the two are somewhat differently distributed in the body, and this may explain in part the great variation in tumorigenesis in relation to quantity of radioactivity found in the body.

Looney reviewed 36 patients who were treated with radium chloride and fourteen luminous dial workers (58). All patients who have 1 μg. or more of Ra in their bones have roentgenographic evidence of changes in bone density. Thus far, four malignant bone tumors have developed in the 36 patients given Ra medically and three malignant bone tumors in the fourteen luminous dial workers (Table 1).

Autoradiographs (60) show a random distribution of radium in trabecular bones and concentration of radium in the cementing lines and Haversian systems of compact bone (Fig. 1). The radium seems to be deposited in areas that were metabolically active at the time of administration or redistribution of Ra. The areas of more uniform and less dense deposition were probably the result of inorganic ion exchange (80). The areas of microscopic bone destruction do not always correspond with those of radium deposition.

In general, the tumor incidence (20 per cent) and average latent period (19.5-31 years) in persons with Ra and MsTh poisoning varied but little with different degrees of radioactivity (1 to < 10 μg.). The problem of radium storage in relation to tumor incidence is interesting but involved. Patients vary in their ability to store radium and in their response to it. Aub et al. (5) cited cases of three patients in whom radium contents of 10-23 μg. were stored for from 20 to 25 years without serious interference with health, while tumors developed in other patients with a Ra burden of but 1 μg. Individual differences in sensitivity, or perhaps the relative concentrations of MsTh and Th admixed with Ra, account for these remarkable differences. There is some uncertainty about the doses because of absorption of Rn on glass surfaces and errors in technics.

From the physical standpoint, Evans (23) and, more recently, Spiers (84) made a thorough study of these cases, and much of our present knowledge of energy levels of bone-seeking isotopes that are carcinogenic is based on their calculations. Some of the essential data in relation to tumor induction by Ra in man are stated by Aub et al. (5). Ra, much like Ca, is semipermanently deposited in bone.

According to Aub et al. (5) and Evans (22) the daily rate of Ra excretion is estimated at about 0.005 per cent of the total present in the body. The total Ra content in fatal cases was 1-5 μg. The average Ra content of dry bone was 1.5 X 10^9 gm. Fifty-five per cent of Rn and its decay products (RaA, RaC) were retained in bones. Two to 10 rep (roentgen equivalent physical) of alpha/day for 10-15 years is estimated to cause cancer in one-half to one-tenth of the exposed people; this delivers a total of about 7000 rep = 35,000 rem. The Ra burden of one-fifth of these produced cancer in man.

The maximum permissible burden of a bone-seeking alpha-emitter, expressed as Ra, was reconsidered by Spiers (84) in the light of the calculated dose rates to osteocytes and of the relative biological efficiency of alpha radiation, for which a factor of 20 is proposed by the International Committee of Radiation Protection. Difficulties of calculation result in part from lack of uniformity of radiation. The radiation dose to osteocytes

TABLE 1

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Ra (μg.)</th>
<th>Exposure type</th>
<th>Death (Years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma, humerus</td>
<td>8-9</td>
<td>Therapeutic injection</td>
<td>23</td>
</tr>
<tr>
<td>&quot; , tibia</td>
<td>6.3</td>
<td>Dial painting</td>
<td>27</td>
</tr>
<tr>
<td>&quot; , finger</td>
<td>0.8</td>
<td>Therapeutic injection</td>
<td>28</td>
</tr>
<tr>
<td>Giant-cell sarcoma, jaw</td>
<td>1.0</td>
<td>Dial painting</td>
<td>15</td>
</tr>
<tr>
<td>Fibrosarcoma, knee joint</td>
<td>5-6</td>
<td>Therapeutic, oral</td>
<td>17</td>
</tr>
<tr>
<td>Squamous carcinoma, sinus</td>
<td>10</td>
<td>Dial painting</td>
<td>19</td>
</tr>
<tr>
<td>Squamous carcinoma, sinus</td>
<td>2-9</td>
<td>&quot;</td>
<td>34</td>
</tr>
<tr>
<td>Squamous carcinoma, sinus</td>
<td>1.0</td>
<td>&quot;</td>
<td>34</td>
</tr>
<tr>
<td>Osteosarcoma, femur</td>
<td>3.8</td>
<td>&quot;</td>
<td>32</td>
</tr>
<tr>
<td>&quot; , elbow</td>
<td>0.5</td>
<td>&quot;</td>
<td>30</td>
</tr>
<tr>
<td>&quot; , ischium</td>
<td>1.3</td>
<td>&quot;</td>
<td>30</td>
</tr>
<tr>
<td>Fibrosarcoma, foot</td>
<td>1.3</td>
<td>Therapeutic injection</td>
<td>22</td>
</tr>
<tr>
<td>Osteosarcoma, tibia</td>
<td>0.8</td>
<td>&quot;</td>
<td>24</td>
</tr>
<tr>
<td>&quot; , vertebrae</td>
<td>6.8</td>
<td>&quot;</td>
<td>?</td>
</tr>
<tr>
<td>&quot; , tibia</td>
<td>5.6</td>
<td>&quot;</td>
<td>24</td>
</tr>
</tbody>
</table>

* After exposure.
was calculated by Hoecker and Roofe (44), utilizing alpha track radiographs made on preserved bones of dial painters who had died 20 years earlier. The maximum concentration in their samples was 7 times more than the average for the skeleton as a whole. If osteocytes are regarded as a "limited volume of tissue" to which the higher permissible dose rate of 1.5 r/week is allowed, the permissible Ra burden may be 0.1 µg. (Spiers [84]). This burden in the skeleton will deliver to osteocytes 1.6 rem per week -0.08 rep). An estimated 0.4 rem/week will be delivered to bone marrow and 0.03 rem/week to blood.

The relative efficiency of a-rays for carcinogenic action is not precisely known, nor is the mechanism by which radiation induces malignant changes, and therefore all estimates are crude. Ionizing radiations are known to produce gene mutations and structural damage to chromosomes. According to Lea (56), a-rays may be one-third as effective as x- or γ-rays in the production of mutations, but, according to Gray (41), they are more effective in causing chromosome damage.

Similarly, little is known about the morphogenesis of bone tumor development. Since bone tumors induced by radioisotopes are autonomous, the basic change is to be sought in an irreversible change in osteocytes. Modifications in osteocytes as a consequence of irradiation have, to our knowledge, not been investigated, and the known radiation-induced non-neoplastic changes in bones may be merely incidental. The latter may be caused by damage to nutrient vessels. One such lesion is aspetic necrosis of bone. The other, so-called "radiation osteitis," is a diffuse fibrosis of the marrow with disorganization of hemopoietic structures, infiltration of inflammatory cells, resorption of bone by osteoclasts, and some atypical bone formation. Neither of these lesions is localized entirely to regions of greatest alpha activity.

Experimentally, numerous investigators have demonstrated the ability of Ra and MsTh to cause osteosarcoma by intravenous administration in rabbits (see 30) and by oral administration in rats (see 30). In these animals tumors appeared as early as 1 year after administration of the carcinogen, while in man tumor formation required 10 years.

Implantation of Ra- or Rn-filled sealed tubes caused fibrosarcoma and carcinoma but not bone sarcoma. Bone sarcoma is favored only by intimate contact of "bone seekers" with osteoblasts.

While Ra is essentially a bone-seeker, some decay products of Rn, notably Po, cause severe, often fatal, kidney damage. Hyperchromatic cells, many with bizarre giant nuclei, are present in these kidneys, but these cells do not seem to proliferate (Hollcraft et al. [45] and Casarett [18]) (Fig. 2). This change is analogous to that seen in thyroids damaged by I131 and other sites of radiation in that they possess hyperchromatic, large, often bizarre-shaped nuclei (cf. 64, 65) (Figs. 3 and 4). The abnormal cells resemble neoplastic cells, but are not known to give rise to tumors. It is possible that they are permanently altered cells (radiation mutants) but do not possess the intrinsic growth power of fully autonomous cells, or are restrained from proliferation by the desmoplastic reaction caused by irradiation. (The latter could be tested experimentally by transplantations in normal hosts.) Similar, but reversible, chromatin abnormalities can, however, also be induced by folic acid deficiency.

In the experiments of Casarett (18), the nephrosis caused by the alpha-emitting Po terminated in nephrosclerosis, with formation of adenomas. Did these adenomas result from attempted regeneration of injured tubules or from radioactivity? They remind us of the renal tumors induced in hamsters by estrogens and of adenomas in sclerotic human kidneys. The character of these renal tumors and those in the adrenal medulla, described by Casarett (18) as late effects of Po damage, require elucidation.

**Thorium Dioxide (Thorotrast)**

Introduced in 1928 as a contrast medium in radiography, ThO2 became the most widely used radioactive substance before artificial radioisotopes were available. When injected into the blood stream, it is phagocytosed by the reticulo-endothelial (RE) system, chiefly of liver and spleen. Very recently, Looney et al. (58, 59) reviewed the status of 35 people who received 3–15 gm. of thorotrast intravenously for diagnostic purposes. With increasing time, larger and larger aggregates of thorotrast were demonstrated in the RE cells. These aggregates were usually 10–100 microns in diameter, but some were as large as 1–2 mm. Because of the short range of the alpha tracks, aggregation of thorotrast particles is accompanied by marked reduction of biologic efficiency. Evans (23) calculated the liver dose of alpha radiation after intravenous injection of thorotrast to be 1.5–5 rem/day. Tissue containing 1 per cent thorotrast would then receive 3000 rep or 15,000 rem in 10 years, an amount comparable with the carcinogenic dose in chronic radium poisoning.

MacMahon et al. (63) described a patient with endothelial-cell sarcoma of the liver in the vicinity of thorium deposits, who died 12 years after receiving thorotrast. This was the first well docu-
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mented instance of tumor induction by this isotope.3

Because the greatest concentration of ThO2 is in the spleen, it might be expected that neoplasms would occur most frequently in this organ, as Looney et al. remarked (59), but no tumors have been reported in the spleen; nor have they been noted about the dense granulomas which formed at sites of extravasations at sites of injections (59). On the other hand, five neoplasms have been reported about ducts or sinususes into which thorotrast was injected: two in the lacrimal duct, one in the maxillary sinus, one in the renal pelvis, and one in the mammary duct. In the liver, five tumors were observed (Table 2).

The long latency of carcinogenesis by ThO2 is evident from all reports. Cancers are still appearing in scattered regions of the body three decades after use of the isotope. The tumor induction rate is low, for, considering the large number of people who have received ThO2, the total number developing tumors is small. Squamous-cell carcinoma developed on the eyelid of a man 85 years after injection of ThO2 in the lacrimal duct. The excised tissue was estimated to have delivered 1.5 r/day or 20,000 r in 25 years (Rudolph [80]). A similar tumor was found in the maxillary antrum of another man 10 years earlier (Hofer [43]); a carcinoma of the lung was noted 18 years after bronchography with ThO2 (1). These and other cases have been well reviewed by Looney et al. (59), who have also discussed the uncertainty of the causal relation between leukemia and administered thorotrast in the few reported cases.

ThO2 administered to man for visualization of vessels caused vascular changes that are likened to thromboangiitis obliterans and arteriosclerosis. The vascular changes may, to some extent, have counteracted the tumor-producing properties of the ThO2.

Before the discovery of the carcinogenic hydrocarbons, ThO2 was perhaps the best available carcinogen. Carcinomas and sarcomas, including osteosarcomas, were induced with it in rats, guinea pigs, and rabbits. This early work (see 30) demonstrated the relative responsiveness of different adult tissues to this radiocarcinogen. The basic findings were duplicated later with hydrocarbons and more recently with artificial radioisotopes.

ARTIFICIAL RADIOISOTOPES

While the old observations were empirical, and mainly qualitative, research in the post-nuclear fission era has become more quantitative. Present-day projects are apt to be designed to yield information on tumor production in relation to dose, dose rate, type of radiation, on biologic effectiveness, and on synergistic, antagonistic, and other factors which modify the biologic effectiveness of radiation.

Table 3 shows the quantity and kind of isotopes shipped by the AEC for medical and industrial uses since 1946 and their reported carcinogenicity.

With the exception of Co60, which is used only in sealed containers for external irradiation, all those detailed have been tested for carcinogenicity. C14 is not carcinogenic and Au198 colloid causes only adenomas of the liver.

### TABLE 2

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Site</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma</td>
<td>Kidney pelvis</td>
<td>16</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Lacrimal duct</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>Maxillary sinus</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Mammary gland</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>?</td>
</tr>
<tr>
<td>Cholangioma</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Hemangi...</td>
<td>endothe...</td>
<td>23</td>
</tr>
</tbody>
</table>

* Abbreviated from Looney et al. (59). † After administration of thorotrast.

**Phosphorus-32.**—P32 is one of the radioisotopes most frequently used clinically. Will it increase the leukemia incidence in man? Leukemias developed in four (3 per cent) of 148 polycythemic patients treated with P32 and observed by Stroebel and Pease (85) over a 10-year period, one of chronic and three of acute myeloid type. This is not a convincing figure, for polycythemia sometimes terminates in myeloid leukemia as if the latter were a natural developmental phase of polycythemia. There are not enough data to know how often this occurs: (a) without any treatment, (b) after use of an erythrolytic agent, (c) after total or partial body x-radiation, and (d) after use of P32.

The fact that all four leukemias observed by Stroebel and Pease were myeloid could relate these to either polycythemia, a disease of the marrow, or to irradiation. Most leukemias among the Japanese exposed to atomic bomb were myeloid, and most of them were acute (54, 68).

Life-span studies in animals on the carcinogenicity of internally administered P32 were conduct-
ed in two laboratories, one by Koletsky et al. (51)
in rats, the other by Brues et al. (12) in mice.

Brues et al. (12) showed that, with respect to
leukemogenic effects in mice, P³² is a carcinogenic
stimulus comparable with x-rays. It is effective
whether given in single or in fractionated doses.
Increasing doses are more effective until a satura-
tion value is reached. There is also evidence for a
threshold dose and dose rate below which tumors
was a distinct reduction of the latent period when
the dose was increased. The threshold was sharp, 1
µc/gm causing tumors in 32 per cent of the rats,
and 0.5 and 0.25 µc/gm producing none. All squa-
mous-cell carcinomas occurred in rats receiving the
largest dose and, with one exception, originated
about the nasopharynx. It is noteworthy that in
the rat P³² caused the development of bone tumors,
to which the strain used shows some susceptibility,

### TABLE 3

**Radioactive Isotope Distribution Data**

(August 2, 1946 to May 31, 1955)

<table>
<thead>
<tr>
<th>Isotope, Half-life</th>
<th>Radiation MEV</th>
<th>Cumulative Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine-131 8.0 days</td>
<td>0.303</td>
<td>285</td>
</tr>
<tr>
<td>Phosphorus-90 14.3 days</td>
<td>0.695</td>
<td>86</td>
</tr>
<tr>
<td>Carbon-14 5740 years</td>
<td>0.050</td>
<td>3</td>
</tr>
<tr>
<td>Sodium-24 14.9 hours</td>
<td>0.540</td>
<td>3</td>
</tr>
<tr>
<td>Gold-198 2.69 days</td>
<td>0.320</td>
<td>104</td>
</tr>
<tr>
<td>Tritium-3 0.006</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Strontium-89 125 days</td>
<td>0.500</td>
<td>30</td>
</tr>
<tr>
<td>Strontium-90 25 years</td>
<td>0.320</td>
<td>1</td>
</tr>
<tr>
<td>Cobalt-60 5.2 years</td>
<td>0.099</td>
<td>5900</td>
</tr>
<tr>
<td>Cesium-137 37 years</td>
<td>0.170</td>
<td>219</td>
</tr>
<tr>
<td>Iridium-192 70 days</td>
<td>0.250</td>
<td>236</td>
</tr>
<tr>
<td>Polonium-210 138.3 days</td>
<td>0.8</td>
<td>113</td>
</tr>
</tbody>
</table>

**Experimental Carcinogenicity**

<table>
<thead>
<tr>
<th>Isozors</th>
<th>Half-life</th>
<th>Energy</th>
<th>Cumulative Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid, pituitary</td>
<td>8.0 days</td>
<td>0.303</td>
<td>285</td>
</tr>
<tr>
<td>Bone, skin, leukemia</td>
<td>14.3 days</td>
<td>0.695</td>
<td>86</td>
</tr>
<tr>
<td>Liver (adenoma)</td>
<td>125 years</td>
<td>0.320</td>
<td>1</td>
</tr>
</tbody>
</table>

### TABLE 4

**Carcinogenicity of P³² in Rats**

<table>
<thead>
<tr>
<th>Dose (µc/gm wt.)</th>
<th>No. positive</th>
<th>Per cent positive</th>
<th>Squamous carcinoma</th>
<th>Osteosarcoma</th>
<th>Latency (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.52</td>
<td>9/19</td>
<td>73</td>
<td>3</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>3.5; 3.0</td>
<td>12/24</td>
<td>36</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>4/13</td>
<td>31</td>
<td>0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>6/19</td>
<td>32</td>
<td>1</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>0.5; 0.25</td>
<td>0/43</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*From Koletsky et al. (52), abbreviated.*
† Shortest latency, 7.5; longest, 25+ months.
‡ 18,000 rep = LD₉₀ for mice; 10× therapeutic dose in man.

are not induced. More recently, Finkel³ noted that
P³² also causes a few osteogenic sarcomas in mice.

In rats, on the contrary, P³² readily produces
osteogenic sarcomas and squamous carcinomas but
no leukemias (Table 4). Koletsky and Christie (52)
found that single doses of P³² in the LD₉₀ range
(4.5 µc/gm body weight) and smaller doses pro-
duced osteogenic sarcomas or squamous-cell car-
inomas, or both, in more than one-third of the
animals tested. The threshold tumorigenic dose
was about one-fifth of the LD₉₀ (0.5–1 µc). There

³ M. P. Finkel, personal communication to the authors.

while in mice it caused leukemias, to which the
strain used was susceptible. In assaying a radio-
active substance for carcinogenicity, it may be
worth using many strains of animals of different
species with different liabilities. Not the specific
isotope, but the quantity incorporated per cell, the
type of cell, and the stage at which it is affected
are the determining factors in the host response.
The 0.5-µc. dose (that is, one-half of a strongly car-
icinogenic dose in rats) approaches the average
therapeutic dose in man. If the calculations indi-
cating that man is more sensitive to bone tumor
induction than small laboratory animals are ac-
cepted, the therapeutic dose for man may well be
within the carcinogenic range. The use of different
strains and species may disclose an even broader
spectrum of carcinogenicity of P³².

Moore et al. (70) attempted to produce adeno-
carcinomas by instilling P³² into the stomach of
mice in thin latex balloons. All five tumors pro-
duced were squamous carcinomas, arising from the
forestomach. The only consistent change provoked
in the mucosa of the glandular stomach was that
of degeneration and radionecrosis. Adenocarcino-
mas of the stomach are yet to be produced by any
Gold-198. — When colloids of relatively large particle size gain entry into the blood stream, they readily disappear from it and are deposited in the liver and spleen. Those of smaller particle size disappear much more slowly and are deposited primarily in the bone marrow and spleen, and to a lesser degree in the liver. Colloids of Au¹⁹⁸ and of other radioactive elements are being used in experimental therapy. They are introduced by different routes chosen to provide greater concentration of radioactivity at desired sites. The possibility of producing neoplasms of Kupffer cells by sublethal doses of colloidal Au¹⁹⁸ has been explored without success (88), with a strain of mice in which reticulum-cell sarcoma is common. Cirrhosis was produced (53), as was done earlier in the dog by Hahn et al. (42). Benign liver cell tumors developed in 10–25 per cent of the mice in the series of Upton et al. (88), but there were no carcinomas. Cirrhosis and adenomas of the liver are precancerous lesions, and it is still possible that, by repeated administration of Au¹⁹⁸ colloid with the proper host, dose rates, and stimulating co-factors well chosen, liver carcinomas and reticulum-cell sarcomas could be induced.

The cells in which the radioactive substances localize must receive a tremendous amount of radiation. If the dose is large, these cells die, the radioactive substance is released, recirculated, and taken up again by similar cells. This sequence of events has been demonstrated by Gabrieli and Cutler with colloidal Cr¹⁹³O₄ (53). It is remarkable that, in spite of the heavy exposure of RE cells to varied quantities of radioactive substances, neoplasms of these cells have not been induced.

While Au¹⁹⁸ colloid by itself has little carcinogenic power for the liver, when combined with an azo-dye carcinogen it enhances the carcinogenicity of the latter (Williams et al. [90]). The situation is remarkably similar to the carcinogenic activity of I¹³¹ in the thyroid. I¹³¹ given alone is only mildly carcinogenic, but when combined with goitrogen it becomes highly carcinogenic to the thyroid.

The tentative generalization may be worth considering that carcinogenesis by ionizing irradiation is a multi-stage process. Ionizing irradiation may produce a chromosomal alteration allied to mutation, and some cells so altered may be potential cancer cells. Without further stimulation they remain in situ, may produce a few abnormal cells, but ultimately die without producing a cancer. When, however, such cells are subjected to a growth stimulant of the respective cell, a cancer eventuates. This concept is similar to that postulated for cutaneous carcinogenesis by different agents by several investigators (Rous and Kidd [76], Rusch [78], Tannenbaum [86], Berenblum [7], etc.).

Iodine-131. — The widespread use of I¹³¹ in treatment of carcinoma of the thyroid and depression of thyroidal function in hyperthyroidism and hypertensive heart disease raises the question whether cancer of the thyroid or of adjacent organs might result from the therapeutic use of I¹³¹. Thus far it has not, but the possibility of such a change in man is recognized.

There are numerous reports of the effects of I¹³¹ alone, in rats, mice, and other species, but only one on the development of carcinoma of the thyroid. Therefore, the report by Goldberg and Chaikoff (35, 36) is worth closer scrutiny. In seven of 25 young rats of the Long-Evans strain that received a single injection of 400 μc. of I¹³¹, carcinomas developed, some with metastases, 1.5 years to 2 years after injection. Adenomas occurred in two others. In contrast, larger numbers of rats that were given radioiodine by other investigators and observed for adequate periods of time had many thyroid adenomas but no carcinomas. It is possible that the thyroid of Long-Evans strain is especially sensitive to ionizing radiation, or that some undetected co-carcinogenic force was at play. The work of others has amply shown the synergistic effect of goitrogens. The dose of I¹³¹ was well chosen by Goldberg and Chaikoff (35). It is one that causes profound damage but also leaves some thyroid tissue apparently unchanged. These conditions are also fulfilled in the treatment of patients with I¹³¹ for hyperthyroidism or heart disease. Some thyroid epithelial cells are killed, but others are not harmed. Those receiving in-between doses are most likely to undergo a malignant change.

Are the carcinomas induced in rats by a direct mutagenic effect of I¹³¹, or do excessive amounts of thyrotropin (TSH) play a significant role in their genesis as they do in cancers arising in goiters? Most residual cells are atypical. A few cells appear stimulated, and a high blood level of thyrotropin is known to follow thyroidectomy. The lack of high TSH levels in patients with autonomous thyroid carcinomas is not surprising, since malignant cells often free themselves from the forces controlling normal growth and secrete less hormone than do their normal precursors. On the other hand, this finding does not exclude some role of TSH excess in their genesis. Regenerated functioning thyroid follicles would inhibit TSH production, and thus normal and abnormal thyroid cells could co-exist.

In partially radiothyroidectomized animals, ab-
sence of thyroid hyperplasia in spite of TSH excess appears to be the rule. The rudimentary and abnormal thyroid follicles are usually embedded in excessive connective tissue, and the nutrient arteries are markedly stenosed. These changes may in part be responsible for lack of adequate compensatory hyperplasia. Maloof et al. (64, 65) found that these thyroids fail to enlarge in response to the administration of thiouracil in spite of persistent hypertrophy of some cells. They found only one adenoma of the thyroid in 500 rats studied, indicating that radioiodine lowers the proliferative capacity of thyroid cells.

Bizarre thyroid cells in I\textsuperscript{131}-treated animals were noted by all investigators. Thiouracil accentuates atypicity (Doniach [19]). Some cells appear to be somewhat functionally active and capable of undergoing hypertrophy but seldom hyperplasia, so that the compensated thyroid will be small with large cells.

Following subtotal surgical resection, remnants of the thyroid fail to regenerate into a normal-sized gland. The compensating organ is small with hyperfunctioning cells, usually in adenomatoid arrangements. The bizarre hyperchromatic cells of the irradiated thyroid are lacking.

The induction of carcinoma in thyroid after administration of I\textsuperscript{131} is not a simple matter of direct carcinogenesis by ionizing irradiation. Maloof et al. (65) and Doniach (19) estimated that in rats 50 \textmu C. delivers a total dose of 80,000 rep, and 100 \textmu C. 60,000–197,000 rep. Were direct radiation alone responsible for the induction of malignant thyroid tumors, they would have occurred in many rats and mice receiving doses larger than 50 \textmu C.

Administration of I\textsuperscript{131} is often combined with an antithyroidal drug. Doniach (19) tested the carcinogenic potency of 5, 30, and 100 \textmu C. of I\textsuperscript{131} on the thyroid of rats, alone and in combination with a subsequent course of methylthiouracil. Thiouracil itself produced adenomas only. I\textsuperscript{131} increased the formation of adenomas in the 5- and 30-\textmu C. but not in the 100-\textmu C. group. In five of the twenty rats that had been given 30 \textmu C. of I\textsuperscript{131} and methylthiouracil, carcinomas developed. The radiation dose range to the thyroid in the 30-\textmu C. group was 2,270–16,200 rep. The 9,000 rep usually given to patients with Graves' disease is within this range. Apparently, ionizing radiation causes an irreversible pre-neoplastic alteration in the thyroid cells which becomes evident when these cells are brought to proliferation by a second agent which is a powerful growth-stimulant but has, in itself, only minimal carcinogenic capacity.

Carcinomas originating in I\textsuperscript{131}-treated rats are likewise dependent tumors. It is noteworthy in this connection that most tumors induced by endocrine imbalance are dependent neoplasms. This points to a probably basic difference in the character of thyroid tumors induced by goitrogens and those induced by ionizing irradiation. The former are probably dependent and are induced by an abscopal mechanism, while the latter are autonomous and are probably induced by a direct mutagenic effect.

Doniach estimated that the 8,000–10,000 rep dose required to cause remission in Graves' disease in man is in the carcinogenic range, and the possibility of late development of thyroid carcinoma in patients given thyroid-depressing doses of I\textsuperscript{131} must be reckoned with. Nevertheless, this hazard alone should be no more of a deterrent to the use of I\textsuperscript{131} than is the rare occurrence of carcinomas and sarcomas at sites of irradiation following therapeutic use of x-rays. However, treatment with thiouracil combined with radiation appears highly hazardous.

It is remarkable that in mice I\textsuperscript{131} does not produce carcinoma of the thyroid. The number of animals exposed by different investigators within the theoretically effective dose range and observed for 1–2 years probably amounts to several hundred. The most likely carcinogenic dose in mice is about 10–50 \textmu C. In our experience small adenomas are common, but not carcinomas. Although the abnormal cells morphologically resemble cancer cells, they do not seem to possess the intrinsic power to proliferate as cancer cells. Their functional inadequacy is indicated by failure to capture I\textsuperscript{131}.

The carcinogenic hazard of radioiodine therapy appears to be due in part to direct neoplastic transformation of thyroid epithelium and to the production of some irreversible change of thyroid epithelium which renders it sensitive to excessive stimulation. Interference with thyroxin synthesis or mere lack of I\textsuperscript{131} (6) causes increased output of TSH, which is a specific growth stimulus to the thyroid.

Once a chromosomal alteration is introduced in a cell, time is needed for that cell to unfold all the potentialities conferred upon it. In the mouse, the life span is about 2 years, but for theoretical purposes the period of exposure can be prolonged by grafting the exposed thyroids on new hosts similarly stimulated. By this technic, the changes which occur in one generation can be simulated in a host with longer life expectancy. Making use of this method, Morris et al. (71) were able to produce malignant tumors in mice with thiouracil alone. But even these tumors were conditioned neoplasms at the start. In man, there are decades available for disclosure of malignant features in...
the original host. Several decades will be required before it will be known whether radiothyroidectomy is carcinogenic in man.

In the meantime the principles for I\textsuperscript{131} treatment enumerated by Doniach (19) are worth citing: (a) treat patients under 45 only if other methods have failed or when life expectancy is under 80 years; (b) minimal dose of I\textsuperscript{131} should be administered; and (c) thyroxine medication should be instituted after the thyrotoxic symptoms are relieved in cases of Graves' disease, or after all responsive cells are destroyed in cases of cancer. It should be remembered that thyroxine counteracts and TSH promotes this type of carcinogenesis.

Structures adjacent to the thyroid also receive near-carcinogenic quantities of irradiation. Cancer of the larynx was described occurring 8 weeks and 11 months after treatment with 180 and 51 \mu c. of I\textsuperscript{131}, respectively (87). The latency period of tumor development was too short in these cases to accept radiothyroidectomized C57BL mice, which are highly susceptible to leukemogenesis by ionizing radiations.

It should be recalled that x-ray therapy of the thyroid is also not without carcinogenic hazard. Sarcoma developed in the thyroid region in a woman 30 years after radiotherapy for thyrotoxicosis, squamous-cell carcinoma of the hypopharynx and larynx in another patient, and a fibrosarcoma of the esophagus in a third (see 30, 31). 

**Pituitary tumor induction by I\textsuperscript{131}.**—Although I\textsuperscript{131} fails to induce thyroid tumors in mice, it regularly produces pituitary tumors (Figs. 5, 6) when given in doses causing complete or nearly complete destruction of the thyroid (37, 38). The relation of dose of I\textsuperscript{131} to tumor induction is shown in Table 5. Thyroid implants or adequate thyroxin treatment will prevent the appearance of these tumors. Gorbman (39) believes that ionizing radiation aggravates or synergizes the thyroidectomy in its tumorigenic action on the pituitary gland.

A limiting factor in the therapeutic use of I\textsuperscript{131} for thyroid carcinoma is the incidental general irradiation with severe depression of the bone marrow. Therapeutic doses are within the leukemogenic range. Two of fourteen patients described by Seidlin et al. (81, 82), who received 1,450 and 1,600 \mu c. of I\textsuperscript{131} for thyroid cancer, died with subacute myeloid leukemia 5 years after initiation of I\textsuperscript{131} treatment. The cumulative blood radiation dose of one patient was about 600 rep, that of the second probably greater. The incidence of two cases of myeloid leukemia in a small series of fourteen, after a compatible latency period, speaks for a possible causal relationship between the I\textsuperscript{131} therapy and leukemia. On the other hand, an increased incidence of leukemia has not been reported in radiothyroidectomized C57BL mice, which are highly susceptible to leukemogenesis by ionizing radiations.

<table>
<thead>
<tr>
<th>Dose (\mu c.)</th>
<th>No. in Pituit. Tumor</th>
<th>Number of Days after Treatment with I\textsuperscript{131}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C 150–299</td>
<td>C 300–399</td>
</tr>
<tr>
<td>25</td>
<td>–</td>
<td>18</td>
</tr>
<tr>
<td>50</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>100</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>200</td>
<td>–</td>
<td>3</td>
</tr>
</tbody>
</table>

\(\text{C} = \text{normal or early thyroidectomy changes}; \text{C} = \text{microscopic or gross tumors.}\)

Italics indicate the occurrence of gross tumors in the respective group.

<table>
<thead>
<tr>
<th>TABLE 5 RELATION BETWEEN DOSE OF I\textsuperscript{131} AND SEX TO INDUCTION OF PITUITARY TUMORS IN MICE (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (\mu c.)</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td></td>
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<tr>
<td>25</td>
</tr>
<tr>
<td>50</td>
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<tr>
<td>100</td>
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<td>200</td>
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</tbody>
</table>

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Gorbman and Edelmann (21, 40) reported that reducing the amount of I\textsuperscript{131} required to destroy the thyroid by keeping mice on a low-iodine diet will prevent tumor induction even though the thyroid is ablated and that added x-radiation promotes tumorigenesis. Failure to induce pituitary tumors by I\textsuperscript{131} in species larger than the mouse could be explained by the greater distance between the pituitary and thyroid. However, pituitary tumors can be induced in mice by the blocking of thyroxin synthesis with propylthiouracil (69), iodine deficiency (6), and by surgical thyroidectomy (18). In our experience, there is an inverse relationship between completeness of thyroid destruction and pituitary tumor induction in animals given either small doses of I\textsuperscript{131} after low-iodine treatment or large doses after normal diet or after surgical thyroidectomy.
Furthermore, the pituitary tumors that have been induced by total-body ionizing irradiation alone, and were assayed, were either adrenotropie (three out of nine) or mammary gland-stimulating (six of nine), and all were autonomous at the start. Only one of nine tumors assayed had some thyro-tropic combined with marked somatotropic potencies, and all were autonomous, while all the tumors induced by thyroidectomy which were tested were thyrotropic and of the dependent type. None of more than ten primary pituitary tumors induced by radiothyroidectomy in four strains of mice grew on normal hosts, but all could be grafted on thyroidectomized mice. Administration of thyroid hormone to the latter (substitution therapy) restored the resistance of these animals (Table 6). These observations strongly favor the opinion that the prime and often sole cause of the induction of mouse, in response to thyroxin deficiency, is a species characteristic. Experience may reveal whether human thyrotropes behave as did those of the rat or of the mouse. However, this riddle may never be solved, since thyroxin treatment following radiothyroidectomy, as it is now practiced, will adequately prevent development of pituitary tumors in man.

**Fission Products**

The carcinogenic effects of bone seeking and some other fission products have been studied extensively, notably in A.E.C. laboratories.

*Strontium-89.*--The carcinogenicity of radio-strontium has been the subject of a large-scale experiment by Brues (9) and by Finkel et al. (26, 27). Single and monthly intraperitoneal injections in the range of 0.01–7.8 µc/gm were given to 3,083 thyrotropic pituitary tumors by $I^{131}$ is the sustained thyroxin deficiency and that the role of ionizing irradiation is minor and not essential.

In considering this controversy it is worth recalling that both hormone imbalance and ionizing irradiation can produce tumors in diverse organs, but the two together do a better job. The difference with respect to autonomy may not be fortuitous.

This generalization is offered not as a law but as a provocative thought with implications worthy of special research. For example, a parallel study on the character of ovarian tumors induced by ionizing irradiation and hormonal imbalance alone is long overdue. Ionizing irradiation and hormonal imbalance can be additive or synergistic. Ionizing irradiations themselves can act in a dual manner, creating a hormonal imbalance and causing irreversible cellular modifications in the autonomous cancer cell.

It remains to be analyzed why pituitary tumors do not develop in the rat after radiothyroidectomy. It is possible that thyroxin deficiency is incomplete in thyroidectomized rats kept on a normal diet or that proliferation of thyrotropes of the mice. Most tumors induced were osteogenie sarcomas; a few were fibrosarcomas and hemangioendotheliomas (3.7 per cent of each). There were strain and sex differences. Females had 1.5 times as many tumors as males. The number of tumors per animal varied from one to fourteen.

Fractionation of 0.25 or smaller doses did not enhance tumor production. The same number of tumors were produced when these quantities were given as a single dose or in fractions of up to five doses. At higher total doses the number of tumors increased with increasing fractionation (27). The latent period was about 6 months and, surprisingly, was independent of the size of the dose. The number of tumors produced was a function of the dose (Chart 1) up to a certain level, beyond which there was a decrease of carcinogenicity (Chart 2).

This apparent inhibition in tumor induction by larger doses is similar to that observed by others after total-body irradiation. For example, fewer myeloid leukemias or ovarian, pituitary, and other tumors were noted in mice exposed to very large doses than in those exposed to medium doses (32). All these neoplasms have a long latency period. This situation has not been fully analyzed, but two
explanations are plausible; namely, loss of a relatively large number of animals during the latency period and damage to cells and blood vessels to such an extent as to impair proliferative processes.

Relative biological efficiency of six heavy radioisotopes.—Finkel (25) studied in mice the relative biological effectiveness of radium and of five other alpha emitters (Pu239, Po210, U233, U232, Th228).

Relative biological efficiency of an isotope was found to vary with the criterion of effect chosen (25). With respect to causing fatality within 90-100 days, radium was found to be only one-twentieth as effective as the other substances. In comparing ability to reduce life expectancy, at dose levels approaching those that produced no effect, the ratios of the various test substances to radium were 7 for plutonium, 3 for polonium, 2 for uranium-232, and 1 for uranium-233.

The relative carcinogenic potential was found to be 7:1 for plutonium and 2:1 for uranium-232. Uranium-233 and polonium were less effective than radium (Chart 3). In these experiments the latent period of tumor development was independent of the dose level but varied with the isotope. This is not true for Ra in man. Multiple tumors were the rule, especially after administration of plutonium.

The complexity of the problem is well brought out by this type of experiment. Variations in effective dose levels, disintegration schemes, metabolism of daughter products, latent periods, and host response all contribute to biological differences.

The “law” of diminishing returns with excessive doses is also well shown by these data. Of the animals that survived the latent period, tumors developed in 15.4 per cent after a large dose, and 4 times as many after a smaller dose. This inhibition of tumor formation is probably brought about by destruction of tumor-potential tissue by irradiation.

Uranium-232, Uranium-233, Plutonium-239, Yttrium-91.—In view of the rapidly increasing
mining and milling of uranium ores, Hueper et al. (46, 48) found it desirable to assay for carcinogenicity metallic uranium deposited in exposed parts of the body. They injected powdered U\textsuperscript{238} (50 mg.) suspended in lanolin into the bone marrow of rats. In one-third of the rats surviving the minimal period of 6 months, sarcomas developed at the site of injection. Sarcomas were also produced by intrapleural injection of uranium. Note that these tumors induced by U metal at the site of injection were osteogenic. Hueper et al. (46, 48) were uncertain whether the tumors were caused by alpha irradiation of uranium or by the metal itself. Metallic nickel powder injected in the same amount and vehicle, at similar sites, produced tumors of the same histologic appearance after comparable latency periods. Hueper re-emphasized the possibility of metallo-carcinogenesis, first shown by Schinz and Ühlinger (79), who observed malignant tumors in rabbits 4–7 years after intramedullary implantation of small quantities of nonradioactive arsenic, chromium, and cobalt in metallic form.

Similarly, Lisco and Kisieleski (57) implanted plutonium metal subcutaneously into rabbits (670–1,800 μg.) and rats (610–800 μg.). The oxide-coated plutonium quickly disintegrated, and the implants became encapsulated and calcified. Only small amounts of plutonium were absorbed. An osteogenic sarcoma, thought to be due to alpha particles of plutonium, developed in only one rat. It is remarkable that in rabbits no sarcomas developed at the site of Pu implants. The calcium about the Pu fragments may have blocked most of the alpha particles.

Adenocarcinoma of the colon has been produced in four of 33 rats by the feeding of Y\textsuperscript{91} (30) in single doses of from 1.0 to 6.0 μc. The tumors appeared in from 135 to 506 days. A second group of rats received 78 feedings of 0.46, 0.20, or 0.06 μc. over a period of 3 months. Almost all these rats died from carcinoma of the colon in 1–1½ years.

Pu\textsuperscript{239} and Y\textsuperscript{91} produced sarcomas in a large proportion of mice, and the latent period of 200 days could not be shortened by increasing the dose as much as tenfold (Brues et al. [11]). H\textsubscript{2}O and C\textsuperscript{14} are potentially carcinogenic but have not been shown to produce tumors. Tritium oxide (H\textsubscript{3}O\textsubscript{2}) when administered to animals behaves like water and can deliver a total-body dose of as much as 1,200 rep (Jennings and Brues [49]).

Brues and Buchanan (10) concluded that C\textsuperscript{14} offers a comparatively small hazard because, in spite of its long half-life, there is a fairly rapid turnover and loss from the tissue. The quantity retained, chiefly in bones, is small.
served in a single rat. Daily β-ray treatments of 50 rep produced similar results, but 348 exposure days, or a total of 13,400 rep, were required to produce tumors. After daily administration of the 50-rep dose, tumors developed in the skin or hair follicle without gross premortem changes.

Passonneau et al. (72) exposed the skin of rats for 48 hours over a 35 sq. cm. area to β-irradiation of Sr90-Y90. In one series the material was distributed uniformly over the source, while in others it was in the form of point sources (10, 20, or 50 in number). Papillomas began to appear within 4 months and malignant tumors within 7 months. The latter were carcinomas and sarcomas in approximately equal numbers. Formation of skin tumors was greater after exposure to diffusely distributed β-radiations than after exposure to the same amount of isotope in point sources. Perhaps one of the most interesting and surprising of their observations was an up to fivefold increase in the incidence of benign mammary tumors. Mammary tumor development is believed to be due not to extrinsic carcinogens but to estrogens. Mammary tumors developing in mice after total-body irradiation are frequently associated with estrogen-secreting granulosa-cell tumors, but they can also develop in the presence of atrophic ovaries. Guinea pigs have also been shown to be sensitive to the induction of breast tumors by ionizing irradiation, and this carcinogenesis is also unrelated to granulosa-cell tumors (Lorenz [82]). The use of P32 plaques may prove to be a useful tool in the study of the pathogenesis of mammary tumors by ionizing irradiation.

The effects of combined cutaneous application of P32 and Y90 and methylncholantherene were studied by Cloudman et al. (14), who found these agents to be approximately additive in producing most skin tumors, and possibly synergistic in the production of papillomas (Table 7). The sequence of changes (epilation, ulceration, healing of ulcer, and early papillomas formations) occurred faster in the hydrocarbon-treated animals.

In studies with combinations of carcinogens, the outcome depends on the concentration of the agents used as well as on the time relationship in their application. A tissue-destructive dose, or one causing marked atrophy and scarring with sclerosed vessels, may counteract a second carcinogenic agent. Administration of a second carcinogen in a state of heightened mitotic activity may, on the contrary, cause a synergistic effect. Tumor induction by hydrocarbons proceeds faster than by radioactivity, and it is possible that carcinogenesis by the two agents is due to different events. In the experiments by Cloudman et al. (14), the radiation was administered before the chemical. Conceivably, a synergistic effect of greater magnitude might have been found if the sequence had been reversed and optimally timed.

"Fall-Out" Problems

There are two fall-out problems: that of exposure to fission products soon after and close to the area of detonation of an atomic or hydrogen bomb, and that of exposure to increased and accumulated radioactivity on the surface of the globe resulting from repeated and remote detonations of nuclear weapons.

| TABLE 7 |
| P32 and Methylcholanthrene Carcinogenesis in Mice* |

<table>
<thead>
<tr>
<th>Days to:</th>
<th>P32</th>
<th>Methylcholanthrene</th>
<th>P32 + Methylcholanthrene</th>
</tr>
</thead>
<tbody>
<tr>
<td>maximal epilation</td>
<td>22</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>ulceration</td>
<td>22</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>healing of ulcer</td>
<td>107</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>early papilloma</td>
<td>82</td>
<td>45</td>
<td>90</td>
</tr>
</tbody>
</table>

* From Cloudman et al. (14), abbreviated.

The problems of somatic injury are also linked to that of genetic hazard. Most neoplastic changes are allied to mutations caused by exposures of higher intensities. The possible role of "normal" background irradiation with photons and radioactive particles, including that steadily created by cosmic rays, has been the subject of some speculation and experimentation. There is no evidence indicating that it plays a role in causation of spontaneous tumors of man and animals.

The effects from internally deposited fission products are slight compared with the effects of external exposure, because the amount of incorporated radioactivity is relatively small and short-lived. However, both external and internal irradiation from fall-out are associated with some hazard of carcinogenesis.

The fall-out from both A and H bombs is of essentially the same composition, both types deriving most energy from uranium fission. The degree of hazard depends on the power of the bomb, site of detonation, time and duration of exposure, and other variables. As Lapp (55) stated, "The bomb (hydrogen) dislodges millions of tons of earth churned into the fireball and coated with prodigious quantities of radioactivity created by the fission process; fission products adhere to the debris... The "hot" debris is swept upwards to
the stratosphere and is dispersed by the wind. The heavy particles fall out first . . . the tiny particles can be wafted around the world without descending."

The activity in a fall-out ellipse 50 miles wide and 200 miles long would be about 500 roentgen/hour, 1 hour after detonation, dropping rapidly as time passes. This intensity would be subject to considerable fluctuation, depending upon mixing in the bomb cloud, its dispersal in the stratosphere, and the vagaries of meteorology. The radioactive dust observed at considerable distances from the site of nuclear detonation is chiefly of short life and of a low order, adding little to the natural radioactivity of the earth's surface and atmosphere. In an editorial in The New England Journal of Medicine (89, and personal communication) it is concluded that the medical importance of the slight increase in the radioactivity of the earth's atmosphere has been greatly exaggerated in the current press. The Atomic Energy Commission (4) lends support to this conclusion with the statement that "None of the extensive data collected from all the tests shows that residual radioactivity is being concentrated in dangerous amounts anywhere in the world outside the testing areas."

In those areas where actual exposure to and contamination from radioactive fall-out material can take place, a hazard exists. A single instantaneous exposure alone can cause a variety of neoplasms, as the long-term studies in mice exposed at Eniwetok in the 1954 atomic bomb trials (92) indicate. Some tumors have a very low induction rate; others appear after very long latent periods. Thus far, in men exposed to single doses of external total-body irradiation, only leukemias have been observed (54, 68).

The quantity of inhaled or ingested radioactive particles, the amount absorbed from injured contaminated skin, the site of deposition in the body, the rapidity of excretion, and the specific radioactivity characteristics of the material determine the internal hazard. The fate of these elements in the body is expected to be similar to that noted in animals that were given fission products.

In people thus far exposed accidentally, sufficient time has not elapsed since exposure for neoplasms to become manifest. Anemia and the presence of radioactivity in bone, and tardy removal of radioactive substances from the skin, may possibly lead to the development of skin and bone tumors. The generalized character of irradiation makes the development of leukemia a possibility, since leukemia is known to develop after whole-body irradiation in both man and mice. The Marshall Islanders accidentally exposed to fall-out in 1954 have been carefully studied (8, 15, 16, 17 and personal communication). The total body exposure was estimated to range from 14 to 175 r. The general irradiation was intense enough to cause nausea and vomiting. The skin exposure from β-rays was of sufficient intensity to cause epilation, depigmentation, and ulceration. However, all these injuries were transient, and 1 year after exposure only a slight depression of lymphoid levels remained. The internal exposure was considered to be well below the carcinogenic level, the highest internal dose being to the thyroid (up to about 200 rep).

As to the C¹⁴ build-up, rough calculations by Arnold (8), based on the estimated energy release of the fusion tests so far, indicate that these tests will change only negligibly the small percentage of C¹⁴ already present in the atmosphere. Furthermore, C¹⁴ has not been proved to be carcinogenic. Biophysical aspects of the fall-out from bomb clouds have been well reviewed by Andrews in an article which appeared after completion of this paper (2).

There is a vast difference between a carefully prepared program for exploding nuclear devices at places and times chosen to minimize possible injury to man and an all-out war where both sides use such devices in the most damaging ways possible. We share the philosophy of Andrews (2) that if the first alternative helps to prevent the second, we must accept the first, with the uncertainty of some information not yet known on possible radiation injuries to a small number of people.

Closing Comments

Opinions as to future hazard from radioactivity vary widely. A pessimistic picture is seen by Hueper (47), who believes that "Mankind has entered an artificial carcinogenic environment, in which exposures to ionizing radiations of various types and numerous sources will play an increasingly important role in the production of cancers."

To many optimists, on the contrary, with our present control and regulation of safe handling in production and distribution of radioactive isotopes, sealing of sources, safeguarding of disposal, etc., the use of radioactive isotopes does not constitute an unsurmountable carcinogenic hazard.

A realistic view must consider the possibility of future accidents and incidents involving liberation of large quantities of radioactive substances. Furthermore, there is always an element of unpredictability in the use of any new drug. Only by experience shall we learn the threshold carcinogenic doses of radioactive isotopes in man. It is too early to tell how many persons, if any, have already
received an effective exposure to radioactive carcinogens.

REFERENCES


Figs. 5 and 6.—Primary pituitary tumor induced in a mouse by radiothyroidectomy. (Fig. 5) Bulging of the posterior cranium. (Fig. 6) The tumor exposed, showing a bulky mass pushing the optic chiasma forward and occupying more than half of the cranial cavity. (From Furth [38].)


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