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Radionuclide Injury to the Lung

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Radionuclide injury to the lung has been studied in rats, hamsters, dogs, mice and baboons. Exposure of the lung to high dose levels of radionuclides produces a spectrum of progressively more severe functional and morphological changes, ranging from radiation pneumonitis and fibrosis to lung tumors. These changes are somewhat similar for different species. Their severity can be related to the absorbed radiation dose (measured in rads) produced by alpha, beta or gamma radiation emanating from various deposited radionuclides. The chemicophysical forms of radionuclides and spatial-temporal factors are also important variables. As with other forms of injury to the lung, repair attempts are highlighted by fibrosis and proliferation of pulmonary epithelium. Lung tumors are the principal late effect observed in experimental animals following pulmonary deposition of radionuclides at dose levels that do not result in early deaths from radiation pneumonitis or fibrosis. The predominant lung tumors described have been of epithelial origin and have been classified, in decreasing frequency of occurrence, as adenocarcinoma, bronchiolo-alveolar carcinoma, epidermoid carcinomas and combined epidermoid and adenocarcinoma. Mesothelioma and fibrosarcoma have been observed in rats, but less commonly in other species. Hemangiosarcomas were frequency observed in dogs exposed to beta-gamma emitters, and occasionally in rats exposed to alpha emitters. These morphologic changes in the lungs of experimental animals were reviewed and issues relevant to the prediction of human hazards discussed.

Introduction

Inhalation of radionuclides constitutes a potential health hazard to selected occupational groups in the nuclear industry and to the general public from nuclear weapons testing. The association of pulmonary radionuclide exposure and lung cancer has been documented in uranium and fluorspar miners (*1-3*). Since few human data exist, however, with respect to biological effects from inhaled transuranium radionuclides or fission products derived from the nuclear industry, dose-effect studies in experimental animals have been performed in order to predict the health consequences in humans from inhalation of these products. Literature reviews on the pulmonary toxicity of inhaled radionuclides have been presented by Bair and Thomas (*4*), Bair and Thompson (*5*), ICRP (*6*), the Medical Research Council (*7*) and Thompson (*8*). This paper reviews the morphologic changes in the lungs of experimental animals produced by the inhalation of radionuclides and points out some issues relevant to the prediction of human health hazards.

Models for the deposition and retention of radionuclides, based on the anatomy of the respiratory tract, particle size and solubility of the radionuclides, have been presented by the ICRP (*9*). Deposition was separated into the following major compartments: nasopharyngeal, tracheobronchial, pulmonary (alveolar), and thoracic lymph nodes. The fraction of inhaled aerosol particles deposited in the various regions of the respiratory tract was determined as a function of particle size. Particles deposited on the mucus layer of the nasopharyngeal and tracheobronchial regions are cleared, in minutes to hours, by cilia-propelled mucus flow. Particles deposited in the pulmonary region may be phagocytized by alveolar macrophages or by Type I alveolar epithelium, or they may be solubilized, either free in the air space or within macrophages and/or epithelium. Macrophages with engulfed particles may then migrate to the ciliated portions of the respiratory tract and be cleared, whereas soluble particles may pass through the alveolar wall into bloodstream for transport to extrapulmonary tissues. Radionuclides cleared by the mucociliary escalator may be swallowed and then either absorbed from the gastrointestinal tract or passed in feces. Radionuclides absorbed into the bloodstream may be excreted via urine or bile. Bronchial and tracheobronchial lymph nodes may also accumulate a considerable amount of radionuclides.

Retention of inhaled radionuclides in the lung is primarily dependent on the chemical form of the compound. The ICRP (*9*) postulates D, W and Y class compounds having average clearance times from the lung of 0.5 50 or 500 days, respectively. Animal studies have shown that oxides of plutonium, americium, and curium have pulmonary clearance times ranging from 50 to 1000 days. Actinide nitrates and other soluble chemical forms have more rapid pulmonary clearance rates. Oxidation temperature may also influence the

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clearance of oxides, i.e., high-temperature oxidation forms more insoluble compounds.

Retention of radionuclides in the lung is also influenced by particle size and specific activity. The specific activity is related to the amount of energy released per unit mass of the radionuclide, with faster decay rates yielding higher specific energies. Increased particle size, higher specific activities, and increased quantity of material deposited in the lung will cause increased cytotoxicity to macrophages phagocytizing particles. Increased macrophage cytotoxicity is associated with fibrosis that tends to sequester particles in the lung, causing longer retention times. Increased specific activity, however, can influence physicochemical properties of compounds, causing "dissolution" and increased solubility, resulting in shorter retention time in the lung.

The absorbed radiation dose, measured in rad (1 rad = 100 erg/g of lung), can be calculated after determining deposition levels and clearance curves for the radionuclide. Although the absorbed radiation dose is important in making comparisons between radionuclides, the magnitude of biological effects is more closely related to the average energy released per unit track length (termed the linear energy transfer, or LET). For example, alpha particles, generally having track lengths of approximately 40 μm, have much higher LET than beta particles having track lengths extending several millimeters in tissues.

The spatial-temporal considerations are also important in radionuclide toxicology. For example, the average radiation dose to the lung, measured in rad, does not reflect the possibility of nonuniform distribution. Very high amounts of energy released in the area of a few cells could have less biological effect, due to wasted energy, than if this energy were distributed over the entire lung. Factors such as lung cell movements, particle movements, solubility, and particle size tend to average the dose-distribution pattern in the lung for inhaled radionuclides from the initial nonhomogeneous pattern to a more homogeneous one. The degree of dose nonhomogeneity is greater for insoluble, alpha-emitting transuranic oxides than for more soluble transuranics or for beta-gamma emitters. A comprehensive assessment of radiation dose from inhaled plutonium, however, indicated that averaging the absorbed alpha radiation dose provided a sound basis for predicting health hazards (*10*).

Types of Injury

General

Exposure of the lung to high dose levels of radionuclides produces a spectrum of progressively more severe functional and morphological changes, ranging from radiation pneumonitis and fibrosis to lung tumors. These changes are somewhat similar for different species. Their severity can be related to the radiation dose produced by the alpha, beta or gamma radiations emanating from various deposited radionuclides (*11*, *12*). As with other forms of injury to the lung, repair attempts are highlighted by fibrosis and proliferation of pulmonary epithelium. Lung tumors are the principal late effect observed in experimental animals following pulmonary deposition of radionuclides at dose levels that do not result in early deaths from radiation pneumonitis or fibrosis.

Replicating cells may be more susceptible to cancer formation than resting cells. In the rat, the alveoli continue to multiply throughout life; bronchiolar and alveolar epithelium turn over every 30 days or less (*13*, *14*). Mechanical irritation; chemical, physical, and infectious agents; and vitamin A deficiency may result in squamous cell and adenomatous metaplasia in the lung (*15*,*16*). Continuous irritation to the lung may provide the promotional stimulus needed for development of lung tumors (*17*).

The concept of progression in neoplasms was evaluated by Foulds (*18*). According to Saccomanno et al. (*19*), the properties of a tumor cell are acquired serially in a kind of cellular evolution. Mechanisms have probably evolved to protect the body from the evolution of altered cells in rapidly regenerating epithelial tissues. It may be necessary for a certain number of cells to form a malignant "focus" before tumor growth occurs in the lung (*20*, *21*). There appears to be a relationship between the incidence of radiation-induced tumors in the lung and ionizing events in each cell, multiplied by the number of cells irradiated in the lung (*22*,*23*).

Rats

The rat's susceptibility to injury from inhaled radionuclide, along with its ready availability, small size and short lifespan, have contributed to its popularity for studying the inhalation hazards of radionuclides. In addition to being used to study basic mechanisms involved in reaction to injury, an abundant amount of data have accumulated on the relative toxicity of different radionuclides in rats. Pour et al. (*24*) described the various types of spontaneous and induced tumors in the lungs of rats. Rats rarely develop spontaneous lung tumors, except for lymphoreticular neoplasms, which may be confused with chronic murine pneumonia. Epithelial tumors of the lung in rats have been classified as adenocarcinoma, bronchioloalveolar carcinoma, undifferentiated carcinoma, anaplastic carcinoma, well differentiated carcinoma or squamous cell carcinoma. Following exposure to transuranics, most induced lung tumors are well-differentiated adenocarcinomas and squamous cell carcinoma. Hemangiosarcoma, fibrosarcoma, and mesothelioma are less frequently observed following exposure to transuranics.

Stuart et al. (*25*) evaluated the acute effects of inhaled plutonium dioxide. Rats exposed to very high doses of $^{238}PuO_2$ or $^{239}PuO_2$ (6 to 20 μCi/g of lung) died,

with severe pulmonary edema, as early as 6 to 7 days after exposure. At lower doses (~ 0.2μCi/g) survival was longer, with less alveolar edema and deposition of fibrin, but with early proliferation of bronchiolar and alveolar epithelium. The phagocytosis of inhaled plutonium particles has been documented in alveolar macrophages (*26-29*) and in alveolar Type I cells of rats (*29*).

In rats exposed to inhaled $^{239}PuO_2$ (*30*), a progressive radiation pneumonitis developed. It was characterized by damage to pulmonary endothelium and septal wall thickening, caused by interstitial accumulation of collagen and elastin. Pulmonary connective tissue modifications in rats after inhalation of $^{239}PuO_2$ have also been studied (*31*). Biochemical determination of protein, collagen, and uranic acids were related to dose and time. Increased collagen content in the lung was maximal at 200 days after exposure, but returned to pre-exposure values after 400 days in rats receiving the same total rad dose. Since histological examination showed no observable decrease in focal scars between 200 and 400 days after exposure, it was concluded that the decrease in connective tissue components observed with biochemical methods at 400 days after exposure must be correlated with a fine, diffusely distributed connective tissue alteration.

Adenocarcinomas are the lung tumor most frequently seen in rats exposed to alpha emitters such as $^{239}PuO_2$ (*32,33*) and $^{238}PuO_2$ (*34*). Adenomatous metaplasia and adenomas appeared to precede the development of malignant tumors, suggesting that these lesions may be precursors of malignancy. The adenomatous metaplasia consisted of cuboidal epithelial cells lining groups of alveoli and alveolar ducts. With adenomas there was an irregular proliferation of cuboidal epithelial cells forming papillary patterns, replacing the normal architecture of the pulmonary parenchyma. The malignant designation, adenocarcinoma, was reserved for tumors that invaded pleura, blood or lymphatic vessels; invaded other nonparenchymal tissues; metastasized; or histologically resembled invasive or metastatic tumors. Adenocarcinomas generally arose in peripheral areas (frequently subpleural or peribronchiolar) and were associated with areas exposed to high doses of radiation (*35*), but were not always associated with fibrosis. Mucus production by tumor cells was seen in about a third of the tumors (PAS-positive stains). Ultrastructural studies indicated that few tumors arose from Type II pneumocytes. Most tumors appeared to originate from bronchiolar epithelium, presumably in terminal regions, and ultrastructurally resembled bronchiolar Clara cells. Metastases were observed within the mediastinum, and occasionally to kidney. Metastasis to kidney and/or lymph nodes was more frequent in Fischer strain than in Wistar strain rats.

Epidermoid carcinomas in rats consisted of irregular proliferation of stratified squamous keratinizing epithelium, often replacing entire lobes. Foci of squamous metaplasia frequently occurred in association with radiation-induced fibrosis prior to the appearance of lung tumors. Squamous metaplasia and neoplasia were more frequently associated with areas of radiation fibrosis than were adenocarcinomas. Epidermoid carcinomas in rats were more likely to metastasize to distant sites such as kidney. Occasionally, rats developed other primary epidermoid carcinomas and adenocarcinomas.

Hemangiosarcomas were also seen after inhalation of transuranics, more frequently with $^{239}PuO_2$ than with $^{238}PuO_2$ or other radionuclides. Hemangiosarcomas, which arose from central regions of the lung, comprised large solitary masses, composed of dilated vascular spaces, filled with blood and large thrombi, and lined with endothelial cells. The tumors may have originated from venous-arterial shunts associated with radiation-induced scar tissue; they often filled large areas of lobes and contained anaplastic endothelial cells. Metastasis, however, did not occur.

Malignant mesotheliomas grew from the pleural surface, often into large areas of the pleural cavity, and occasionally were implanted in the heart. The tumors had papillary patterns with cuboidal epithelial cells, or combined spindle cell and epithelial patterns. Mesotheliomas induced in rats by intraperitoneally administered $^{239}PuO_2$ have been extensively studied. They were similar in morphogenesis and origin to mesotheliomas induced by intraperitoneal injections of chrysotile asbestos (*36*).

The spectrum of radionuclide-induced lung tumors observed in rats, as described above, is similar to that observed after inhalation of soluble plutonium (*37*), radon-222 and its daughter products (*38*), ^{239}Pu (*39*), ^{241}Am (*39*), $^{244}CmO_2$ (*40*), $^{243}EsCl_3$ (*41*), ^{210}Po (*42*), and $^{144}CeO_2$ (*43*). Differences in radiation dose and dose distribution, however, altered the types of tumors produced. Squamous cell carcinomas predominated at high doses of insoluble $^{238}PuO_2$ or $^{239}PuO_2$ particles; adenocarcinomas predominated at lower doses. For more soluble transuranics, such as $^{244}CmO_2$ and soluble ^{238}Pu, adenocarcinoma predominated at all doses. A series of studies with beta- and gamma-emitting radionuclides implanted by various means into the lung produced squamous cell carcinomas (*44*).

In another series of studies, Wistar rats were exposed to aerosols of $^{238}PuO_2$, $^{239}PuO_2$ or $^{244}CmO_2$ (*33*). Alveolar depositions of transuranics ranged from approximately 0.1 nCi to 1000 nCi. No lung tumors were found in 230 unexposed rats. Thirty-three lung tumors were found in 294 rats exposed to high-fired $^{238}PuO_2$; 16 lung tumors were found in 92 rats exposed to $^{238}PuO_2$ produced from crushed microspheres in saline for several months prior to exposure; 56 lung tumors were found in 295 rats exposed to high-fired $^{239}PuO_2$; 12 lung tumors were found in 61 rats exposed to air-oxidized $^{239}PuO_2$; and 23 lung tumors were found in 240 rats exposed to high-fired $^{244}CmO_2$. A statistically significant increase in the incidence of lung cancer was calculated at an estimated radiation dose to the lung of 56 rad for ^{238}Pu, 32 rad for ^{238}Pu, 78 rad for ^{239}Pu, 50 rad for ^{239}Pu and

27 rad for $^{244}CmO_2$. In each study, individual rats developed lung tumors at lung doses of less than 10 rad. The incidence of lung tumors at these low doses was not significantly different from that of controls, but tumors were consistently found.

The type of induced lung cancer was a function of dose-distribution patterns (*33*). Further analyses of risk were performed on published data, consisting of radiation dose to lung and percent of lung tumors taken from 19 lifespan studies in over 5000 rats given a single inhalation exposure to alpha-emitting radionuclides. The data were analyzed in three groups: (1) plutonium oxides and nitrates; (2) plutonium citrate and ammonium plutonium pentacarbonate; and (3) americium, curium, and einsteinium nitrates and oxides. The spontaneous lung tumor incidence for unexposed rats was 0.14% (based on one observed tumor). The predicted total percent of lung tumors at 1.5 rad to lung was usually between 0.3 and 0.7% for all groups; none of the groups gave a predicted value statistically different from that of the other groups.

Studies on the histogenesis of lung tumors induced in rats by inhalation of alpha emitters have recently been reviewed by Masse (*45*). These investigators divided adenocarcinomas into two main types: bronchogenic (B) and bronchioloalveolar (BA) carcinomas. Ultrastructurally, the B tumors were characterized by irregular nuclei, a developed complex of rough endoplasmic reticulum, often filled with electron-lucent material, mucus granules, conspicuous desmosomes, and, under the apical edge, bunches of filaments with slender microvilli. In an adenoacanthoma variety, there were intracellular spaces similar to those observed in humans by McDowell et al. (*46*), but few mucous granules. When two B tumors were transplanted, epidermoid differentiation was observed, with loss of the glandular pattern.

The BA tumors described by Masse exhibited papillary growth spreading along the margin, were peripherally located, and exhibited early invasion of pleura and mediastinum. Although some BA tumors were mucus-secreting, none exhibited epidermoid differentiation on metastasis or transplantation. The cells were columnar or cuboidal, and the nuclei appeared round or oval, with membrane infolding. Ultrastructurally, apical bunches of filaments were lacking, desmosomes were not conspicuous, and there was no protrusion of the apex into the cytoplasm. The lamellar bodies identified in 37% of BA tumors indicated that they were derived from Type II pneumocytes. Other BA tumors were thought to originate from Clara cells.

Hamsters

The Syrian golden hamster has a low incidence of spontaneously occurring lung tumors (*24*). In addition, the hamster is considered to be resistant to pulmonary infections (*15,47*). There appear to be some species differences between rats and hamsters with respect to pulmonary carcinogenesis from inhaled radionuclides. Moreover, there appears to be a significant difference in the susceptibility of the hamster to pulmonary carcinogenesis by inhalation versus that from serial intratracheal instillation of radionuclides on "inert" carrier particles. Inhalation of alpha emitters (^{239}Pu) produced few lung tumors in hamsters (*48*), whereas intratracheal instillation of alpha-emitters (^{210}Po) in saline resulted in numerous lung tumors at low doses (*49,50*). This indicated that both spatial-temporal dose distribution patterns and apparently innocuous stimuli such as saline may greatly influence pulmonary carcinogenesis (*51-53*).

Altered collagen metabolism in plutonium-induced interstitial pulmonary fibrosis has been studied in the hamster (*54*). A similar study in hamsters that inhaled beta or gamma emitters showed both synthesis and degradation of collagen within a 2-week period and histologically observed fibrosis by 2 months after exposure (*55*). Autoradiographic studies showed that collagen stain observed on tissue slides accumulated preferentially in areas immediately surrounding individual plutonium particles and in regions of high particle concentration (*56*).

An incidence of lung tumors in hamsters of as much as 92% was seen at lung doses of 4500 rad, and 43% at 225 rad following instillations of ^{210}Po on carrier particles of ferric oxide (*57*). This method of pulmonary deposition produced the greatest radiation dose in the bronchiolo-alveolar region, the region where the tumors arose. The tumors, observed by light microscopy, had features of both epidermoid and adenocarcinomas, and were therefore classified as "combined tumors." In an elegant histochemical, light and electron microscopy study of hamsters exposed to ^{210}Po and serially sacrificed, the bronchiolar Clara cell was identified as the probable cell of origin of these lung tumors (*58*). A rapid progression from hyperplasia to bronchiolar-cell malignant tumors was described (*59*).

Other investigators have shown that hamsters are refractory to the induction of lung tumors with radionuclides. In a series of studies in Syrian golden hamsters exposed to the inhalation of radon daughters and uranium ore dust (*60*), lung tumors developed in only a few hamsters, and only in those animals receiving very high dose levels. The uranium ore dust induced inflammatory and proliferative changes in the lungs, consisting of macrophage accumulation, alveolar cell hyperplasia, and adenomatous lesions which did not progress to tumors. Exposure to radon and radon daughters was associated with bronchiolar epithelial hyperplasia, and metaplastic changes of alveolar epithelium. Squamous carcinoma developed in four hamsters, with incidences of approximately 3% of hamsters exposed to radon and radon daughters, and 1% of hamsters exposed to radon and radon daughters plus uranium ore dust. The development of squamous metaplasia and development of carcinoma were considered related. Because of the very low incidence of lung cancer resulting from

exposure to radon and radon daughters, it was concluded that an animal model "other than the hamster would be more appropriate for study of the pulmonary carcinogenic potential of uranium ore alone."

In order to make a comparison of pulmonary carcinogenesis between rats and Syrian golden hamsters, hamsters were exposed by inhalation to $^{239}PuO_2$ or $^{238}PuO_2$ at doses that caused lung tumors in rats. Hobbs et al. (*61*), using $^{239}PuO_2$, and Mewhinney et al. (*62*), using $^{238}PuO_2$, did not observe lung tumors. Sanders (*48*) reported a lung tumor incidence of 3 in 292 Syrian golden hamsters that inhaled $^{238}PuO_2$ or $^{239}PuO_2$. Although, in hamsters, the inhaled plutonium produced a dose-dependent increase in adenomatosis that could be considered premalignant, the adenomatosis lacked histopathologic criteria for malignancy, and did not affect mortality. Several investigators have described the development of adenomatosis in the lungs following treatment with a chemical carcinogen (*63-66*). However, the lack of association between adenomatosis and carcinoma transformation in hamster lungs indicates that either adenomatous metaplasia is not a step in the pathogenesis of pulmonary carcinoma; that a biological control mechanism prevents or inhibits the progress of adenomatous metaplasia into carcinoma; or that a prolonged latent period exists between the appearance of metaplasia and neoplasia, extending beyond the lifespan of the hamster strain used in these studies.

In an imaginative series of studies at Los Alamos Scientific Laboratories, Syrian golden hamsters were intravenously injected with microspheres of 10 μm diameter containing Pu and ZrO_2 ceramic (*51, 67, 68*). The microspheres lodged in the pulmonary capillaries and remained immobile for the life of the hamster. Because of the immobility and the uniformity of the microsphere distribution, radiation doses were very precisely quantified. To the surprise of the investigators, very few tumors were observed. Studies with concurrent intratracheal injections of ferric oxide, however, raised the incidence of primary lung tumors from 5% to 38% (*53*). Similarly, intravenously injected microspheres exposing hamsters to ^{147}Pm beta radiation produced lung adenomas, adenocarcinomas, and epidermoid carcinomas, reaching a 30% incidence at a very high dose rate (15 rad/year); the adenomatous bronchiolar lesion was described as an unreliable estimator of tumorigenicity (*51*). From the work with intravenously injected microspheres, it can be concluded that factors other than radiation are involved in pulmonary carcinogenicity.

Dogs

Dogs are the most common, large, nonrodent, laboratory animal used in inhaled radionuclide studies. Advantages of dogs over rodents include their longer lifespan, which allows translation of radionuclides to extrapulmonary organs, a lung function with respect to inhaled particles that more closely resembles the human, and a greater similarity to humans in some aspects of radionuclide kinetics (*69*).

The lung histopathology following exposure to $^{239}PuO_2$, $^{238}PuO_2$, and $^{239}Pu(NO_3)_4$ appeared to be similar for comparable radiation doses from these various chemical and physical forms of plutonium (*70*). Alveolar depositions of $^{239}PuO_2$ in amounts of 0.1 μCi/g of lung tissue was associated with respiratory failure within 10 months, characterized as pulmonary edema, severe vascular damage, fibrinous accumulations in bronchioles and alveoli, and pulmonary fibrosis. Alveolar deposition in the range of 0.05 μCi/g of lung induced pulmonary fibrosis, bronchioloalveolar cell hyperplasia and metaplasia, alveolar histiocyte proliferation, pleural fibrosis and early "alveolar tumor formation" in 1 to 5 years. In an additional study comparing plutonium-239 and -238 dioxide, lung lesions were related to total cumulative dose (*71*). Autoradiographic studies have shown the plutonium particles to be concentrated in areas of fibrosis (*72*).

Bronchioloalveolar tumors were first described in four dogs surviving more than 855 days after inhalation of $^{239}PuO_2$, with lung burdens at death of 0.6 to 1.4 μCi (*73*). The lungs of these animals had marked amounts of radiation pneumonitis, characterized as diffuse fibrosis, sclerosis, and, in some instances, hyalinized areas in subpleural, septal, and peripheral regions. The authors described a gradual transition from alveolar metaplasia to more anaplastic and, finally, neoplastic forms. The tumors were described as follows: "Infiltrating pleomorphic cells in these regions assumed epithelioid or squamous characteristics, formed frondlike papillary projections, or took the appearance of bronchiolar or acinar structures."

Bronchioloalveolar carcinomas were described in dogs from additional ongoing studies with inhaled $^{239}PuO_2$ (*74,75*). The morphology of $^{239}PuO_2$-induced tumors in 22 dogs were later described (*70*) as mostly bronchioloalveolar carcinomas of peripheral origin, with two peripheral squamous cell carcinomas and three epidermoid carcinomas. Metastases were often demonstrated in the tracheobronchial and mediastinal lymph nodes and, less often, in the mesenteric lymph nodes, liver, kidney, spleen, adrenals, brain, and bone marrow. The high incidence of primary lung tumors was emphasized in a later paper (*76*), which reported that 20 of 21 dogs developed pulmonary neoplasia ~ 4.5 years after a single inhalation exposure to $^{239}PuO_2$, with estimated average cumulative radiation dose to the lungs of 2,000 to 12,000 rad. Using Cutler-Ederer estimates of lung tumor incidence, adjusted for differences in proportional survival, a higher incidence of lung tumors was found in dogs than in rats at earlier times in proportion to their life expectancy. The incidence was significantly higher in the interval from 20% to 50% of lifespan (*77*). Dogs also had a proportionately earlier mean time to tumor occurrence.

The inhalation of beta-gamma emitters produced a slightly different spectrum of changes from those

produced by alpha-emitting plutonium. The effects of aerosols of relatively soluble or insoluble beta or gamma emitters having different radioactive half-lives are being studied to determine the effects of various dose patterns (*78,79*). Yttrium-90, ^{91}Y, ^{144}Ce and ^{90}Sr were fused in aluminosilicate to form particles that were more slowly cleared from the lung. Deaths from radiation pneumonitis and pulmonary fibrosis, similar to those seen after inhalation of high dose levels of plutonium, were seen within the first 500 days after exposure. Survival time appeared to be a function of dose rate.

Changes in collagen constituents in different regions of lung were studied in beagle dogs after inhalation of beta-emitting radionuclides (*80*). Measurements of insoluble native collagen, soluble collagen (tropocollagen or procollagen), and ultrafilterable hydroxyproline peptides indicated that the development of pulmonary fibrosis was directly related to initial dose rate in the lung. The pathogenesis of pulmonary fibrosis following inhalation of radionuclides seemed to be: initial collagen degradation, followed by increased synthesis and accumulation of collagen and, finally, a more normal rate of synthesis and, possibly, degradation. Previous studies by Pickrell et al. (*55*) had shown unchanged elastin content and slight alterations in glycosaminoglycons in lungs of beagle dogs exposed to inhaled radionuclides.

Primary pulmonary hemangiosarcomas, with widespread disseminated metastases, occurred with relatively large doses (23,000 to 48,000 rad) of protracted beta radiation to the lung (*81*). Bronchioloalveolar carcinomas were the most common pulmonary neoplasms at lower dose levels (7,000 to 20,000 rad), delivered in shorter intervals (*79*). As with inhaled insoluble plutonium, pulmonary neoplasms were the predominating cause of death from inhaled beta-gamma emitters, but pulmonary neoplasms occurred less than 2 years after exposure—earlier than after inhaled plutonium. The difference in tumor types may reflect differences in biological responses between the very short-range, high-LET, alpha irradiation and the longer range, low-LET beta-gamma irradiation.

Extrapulmonary lesions often play important roles in inhalation exposure of dogs to radionuclides (*6*). They include some degree of cardiomegaly and congestive heart failure in dogs with pulmonary fibrosis; prominent, sclerosing, tracheobronchial lymphadenopathy resulting from insoluble radionuclides being cleared by the lymph nodes; and neoplasms in other organs that accumulate radionuclides or, in the case of beta-gamma emitters (*79*), are exposed to irradiation. Occasionally, dogs with plutonium-induced lung tumors have developed hypertrophic osteoarthropathy (*76*). Dose-related lymphopenia, as well as evidence of decreased immunologic competence, has been observed in dogs exposed to insoluble radionuclides that concentrate in tracheobronchial lymph nodes (*82*).

Mice

The mouse has been infrequently used as a model for pulmonary radionuclide carcinogenesis. Temple et al. (*83*) described a bronchiolar carcinoma and two squamous carcinomas in mice given $^{239}PuO2$ by intratracheal injection. A reduction in the incidence of urethan-induced pulmonary adenomas after inhaled $^{239}PuO_2$ was reported by Brightwell and Heppleston (*84*). After repeatedly exposing mice to a relatively insoluble form of ^{144}Ce, giving dose rates and cumulative doses to the lung comparable to those produced in dogs, the total incidence of lung tumors was correlated with cumulative dose, not dose rate (*85*).

Baboons

Studies with inhaled transuranics in baboons seem a logical step for the extrapolation of nonprimate animal data to man (*86*). The lesions in the lungs of baboons following $^{239}PuO_2$ inhalation were described as more homogeneous than expected with particulates, and consisted of interstitial pneumonitis, with fibrosis rich in elastic fibers, hyalinized arteries, intense proliferation of Type II pneumocytes and foci of giant cell interstitial pneumonia (*78*). However, the acute mortality observed primarily reflecting the radiation pneumonitis was similar to that of dogs (*87*). The studies in baboons have not progressed long enough to evaluate possible long-term effects such as lung tumors.

Discussion

Studies on pulmonary effects of radionuclides have used many animal models to study basic mechanisms with which the lung responds to injury. Phagocytosis of inhaled or intratracheally injected particles appears as a common initial event. Mitosis-linked cell death is a widespread phenomenon of radiation injury, and is possibly the major response of cells to the physical injury resulting from the radionuclide. This results in cell death or small areas of necrosis, depending on the concentration of particles and the local distribution.

Fibrosis, as a general response to cell death, tends to sequester the source of irritation. Epithelial cell proliferation may result from this fibrosis or, more likely, may occur concurrently as a response to radiation-induced epithelial cell death. The stimulus for epithelial cell proliferation and transformation in association with fibrosis is not known and, at present, the existence of such a stimulus is only speculative. The possibility cannot be excluded that fibrosis may render the proliferation of epithelial cells more susceptible to chemical or physical carcinogenesis.

Despite differences in radionuclides, animal species and experimental procedures, there are many similarities in tumor type and histopathology. The predominant lung tumors described have been of epithelial origin and have been classified, in decreasing frequency of occur-

rence, as: adenocarcinoma, bronchioloalveolar carcinoma, epidermoid carcinoma and combined epidermoid and adenocarcinoma. Mesotheliomas and fibrosarcomas have been observed in rats but less commonly in other species. Hemangiosarcomas were frequently observed in dogs exposed to beta-gamma emitters, and in rats exposed to alpha emitters. Neither oat cell tumors, nor any other type of neurosecretory cell tumor, have been induced by exposing laboratory animals to radionuclides, in spite of the presence of small-cell carcinomas in uranium miners (*19,22,88*).

Major advantages of animal models for studying cellular injury resulting from radionuclide exposure are the ability to relate actual dose and dose rate, instead of merely exposure level, to biological effects. The actual deposition of energy from radionuclides in lung tissue can be estimated from clearance curves. Correlation of biological effects with dose and dose rate allows for greater reproducibility of experiments and for more precise testing of hypotheses. Stochastic microdosimetry is being developed to estimate energy exposures to individual cells.

To summarize, in animals exposed to high levels of radionuclides, death occurs from a variety of lesions characterized as radiation fibrosis. At low exposure levels, but at levels higher than most human exposures, longer survival allows the appearance of pulmonary neoplasia. Extrapolation of animal findings to people must be performed with caution. Ongoing lifespan studies will allow better documentation of the level of risk at very low exposure levels.

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