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FINAL REPORT

ACUTE AND CHRONIC EFFECTS OF RADIOACTIVE PARTICLES ON THE RESPIRATORY TRACT

by

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To

Dr. Shields Warren	Chairman of Panel on Acute and Chronic Somatic Effects of Radiation in Humans. (Deaconess Hospital, Boston, Massachusetts)

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I Introduction

The second meeting of this panel took place at Stanford Research Institute, Menlo Park, California, to evaluate further and to summarize briefly the available information on the effects of inhaled radioactive particles on the respiratory tract. Consideration was given to the sources and nature of such particles and to the numerous physical and biological factors involved. An attempt was made to define known parameters, to determine gaps in existing knowledge, and to formulate recommendations for needed research. Although the primary emphasis was on radioactive particles, it was found necessary to consider also the general problem of the effects of radiation on the lung, whether the source was external or internal.

II Sources and Nature of Airborne Radioactive Particles

Radioactive particles containing the daughter products of radon and thoron* are a normal constituent of our atmosphere and are continually being inhaled by man. Most of the daughter products have short half-lives and thus decay rapidly to insignificant levels. The concentration of the radon and thoron products in the atmosphere does not normally exceed one-thousandth of that level presently considered to be safe for man. (Exceptions occur in some mines and in locations where quantities of radium or thorium are stored.) Mankind is therefore able to breathe continuously air containing small numbers of radioactive particles with no significant harm to health.

With the recent increase in the quantities of artificial radioactive substances produced, the possible sources of airborne radioactive particles have greatly increased. Significant sources include nuclear explosions, nuclear production and power plants, experimental reactors, and industrial and research applications of radioisotopes. The contamination resulting from these sources can be divided into two categories, (1) the world-wide distribution from nuclear explosions, and (2) the essentially local distribution from the other sources.

A. Nuclear Detonations

The characteristics of the radioactive particles from a nuclear detonation and their distribution in the atmosphere are determined by many physical factors, including the type of device, the altitude of the detonation, and the meteorological conditions. The more powerful devices result in the transport of radioactive particles into the stratosphere with subsequent distribution over the face of the earth (1). The small particles, carried to great heights, fall back into our atmosphere months and years after the detonation. In addition to the

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* Radon and thoron gases produced from radium and thorium in the earth's crust.

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world-wide distribution produced by all large-yield devices, low bursts (surface and sub-surface) also create inhalation hazards over local areas (up to 10,000 square miles).

These radioactive particles contain fission products, nonconsumed fissionable material, and activated materials from the environment. This debris is produced in various particle sizes ranging from submicron to millimeter sizes, with the larger particles deposited in the local area of the detonation. Atmospheric contamination at distances of hundreds of miles or more consists largely of particles in the respirable range, although some particles as large as 1000 microns in diameter may be transported similar distances (1). Particles of the order of 1 micron may remain suspended in the stratosphere for years, gradually falling into man's environment, where they may be inhaled.

The rate of radioactive decay of these substances decreases with their age with the initial rate being extremely rapid. Table I illustrates the percentages of fission products remaining at various times following a detonation. In spite of these rapid decay rates, at the end of one year the residual activity of a 20-kiloton device will still be on the order of 100,000 curies (2). The quantities of unconsumed fissionable substances are small in comparison with the fission products but they provide a possible source of very long-lived, alpha-emitting materials. The activated products of a nuclear detonation depend upon the environment of the detonation. In general they consist of both short-lived and long-lived materials, with their qualitative behavior with time similar to that of the fission products.

Table I

PERCENT OF ACTIVITY REMAINING FOLLOWING THE DETONATION OF A NUCLEAR DEVICE (3)

Time Since Formation (t)	% of Activity Present at 1 Minute that Remains at Time, t
1 day	0.016
1 month	0.00028
1 year	0.000014

Because of the immense dilution that occurs in the atmosphere, the probability of inhaling significant amounts of such particles is still exceedingly slight, except in the vicinity of nuclear detonations.

B. Other Sources

The other sources of airborne radioactive particles present a potential hazard to small numbers of people working in and near the area where the operations take place. These particles arise from handling radioactive materials in reactors, nuclear processing plants, research laboratories, and other radioisotope applications.

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The particles may contain any of the hundreds of individual radioisotopes either alone or in combination. In many cases these radioactive isotopes have long half-lives, may have high specific activities, and may vary in size from less than one micron to several millimeters. Although normal control practices protect the workers under most circumstances, the probability of exposure from an accident remains significant. The most spectacular hazard would be the accidental release of large quantities of radioisotopes from a nuclear reactor.

III Description of the Respiratory Tract, Anatomy and Physiology

The descriptive and functional information given below is limited to that pertinent to inhalation of particulate material, and its fate once it enters the respiratory system. The function of the respiratory tract is to convey air to the pulmonary alveoli for oxygen and carbon dioxide exchange. During the passage of the air from the outside to the alveoli, moisture is added to the air and much of the extraneous material present in air, such as dust particles and pollens, which are of no importance in gas exchange, is removed before the air reaches the alveoli.

The nasal passages, trachea, and bronchi through which air passes are lined by a membrane, which constantly secretes mucus and is lined throughout most of its course with ciliated cells which constantly move the mucus away from the terminal bronchi, in the case of the nasal passages toward the throat and in case of the trachea and bronchi toward the pharynx where it is either expectorated or swallowed. The nasal air passages are tortuous and are so constructed that the air must pass over a large surface of this mucus-covered membrane which acts as an effective filter for particles larger than 5 microns. Mouth breathing does not have this protective function.

The trachea is a moderately rigid, cartilaginous structure approximately 2 cm in diameter in the adult male; it extends from the pharynx into the thorax, where it divides into two major bronchi which convey air to the lungs. These bronchi penetrate the lungs, repeatedly divide, and with each division decrease in size until they enter the pulmonary lobule, at which point they are 0.15 to 0.20 mm in diameter. The bronchi and bronchioli, except the "respiratory bronchioli," are lined with ciliated and mucus-secreting cells.

In the normal healthy repiratory tract foreign particulate material that penetrates no farther than the terminal bronchi is moved out of the lung by ciliary action, but that which passes beyond the terminal bronchi is handled by a different mechanism.

The primary lobule of the lung consists of a terminal bronchus surrounded by alveoli (air sacs) in which exchange of gases between the air and blood takes place. The alveoli consist of capillaries lined with endothelium, which is in contact with the blood, and epithelium, which is in contact with air. Also within the alveoli there are phagocytic cells (septal cells).

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The lymphatics consist of a closed, endothelial tubular structure, somewhat resembling a vascular system; it collects interstitial fluid (lymph)and cells,passes through lymph nodes and finally into the vena cava. The lymph nodes function as a filtering structure and remove from the lymph phagocytic cells containing foreign or endogenous particulate material. The alveoli probably do not contain lymph vessels, the smallest and first lymph vessels being found in the walls of the terminal bronchi. From this point the vessels pass either along the pulmonary arteries and bronchi or to the surface of the lung and form the pleural plexus. In either case the lymph ultimately passes through the plexuses about the large bronchi and trachea. Surrounding the bronchi there are a large number of lymph nodes through which the lymph must pass before it reaches the thoracic duct.

Particulate material which reaches the alveoli may be engulfed by phagocytic cells. These cells migrate to the lymphatic vessels and are carried with the lymph to the nodes at the hilum of the lungs. Some phagocytic cells may migrate to the bronchi and be carried upward in the bronchi by ciliary action. Small amounts of particulate material become lodged free in the interstitial tissue usually at points of bifurcation of bronchi and blood vessels and about the lymphatics of the pleura. Particulate material may remain in the lung for some period of time, depending on the chemical and physical properties of the material.

IV Fate of Inhaled Particles

A. General Statement

Evaluation of the potential hazard from inhaling radioactive airborne materials requires careful consideration of numerous physical factors and of the physiological functions of the respiratory system. Among the physical factors the more important are: (1) particle size, (2) solubility, (3) density, (4) aggregation of particles, (5) the relative amount of radioactivity in particles of the respirable size range, (6) duration of exposure, and (7) the chemical and physical nature of the radioactive particles. The more important physiological factors concerned in the removal and absorption of inhaled particles include: (1) mouth versus nose breathing,(2) minute volume, (3) filtering effect of the upper respiratory passages, (4) various clearance mechanisms, and (5) vascularity of capillary beds in the respiratory mucosa.

Most particles larger than five microns in diameter adhere to the mucous membranes of the nose and larger bronchi,especially at the points of angulation or branching of the respiratory tree, and do not penetrate to the deeper air passages. As the particle size decreases, a larger and larger fraction of the inhaled material reaches the alveolar ducts and sacs. Much of this is exhaled again, but appreciable fractions may be retained. The amount finally retained in the lung is determined in part by the shapes of the particles (e.g. a long,thin asbestos fiber may be retained while spherical or cuboidal silica particles may not) and

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their density, but is largely dependent on chemical factors. Readily soluble materials enter the circulation and are carried to other organs by the blood stream,whereas insoluble materials may remain in the lung for long periods. The removal of the latter depends on the physiological mechanisms for removal of foreign bodies from the respiratory system. These include (1) reflex coughing and sneezing, (2) the constant activity of cilia in the bronchiolar epithelium, which brings material from the deeper respiratory passages to the mouth where they are either expectorated or swallowed, (3) engulfment by phagocytic cells with subsequent movement either up the respiratory tract as in (2) or to the lymphatic system with possible concentration in lymph nodes or other sections of the lymph drainage system, (4) entanglement and dilution in mucus lining the respiratory tree and propulsion with the mucus as above, and (5) possible direct entry into the lymphatic system without the mediation of phagocytic cells.

Since the upper respiratory passages act as a filtering mechanism for larger particle sizes, they may accumulate appreciable quantities of inhaled material if the mean particle size is large (greater than 5 microns). On the other hand, the lung itself may be exposed to the highest concentrations of a material of a smaller size, especially if it is also insoluble. Other organs of the body will receive material from lungs or upper respiratory passages if it is (1) soluble or (2) brought to them as a result of the lung clearance activities described above. If exposure is repeated, both the lung and other organs may contain appreciable amounts simultaneously. Also, on repeated exposure to insoluble substances the amount permanently retained in the lower respiratory passages may increase considerably with time.

The general relationships described above are documented specifically in the following sections, but mention should be made here of the compendia and reviews by Dalla Valle (4), Davies (5), Drinker and Hatch (6) and Eisenbud (7), and to the studies of Drinker and colleagues (8), Landahland Hermann (9), etc.

The radioactive elements formed in nuclear fission are predominantly oxides which have a limited solubility in body fluids. Further, the airborne particles with which radioactivity is associated are for the most part considerably larger than the optimum size for deposition and retention in the alveolar tissue of the lung. Thus, the probability of long-term retention of significant amounts of inhaled fallout material in the lower respiratory passages is not appreciable following an acute exposure. However, the amount of inhaled radioactive material which can produce injurious effects may be minute because of the close proximity of the particles to the tissue which they irradiate and their high specific activities. There is, in fact, some preliminary evidence that single active particles of plutonium lodged in the mouse lung can induce epidermoid carcinoma (10).

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chromate, nickel carbonyl

B. Clinical Experience

A considerable body of clinical data has been gathered on human inhalation of various particulate materials. Some of these agents produce diseases which have a fairly characteristic clinical course and pathological structure. Examples of these are silica and asbestos, causing pulmonary fibrosis; beryllium, causing granulomatosis; and ~~cobalt, arsenic, nickel~~, and asbestos, leading to carcinoma of the lung. Many particulates, such as non-crystalline silica, carbon, and iron, have been demonstrated to be biologically inert and not to lead to disease in the respiratory system.

Investigations of dust hazards in industry have yielded some information on the fate of the inhaled particles in the human respiratory tract. The majority of these investigations pertain to the total quantity of dust retained under a very generally defined set of conditions. Very divergent results have been obtained, as is summarized by Davies (5). Properties such as particle size distribution and the physical properties of particles which determine their impaction and settling rates are important, and the breathing characteristics of the subject may exert a modifying influence. Although we have gained a general picture of the fate of inhaled materials in the respiratory tract from such work, quantitative information is not in general available. The impression is always that individual substances pose individual problems and that simplifying generalizations have not been possible.

Because of the greater ease of measurement, especially in the presence of an energetic gamma component, the fate of radioactive dust may be followed somewhat more easily in man than that of non-radioactive materials. However, work is just starting in this field. Marinelli, Norris, et al. (11), could follow the clearance of radium sulfate from the lungs of six persons who suffered accidental exposure to radium sulfate dust. They used a gamma-ray scanning device. There was an early rapid elimination from the lung followed by a progressively slower loss. The half-time for retention varied from 32 days initially to 140 days within six months after exposure. Albert and Arnett (12), measured rates of loss from the lungs of thoron daughter products adsorbed on kaolin and of a radioactive iron dust. These substances left the lung much more rapidly than the radium sulfate cited above. The retention half-time was about 9 hours. Two distinct phases appeared in this early bronchiolar clearance, a very rapid one ending in 2 to 4 hours, and a second phase ending in about 30 hours. Their relative importance varied with the average particle size.

Recently, interest has developed in the possibility of bringing therapeutically effective radiation dosages to regional lymph nodes by administering radioactive colloids intratracheally. Hahn, et al. (13), have shown that such colloidal suspensions may remain fixed locally for long periods. This is in line with earlier information obtained with colloids of thorium (e.g. thorotrast) which have been found to remain

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in situ for period of years. Finally, preliminary studies of the rate of transfer of insoluble plutonium deposited in the lungs of humans indicate movement with half-times of the order of two years (14).

Thus, the information on deposition and retention in human lungs is scanty in many particulars and permits few generalizations. Indeed, in all probability each substance represents a separate situation, and generalizations to a broad evaluation of the hazard of inhaling radioactive materials cannot be made at present.

C. Experimental Observations in Animals

Obviously, much detailed information regarding the deposition, retention, and clearance of inhaled materials that cannot be obtained from clinical observations can be obtained from experimental work with animals. Although the difficulties of transfer of experimental information from animals to man are recognized, a short summary of the current status of information in this field may be useful.

1. Non-Radioactive Materials

Exposure of animals to dusts of the type important in industrial medicine has yielded valuable basic information on the fate of various substances (Gardner (15) and Lanza (16)). Clearance mechanisms previously discussed provide important physiological safety factors in respect to the potential radiation damage to the respiratory system. The efficiency of these mechanisms varies, as stated above, with the physical and chemical properties of the particulate material and the components of the respiratory system. This has been reviewed adequately by Eisenbud (7). In general, foreign particles are rapidly removed from the nasal passages and bronchial tree during the first few hours or days by ciliary action and mucus secretion. Materials initially deposited in lung parenchyma distal to the ciliated air passages remain in these areas for a longer period (weeks or months) and are removed more slowly and less efficiently by phagocytosis. They may be subsequently translocated to organs of the reticulo-endothelial system by way of the pulmonary lymphatics (17). Insoluble materials of unit density, such as bacterial spores (18), india ink, and prodigiosin (19), are more rapidly and effectively removed from both major compartments of the respiratory system than are similar particulate materials of greater density (20) such as silica and beryllium sulfate. With unit density materials, the upper passages are cleared within a few hours and the lower passages within a few days. With the higher density materials, although the upper passages are still cleared in hours, removal from the lung parenchyma requires much longer periods. The most important aspect is that in these cases a small percentage of the material initially deposited in the distal part of the pulmonary tree is retained for very long periods. Furthermore, on repeated inhalation exposures, there is a gradual increase in the amount permanently retained (21).

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A clear demonstration of the importance of particle size to toxicity is found in the studies of Wilson, et al., on uranium dioxide dust (22). Using lung damage, lung weight, body weight loss, and evidence of kidney damage as criteria, they showed in rats and rabbits, that uranium dioxide dust with a mass-median particle diameter of 0.5 micron was considerably more toxic than the same inhaled concentration having a mass-median particle diameter of 2.3 microns. Similarly, the ability of beryllium oxide (23) to produce an acute pneumonitis and of silicon dioxide to induce silicosis in animals (24) is found to increase as average particle size decreases. This may be related to the larger surface area of the smaller particles.

2. Radioactive Materials

During the war years, experimental studies were made of the retention and fate of inhaled fission product aerosols and of various individual radioactive materials, including alpha emitters. These were primarily acute exposures and provided useful preliminary figures regarding retention and subsequent distribution to tissues. Abrams, et al., (25) showed that Strontium 89 left the lungs quite rapidly but that Zirconium 95, Yttrium 91, and Cerium 144 were eliminated much more slowly. Translocation to the skeleton occurred in each case. These same authors investigated the fate of inhaled plutonium aerosols (26) and showed that valence state and the presence of complexing agents are important in pulmonary retention. The deposition and fate of plutonium, uranium, and their fission products were studied in detail by Hamilton and his associates (27). The distribution of Polonium 210 inhaled by rats was found by Fink, et al. (28) to be similar to that which occurs after intravenous injection.

Another aspect of the problem is illustrated by work with radon. Radon itself is a noble gas and behaves in the body in accordance with its solubility in body fluids. The gas itself remains in the lungs for relatively short periods and constant exposure would be necessary to produce significant lung damage. The same would apply to the radioactive gases occurring in nuclear fission. However, as was first pointed out by Bale (29) and subsequently shown experimentally by Cohn, et al. (30) and by Shapiro and Bale (31), the decay products of radon may deposit on atmospheric dust and be of primary importance. The dust particles with their contained radon decay products may remain in the respiratory tree, being distributed more or less as a function of particle size, and contribute much larger radiation doses than radon itself. Although this is of more importance to mining and ore processing operations than to fission product "fallout," the importance of considering carrier dust and decay products is illustrated by this work.

All of these acute studies indicate that evaluation of the hazard to the lung depends upon the compound inhaled and its physical-chemical state. This has been borne out by more recent work, in which animals have been exposed to "fallout" or simulated fallout and fission products as reviewed in the succeeding paragraphs.

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Studies involving the exposure of animals to airborne radioactive particles have been made both in the field and in the laboratory. The results of tests conducted at the Nevada Proving Grounds during the past few years indicate that the retention of particulate matter in the respiratory system of exposed animals was insignificant, even in the presence of an appreciable external radiation flux (20).

In the Pacific test of March 1, 1954, a large number of human beings and animals were accidently exposed to fallout from nuclear detonation (32, 33). In this situation considerably larger amounts of radionuclides were taken up and retained than in the continental tests. In the Pacific exposure, the type of detonation and the carrier material of the fallout differed from those encountered in the Nevada tests.

Studies of the animals exposed to the fallout from the abovementioned Pacific nuclear detonation provided data on the uptake, distribution, and retention of the various fission products (33). Routes of entry for the material were both inhalation and ingestion, with the latter the more important.

Although a large number of fission products were present in the environment, relatively few gained entry into the body. These included Strontium 89, Barium 140, Iodine 131, and some of the rare earth elements. The elements which enter the body are characterized chiefly by their solubility. Biological removal and radioactive decay reduced levels of radioactivity in the lungs of pigs rapidly, so that at three months only 0.02% of the beta-ray activity of the entire body was present in the lungs. At six months after the detonation, the radioactivity levels in the lungs of pigs were barely detectable.

The amount of fission products deposited in the body from inhalation and ingestion of this fallout material was insufficient to contribute to the acute radiation effects observed. The possibility of delayed effects occurring from internally deposited radioactive material is very small.

Studies in the laboratory designed to provide data on the results of exposing small animals to fallout material have been of two types: those which utilize pulverized radioactive material from the field, and those which attempt to reproduce fallout material.

In the former studies, rabbits were exposed to aerosols (0-3 microns in diameter) developed from materials collected from the Nevada Proving Grounds (21). The materials were used several months after the contaminating event, so that only the long-lived fission products were present. The materials were further characterized by the fact that they were siliceous and therefore highly insoluble (one percent in water).

Following single 4-hour exposures to a dust concentration of $1 \mu c/m^3$ with particles having a mean diameter of 0-3 microns, the amount initially retained in the lungs (369 d/s) was about one-ninth that found

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in the stomach (2326 d/s). Clearance from the lung and the gastrointestinal tract was practically complete by 96 days (0.8 d/s and 5.2 d/s respectively). Values for the clearance from both systems were parallel, and followed an exponential function, with about 85% lung clearance in 7 days and about 95% clearance from the gastrointestinal tract in the same time.

Products from two-day-old neutron bombarded uranium were employed in the various simulants used in the laboratory experiments, designed to re-create various types of fallout (34, 35). In this inhalation experiment the animals received many of the short-lived fission products in addition to the longer-lived radiosiotopes. The distribution and retention of the fission products in these animals confirmed that fact mentioned previously that the uptake and metabolism of the inhaled radioactive particles depends largely on the physical and chemical characteristics of the carrier material. It was found that the retention and metabolism by the lungs and other tissues could be altered by the injection of the chemical, zirconium citrate, immediately preceding or soon after exposure (35).

The quantity of fission products retained by the mice as a result of inhalation exposure was proportional both to the length of exposure and to the concentration of airborne radioactivity. The internally deposited radioactivity in the lungs, as well as in the skeleton and soft tissues, decayed rapidly. This resulted from the fact that the activity of the aerosol was contributed chiefly by radioisotopes of short half-lives, and that the biological turnover in the lungs and soft tissues was rapid.

The accumulated evidence from these controlled experiments in the laboratory and field studies all point to the conclusion that the internal radiation hazard following an acute exposure to fallout is very small in comparison with the overwhelming external dose. This conclusion, of course, applies to the inhalation hazard immediately following exposure to a nuclear detonation, and would not necessarily apply to the effects produced by acute exposure to long-lived radioisotopes such as Strontium 90 and Plutonium 239, or to chronic exposure to small amounts of long-lived fission products.

In repeated exposure studies (21), in which rabbits and rats were given as many as 60 6-hour exposures five days each week to the siliceous radioactive material (from Nevada) using dust concentrations of 0.01 $\mu c/m^3$, pulmonary retention increased in proportion to the number of exposures. Lung clearance values were much lower than for animals subjected to a single exposure, being only about 30% in 30 days, and 70-75% in 60 days.

V Radiation Effects on the Respiratory Tract

Insofar as is known, the amount of damage suffered by any tissue depends upon the amount of energy absorbed. The determinants are:

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1. The nature and intensity of the source

2. Time

   a. Duration of exposure
   b. Rate
   c. Whether exposure is continuous or intermittent.

As regards such late effects as neoplasia, when the radioactive particle has an indefinite biological half-life, and is fixed by some mechanism within the tissue, the total volume of tissue affected may be small, but nevertheless of great significance; it is theoretically possible that a single cell exposed to a single radioactive particle may be the source of a neoplastic cell lineage that can ultimately destroy the host. Of course, with larger numbers of cells exposed, the statistical chance of such an event becomes greater.

Within the above parameters the effects to be expected may be classified as acute or chronic.

A. Acute Effects

Acute effects may be arbitrarily defined as effects occurring within the first six weeks.

Information that has accrued on the pathology of acute effects is largely based on changes produced by externally applied x-rays in the treatment of cancer of the breast. With adequate exposure, two or three thousand to fifteen thousand roentgens, some cases showed lesions that consisted of alterations in the cells of distal air passages. There was enlargement of the passages, and sometimes an increased basophilia of the cytoplasm. The nucleoli likewise became very prominent.

Distinctive acidophilic hyaline membranes were often formed early in the tissue response to irradiation of the lung. These underwent absorption finally but not organization.

A characteristic and early change was edema of the alveoli together with congestion. The cellularity of the walls of the alveoli was increased, in part by swelling of the lining cells and endothelial elements, and sometimes by infiltration of small numbers of lymphocytes, plasma cells, and large mononuclear elements.

Pulmonary scarring occurred only with the larger doses of x-rays.

The lymphatics and small blood vessels became congested early. With large doses, the large vessels showed a striking edema of their walls, and occasionally cellular infiltration. The elastica may become reduplicated and focally coarsened. The lymphoid tissue within the lungs may atrophy, as elsewhere, but when the doses are appropriately spaced regenerative activity may keep pace with the destructive action of the ionizing radiations.

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From available data, it would seem that single doses applied locally in excess of 2000-3000 roentgens at 150 to 200 kv are necessary to produce these acute tissue responses in the lung. It has been found that when rats are injected with 30 to 159 microcuries of Phosphorus 32, changes resembling those of the acute tissue response in the lung to x-rays appear within seven days.

B. Long-Term Effects

Experiments of Lorenz, et al. with strain A mice chronically exposed to gamma rays for a total of 2000 rad have shown an incidence of lung tumors 50% higher in experimental than in the control mice at nine and one-half months (37). It has long been known that extremely small doses of radioisotopes can produce neoplasia. A classical example is sarcoma of bone after the retention of as little as 1 microcurie of radium. Even lesser amounts, of the order of 0.4 microcurie, have recently been shown to produce bone necrosis in man (38). These studies, together with unreported work by other groups, suggest that occupational exposure to appreciable amount of ionizing radiation has been common among miners and has existed for a long time (39). Earlier reports indicated that radon inhalation by the Jackymov miners resulted in lung carcinoma (40). Unquestionable evidence that carcinoma resulted from exposure to radon in these miners does not exist.

C. Effects of Radioactive Particles (Internal Emitters) on the Respiratory Tract

Available experimental data include the production of epidermoid carcinoma (10) of the lung within one year in mice of the BAF_1 strain (a strain known to have a low prevalence of naturally occurring lung tumors) by as little as 0.06 microcuries of colloidal plutonium oxide administered intratracheally. An early response to this material that occurred within three months was fibrosis and atypical epthelial proliferation in the terminal respiratory passages. Within three months, mice exposed similarly to Ruthenium oxide ($Ru^{106}O_2$) in doses of 1.5 to 2.5 microcuries, showed focal scarring of the pulmonary parenchyma. At one year there was apparently no progression in the scarring (10). In the lungs of rats exposed by Cember and his group (41) to Barium sulfate ($BaS^{35}O_4$) particles for a period of a year there were doubtful minute foci of fibrosis. No neoplastic changes were observed. A number of 1-2 year experiments in which animals were exposed daily to varying doses of x-rays and neutrons have produced no demonstrably pulmonary effects (42). Another pertinent, although negative, experiment may be cited: 5½-mm particles of siliceous atomic debris from a Nevada test site each particle containing 10^{-5} microcuries of alpha emitters and 10^{-2} microcuries of beta emitters per particle, were implanted in the lungs of rats. Only a foreign body response comparable to that of non-radioactive siliceous material occurred after one year (21).

Information obtained with other tissues may given an indication of the mechanism for the damage to the respiratory tract produced by radio-

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active particles. For instance, Passonneau (43) has performed some experiments to determine the incidence of skin tumors in rats exposed to beta radiation from point sources of Strontium 90-Yttrium 90. The efficiency of tumor production in these rats decreased as the amount of radioactive material in the individual point sources was increased (44). This decrease in efficiency is presumably dependent on the wasting of radiation energy on those tissues which are killed by the high radiation levels present at short distances from the point sources. Calculations (45) indicate that if the tumor production is a linear function of the radiation intensity, the efficiency of tumor production will increase as the amount of radioactive material in the individual point sources is decreased. If the tumor production depends upon the square or higher power of the radiation intensity, the efficiency of tumor production will exhibit a maximum for some definite amount of radioactive material in the point sources.

VI Conclusions

1. With reference to fallout from nuclear detonations, consideration of physical factors (such as strength and type of detonation, particle size distribution, decay rates, meteorological factors, airborne radioactivity levels, and percentages of radioactivity in the respirable size range), and actual experience, indicate that the acute external beta-gamma radiation hazard is many times greater than that from inhalation.

An additional safety factor for the lung (of perhaps 10) is represented by the respiratory clearance mechanisms.

2. In industrial or research work with nuclear reactors and radioisotopes, situations may occur wherein relatively small numbers of people may receive significant radiation exposure to parts of the respiratory system from inhaling radioactive particles containing long-lived isotopes of high specific activity, without simultaneously exceeding tolerance levels for whole body exposure.

3. Little information is available on the potential hazard to the respiratory system and other organs following chronic exposure to small amounts of long-lived radioisotopes such as Strontium 90 and Plutonium 239. The occurrence of epidermoid carcinoma in the lungs of mice after exposure to plutonium particles suggests that accumulations of such materials may present a similar hazard to man.

VII Recommendations

1. More information should be obtained on storage and clearance mechanisms, immediate and long-term, in respect to various radioisotopes in various chemical forms and particle sizes, in both the upper and lower respiratory tracts.

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2. A concerted effort should be made to compare the behavior and effects of inhaled radioactive and non-radioactive particles with the objective of utilizing the large amount of data already available on non-radioactive materials.

3. Possible cumulative storage within the respiratory tract, following repeated exposure to long-lived isotopes, should be given special attention.

4. Analyses of human lungs for radioactive particles should be made; the study of lungs containing tumors may be especially fruitful.

5. Spatial-dose relationships should be further worked out and carefully considered in studying the chronic effects of particles containing long-lived radioisotopes on tissues in general and on the respiratory tract in particular.

6. Species differences must be considered in evaluating the effects of ionizing radiations on the lungs; special attention should be paid to species with a long lifespan in consideration of time-intensity factors.

7. Further studies should be made of the combined effects of external and internal radiations on the lungs.

8. Further work should be done on the development of instruments for the preparation and collection of radioactive aerosols with particular attention to the physical parameters needed for interpreting biological experiments.

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