Chapter II

THE RESPIRATORY TRACT

How particles are deposited in the lung and how long they remain depend on the properties of the particles and on the nature of the lung. This description of the respiratory tract and its functions is limited to information pertinent to the inhalation of particulate material and to the fate of this material after it enters the respiratory system. Detailed information on the anatomy and physiology of the lung can be found in other sources[1, 2]. The function of the respiratory tract (shown in Fig. II-1) is to convey air to the pulmonary alveoli for exchange of oxygen and carbon dioxide. During 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, is removed before the air reaches the alveoli.

The nasal passages, trachea, and bronchi through which air passes are lined by a membrane that constantly secretes mucus. The membrane is lined throughout most of its course with ciliated cells that constantly move the mucous toward the pharynx, where it is either expectorated or swallowed. The nasal air passages are so constructed that the air must pass over a large surface of this mucous-covered membrane, which acts as an effective filter for particles larger than 5 μ.

The trachea is a moderately rigid, cartilaginous structure 2 to 3 cm in diameter in the adult male; it extends from the pharynx into the thorax, where it divides into two major bronchi that convey air to and from the lungs. These bronchi penetrate the lungs, repeatedly divide, and with each division decrease in size until they enter the pulmonary lobule. The mucosa of the major bronchi is composed of tall columnar cells that are mucous-secreting or ciliated, and smaller basal and intermediate cells. The thickness of the epithelial layer of the major bronchi varies considerably but averages approximately 40 μ.[3] As the bronchi become smaller in diameter the epithelium becomes thinner; in the terminal bronchioles, 0.15 to 0.20 mm in diameter, it consists of a single layer of cuboidal cells only a few microns thick. The "respiratory bronchioles" are not lined by mucous-secreting or ciliated cells. As the mucous stream, propelled by the ciliae, moves upward from the terminal bronchioles to the pharynx, relative stasis occurs where the stream divides to pass around entering bronchi and around vocal cords. Small whirlpools of mucous have been observed at these points, where prolonged exposure from radioactive particulates and colloids could occur. Also, islands of (non-ciliated) squamous metaplasia and areas in which columnar epithelium are denuded of ciliae have been observed; mucous on these is removed more slowly by traction[4].

The primary lobule of the lung consists of a terminal bronchiole, respiratory bronchiole, alveolar ducts, and 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 a membrane of lining cells, which is in contact with air[5, 6]. Nucleated cells are not normally seen to form a continuous lining of the adult alveolus; however, many pathologic conditions are associated with

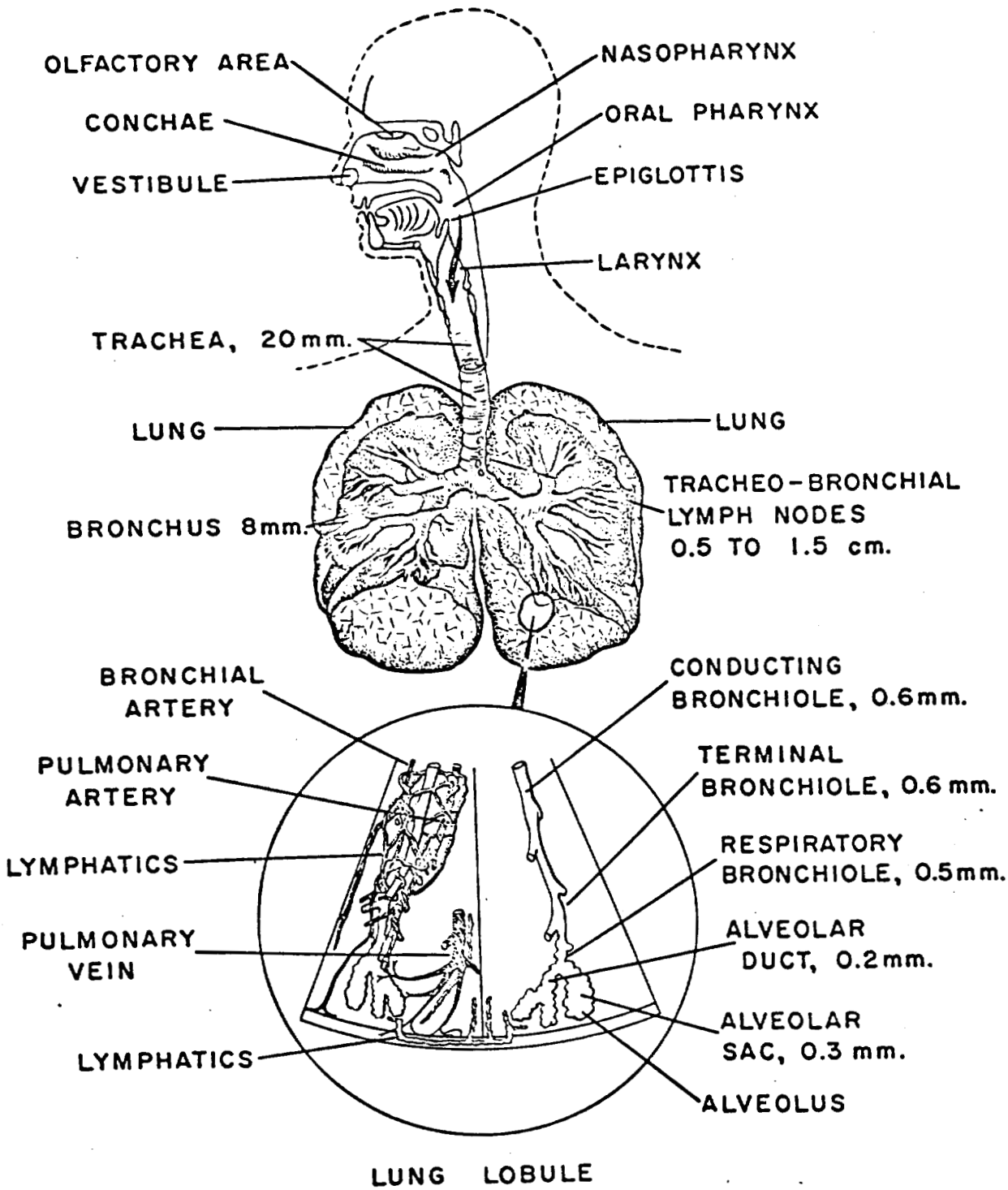

Figure II-1.

the clear appearance of nucleated lining cells. Alveolar macrophages are mononuclear cells approximately 8 to 12 μ in diameter, although they can become large and multinuclear under abnormal conditions. Their main characteristics are ameboid motility and the ability to engulf particles and bacteria. These cells have some staining properties in common with cells of the reticulo-endothelial system[7].

Phagocytes have been observed both in the air sacs and on the alveolar wall. They may migrate to the bronchi and be removed by ciliary streaming, or they may migrate to interstitial spaces and thence to the lymphatics. The constant removal of these cells from the lung is accompanied by a constant production of new cells, and it is estimated that the entire population is renewed about once a week[8]. Production of phagocytic cells is stimulated by the presence of particulate material in the air sacs.

The lymphatic system consists of a closed, endothelial tubular structure, somewhat resembling the vascular system. Its function is to remove from the tissue fluid substances that cannot readily gain entry into the blood capillaries. Interstitial fluid and cells collected by the system pass through lymph nodes and finally into the vena cava, a large vessel leading into the heart. In the anesthetized dog, the rate of lymph flow from the right thoracic duct is about 5 to 10 milligrams per minute[9]. 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 bronchioles. 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, a network of lymph vessels. In either case the lymph ultimately passes through the plexuses about the large bronchi and trachea. Surrounding the bronchi are a large number of lymph nodes through which the lymph must pass before it reaches the thoracic duct.

The volume of tissue in the lung, other than blood and lymph vessels, is largely composed of extravascular space. Its size has been variously estimated. In one study using radiosodium, the extravascular space was estimated to be approximately three times the volume of blood plasma in the lung[10]; in another study, 190 cm^3 in the normal adult[11]. All of the studies indicate a rapid exchange of water and ions between the plasma and extravascular space[12].

Estimations of the volume of blood in the pulmonary circulation have varied widely, but many of the data indicate a volume of approximately 500 cm^3 or 10 percent of the total blood volume[13]. The blood flow of pulmonary circulation in a 70-kg man under basal conditions is around 5200 cm^3/min.[2]

The importance of considering the volume of blood, extracellular fluid, and lymph in making dosage calculations is not certain, because all of the constituents are in rapid exchange with the total blood volume of the body. The weight of the lungs, however, is important in the calculation of radiation doses to the lungs. The usual figure given for the lung weight of a 70-kg man is about 1000 grams[1, 2, 14]. This figure is an average of weights of lungs obtained at autopsy. It may be misleading since many of the lungs seen at autopsy are involved in various pathological processes, practically all of which increase the weight of the lungs. The average weight of the lungs in 6 electrocuted adult males was found[15] to be 534 g; this figure is probably as close as it is possible to determine for the lung in a relatively

"bloodless" state. Using lungs from accident victims, the average density of inflated healthy lungs was recently determined[16] from formalin-fixed sections and found to be 0.26 ± 0.03 g/cm^3. These authors made a survey of values obtained from the application of other techniques and concluded that the correct value was not higher than 0.3 g/cm^3.

Normal lung volumes and capacities have been defined by Comroe et al.[17], who have also given values for a healthy, resting, recumbent young male. The authors first list the four primary volumes measured: (1) Tidal Volume (500 ml), the volume of gas inspired or expired during each respiratory cycle; (2) Inspiratory Reserve Volume (3.1 liters), the maximal amount of gas that can be inspired from the end-inspiratory position; (3) Expiratory Reserve Volume (1.2 liters), the maximal volume of gas that can be expired from the end-expiratory level; and (4) Residual Volume (1.2 liters), the volume of gas remaining in the lungs at the end of a maximal expiration. There are four capacities, each of which includes two or more of the primary volumes: (1) Total Lung Capacity (6 liters), the amount of gas contained in the lung at the end of a maximal inspiration; (2) Vital Capacity (4.8 liters), the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration; (3) Inspiratory Capacity (3.6 liters), the maximal volume of gas that can be inspired from the resting expiratory level; and (4) Functional Residual Capacity (2.4 liters), the volume of gas remaining in the lungs at the resting expiratory level. The relationships between volumes and capacities are best understood by reference to a diagram such as given in Fig. II-2, taken from Comroe et al[17].

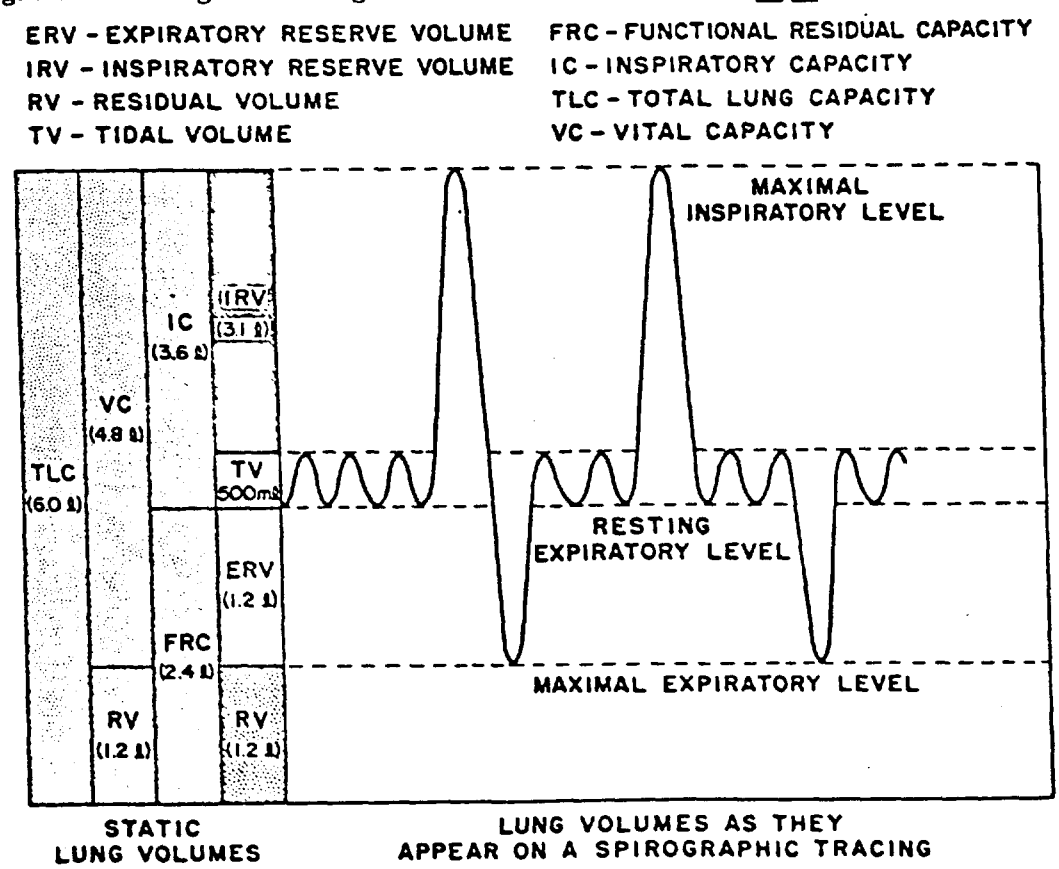

Figure II-2.

The volume of the respiratory passages is about 150 ml and is referred to as the anatomical dead space, because air in this space does not exchange gases with the blood. At the end of expiration the air passages are filled with alveolar air; during inspiration this air is driven back into the depths of the lungs by the incoming air. Upon inspiration an increase in lung volume takes place, principally in the atria or air chambers of the primary lung lobules, and the air passages increase in volume in proportion to their lengthening. The incoming air, which represents about 15 percent of the air already present, mixes with the normal capacity air and ultimately reaches the alveoli by gaseous diffusion.

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Chapter III

DEPOSITION AND REMOVAL OF INHALED PARTICLES

When inhaled particles enter the respiratory tract, a certain fraction is deposited and the remainder goes back out with the expired air. Some of the deposited material is removed from the site of deposition quickly, but some may remain for appreciable periods. There has been much confusion in the literature regarding terminology for these fractions and the processes responsible for them. For our purposes, the term deposition refers to the initial processes determining how much of the material in the inspired air remains behind after expiration. The term retention applies to the amount or fraction of deposited material that remains in the respiratory tract at any given time. The transport of materials out of the lung is usually referred to as clearance, and the movement of material to other tissues can be referred to as translocation.

A. Deposition

The processes responsible for deposition of particles are basically the same (though differing in relative importance) both inside and outside the respiratory tract, as shown in Table I-1. The amount of material actually deposited in the respiratory tract depends not only on the physical properties of the aerosol, but on the anatomical and physiological characteristics of the recipient.

Although relatively few data on lung clearance of radioactive materials have been obtained from clinical experience, a considerable amount of information on retention and clearance of inhaled radioactive material has been obtained from experimental work with animals. The difficulties in applying this experimental information to man are recognized; however, this extrapolation has been found to be very reasonable in some situations. Palmes, for example, found that for the same atmospheric concentration of 1 μ clay particles, the fraction of inhaled material deposited in the alveoli was the same for both man and guinea pig[1]. Morrow et al. have obtained almost identical results for total deposition of submicronic particles in man and dogs[2, 3].

Impaction will be of primary importance where the air passages change direction abruptly and air flows are high. This would occur primarily in the upper respiratory tract and with moderately large particles. Lower in the respiratory tract where the air velocity is low, sedimentation will be of greater importance, except with the smallest particles (less than 0.1 μ) where diffusion or Brownian motion will be the principal processes. The latter process occurs primarily in the alveoli. Aggregation during the process of inhalation may influence the deposition of all respirable sizes. Condensation of moisture on particles being inhaled may alter their size and other properties. Thermal and electrostatic forces are of little importance except insofar as they contribute to aggregation. Particles larger than 30 μ seldom enter the respiratory tract; it is usual to consider 10 μ as the largest size of any real importance in normal inhalation exposures. As the size of inhaled particles increases beyond a few microns, deposition in the upper respiratory tract increases, and that in the lower tract decreases.

Pathologic conditions or physiologic differences among individuals considerably modify the quantity and the deposition pattern of material in the respiratory system. For example, the different air velocities and alveolar ventilation rates in a fast, shallow breather and a slow, deep breather cause differences in the total amount deposited and probably in the distribution to specific areas of the respiratory tract[2]. Further, the distribution of air to the various lung lobes is not necessarily in proportion to their volumes, so that some lobes may be much more adequately ventilated than others. This has been indicated by autopsy findings and by experiments with radioactive materials[4].

Hultqvist[5] has assembled theoretical and experimental findings on deposition as a function of particle size. From this he constructed two graphs, one showing deposition in the entire lung, and the other deposition in the lower respiratory tract. Figures III-1 and III-2 are adapted from his paper. They show the fraction of the mass (as a percentage) of an inhaled aerosol that would be expected to deposit at each of several arbitrarily selected mean sizes. The fraction deposited in the lower respiratory tract is shown to be greatest on the average at about 2 μ and goes through a minimum in the range 0.2 to 0.5 μ.

It will be noted that the data plotted divide about equally between calculated points based on an idealized lung model and recent experimental findings. Recent experimental investigations in the smaller particle size ranges using electron microscopy[6, 7] have confirmed that minimum deposition occurs at particle sizes between 0.5 and 0.2 μ, although the increase at still smaller sizes was not always observed. The data of Dautrebande[7] do indicate a rise in deposition at sizes below 0.5 μ. Still more recently, the deposition of submicronic particles in man and dog has been studied by Morrow et al.[2,3]. They found that as much as 65 percent of the inhaled aerosol was deposited, even more than the predicted mass deposition (45 percent) for the particle size range used.

The influence of the breathing pattern of an individual can be seen also in the curves of Figs. III-1 and III-2. The fast, shallow breather appears to deposit relatively less material than the slow, deep breather, other factors being equal. This is of considerable importance since these physiologic parameters can evidently exert about as much influence as particle size (compare curves 6 and 7, or 8, 9, and 10 in Fig. III-1). This same effect has been seen at sub-micronic particle sizes[2, 8].

The above data refer largely to particles of unit density or slightly above. Most studies in the past have used dusts or nebulized aerosols having densities of 1 to 2.5 g/cm^3. Heavy metals, such as uranium and plutonium, have densities greater than 10. At particle size ranges where impaction and sedimentation are important, the density factor may affect the deposition sufficiently to shift the curves of Figs. III-1 and III-2 significantly to the left. Thus, as Eisenbud has pointed out[9], a 2-μ uranium particle might act like a 5- to 7-μ particle of silica dust. The magnitude of this effect has not been evaluated for radioactive aerosols.

At submicronic sizes, density plays a less important role. This would also be true when radioactivity is carried largely on a vector dust. It is interesting to note also that aerosols of $Ru^{106}O_2$ and $Pu^{239}O_2$ do not show large differences in deposition despite the density difference, probably because of the wide range of particle sizes used and of other factors (see Table III-1). This problem is important in hazard evaluation and requires further study.

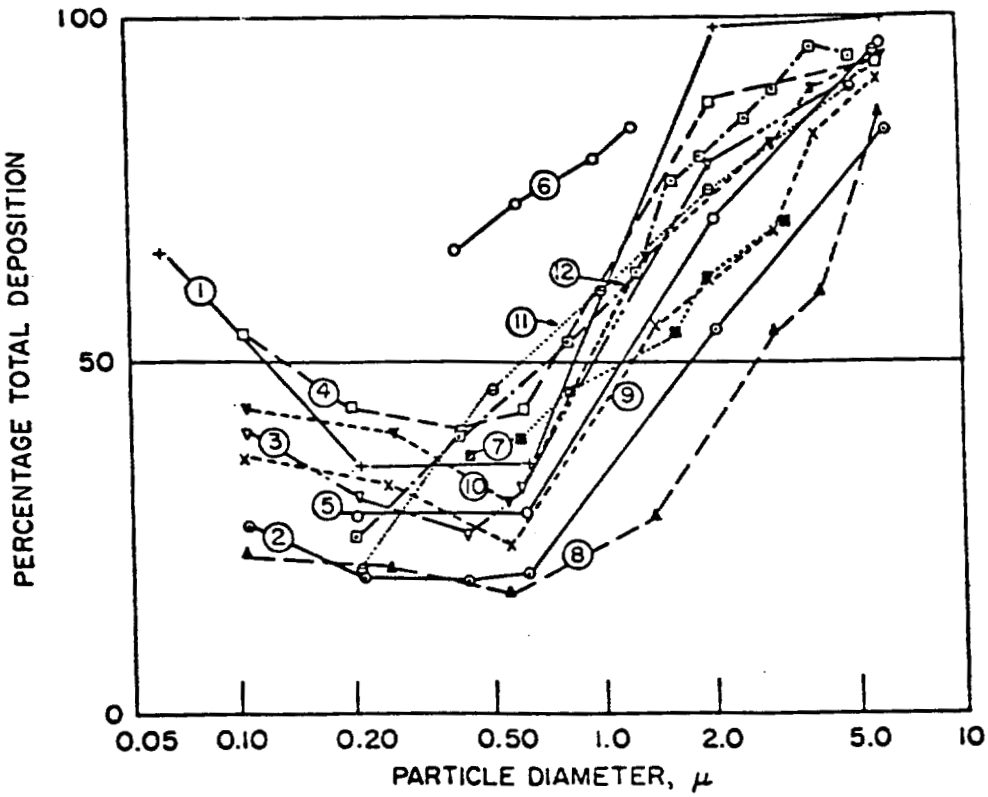


Figure III-1. Total Deposition in the Respiratory Organs (Adapted from Reference 5)

Curve No.	THEORETICAL DATA
1.	Findeisen (60): Postulated flow rate, 200 cm^3/sec; 14 cycles per minute.
2.	Landahl (61) and Landahl et al.(62): Flow rate, 300 cm^3/sec; 15 cycles per minute, tidal air volume, 450 cm^3.
3.	ibid. Flow rate, 300 cm^3/sec; 7-1/2 cycles per minute; tidal air volume, 900 cm^3.
4.	ibid. Flow rate, 300 cm^3/sec; 5 cycles per minute; tidal air volume, 1350 cm^3.
5.	Landahl (61): Flow rate, 1000 cm^3/sec; 15 cycles per minute; tidal air volume, 1500 cm^3.

Curve No.	EXPERIMENTAL DATA
6.	Wilson and La Mer (63): 5-1/2 cycles per minute.
7.	ibid. 20 cycles per minute.
8.	Landahl et al.(62): 15 cycles per minute; tidal air volume, 450 cm^3.
9.	ibid. 7-1/2 cycles per minute; tidal air volume, 900 cm^3.
10.	ibid. 5 cycles per minute, tidal air volume, 1350 cm^3.
11.	Brown et al.(64): Each point represents the mean of many values.
12.	Van Wijk and Patterson (65): 19 cycles per minute.

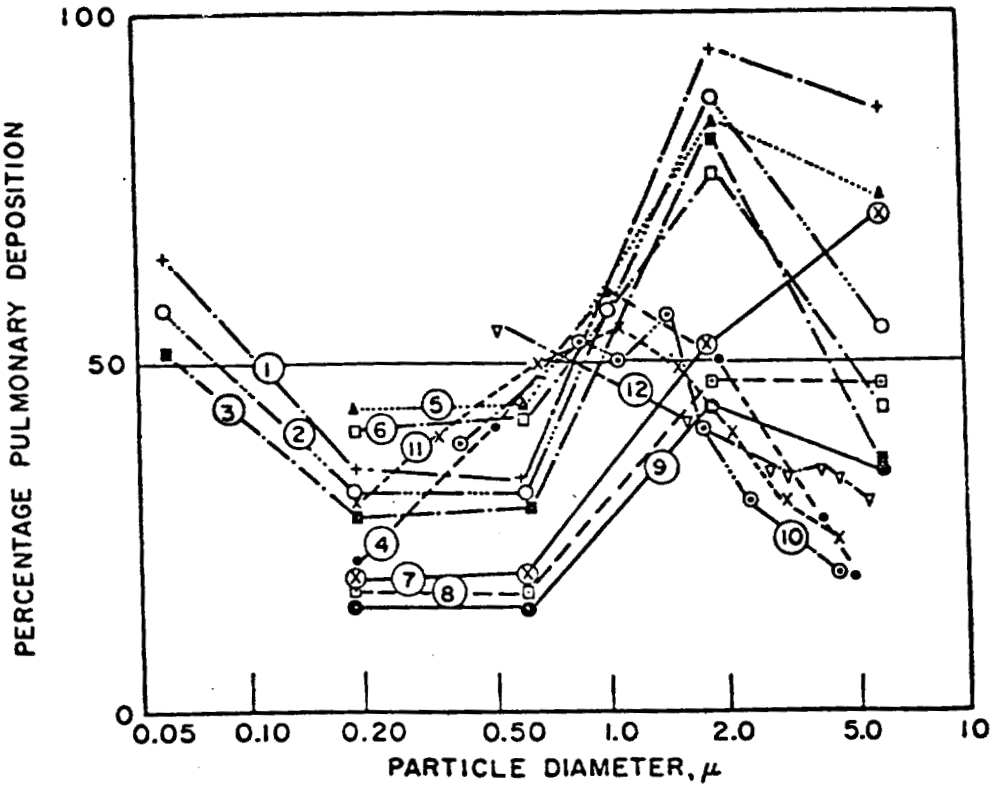


Figure III-2. Deposition in the Lower Respiratory Tract (Adapted from Reference 5)

Curve No.

THEORETICAL DATA

1. Findeisen (60): Retention in third order bronchi and smaller airways; 14 cycles per minute.
2. ibid. Retention in respiratory bronchioles and smaller airways; 14 cycles per minute.
3. ibid. Retention in alveolar ducts and alveolar sacs; 14 cycles per minute.
4. Hatch and Hemeon (66).
5. Landahl (61): Retention in third order bronchi and smaller airways; flow rate 300 cm^3/sec; 5 cycles per minute; tidal air volume, 1350 cm^3.

Curve No.

8. ibid. Retention in respiratory bronchioles and smaller airways; flow rate, frequency, and tidal air volume as for curve No. 7.
9. ibid. Retention in alveolar ducts and alveolar sacs; flow rate, frequency, and tidal air volume as for curve No. 7.

EXPERIMENTAL DATA

10. Wilson and La Mer (63): Mean for seven persons; number of cycles per minute between 5-1/2 and 20.

TABLE III-1
Pulmonary Retention of Radioactive Particles

Materials	Particle Size (μ)	Species	Duration of Observations (days)	Biological half-life[a]	Expressions for Retention	Ref.
I^{131} (b)	-	Mouse, sheep	2	3 hours	-	53, 54
AgI^{131} (b)	-	Mouse, sheep	4	5 hours	-	53, 54
$Zr^{88}O_2$	-	Man	-	30 hours	-	21
Thoron daughters (on Kaolin)	1.2[c]	Man	2	60 hours	-	20
Indium^{114}	-	Rat	6	2 - 4 days		55
$Po^{210}OH$(colloid)[e]	0.28[c]	Rabbit	30	5.7 days	$R_t=78e^{-0.118t}$	23
Po^{210}(-tagged Ag particles) [d]	0.10	Rabbit	30	4.4 days	$R_t=100e^{-0.25t}$	23
Po^{210}(on NaCl)	0.1[c]-0.4[d]	Rat	60(30)	10 - 60 days		24, 43
Po^{210}(on NaCl)	0.05[c]-0.2[d]	Rat	30	17 days		43
$Hg^{203}S$	-	Rat	-	30 days		26
$Sr^{90}SO_4$[f]	0.3	Mouse	140	2 days		28
$Sr^{85}Cl_2$ (on Kaolin)[f]	-	Rat	28	0.3 - 17 days	$R_t=0.34e^{-2.31t}+0.15e^{-0.04t}$	25
$Fe^{59}O_2$	2 - 3.5[c]	Man	70-100	100 days		20
$Pu^{239}O_2$	0.2	Mouse	140	3, 20, and 460 days	$R_t=70e^{-0.23t}+25e^{-0.034t}+4e^{-0.0015t}$	28
$Pu^{239}O_2$	0.1	Dogs (2)	280	1400 and 1600 days[g]		49
$Pu^{239}O_2$	1.0	Rat	350	180 days		30
CeO_2	-	Rat	210	80 days		30
UO_2	0.45	Rat	-	250 days		56
U_3O_8	2.6	Rat	-	90 days		56
$RaSO_4$	-	Man	365	32 - 140 days		22
$Ru^{106}O_2$	0.23	Mouse	500	7, 28, and 230 days	$R_t=83e^{-0.094t}+15e^{-0.024t}+2e^{-0.003t}$	28

(a) When the retention is characterized by two or more phases, the half-life of the early rapid phase is omitted. (b) Rapid translocation to thyroid. (c) Mass median diameter. (d) Count median diameter. (e) Intratracheally injected. (f) Rapid translocation to bone. (g) Determined from excreta data; includes retention in lymph nodes.

It is important to note that the data plotted in the graphs are percentages of the mass deposited, and do not necessarily represent the relative amounts of radioactive material deposited as a function of particle size. Only under the condition that the ratio of radioactivity to mass of particle is constant do the curves indicate the fraction of radioactivity that will be deposited. If, on the other hand, the aerosol is heterogeneous in that it contains a large fraction of small particles of relatively high radioactivity, then the contribution of these particles to the radiation dose, despite their relatively low deposition, may produce a major fraction of the total dose.

B. Pulmonary Clearance

1. Mechanisms

The processes governing retention, clearance, and translocation of inhaled particles are largely physiologic, although physico-chemical properties such as solubility and particle size strongly influence the rates of removal of material in the respiratory tract. The rates of clearance of radioactive particles are important because they influence the tissue exposure time and the degree of radiation hazard to the lung. Although the conditions for determining clearance rates have not been clearly delineated, removal of particulate material from the respiratory tract is thought to involve at least four mechanisms: ciliary action, transfer of soluble material across the alveolar membrane, phagocytosis, and, possibly, physical transport of particulates through the lung parenchyma. These are described in Chapter II.

The action of ciliated epithelium in combination with mucous secretion results in a rapid upward movement of the material deposited in the respiratory tract above the terminal bronchioles. Ciliary action is a continuous process and accounts for the removal of the largest fraction of particles from the respiratory tract. This is particularly true of those particles deposited in the upper respiratory tract and those that have not penetrated the lung beyond the terminal bronchioles. The linear velocity of particles moving up the bronchi is 0.25 to 1 cm/min[10, 11]; in the trachea, rates of up to 3 cm/min have been measured[12]. For obvious reasons this process is sometimes likened to an escalator and termed the "mucous-cilia escalator".

Transfer of relatively soluble material across the alveolar membrane into the blood stream is the second mechanism of respiratory tract clearance. "Soluble"* material enters the systemic circulation relatively rapidly. Substantial amounts of "insoluble"* materials may be trapped and removed by the mucous-cilia escalator, but small amounts (<10 percent) of materials as "insoluble" as PuO_2 are rapidly solubilized and deposited eventually in the skeleton and liver. For example, even at 10 to 20 days after inhalation, PuO_2 is found to be entering the blood stream from the lungs. However, the quantity that enters the blood is only a very small fraction of the amount in the respiratory tract.

The third mechanism for removal of particulate material from the tract is phagocytosis[13]. The rate of phagocytosis for any given particle has been found[14, 15] to be a function of particle size. Larger particles may be phagocytized more rapidly than smaller particles. Phagocytic activity also depends on the physico-chemical properties of the particulate matter, as illustrated by the observation that carbon particles were phagocytized faster than quartz particles in vitro. A phagocytized

* The terms soluble and insoluble are placed in quotes since simple solubility in pure solutes need not be a measure of solubility in the lung (see Chapter I).

particle may be moved into an alveolus and transported upward, or the phagocyte may enter the lymphatics and be transported to the lymph nodes. Significant quantities of material may be found in the lymphatics. For example, with radioactive AgCl colloids, the material was found[16] to be concentrated to a large extent in the lymphatic system draining the pulmonary region.

It has been postulated[17] that some particles may penetrate the respiratory membrane and migrate around vascular and bronchial positions without the mediation of phagocytic cells. Penetration of the respiratory membrane is thought to occur in multiple, small, scattered foci near the juxtaposition of alveoli and large vessels and bronchi. It has also been suggested[17] that the penetration of the respiratory membrane occurred through defects in the membrane. Direct penetration of the alveolar lining by sufficiently fine particles is also a possibility. Important physical factors in the penetration of the respiratory membrane and the migration of particles may be the fluctuating pressures in the lung during the respiratory cycle. However, proof of the existence of this mechanism is not as strong as for the others.

Relatively few data are available regarding the fate of radioactive particles initially deposited in the nose and upper respiratory passages, but it is likely that a considerable amount of the absorbable material in both radioactive and non-radioactive particles can enter the blood from this area[18]. The clearance mechanisms for removing insoluble particles from the upper respiratory tract are similar to those in the lower portions of the tract. Removal rates are usually faster, probably because the entire upper respiratory tract, except the anterior third of the nose, is lined with ciliated epithelium. In view of the frequency of pathologic and anatomic defects and the relatively large size and concentration of particles found, the nose and postnasal sinuses should also be considered in studies of the possible development of neoplasm following inhalation and long-term retention of radioactive particles. There were nasal sinus cancers in the radium dial painters[19].

The clearance of activity from the respiratory tract can usually be described by at least two different rate processes. Initially there is a rapid removal of activity up the respiratory tract with a half-life of minutes to hours, probably due mainly to ciliary action. There is also a slower process that probably involves removal of material deeper in the tract. This latter process has a half-life ranging from days to months, depending on the nature of the material. These rates of clearance are of considerable consequence in determining tissue exposure and consequent radiation damage. Frequently, there may be no single rate constant which can characterize these processes over long periods.

2. Clinical Studies

Few data on lung clearance are available from studies on humans exposed to radioactive aerosols because most of the exposures were accidental and only incomplete information could be obtained. There have been a few experimental studies on human beings, however, involving tracer levels of radioisotopes. Their main objective was usually the determination of the turnover rate of the inhaled material. Results of one clinical study[20] showed a 60-hr biological half-life in the lung following the inhalation of thoron daughters adsorbed on kaolin particles. Lung clearance studies[20] with radioactive metallic iron dust suggested two phases in the early bronchial clearance of particles: a very rapid phase ending in 2 to 4 hrs. and a second phase ending in about 30 hrs. Following the inhalation of another

radioactive aerosol, $Zr^{89}O_2$, all but 2.2 percent of the radionuclide inhaled was deposited[21]. A total of 32 percent of this deposited material was removed by the bronchial route.

Lung clearance rates were studied[22] in several individuals exposed to radium sulfate dust as a consequence of industrial accidents. Half-lives varying from 32 days initially to 140 days within six months after exposure were obtained by such methods as determination of the amount of radon exhaled, measurement of the gamma-ray activity from the thorax and from the whole body, and measurement of radium in the excreta. Clearance of particles from the bronchial mucosa, as determined by external gamma counting techniques, demonstrated the effectiveness of the ciliary mechanism. However, the retention of small quantities of insoluble materials in the lung for long periods of time was also demonstrated.

3. Animal Studies

A number of experimental studies using laboratory animals have been carried out on the retention and fate of inhaled fission product aerosols and of various other radioactive materials. Single inhalation exposures were primarily studied, to obtain data on retention in the lung and translocation of material to other tissues. These studies illustrated the complex kinetics of lung clearance, due both to the physical and chemical properties of the inhaled particles and to the physiologic characteristics of the animal.

The kinetics of the retention of material in the lungs can often be described by a series of exponential functions ($R_t = R'_1 e^{-k_1 t} + R_2 e^{-k_2 t} .... + R_n e^{-k_n t}$). Often a power function ($R_t = At^{-n}$) can also be used to describe the data and may be particularly useful for determining body burdens from excretion data over a long period of time.

Data from both animal studies and tracer studies with man are summarized in Table III-1. Pulmonary retention is expressed as biological half-life, the time required for the lung burden to be reduced by half. Data are given for several materials tabulated according to relative half-life values and include (when available) particle size, the duration of the observations, and equations expressing the retention. Clearance rates differ markedly for the different compounds, usually being consistent with known solubility characteristics, yet in some instances being entirely unpredictable. Some materials, I_2^{131}, AgI^{131}, $Sr^{89}Cl_2$ and thoron daughters (on kaolin particles) were cleared almost immediately from the lung, probably due to rapid solubilization, though silver iodide is considered an "insoluble" material. Other materials, though also very "soluble", are not so rapidly cleared from lungs but are cleared within a few days. For example, a Po^{210} hydroxide colloid (40 Å in diameter) intratracheally administered in rabbits was rapidly transferred from the lung with a biological half-life of 5 days[23]. The main route of redistribution from the lung in this case, contrary to the usual findings, did not appear to be via the tracheal-bronchial tree into the gastrointestinal tract. It was suggested that polonium was eliminated through the lung parenchyma by diffusion and by the participation of the lymphatics. In another part of this study[23], the same lung clearance rates were observed following intratracheal administration of Po^{210}-tagged silver particles less than 10 μ in diameter, despite the marked differences in size and physical form. In inhalation studies using a Po^{210}-contaminated NaCl aerosol[24], half of the inhaled aerosol was deposited in the animals, equally divided between the lung, trachea, and gastrointestinal tract. The quantity of polonium present after the exposure

was described by a function containing two exponentials representing biological half-lives of 10 and 60 days. Further, the tissue distribution of the aerosol after inhalation was quite different from that observed after intravenous, oral, or intratracheal administration. In these studies the distribution and excretion of the Po^{210}-NaCl aerosol after inhalation represented a balance between that observed after intratracheal administration and oral administration.

Lung retention, during a 28-day period, of a very "soluble" aerosol ($SrCl_2$) adsorbed on clay particles was described[25] by the sum of two exponential functions: $R_t = 0.34\ e^{-2.31t} + 0.15\ e^{-0.04t}$. The first exponential indicated an initial rapid clearance of material considered to be associated with the ciliary mechanism and direct absorption in the blood stream. The second component may be associated with the slower rate of loss of particles "fixed" in the alveolar tissue, combined with the loss of material resulting from the solubilization of strontium and absorption into the systemic circulation. The biological half-lives for the two components were 0.3 and 17 days, respectively. In these studies, the rate of clearance of activity from gastrointestinal tract and most internal organs during the 28-day period could also be described by the simple sum of two exponentials. Clearance from rat lungs of $Hg^{203}S$ particles, ordinarily considered very "insoluble", was also investigated.[26] The biological half-life of the material in the deep respiratory tract was found to be only 30 days, thus emphasizing again that behavior in the lung cannot always be predicted from solubility in pure solutes.

Of major concern are the materials that are truly "insoluble" in lung tissues and are retained for a long time. In addition to radium sulfate, these include several fission products and fissionable materials.

A study was made[27] of the uptake and retention of a very "insoluble" thorium compound administered intratracheally. Negligible urinary excretion of the thorium was observed. Most of the material was concentrated in the lung.

In inhalation experiments[28] with $Ru^{106}O_2$, pulmonary retention in mice during a 500-day period after exposure was described by a series of exponentials (Table III-1). Fractions of the originally deposited material showed long half-lives; for example, 2 percent of the deposited dose showed a half-life of 230 days. Similar studies with $Pu^{239}O_2$ in mice were also reported[28]. The half-life for 4 percent of that deposited in the lung was 460 days.

The lung clearance of PuO_2 in rats (after the first 10 days) was expressed[29] by a single power function: $R = 6.4t^{-0.8}$. The same PuO_2 lung clearance data have been represented by two exponential functions over a one-year period[30]. Pulmonary retention studies in rats with $Ce^{144}F_3$, a more "soluble" compound than PuO_2, indicate that the lung clearance rate over an 8-week period can also be described by a series of exponential functions[26]. As with PuO_2, the clearance rate of the CeF_3 particles from the deep respiratory tract over a longer period of time can be described by a power function of time.

Although one would predict that whole-body radiation injury would cause impairment of the clearance mechanisms, studies in rabbits[31] have shown that inhaled insoluble particles are removed from the lungs and respiratory tract even more rapidly and completely in the irradiated (800 r) animals than in the normal controls. These findings were attributed to the associated increase in mucous secretions and

ciliary activity in the first two weeks after radiation exposure and to a secondary increase in phagocytic activity during the third and fourth weeks.

From the data summarized here, a few general principles can be derived. First, radionuclides in forms that are very "soluble" in body fluids are cleared from the lung very rapidly (1 hr or less) and appear equally rapidly in the organ of ultimate deposition, the skeleton in the case of Sr^{90} and the thyroid in the case of I^{131}. The mechanism of lung clearance primarily involves the second process described above; namely, solution of the aerosol and direct passage into the systemic circulation. The radiation dose to the whole lung from such a "soluble" aerosol as $Sr^{90}Cl_2$ is much less than that received by bone and bone marrow. Second, slightly "soluble" radionuclides ($Ce^{144}O_2$) are cleared from the lung at lower rates --- within a few days. Third, a relatively "insoluble" particle such as PuO_2 is removed from the lung by at least two different processes. (The retention half-life of PuO_2 may be 500 days or longer (Table III-1.) The lung clearance mechanism involved here is primarily ciliary action, although a small fraction of the material (much less than 10 percent) is absorbed across the alveolar membrane. Important, too, is the fact that slightly "soluble" material may enter the systemic circulation across the alveolar and gastrointestinal membranes[32]. Finally, the lung clearance of a material is not always predictable from its behavior in pure solutes.

4. Deposition and Clearance Following Exposure to Radioactive Fallout

a. Field Studies. Studies involving the short-term exposure of animals to radioactive fallout have been made both in the field and in the laboratory. In field tests conducted at the Nevada Test Site[33], the retention of particulate matter in the respiratory system of exposed animals was small. The lungs of rabbits exposed to fallout, at distances from 7 to 106 miles from ground zero, had no detectable radioactivity, while the intestines from the same animals had barely detectable levels of activity. The integrated internal dose could be expressed in millirads, even in close-in stations where the integrated external dose was 14 to 32 r.

In the Pacific Nuclear Weapon test of March 1, 1954, a number of human beings and animals were accidentally exposed to airborne fallout[34, 35]. The amounts of radionuclides taken up and retained were considerably larger than in the continental tests, partly because the Pacific test involved a different type of detonation, and the carrier material of the fallout was considerably more "soluble" than that encountered in the Nevada tests. Although a large number of fission products were present in the environment after the Pacific test, only a few were found to have entered the body. These included Sr^{89}, Ba^{140}, I^{131}, and some of the rare earth elements. The routes of entry were both inhalation and ingestion. Biological removal and radioactive decay rapidly reduced levels of radioactivity in the lungs of exposed animals (pigs); after 3 months only 0.02 percent of the beta-ray activity of the entire body was present in the lungs. Six months after the detonation, the radioactivity levels in the lungs were barely detectable. Other field studies[36] particularly concerned the inhalation of alpha emitters.

b. Laboratory Studies. Laboratory studies designed to provide data on the uptake and clearance of inhaled fallout material have been of two types: those which use deposited radioactive fallout material from nuclear testing sites, and those which simulate fallout material. In studies of the first type, rabbits were exposed to aerosols produced from materials collected at the Nevada Test Site[33]. The materials were

used several months after the contaminating event, so that only the longer lived fission products were present. Further, the materials were siliceous and therefore highly "insoluble" (one percent in water). Following single 4-hr exposures to a dust concentration of 1 $\mu c/cm^3$ of particles with a mass median diameter of 0.3 μ, the amount initially retained in the lungs was about one-ninth that found in the stomach. Clearance from the lung and gastro-intestinal tract was practically complete by 96 days. The clearance rates from both were very similar and followed an exponential function, with about 85 percent lung clearance in seven days and about 95 percent clearance from the gastrointestinal tract in the same time.

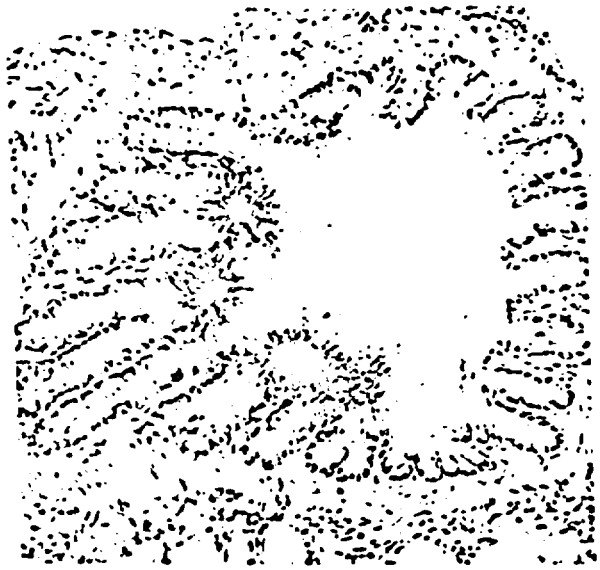
In repeated exposure studies[33] in which rabbits and rats were given as many as 60 separate 6-hr exposures (5 days each week) to the siliceous radioactive material from the Nevada Test Site, using concentrations of 0.01 $\mu c/cm^3$, the pulmonary burden increased as the number of exposures was increased. Lung clearance values following these multiple exposures were much lower than values obtained following a single exposure. About 30 percent of the material deposited immediately after termination of exposure was cleared in 30 days, and 70 to 75 percent in 60 days.

In laboratory experiments designed to reproduce fallout from various types of nuclear detonation, products from 2-day-old neutron bombarded uranium associated with various types of carriers were employed as fallout simulants[37, 38]. In these inhalation experiments the animals (mice) received many of the short-lived radioisotopes. The distribution, retention, and clearance of the fission products in these animals confirmed the fact that the uptake and metabolism of the inhaled radioactive particles depends largely on the physical and chemical characteristics of the carrier material. It was also found[39] that the retention and metabolism of these fallout simulants by the lungs and other tissues could be altered by the injection of zirconium citrate immediately preceding or soon after exposure. 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 because the activity of the aerosol was contributed chiefly by short-lived radioisotopes, and the biological loss of the material from the lungs and soft tissues was very rapid.

5. Influence of Physiologic and Pathologic Factors

While the influence of physiologic factors (ventilation rate, air velocity, etc.) on deposition has been studied in some detail, the influence, if any, of these factors on pulmonary clearance has not been determined for radioactive materials. However, it is known from studies of infection, etc., that pathologic processes that alter structure and/or function can modify the clearance process. For example, Hilding[40] has demonstrated ciliary insufficiency and resultant accumulation of mucus and debris in cases of asthma and other respiratory diseases. He has noted[41] an apparent tendency for bronchiogenic carcinoma to occur in areas most likely to be deficient in ciliary activity. Accumulation of mucous and other materials at points of branching was noted by Miller[42]. More recently, results obtained using autoradiographic techniques[43] have indicated that radioactive materials accumulate near bronchiolar openings and in other areas in the normal rat, as seen in Fig. III-3. This process might be accentuated when normal ciliary epithelium is replaced by other cell types.

Po^{210} Aggregates
in Small Bronchiole
2 Hours after Inhalation



Po^{210} Particles at Points of Entry
from Smaller to Larger Bronchioles
12 Hours after Inhalation

It has been reported recently[44] that the simultaneous administration of moderate amounts of inert dust can accelerate the removal of the biologically active particles from the lung when the latter are present in small amounts. It was suggested that this effect was due to a greatly increased stimulus to phagocyte release provided by the greater lung burden.

C. Translocation and Excretion

Regardless of the nature of the inhaled material, a significant degree of translocation of radionuclides occurs from the lungs to other organs and tissues. Thus, there is not only a direct radiation hazard to the lung from inhaled material, but also a systemic radiation hazard from inhaled material, absorbed and subsequently deposited in other tissues.

Once the lung-deposited material enters the systemic circulation through the alveolar or gastrointestinal membrane, the tissue distribution is expected to be qualitatively similar to that of the same material injected intravenously. There may be some exceptions to this generalization, however. For example, following the intratracheal administration of Po^{210}, the metabolism of the material that entered the body through the lungs, even though a soluble salt, is quite different from that following intravenous or oral administration[45].

With a soluble compound ($Sr^{90}Cl_2$), the absorption across the alveolar tissue following inhalation is approximately equal to the absorption across the gastrointestinal tract following oral administration. Further, following exposure to an aerosol of $Sr^{90}Cl_2$ or $La^{140}Cl_3$ adsorbed on a clay particle, the ratio of activity in the gastrointestinal tract to that in the respiratory system was approximately 100.[25] This high concentration of activity in the gastrointestinal tract and the high solubility of $SrCl_2$ across the gastrointestinal membrane suggest that for soluble aerosols, the gastrointestinal tract can be an important route of entry of inhaled material into the systemic circulation[25]. Thus, evaluation of the internal hazard associated with inhalation exposures to soluble aerosols requires the consideration of those parameters that influence transport of material across the gastrointestinal membrane.

In general, following the inhalation of "insoluble" or slightly "soluble" compounds, the respiratory tract or a portion of the gastrointestinal tract is the critical organ (i.e., the organ containing the highest concentration of radioisotope). If a "soluble" particulate material is inhaled, the upper respiratory tract or gastrointestinal tract may initially be the critical organ. During the period of inhalation of the radioisotope, the gastrointestinal tract is usually the critical organ, although with alpha emitters, the radiation originating within the contents of the intestines does not seem to be effective in causing acute damage to the intestinal wall[46]. The dose to the lung from inhalation of "soluble" compounds is usually less than the dose to the gastrointestinal tract.

Recent work[36, 47, 48] indicates that radioactive particles removed from the lungs may be collected in the tracheobronchial lymph nodes and remain there for long periods. The data in Table III-2 show that the concentration of material in the lymph nodes may sometimes greatly exceed that in the lung[36, 47]. These data were obtained both in laboratory experiments and from a field exposure to an "insoluble" alpha emitter. Pulmonary-lymph-node-to-lung ratios greater than 1 indicate that the nominal dose rate to the lymph node exceeds those to the rest of the lung. This

TABLE III-2

Ratio of Pulmonary Lymph Node (PLN) to Lung Concentration

Material	Relative Soly. of Compound	Species	Type of Exposure	Time		PLN/Lung[a]	Ref.
				Exposure	Post-Exposure		
UO_2	Insoluble	Monkey	Inhalation	93 days	Short	49	51, 57
UO_2	"	Dog	"	6 months	"	1.5	51
UO_2	"	Dog	"	12 months	"	6.2	51
UO_2	"	Dog	"	24 months	"	13.8	51
UO_2	"	Rat	"	6 months	"	0.3	51
UO_2	"	Rat	"	12 months		1.95	51
UO_2	"	Rat	"	12 months	6 months	13.2	51
UO_2	"	Dog	"	1 year	Short	22	58
UO_2	"	Dog	"	1 year	"	1.3	58
U Nitrate	Soluble	Dog	Inhalation	Few months	8 years	53	51
ThO_2	Insoluble	Dog	Inhalation	5 hrs	10 days	0.05	24
Po^{210}	Soluble	Rat	"	5 hrs	57 days	0.26	24
Oxide on	"	Rat	"	20 min	5 days	0.06	43
NaCl	"	Rat	"	20 min	20 days	0.10	43
crystals	"	Rat	"	20 min	30 days	0.19	43
	"	Rat	Intratracheal injection	Immed.	2 days	0.12	45
	"	Rat	"	Immed.	10 days	0.40	45
	"	Rat	"	Immed.	30 days	4.1	45
	"	Rat	"	Immed.	62 days	2.8	45
$Pu^{239}O_2$	Insoluble	Dog	Inhal. (field)	160 days	4 hours	12.5[b]	36
	"	Burro	"	160 days	4 hours	17.8[b]	36
	"	Dog	Intratracheal injection	Immed.	10 days	0.06	58
	"	Dog	Inhalation	Immed.	10 months	10 to 100	49

(a) Ratio of concentrations in pulmonary or tracheobronchial lymph nodes/lung parenchyma on a per gram basis.
(b) Using median.

can result from longer retention of particles in the lymph nodes than in the rest of the lung and from gradual movement of particles in the lung to lymph nodes. That movement of particles to lymph nodes occurs with the passage of time has been recently shown[49]. Two weeks after beagle dogs were exposed to plutonium oxide, the ratio of plutonium concentration was found to be about 0.1. Forty weeks after they were exposed, the ratio was about 50. Autoradiograms (Figs. III-3 and III-4) also show accumulation of "insoluble" alpha emitting particles in the bronchioles and in the lymphoid tissue of the lung[47, 43]. The importance of this concentration in the lymph nodes in evaluating the inhalation hazard must be further investigated[48].

Figure III-4. Autoradiogram Showing Alpha Tracks in Lung and Lymph Node of a Mouse 100 Days after Intratracheal Administration of 2.5 μc $Pu^{239}O_2$ (18X) (Ref. 47)

D. Models for Deposition and Retention

1. ICRP Lung Model

To provide a consistent and conservative basis for estimating the accumulation of radioactive material in the lung, the International Commission on Radiological

Protection[50] derived a model for the respiratory characteristics of the standard man. The model, reproduced here as Table III-3, shows these characteristics in terms of single numbers which presumably provide an estimate of maximum hazard.

TABLE III-3

Distribution of Inhaled Particles
(Ref. 50)

Distribution	Readily "soluble" compounds (%)	Other compounds (%)
Exhaled	25	25
Deposited in upper respiratory passages and subsequently swallowed	50	50
Deposited in the lungs (lower respiratory passages)	25(a)	25(b)

(a) This is taken up into the body.
(b) Of this, half is eliminated from the lungs and swallowed in the first 25 hours, making a total of 62.5 percent swallowed. The remaining 12.5 percent is retained in the lungs with a half-life of 120 days, it being assumed that this portion is taken up into body fluids.

According to the model, 75 percent of the inhaled material is assumed to be deposited, with 25 percent deposited in the lower respiratory tract for either "soluble" or "insoluble" material. The 50 percent deposited in the upper respiratory tract is eliminated rapidly and subsequently swallowed. All of the "soluble" material reaching the lung is dissolved and enters the blood, while only half of the "insoluble" material is eventually removed from the lung, at a rate governed by a 120-day biological half-life. This model was devised and was intended for use only when information was lacking to provide a more realistic estimate.

It is apparent from Figs. III-1 and III-2 that the deposition is a function of the particle size on which the radioactive materials are carried. If one can assume uniform quantities of radioactive materials per unit mass of particle, then deposition will be least for particles in the size range 0.2 to 0.4 μ. There is no assurance, however, that all sizes will be uniformly contaminated; in the extreme case, it is possible that all the radioactive materials could be carried on the sizes giving maximum pulmonary deposition. Thus, complete evaluation of the effects of inhaled radioactive materials requires measurement of the total quantity of radioactive materials carried by particles of various sizes. By comparison with the data in Fig. III-1, the total deposition value of 75 percent used by the ICRP is relatively conservative for most size ranges. Obviously, it can only underestimate the quantity deposited by about 30 percent, although it could overestimate by a factor of 5 to 10 in particular situations. The 25 percent deposition assumed for the lower respiratory passages is based

upon results of animal studies and is more tenuous. Note that Morrow et al[2, 3] have indicated that deposition of small particles in the lower respiratory passages may be as high as 70 percent of the inhaled material.

Clearance mechanisms, although described qualitatively, have not been investigated in sufficient detail to permit adequate quantitative models that describe the clearance rates for the more important variables. It is generally agreed that materials deposited in the ciliated upper portion of the respiratory tract are removed to the gastrointestinal tract within a matter of days or hours. "Soluble" materials reaching the lung are absorbed as easily or more easily than from the gastrointestinal tract, but the rate of absorption from the upper respiratory tract is a matter of conjecture. From this standpoint, the 25 percent absorption of inhaled "soluble" materials is reasonable and, in general, the radiation dose to the respiratory tract from easily absorbed materials is relatively low. There is additional need to investigate the concept of solubility in this respect, since it is known that "insoluble" materials such as strontium sulfate or silver iodide are rapidly removed from the lung and moved into the bloodstream. An adequate definition of the variables here could define more clearly the importance of the lung as a factor in estimating the maximum permissible concentrations for "soluble" radioisotopes in air.

The retention of 12.5 percent of the inhaled "insoluble" materials in the lung with a biological half-life of 120 days is a reasonable assumption, for lack of other information. Certainly the retention and half-life depend upon both the physical and chemical nature of the particle, and variations would be expected, even for the same element from different sources.

Present data on the elimination rate from the lung are confusing from the standpoint of the mathematical model best suited to describe the rate. Some experiments indicate a fit to an exponential retention curve (i.e., a constant fractional removal per unit time), while others indicate a decrease in the fractional rate of removal. This again may be influenced by the physical and chemical form of the particles but completely satisfactory estimates of the radiation dose cannot be made before this factor is known.

The model does not mention the possible accumulation of "insoluble" particles in the lymph nodes, a process recently demonstrated[51] with chronic uranium and thorium exposures.

The studies on deposition and retention, as well as the ICRP model, are primarily related to the "normal" man (i.e., an individual with an intact, healthy respiratory system). It is known that many individuals have defects, either hereditary or disease-induced, in the respiratory tract. Many of these defects could change the deposition and retention patterns noted earlier to the extent that a larger fraction of the inhaled material is deposited and the rate of elimination is reduced. If, as is believed, this group constitutes a sizeable fraction of the population, the "standard man" should be based on estimates valid for these individuals; otherwise, some people would receive significantly higher doses than those intended in the establishment of present limits.

2. Criteria for a Revised Model

Although the ICRP model serves well as a guide for practical inhalation hazards control, a refined model may soon be derivable. New knowledge is rapidly becoming

available of the variables that affect deposition, retention, and toxicity of radioactive particles. All three of these parameters, necessary to a refined model, may be expected to vary, depending on the physiologic state of the individual. It may be envisioned that a future model will take into account age and condition of the lungs, but little can be said about these factors now because of the paucity of knowledge.

Aside from the problem of accounting for individual variation among humans, some progress in establishing a model can be achieved. For describing deposition mathematically, the respiratory tract could be arbitrarily divided into a series of compartments, such as alveoli, bronchioles, bronchi, trachea, etc., with separate deposition-versus-size curves assigned to each. To do so would require data not yet available, and would be so complex as to be impractical for use. Figures III-1 and III-2 suggest a similar but simpler approach. A composite of the two figures appears in Figure III-5. This suggests a model for deposition divided into only two compartments, the upper and lower respiratory tracts. (The latter is defined as that portion of the tract which consists of alveoli and bronchioles; the upper tract is what remains.) The influence of variables that affect deposition --- respiration rate, particle size, and particle density --- is indicated. Although such a deposition model is not yet sufficiently quantitative to allow complete confidence in applying it, it does suggest that some progress can be made in more accurately estimating deposition for particles of known size and density.

Similarly, it should soon be possible to more accurately describe retention than by a single half-life, and to better define the critical organ. Turnover data summarized in Table III-1 suggest that some increase in precision of estimates can be presently achieved. Table III-2 suggests that sufficient evidence might be available in the near future to indicate that the critical organ is not the whole lung but the pulmonary lymph nodes.

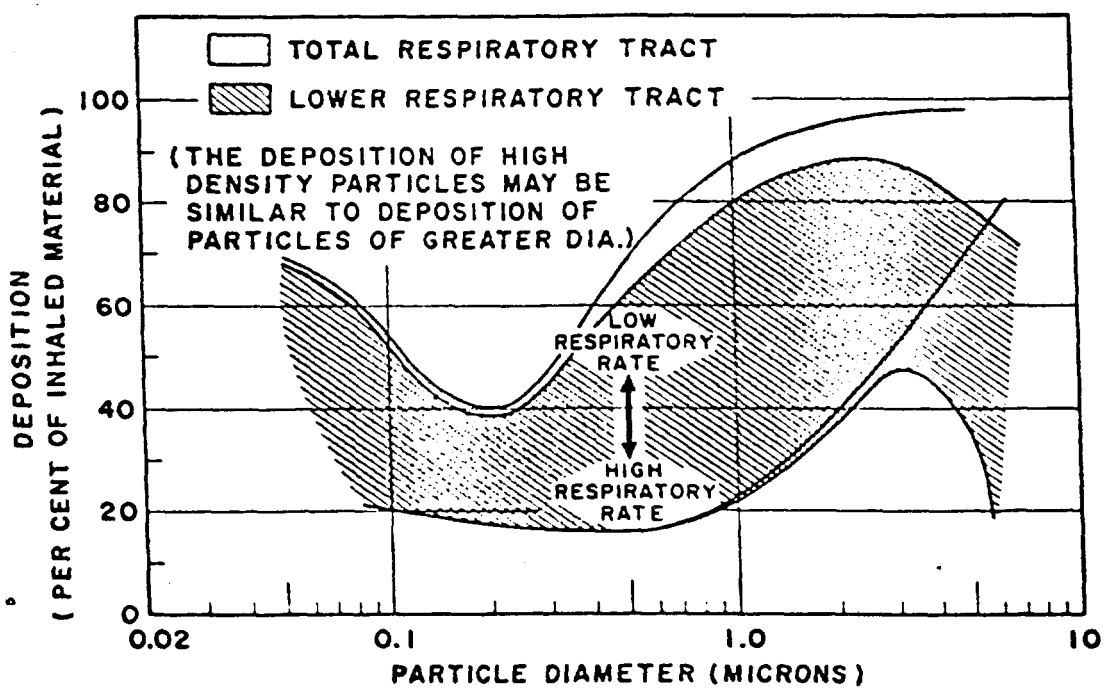


Figure III-5. Deposition in Respiratory Tract

Finally, the toxicity caused by radioactive particles deposited in the lungs is becoming better known as research progresses. The accurate correlation of dose distribution to biological effects is required by the eventual model for assessing inhalation hazards; subsequent chapters indicate that steps toward making such a correlation should soon be possible.

E. Estimation of Lung Burden

The estimation of lung burdens of inhaled radioactive material in humans is usually difficult. The two approaches used are the direct and indirect methods.

For gamma emitters, the direct approach makes use of collimated gamma scintillation spectrometers in heavily shielded whole-body counters[22]. Using appropriate phantoms, it is possible to calibrate the counters to read absolute levels of lung-deposited gamma emitters. The application of these external counting techniques to the measurement of lung burdens of pure beta emitters is made difficult by the characteristics of the radiation emitted, although theoretically such measurements are feasible.

The indirect method estimates the lung burden from the measurement of radioactive material excreted. If the radionuclide in the lung decays to a radioactive daughter that is exhaled, the burden can be estimated from measurements of the daughter's concentration in exhaled air. Such a method was one of those used for determining retention of radium in humans[22].

Since an inhaled "insoluble" material is removed from the lungs primarily via the gastrointestinal tract, it has been suggested[29] that the lung burden of an "insoluble" material can be estimated from the fecal excretion rate. In another model suggested for estimating lung burdens of PuO_2, both fecal and urinary excretion rates were used[52]. It was assumed that a constant fraction of the PuO_2 present was daily transferred from the lungs to the systemic circulation and that the urinary and fecal excretions could be described by power functions. The success with which such mathematical models can be used to accurately relate concentration of radioactive material in excreta to lung burden is not proven.

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Chapter IV

LUNG DOSE CONSIDERATIONS

To provide some basis for understanding the observed effects of inhaled radioactive substances and to compare these with the effects of externally applied radiation or with the effects of nonradioactive materials, it is necessary that the distribution of the energy from the material be known with some detail. If the actual distribution of radioactive material is known, and if the properties and rate of production of ionizing radiation from this material are known, it is theoretically possible to calculate the dose distribution. This is usually impractical, however, especially in the case of particulate materials which may not have a permanent location in the lung.

Despite the difficulty in determining the distribution of radioactive material in the lung, there are some calculations that can be performed to provide indices for comparisons between different kinds of observed damage.

A. Uniform Distribution

In the simplest case for evaluation of the dose or dose rate, the radioisotope is assumed to be deposited uniformly through the volume of an organ that is large compared with the range of the radiations involved. Under these conditions, it may be assumed that the rate of energy emission from a given volume is equal to the rate of energy absorption in the same volume. Thus, the dose rate is:

$$D' = \frac{q \times 3.7 \times 10^4 \times 86,400 \times \overline{E}}{m \times 6.24 \times 10^5 \times 100} \qquad (1)$$

$$D' = 51 \frac{q\overline{E}}{m} \text{ rads/day}$$

where

q = quantity of radioactive material in the organ (μc)

3.7×10^4 = disintegration per sec per μc

86,400 = seconds per day

$\overline{E}$ = average energy released per disintegration (Mev)

m = mass of the organ (g)

6.24×10^5 = Mev/erg

100 = ergs/g/rad.

The above formula gives only the dose rate; the total dose over any given period of time can be determined by integrating over the time allowing for the change in dose rate with time for both the radioactive decay of the material as well as for its removal from the lung.

If the rate of removal of the material can be represented by an exponential, then the total dose due to one radioactive species from time of inhalation to infinity is given by

$$D = 51 \frac{q \overline{E}}{m \lambda_e} \qquad (2)$$

where $\lambda_e = \lambda_b + \lambda$, in $days^{-1}$

λ_b = biological elimination constant

λ = radioactive decay constant

These formulas are applicable only to those elements of the organ with dimensions greater than the range of the radiations. At the surface of such an organ and the layer of other tissue surrounding the organ, the dose rate and the dose due to the contained radioisotope will approach one-half the above values.

If gamma radiation is present or if the organ is smaller than the range of the radiation, a correction must be made for the fraction of radiation that escapes. In small animals the gamma dose can be neglected. In man, since the lung is a relatively large organ, it may be necessary to consider the gamma radiation, particularly where the gamma energy emission is large compared to the beta energy. These corrections are made by integrating the absorption of gamma rays originating in each element of the tissue over the volume of the organ. In general, such procedures are complex for non-regular shapes and must be carried out through numerical techniques. An approximation of the gamma absorption may be obtained by assuming the organ to be spherical and solving for the dose rate at the center. Again the distribution of gamma dose through the tissue mass is non-uniform, with a maximum at the center and a minimum at the edge.

B. Focal Distribution

The presence of discrete particles containing radioactive materials produces a non-uniform pattern of radiation dose in the surrounding tissue. This pattern is characterized by an inverse square relationship modified by the rate of energy loss along the path of the radiation, and by prior energy absorption.

The calculation of these dose rates has been investigated in detail by Loevinger[1], who formulated an empirical function for the absorption of energy from beta particles, and by Roesch[2], who applied the age diffusion theory to problems of beta dose rates. *

* Age diffusion theory was originally developed by Fermi to explain the diffusion of neutrons in various reactor media. It is analogous in many respects to thermal diffusion theory, for example. The particular significance of age as applied to diffusing neutrons is that neutrons with a large age have less kinetic energy than do those with a small age. Energy loss of electrons "diffusing" in tissue is described by Roesch on a similar basis.

The age diffusion theory is applicable at distances greater than one mean free path. An alternate approach suggested by Healy[3] is to integrate the rate of energy loss for the various energies of particles over the beta spectrum. The Fermi spectrum for the allowed transition is used to describe the energy distribution of the initial particles.

$$N(E^*)\,dE^* = KE^* \sqrt{E^{*2} - 1}\,(E_o^* - E^*)^2\,dE \qquad (3)$$

where $N(E^*)dE^*$ is the number of electrons in the energy range dE^* located at energy E^*, and E_o^* is the maximum energy of the beta spectrum in units of mc^2. E^* is the total energy of the electron, including both the rest energy and the kinetic energy. The range of beta particles in air as given by the International Commission on Radiological Units and Measurements[4], is shown in Fig. IV-1. An empirical relation which closely approximates this function is:

$$R = 0.556 - 0.0841(1-e^{-6.50E}). \qquad (4)$$

In this equation, R is the range in centimeters for tissue and E is the kinetic energy of the beta particle in Mev. From eq. (3) the rate of energy loss in tissue $\frac{dE}{dR}$ is given by:

$$\frac{dE}{dR} = \frac{1}{0.556 - 0.546\,e^{-6.50E}} \cdot \qquad (5)$$

By subtracting the energy loss for travel through an increment of distance from each incremental part of the energy spectrum, a modified energy spectrum is obtained which, in connection with eq. (3), can be used to obtain the average rate of energy

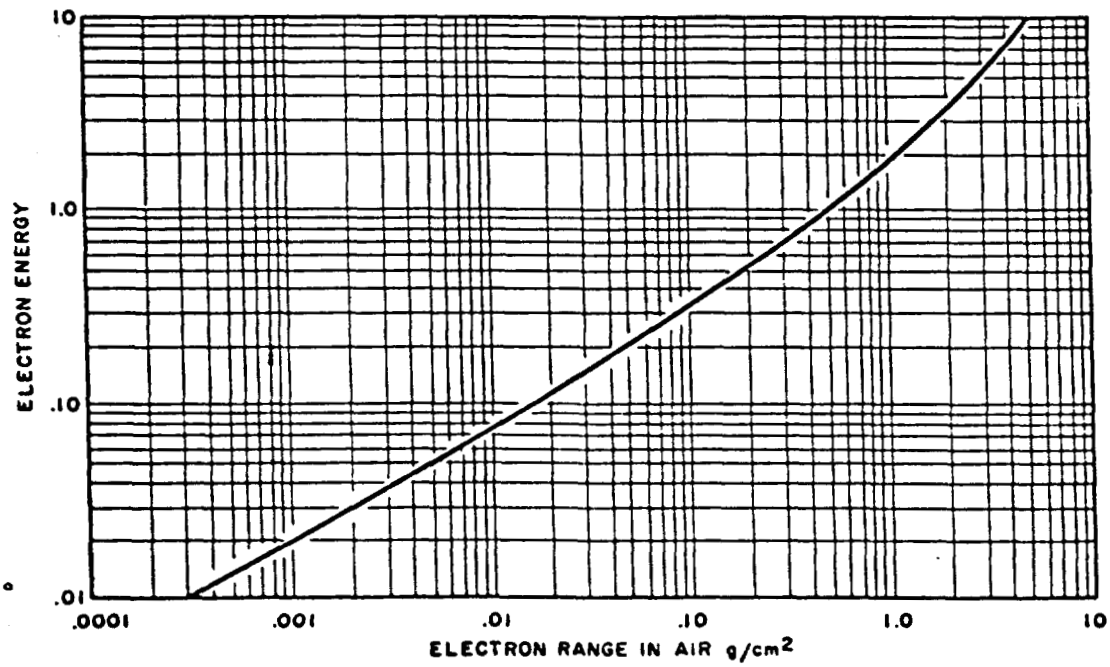

Figure IV-1. Approximate Range-vs.-Energy Curve for Electrons in Air, Calculated by Nelms (Ref. 12)

loss through that distance. Repeated calculations then can produce the energy loss over the whole range of the radiation.

A comparison between the various methods of calculation and experimental values of Marinelli[5] is given in Fig. IV-2. The data are plotted as dose rate times distance in soft tissue squared to eliminate the very rapid inverse square decrease.

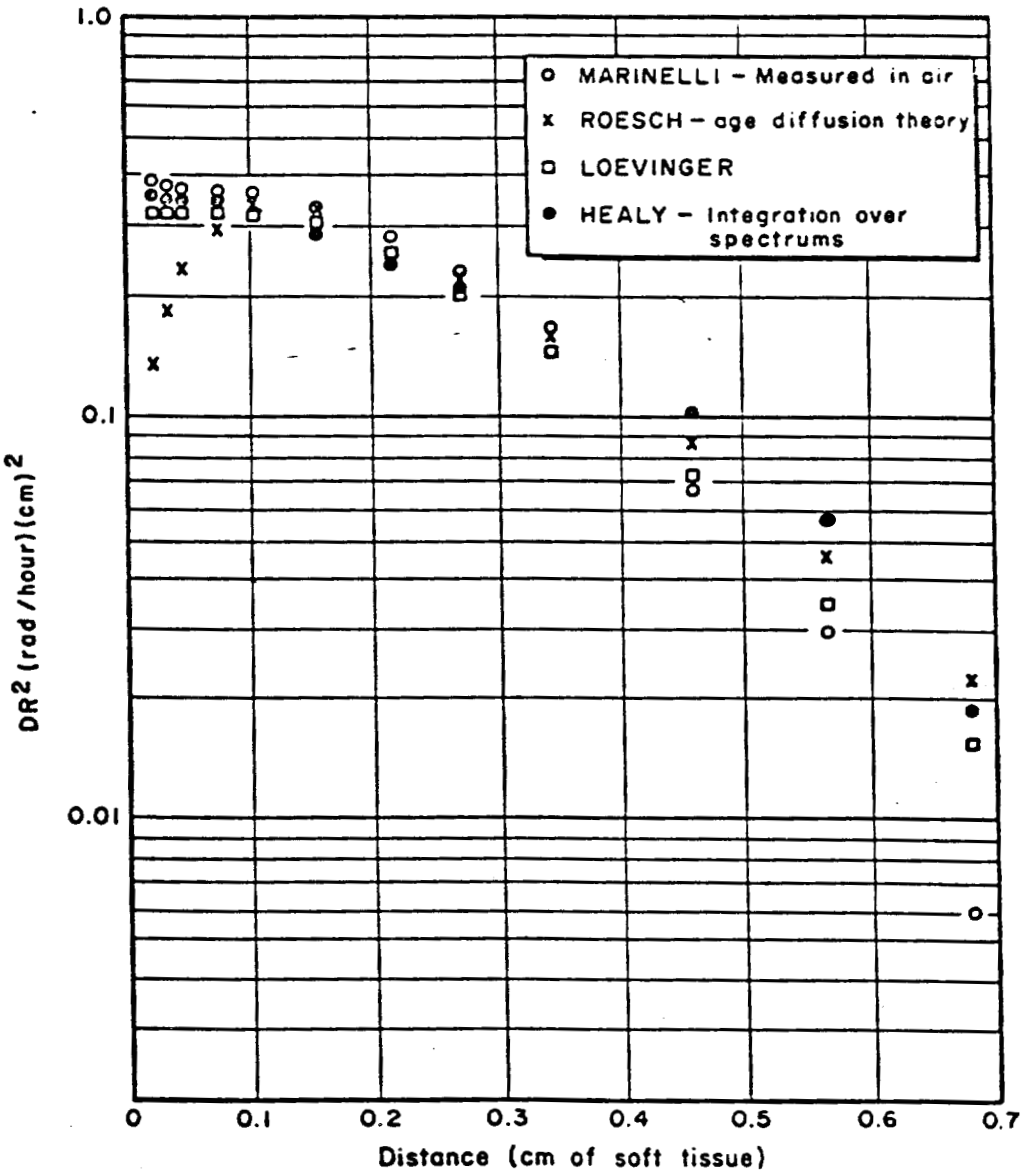

Figure IV-2. P^{32} Point Source Dose Rate Per Microcurie Plotted as a Function of Distance from Source

Table IV-1 presents the calculated dose rate at various distances in soft tissue around 1-μc sources of several different radioisotopes with differing energy spectra.

The extremely high dose rates are thus in the region within a few cells of the particle, while the total volume influenced by the particle is strongly dependent upon

TABLE IV-1

Dose Rate in Tissue Around 1-μc Particle

Distance (μ)	Dose Rate (rads/hr)			
	C^{14}	Sr^{90}(a)	P^{32}	Y^{90}
10	2,000,000	530,000	380,000	270,000
100	1,500	5,000	3,700	2,700
200	40	1,100	930	680
400	0.03	200	230	160
600		60	100	70
1,000		10	30	26
2,000		0.03	7	7
4,000			0.7	1
6,000			0.1	0.3
8,000			0.01	--
10,000				0.02

(a)Anomalous spectral distribution; does not include Y^{90} daughter.

TABLE IV-2

Average Dose Rate for 1-μc Particle

Radius of Sphere (cm)	Volume of Tissue (cm^3)	Average Dose Rate (rads/hr/μc)			
		C^{14}	Sr^{90}	P^{32}	Y^{90}
0.01	4.2×10^{-6}	2.1×10^{4}	1.5×10^{4}	9.4×10^{3}	9.0×10^{3}
0.1	0.0042	25	87	110	79
0.62	1.0	0.096	0.43	1.4	1.7
1.0	4.2	0.023	0.10	0.36	0.48

the energy of the beta particles emitted. These very high dose rates are of considerable importance because there is some possibility that the damage caused by radiation could vary more rapidly than as a linear function of dose rate, as will be shown in Chapter V.

Also of interest is the average dose rate over a given volume of tissue, as shown in Table IV-2. This has been estimated by integrating the energy absorbed over a sphere of defined radius.

The rate of energy absorption from alpha particles is given by the Bragg curve, which shows a marked increase toward the end of the range. The total range of the alpha particle is on the order of 30 to 70 μ, so that the energy is dissipated close to the particle. Dose rates around a particle emitting 5.5-Mev alpha particles were calculated from energy loss data given by Lea[6]. These results are tabulated in Table IV-3.

TABLE IV-3

Dose Rates at Given Distance, and Average Dose Rate in Sphere for 1-μc Particle Emitting 5.5-Mev Alpha

Distance (μ)	Dose Rate at Distance (rads/hr)	Average Dose Rate in a Sphere of Given Radius (rads/hr)
10	1.7×10^8	4.7×10^8
20	5.2×10^7	1.3×10^8
41	0	4.0×10^7
1,000	0	2.8×10^3
6,200	0	12
16,000	0	2

For particles larger than a few microns in diameter, the absorption of energy within the particle (self-absorption) will decrease the values listed in Table IV-3. It is of interest to note that the average energy delivered to the 1 g of tissue immediately surrounding the particle is 5 to 10 times that delivered by beta particles, but the alpha particle energy is concentrated in only about 10^{-7} g or a few hundred cells.

C. Aggregations of Small Particles

The dose rate to individual cells from an aggregation of small particles in the region (or from other types of non-localized deposits) can be computed in detail only by considering the contribution of each particle to the tissue element in question. Since such localization does not usually occur in a regular pattern, this task can be carried out only through tedious individual calculations for each source and tissue volume. Approximations of the dose could be made by assuming a regular pattern of deposition (such as each particle arranged in a cubic lattice with each particle containing an average quantity of radioactive material). Such approaches are similar to those which have been used by Spiers[7] to calculate the dose rates to soft tissue in the bone as a result of radium deposition.

A number of authors have investigated the radiation dose to the lung from the daughter products of radon. Several representative values are compared in the following table.

Author	Radon Conc. ($\mu c/cm^3$)	Dose Rate	Dose Rate for 10^{-10} $\mu c/cm^3$ (rads/yr)
Morgan[8]	9×10^{-9}	15 rem/yr	0.17
Shapiro[9]	1×10^{-8}	0.78 rep/yr 7.8 rem/yr	0.08
Chamberlain and Dyson[10]	3×10^{-10}	0.22 rem/yr	0.07
Hultqvist[11]	3×10^{-10}	0.15 rem/yr	0.05

These values have been calculated with some assumptions as to the distribution of particles, and generally represent dose rates to the bronchi. The calculations further assume various degrees of equilibrium between radon and the daughters in the atmosphere. In general, it is believed that less dusty atmospheres will result in lower doses. Similarly, rapid changes of the air in mines will reduce the fraction of equilibrium attained and thus will reduce the dose rates to the lungs.

At present, there are no practical methods of directly measuring doses to the lung due to radioactive materials in the lung, although insertion of small ionization chambers might be possible where only gamma radiation is involved. With alpha and beta radiation, doses can only be calculated. For these calculations, a knowledge of the radiation involved and the distribution of the sources of these radiations in the lung is necessary.

Such calculations of dose rate and dose are useful primarily for intuitive comparisons of situations, since the dose is only one of the factors involved in the tissue damage, and experience with irradiation of single cells, small tissue masses, or portions of an organ is generally inadequate to permit complete evaluation of damage. One of the chief purposes in calculating such doses in experimental situations is to build up our knowledge of the interrelations so that realistic assessments of damage in other situations may be made.

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*See key to report abbreviations at end of this report.

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