In which iodine and indicate that the gland is but is totally incapable of contain iodine in any hours after administration after an injection, goitrogenic substances able to prove that iodine produced in the thyroid interesting to note that it y sulfaguanidine.

wise in patients with avidity for iodine. As alone is not capable of exophthalmic goiter reached when iodine is This would agree with Rawson, who demonstration of thiouracil is store radioactive iodine

s with the clinical pic-

stage of operation the stage, while the histo-

v (basal metabolic rate + 15 before and

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colloid transforma-

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der DEPOSITION AND FATE OF PLUTONIUM, URANIUM AND THEIR FISSION PRODUCTS INHALED AS AEROSOLS BY RATS AND MAN

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THE MANNER in which foreign materials are eliminated from the lungs has long been of interest. Robertson has summarized previous investigations. In general, it has been shown that particles inhaled into the lungs may be eliminated in two ways. In both mechanisms the particles are engulfed by phagocytes. Following this, some particles, such as silica, are carried into the lymphatic system of the lung by phagocytes migrating through the alveolar lining. Concerning the other mechanism of elimination it is postulated that particles are transported as far as the ciliated epithelium of the respiratory bronchioles, where they are swept out by ciliary action. The cells responsible for transporting them to the respiratory bronchioles have been identified as dust or septal cells. Fried expressed the belief that they are mesenchymal in origin.

McCUTCHEON’S studies of chemotaxis have shown that the phagocytes of the lung are specialized with respect to the kind of particle which they will engulf. He listed polymorphonuclear cells as being positively chemotactic to collodion particles, bacteria, and tissue proteins, negatively chemotactic to aluminum silicate and indifferent to carbon particles. In this respect they are in contrast to dust or septal cells, which phagocytose carbon. Dust cells and monocytes do not display positive chemotaxis but accomplish their work by means of random locomotion.

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The hazards of various industrial materials in the lungs have been of concern for many years. Pulmonary elimination and/or absorption of materials became a matter of even greater concern with the release of nuclear energy and the attendant possibility of the accidental release of the products of nuclear fission. However, the production of fission products and fissionable materials had its compensations as far as radiation hazards were concerned, in that the materials which were possible sources of danger because of their radioactivity were by the same token useful tools in the study of the function of the lungs.

Of the several technics available for studying the transport of radioactive materials in the body two were used in these studies. One was the quantitative determination of the behavior of the radioactive materials administered by observing the fate of a known amount of active material introduced into the lungs. This was done by measuring the radioactivity of the animal tissues and excreta with a Geiger-Müller counter in the detection of beta and gamma radiation and the parallel plate linear amplifier combination in that of alpha particles. The second was the determination of the exact location of the particles in lung tissue. This can be done through the use of the technic of radioautography. Radioautographs were taken of lung sections at several periods of time after the lungs had been exposed to the radioactive aerosols used in these studies.

The information gained from these two methods places the investigation on a quantitative basis. Since the materials can always be followed because of their radioactivity, it is possible to determine the various fractions following any particular route as well as the time it takes for translocation to occur.

The elements used were administered as smokes and sprays. The smokes and sprays were composed of particles of plutonium, uranium and the fission products of both of these materials. The mixture of radioactive fission products contained principally strontium (Sr), yttrium (Y), zirconium (Zr), columbium (Cb), ruthenium (Ru), barium (Ba), lanthanum (La), cerium (Ce), cesium (Cs), praseodymium (Pr), neodymium (Nd) and element 61 at the time of the assay of radioactivity in organs, liver, and excreta. Zirconium and protoactinium (Pa) were studied separately as well.

METHODS OF STUDY

The manner in which radioactive material is assayed when present in biologic tissues has been adequately described elsewhere.5

The methods which were used to deposit radioactive aerosols in the lungs of rats are as follows: With the exception of the one study of a human subject, young rats weighing between 200 and 300 Gm. were used in all experiments. The rats were prepared for exposure with an intraperitoneal injection of pentobarbital sodium. The dose was 40 mg. per kilogram of body weight for male rats and 30 mg. per kilogram for female rats. After the rat was anesthetized, the whiskers on the nose were closely clipped. The lips were fastened together with a three-cornered stitch between the lower lip and the two halves of the upper lip. The mouth was further sealed up with celloidin (a concentrated pyroxylin), and at the same time the glass nose piece was cemented in place (fig. 1). This procedure completely sealed off the openings of the mouth and directed the rat's respiration through the nasopharynx. In order to complete the exposure, the glass nose piece of the rat was plugged into the aerosol chamber with gum rubber tubing (figs. 2

Fig. 1.—A rat prepared for exposure to aerosol, with nose piece in place and mouth sealed with celloidin.

and 3). After being exposed to the aerosol under study, the rats were placed in metabolism cages so that fecal and urinary excretions could be collected separately. The animals were killed at varying times after exposure, and their tissues, urine and feces were assayed for the element being studied.

The animals used in these studies were given the following materials as aerosols.

1. Plutonium oxide (PuO₂) produced by burning both the metal and the salts of plutonium.
2. Plutonium nitrate (PuO₂(NO₃)₃) as a spray.
3. Fission products combined with their parental elements, plutonium and uranium, which had been previously exposed to intense and prolonged neutron
irradiation. Both the plutonium and the uranium were burned in the metallic state, thus producing aerosols of their oxides and the oxides of most of the fission products.

4. Carrier-free fission products, free of uranium and plutonium and containing very small amounts of inactive isotopic elements. They are described as being carrier free because of the fact that they were prepared without inclusion of their stable isotopes during their chemical separation from uranium and plutonium. Most of these also were primarily in the form of their oxides.

5. Aerosols of carrier-free zirconium or zirconium oxide (ZrO₂).

6. Aerosols of protoactinium as protoactinium oxide (Pa₂O₅).

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Fig. 2.—The exposure chamber used to produce aerosols by burning the radioelement, deposited on graphite electrodes, in an electric arc. This was done in an atmosphere of pure oxygen in order to prevent the formation of poisonous amounts of carbon monoxide. The bakelite leads were connected to the rat's nose piece with gum rubber tubing. The exposure was made by striking an electric arc between the two electrodes. The exposure time was about 30 seconds.

The specific aerosols used in these studies were prepared as follows:

1. Plutonium nitrate as PuO₃(NO₃), is soluble in ethyl ether. Advantage was taken of this property by introducing the plutonium nitrate into the exposure chamber as a spray. Very small particles free from ether were produced by forcing the ether-plutonium solution through a gold jet after it had been allowed to come into equilibrium with carbon dioxide at a pressure of 760 pounds per square inch.
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plutonium and containing
are described as being
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uranium and plutonium.
ides (ZrO₄).
PaO₃).

by burning the radio-
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ion of poisonous amounts
the rat's nose piece
striking an electric arc
30 seconds.

red as follows:
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nitrate into the exposure
were produced by forcing
been allowed to come
pounds per square inch

Fig. 3.—Diagrammatic sketch of the equipment used to produce aerosols of
plutonium nitrate (PuO₂(NO₃)₂). The plutonium nitrate dissolved in ether, with
carbon dioxide in the lower chamber, is forced through the gold jet at 760 pounds of
pressure into the upper exposure chamber. As the ether evaporates in the warm
chamber, the plutonium nitrate aerosol is suspended. Its droplet size is further
reduced by the extreme effervescence of the carbon dioxide in the ether at
atmospheric pressure.

The drawings in figures 2 and 3 were made by Mr. Gaines Heim.
An effervescent ether-plutonium solution was produced when the jet was directed into the warm exposure chamber, the temperature causing the ether to evaporate. The plutonium yielded to the rat was about 10 per cent of the total plutonium used in the spray. The latter amounted to about 300 micrograms of plutonium per exposure. The exposure time was 3 to 4 minutes. The equipment devised to produce the plutonium nitrate aerosols is shown in figure 3.

2. Aerosols of plutonium in the plus four state as plutonium oxide (PuO₂) were produced by burning the plutonium salts and the plutonium metal itself. In the former instance, the solution was evaporated on graphite electrodes, and in the latter the metal was embedded in holes drilled in the centers of the 1/16 inch graphite rods. In both cases the electrodes plus the plutonium were burned in an atmosphere of oxygen in an electric arc. Two hundred micrograms of plutonium were burned for each exposure. The amounts yielded to the rats varied from 4 to 7 per cent of the material burned. The exposure consumed 30 to 60 seconds. One type of equipment used is shown in figure 4.

3. Aerosols of fission products occluded in uranium as uranium oxide (U₃O₈) and plutonium as plutonium oxide (PuO₂) were produced in a similar manner. At the time of exposure the radiations from the fission products predominated. The ratio of fission product disintegrations to the alpha particles arising from the uranium was about 20,000 to 1. The age of the fission products was 2 to 3 months. About 80 mg. of uranium metal was burned at each exposure of 30 seconds' duration. The yield to the rats was about 1 per cent.

4. Carrier-free fission products were also prepared as an aerosol by evaporating the uranium-free solution on graphite rods and burning these. The solution of fission products used was 6 months to 1 year old. Owing to this fact, the fission products with short half-lives had decayed away. The fission elements remaining then were composed primarily of Sr⁹⁹ and Sr⁹⁰, Y⁹¹, Zr⁹⁰, Cb⁹⁵, Ru¹⁰⁸ and Ru¹⁰⁸. Cs¹³⁴, Ce¹⁴⁴, and element 61¹⁴⁷.

5. Zr⁹⁰ was used in a study of a human subject (one of us). The short half-life of this material, as well as the absence of long-lived radioisotopes, precluded any danger of excessive amounts of radiation to the subject. The active material was suspended as an aerosol in argon as follows: The Zr⁹⁰ solution was evaporated on two concave gold buttons 1 cm. in diameter. It was then dispersed in argon by passing 15,000 volts between two electrodes which were placed 5 mm. apart. A 0.01 microfarad condenser was connected across the high voltage line. Oxygen was avoided in the chamber because of the production of undesirable amounts of ozone. Approximately 1 microcurie of Zr⁹⁰ was inhaled by placing in the left nostril a short rubber tube which was also connected to the generator. The inhaled Zr⁹⁰ was exhaled through the mouth into a glass wool filter, followed by several breaths of inactive air, so that the percentage of material exhaled could be calculated.

6. Carrier-free protoactinium, which has a 30 day half-life, was prepared as an aerosol by sparking evaporated Pa²³³ solution on a gold electrode in a high voltage electric discharge. This was administered to rats in the same manner as Zr⁹⁰.

Except in the Zr⁹⁰ and protoactinium studies, the size of the particles produced by the aerosol generators was determined by collecting representative samples on amyl acetate films. The particle size was estimated with the aid of an electron microscope.

The lungs, kidneys, liver, spleen, skeleton, gastrointestinal tract, head, skin and the balance of the rat, as well as the separated excreta, were assayed for the radioactive material which was administered either as an aerosol or included...
fiber-plutonium solution was prepared. In the temper-exposure chamber, the temperature to which the rat was exposed was about 30°. The exposure time was 3 to 4 days. The plutonium nitrate aerosols is plutonium oxide (PuO₂) the plutonium metal itself or graphite electrodes, and in the centers of the 1/16 in. hundred micrograms of plutonium were burned to yield the rats varied exposure consumed 30 to 60 g.

As uranium oxide (U₃O₈) used in a similar manner, products predominated. The particles arising from the products was 2 to 3 months. An aerosol by evaporating the solution of the aerosol, the solution of these. The solution of this fact, the fission produced was 2 to 3 months. The active material was prepared as an aerosol by evaporating a solution of the active material remaining, Zr²⁵, Cb²⁷, Ru¹⁰⁶ and Cf²⁵. The short half-life of these isotopes, precluded any quantitative samples on this aid of an electron microscopy. The paraflin was removed with xylene. A thin protective covering of celloidin was used on the section. Each slide was placed in contact with a

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with the aerosol. These assays were performed on groups of 3 to 7 rats at periods as long as 256 days after exposure. A detailed report of the amounts of the active material deposited in various tissues of the rat as well as the metabolism of these elements is presented elsewhere. Only values obtained for the head, lung and skeletal deposition, the daily rate of excretion, the particle size and the radioautographic studies are included in this report.

Radioautographic Technic

At intervals, as stated in the text, following the inhalation of the aerosol being studied, the rats were killed with chloroform. The lungs were fixed while intact in the animals by injecting 80 per cent alcohol (pH approximately 8) into them through the trachea. Zenker-formaldehyde solution could not be used as a fixative, because it was found to cause fogging of the x-ray film. Formaldehyde solution U. S. P. could not be used, because it leached plutonium from the tissues. After 24 hours' fixation, the lungs were dehydrated in dioxane and embedded in paraffin. Sections 10 microns in thickness were cut and mounted on microscopic slides. The paraffin was removed with xylene. A thin protective covering of celloidin was used on the section. Each slide was placed in contact with a
piece of “no screen” x-ray film and wrapped in black paper to exclude light. Lead weights were used to press the film and the tissue together. The details of the procedure used have been reviewed elsewhere by Axelrod and Hamilton.\(^6\) After the films were exposed and developed, the lung sections were stained with hematoxylin and eosin. Photomicrographs of representative slides and their radioautographs are presented in this report.

**RESULTS**

The aerosols studied here were, in general, deposited in the same respiratory areas of the rats despite their rather different origin and physical and chemical properties. Immediately after exposure the major proportion of them were found to be distributed from the nasopharyngeal region down through the bronchial tree and into the alveoli of the lungs. The rate at which this general region functioned in the removal of the aerosols was composed of two very different time intervals. The presence of ciliated epithelial cells allowed almost complete removal of the active particles in a matter of hours. This relatively rapid removal of material deposited on the ciliated epithelium agrees with the ciliary removal rates reported by Proetz.\(^7\) In the regions of the lungs, such as the ductus alveolaris and the alveoli, the removal of any large percentage of an aerosol consumed a range of time of the order of many months. The route of removal was primarily via the bronchial tree. Since plutonium and the majority of the fission products given are not absorbed in the gastrointestinal tract to any extent, the material excreted via the bronchial tree could be detected in the fecal fraction of the excreta.\(^5\)\(^8\)\(^6\) However, the products of fission which are comparatively recent contain appreciable amounts of Ba\(^{140}\), which has a half-life of 12.5 days. In addition, all the solutions contained Sr\(^{90}\) and Sr\(^{90}\), which have 55 day and 25 year half-lives, respectively. As shown by Hamilton,\(^2\)\(^6\) these two elements would have been absorbed to some extent through the lungs had they been in solution, since they are absorbed from the intestinal tract when administered orally. The absorbed portion amounted to from 5 to 60 per cent of the total amount given. Of the absorbed portion, 65 per cent was found deposited in bone. It follows, then, that a low bone deposition of these fission products suggests that they were locked in insoluble particles when administered as aerosols. In these studies the insoluble particles could have been carbon, plutonium or uranium in combination with their oxides.

**Plutonium Nitrate (PuO\(_2\)[NO\(_3\)]\(_2\)) Sprays.**—Table 1 shows the fate of plutonium nitrate when administered to rats as a spray, the plutonium being in the plus six state. At 10 minutes after exposure the lungs and the head, the latter including the region above the trachea, contained approximately the same amount of aerosol. It can be seen that the plutonium was removed from the head quickly and was found in the fecal fraction. After one day the lungs continued to lose plutonium, but at a rate much more slowly than the head. The plutonium which was transported across the capillary barrier of the alveoli by whatever means eventually found its way to bone. This transport was not a great factor in the elimination of the pulmonary plutonium, since the highest value obtained was 12 per cent of the total 64 days after administration. The total fraction of plutonium absorbed from the lungs was probably of the order of 20 per cent of the amount retained in the respiratory tract, since 60 to 70 per cent of plutonium absorbed after intramuscular injection is deposited in bone.

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In addition, the absorption of plutonium occurred promptly, since there was little additional plutonium deposited in bone after the fourth day. The aerosols were removed from the head and the lungs by being passed up the bronchial tree, since they were detected primarily in the feces. This includes the fraction that was initially deposited on the ciliated epithelium of the upper respiratory tract and was rapidly swept out, as well as that retained and slowly eliminated from the alveoli.

Radioautographic studies were made at 10 minutes and 16 days after exposure. At the 10 minute interval the ciliated passages of the lungs, as well as the alveoli, contain deposits of plutonium (fig. 5A). At 16 days, however, deposition appears to be primarily in areas included in the ductus alveolaris and its primary lobules (fig. 5B). The data shown in table 1 demonstrate a reduction of plutonium for all areas of the lung.

**Plutonium Oxide Aerosols Prepared from Plutonium Metal and Salts of Plutonium.**—Plutonium oxide particles were produced by burning plutonium with graphite in an electric arc in an atmosphere of oxygen. In this case plutonium was presented to the rats in the plus 4 state and probably as some plutonium metal. Its chemistry in the plus 4 state is somewhat similar to the lanthanide series of rare earths. This is in contrast to the plus 6 state of plutonium resulting when the plutonium nitrate sprays were used. The latter compound, PuO$_2$(NO$_3$)$_2$, is more similar in chemical characteristics to uranyl salts of uranium. The particle sizes produced by the electric arc varied from 0.06 to 38 microns. Their average size was 0.49 micron (fig. 6).

<table>
<thead>
<tr>
<th>Percentage of Total per Organ at Given Time</th>
<th>After Exposure of Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>49  40  45  41  49  9</td>
</tr>
<tr>
<td>Head</td>
<td>37  5  1.5  0.8  0.1</td>
</tr>
<tr>
<td>Bone</td>
<td>33  8  11  7.9  12</td>
</tr>
<tr>
<td>Daily rate of elimination</td>
<td>3  3  3  0.9  0.3</td>
</tr>
</tbody>
</table>

Tables 2, 3 and 4 summarize the results obtained with plutonium oxide aerosols. It can be seen that the results are similar to those obtained with the plutonium nitrate sprays with the exception that relatively little of the aerosol was absorbed into the blood stream, as evidenced by minimal deposits in the bones. Consequently, less was found in the organ of primary deposition, bone. Plutonium oxide aerosols are gradually removed from the nonciliated areas via the bronchial tree. This removal takes a much longer time than that of the aerosols deposited in the portions of the respiratory tract above the trachea, which are included in the head fraction, as well as those deposited on the ciliated epithelium of the bronchial tree. The plutonium oxide aerosols are eliminated in the same manner and at comparable rates whether they are produced by the burning of plutonium salts or by the burning of the metal.

The actual amount of plutonium administered to the rats used in these studies varied from 1 to 3 micrograms per animal. This amount would have given the lungs of the rats about 2 roentgens (r) per day. In this case the electron microscope pictures suggest that some of the aerosol existed as the metal. Furthermore, it is worthy of attention that the aerosol particles appear to follow the same path whether they are detected by following the alpha activity of the plutonium or the beta and gamma radiations of the fission products incorporated in the plutonium.
Fig. 5A.—Radioautograph (lower) and lung section (upper) showing pulmonary deposition of plutonium oxide aerosol obtained by burning plutonium chloride and plutonium nitrate. The rat was killed ten minutes after exposure. Plutonium is heavily deposited on ciliated bronchial surfaces and in alveoli. (× 6.)
Fig. 5B.—Radiograph (lower) and lung section (upper) showing pulmonary deposition of plutonium oxide aerosol obtained by burning plutonium chloride and plutonium nitrate. The rat was killed sixteen days after exposure. Plutonium has been almost completely cleared off of the ciliated surfaces and is located in alveolar structures. (×10.)
particles. These results are in agreement with our view that the particles themselves were being followed rather than any one element or group of elements, since the handling of fission products of this age would have been different from that of plutonium (also the carrier-free fission products mentioned on an earlier page). Less than 2 per cent of the total material administered as plutonium was absorbed through the lungs to enter the blood stream and be deposited in the skeleton. With respect to the fission products, the amount thus absorbed was about 7 per cent.

Radioautographic studies suggest that the alveoli were the major area of retention of the inhaled plutonium fission product aerosols after the material laid down on the ciliated passages of the lungs had been expelled (figs. 7 A, B, C and D). At the time of exposure 10 fission product disintegrations were occurring for each alpha particle emitted from the plutonium. The plutonium was prepared by placing plutonium metal in graphite electrodes. These were placed in the dexterium oxide pile at the Argonne National Laboratories. At the time of the production of the aerosols the fission products had an average age of 2 months. We estimate that 25 per cent of the film darkening was due to alpha particles and 75 per cent to fission product particles.

Aerosols Composed of Uranium Oxide Containing Fission Products.—Aerosols similar to those composed of the plutonium oxide fission product particles just discussed were produced by burning uranium wire in an electric arc. Smoke particles produced in this manner would be quite comparable to those which might arise from accidental destruction of a uranium pile. The uranium wire had been previously placed in the Clinton pile at Oak Ridge, Tenn., and the fission products were produced by prolonged neutron irradiation. About 60 days elapsed between the time of their removal from the pile and the production of aerosols for inhalation. Although the particle sizes produced on burning ranged from 0.06 to 9.4 microns, the average particle was larger than those produced from plutonium by about a factor of 2, being 0.97 micron in size (fig. 8). This increase in particle size is apparently reflected in the relatively greater entrapment in the respiratory structures of the head. This greater deposition observed in the head as compared with the lungs agrees with the observations of Barclay and co-workers,8

who showed that bismuth carbonate dust particles 2 to 12 microns in size were not deposited past the respiratory bronchioles and with those of Poliardi, who showed that silica and coal particles larger than 10 to 12 microns were not found in the alveoli of miners. Table 5 summarizes the results obtained by exposing

### TABLE 2.—Fate of Plutonium Inhaled as Plutonium Oxide Aerosols Made by Burning Plutonium Metal Embedded in Graphite

<table>
<thead>
<tr>
<th>Percentage of Total Administered per Organ at</th>
<th>Given Time After Exposure of Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Min.</td>
<td>1 Day</td>
</tr>
<tr>
<td>Lungs...</td>
<td>27</td>
</tr>
<tr>
<td>Head...</td>
<td>56.2</td>
</tr>
<tr>
<td>Bone...</td>
<td>1</td>
</tr>
<tr>
<td>Daily rate of elimination...</td>
<td>23.7</td>
</tr>
</tbody>
</table>

* The relatively higher values obtained for bone 10 minutes after exposure are not considered to be significant, since there is a possibility that the animals were contaminated with the aerosol deposited on the nose and face.

### TABLE 3.—Fate of Plutonium Inhaled as a Plutonium Oxide Aerosol Prepared by Burning Plutonium Metal Embedded in Graphite

<table>
<thead>
<tr>
<th>Percentage of Total Administered per Organ at</th>
<th>Given Time After Exposure of Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Min.</td>
<td>1 Day</td>
</tr>
<tr>
<td>Lungs...</td>
<td>24</td>
</tr>
<tr>
<td>Head...</td>
<td>50</td>
</tr>
<tr>
<td>Bone...</td>
<td>1</td>
</tr>
<tr>
<td>Daily rate of excretion...</td>
<td>23.8</td>
</tr>
</tbody>
</table>

* The values obtained for the skeleton could have been high because of outside contamination of the skeleton occurring when the rats were dissected at 10 minutes, 1 day and 4 days after exposure.

### TABLE 4.—Comparative Fate of Plutonium Oxide Aerosols Containing Products of Fission of Plutonium Metal in a Deuterium Oxide Pile

<table>
<thead>
<tr>
<th>Percentage of Total Administered per Organ at</th>
<th>Given Time After Exposure of Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Min.</td>
<td>1 Day</td>
</tr>
<tr>
<td>As Pu</td>
<td>As F. P.</td>
</tr>
<tr>
<td>Lungs...</td>
<td>41</td>
</tr>
<tr>
<td>Head...</td>
<td>36</td>
</tr>
<tr>
<td>Bone...</td>
<td>2</td>
</tr>
<tr>
<td>Daily rate of excretion...</td>
<td>19</td>
</tr>
<tr>
<td>16 Days</td>
<td>64 Days</td>
</tr>
<tr>
<td>As Pu</td>
<td>As F. P.</td>
</tr>
<tr>
<td>Lungs...</td>
<td>16</td>
</tr>
<tr>
<td>Head...</td>
<td>0.3</td>
</tr>
<tr>
<td>Bone...</td>
<td>2</td>
</tr>
<tr>
<td>Daily rate of excretion...</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* The values obtained for the skeleton could have been high because of outside contamination of the skeleton occurring during dissection of the rats at 10 minutes, 1 day and 4 days after exposure.

rats to uranium aerosols. It can be seen that the elimination of the aerosol is via the bronchial tree and that the rate of elimination is comparable to that of plutonium aerosols. Relatively small amounts of fission products were absorbed and deposited.

Fig. 7A.—Radioautograph (lower) and lung section (upper) showing pulmonary deposition of plutonium oxide aerosol obtained by burning plutonium metal. The rat was killed ten minutes after exposure. The material is deposited on ciliated surfaces and alveoli. (× 6.8.)
The method of aerosol production is similar to that of plutonium, where the material was absorbed and deposited by burning plutonium metal. The rat was killed ten minutes after exposure. The tissue section was mounted directly on alpha particle plates. The photomicrograph shows the alpha tracks from plutonium deposited on the walls of two bronchi and on the alveolar epithelium. (× 290.)
Fig. 7 C.—Radioautograph (lower) and lung section (upper) from rat killed one day after inhalation of plutonium oxide aerosol obtained by burning plutonium metal. No plutonium remains on the surfaces of the bronchial tree, but it is arranged in spots throughout all of the alveolar structure. (× 7.5.)
in the skeleton. These results are in contrast with those obtained when solutions of fission products are admitted to the lungs by intubation. About 0.1 mg. of uranium was deposited in the rats along with the fission products inhaled as an aerosol.

Fig. 7 D.—Radioautograph (lower) and lung section (upper) from rat killed sixty-four days after inhalation of plutonium aerosol obtained by burning plutonium metal. A considerable amount of plutonium remains in the lung scattered throughout the alveolar structure. (X 8.)

This amount of uranium produced no apparent toxic effect; the amount of radiation arising from the fission products was below the accepted tolerance level of 0.1 r per
day. In this case the percentage of fission products deposited in bone was much greater 4, 16 and 64 days after administration, as can be seen from an examination of table 5.

This suggests that the uranium oxide particles occluded the fission products and that detection of the fission products was in reality detection of uranium oxide particles.

The radioautographic studies shown in figures 9A and 9B demonstrate the areas of pulmonary deposition at 10 minutes and at 1 day after exposure to aerosol of uranium oxide containing fission products. The areas of deposition are the same as those previously noted, primarily the alveoli after removal of material deposited on ciliary epithelium.

The aerosols mentioned previously have been composed primarily of the oxides of plutonium, the oxides of uranium, fission products and plutonium nitrate. Additional studies were performed in which the active particles were fission products in the carrier-free state; thus they contained relatively little mass and no plutonium or uranium. Since they were burned with graphite electrodes, the only particulate matter incorporated with the fission products was carbon. The actual number of radioactive atoms which were traced was relatively small, less than $10^{13}$ atoms to each rat. With respect to plutonium, 1 to 3 micrograms was deposited in the lungs of rats during the exposure. About 0.1 mg. of uranium was administered with the fission product uranium oxide aerosols studied. Since the major part of the fission products produce insoluble oxides on burning, they probably remained incorporated with the carbon particles themselves, although this is not certain; they were not disposed of by the lungs in the same manner as fission products admitted to the lungs by the tracheal intubation previously cited. The data obtained on the deposition and the fate of aerosols of this nature are summarized in table 7.

Relatively small amounts of fission products were absorbed into the body and deposited in bone. This statement of course must be qualified with respect to the age of the fission products used. In this case the fission products were 2 to 3 months old when incorporated with plutonium and uranium aerosols. The fission products used in the carrier-free state were from 6 months to 1 year old. For  

10. The carrier-free fission products were prepared at the Clinton Engineering Works, Oak Ridge, Tenn.
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...this reason of age, the most abundant fission products which were present when the radioactive assays were made included strontium, yttrium, zirconium, columbium, ruthenium, cesium, cerium and element 61. Ruthenium and cesium were found to be rapidly eliminated and not retained by the skeleton. The major portion of the material was eliminated via the bronchial tree. The average size of the particles was found to be 0.53 micron and representative pictures are presented in figure 10.

**Table 5.—Distribution of Carrier-Free Fission Products Administered as a Chloride Solution by Pulmonary Intubation**

| Percentage Remaining in Whole Organ at Given Number of Days After Administration |
|-----------------|-----------------|-----------------|
| Lungs..| 4 Days | 16 Days | 64 Days |
| Trachea..| 40 | 41 | 47 |
| Bone..| 35 | 64 | 74 |

**Table 6.—Fate of Uranium Oxide Aerosol in Rats When the Uranium Oxide Particles Are Followed by the Determination of Radioactivity of the Included Fission Products**

| Percentage of Total Administered per Organ at Given Time After Exposure |
|-----------------|-----------------|-----------------|
| Lungs..| 10 Min. | 1 Day | 4 Days | 16 Days | 64 Days |
| Head..| 20 | 10 | 5 | <0.01 | <0.01 | 0.06 |
| Bone..| 0.5 | 1.4 | 1.9 | 1.2 | 1.0 |
| Daily rate of excretion..| 42 | 3 | 5 | 0.1 |

**Table 7.—Fate of Aerosols Composed of Graphite and Carrier-Free Fission Products When Burned in an Electric Arc in an Atmosphere of Oxygen and Inhaled by Rats**

| Percentage of Total Aerosol Administered per Organ at Given Time After Exposure |
|-----------------|-----------------|-----------------|
| Lungs..| 10 Min. | 1 Day | 4 Days | 16 Days | 64 Days |
| Head..| 20 | 10 | 5 | <0.01 | <0.01 | 0.06 |
| Bone..| 0.5 | 1.4 | 1.9 | 1.2 | 1.0 |
| Daily rate of excretion..| 42 | 3 | 5 | 0.1 |

In addition to the studies described to this point, a series of rats was exposed to protoactinium. This radioelement, Pa$^{233}$, in the carrier-free state, was administered to rats as an aerosol by driving it off of gold electrodes in an electric arc in an atmosphere of argon and, of course, eliminating the carbon in the aerosol. Less than 0.001 microgram of protoactinium was administered to these rats, and it was presumably in the form of protoactinium oxide (PaO$_2$). However, this material could have combined with particulate material and/or bacteria, the presence of which has been demonstrated in the lung by Jones.$^{11}$ At any rate, protoactinium, even though in small amount, is not absorbed into the blood stream from the lung.

to any great extent. The results obtained on protoactinium are summarized in table 8.

As with the aerosols discussed earlier, protoactinium aerosols produced in the manner described in the foregoing paragraph are not absorbed into the body from

Fig. 9 A.—Radioautograph (lower) and tissue section (upper) showing the pulmonary deposition of fission product aerosol obtained by burning uranium metal plus fission products. The rat was killed ten minutes after exposure. The fission product mixture was deposited on ciliated surfaces and throughout the alveolar structure. (X 68.)

the lungs but are eliminated rapidly from the head and more slowly from the lungs via the bronchial tree.
Radioactive aerosols produced in the atmosphere are summarized in the absorption and uptake of radioactivity into the body from burned uranium metal. The fission products are immediately cleared from ciliated surfaces and more slowly from the alveolar structures. Fig. 9B—Radioautograph (lower) and tissue section (upper) showing pulmonary deposition one day after exposure to fission products from burning uranium metal. The material is almost completely cleared from ciliated surfaces and is scattered throughout the alveolar structure. (×8.)
It is of interest to know how much of an aerosol is retained during one inspiration and how much is eliminated in the following expiration. It is realized, of course, that the size of particles, the experimental subject used and the velocity of the pulmonary air currents will also modify the results. Some information was obtained from rats exposed under the experimental conditions noted in the section

![Electron micrographs of aerosols of carrier-free fission products evaporated on graphite rods and burned in an electric arc. (X 8,000.)](image)

TABLE 8.—Fate of Protoactinium Aerosols When Produced by High Voltage Electric Discharge Between Gold Electrodes in an Atmosphere of Argon and Inhaled by Rats

<table>
<thead>
<tr>
<th>Percentage of Total Aerosol Administered per Organ at Given Time After Exposure</th>
<th>10 Min.</th>
<th>1 Day</th>
<th>4 Days</th>
<th>10 Days</th>
<th>64 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>42</td>
<td>45</td>
<td>25</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>30</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Bones</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Daily rate of excretion</td>
<td>35</td>
<td>2</td>
<td>3.5</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

under "Methods of Study" by constructing a valve system which allowed the material exhaled by the rat to be collected separately from that inhaled. When plutonium oxide particles were used, 63.4, 87.6 and 66.5 per cent of the total aerosol inhaled was initially retained in the animal. The particles exhaled were 0.5 to 1.0 micron in diameter, and representative electron micrographs are presented in figure 10.
logyn  

Aerosol is retained during one expiration. It is realized, subject used and the velocity results. Some information was conditions noted in the section

carrier-free fission products arc. (x 8,000.)

produced by High Voltage in an Atmosphere of

<table>
<thead>
<tr>
<th>Aerosol Administered per</th>
<th>Time After Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 Days</td>
</tr>
<tr>
<td>Zr</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>0.1</td>
</tr>
<tr>
<td>3.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

system which allowed the from that inhaled. When per cent of the total aerosol exhaled were 0.5 to 1.0. 

Comment 

The preceding experiments demonstrate that particulate material 1 micron in size and smaller, composed of plutonium or uranium and/or their fission products, which include a large series of elements in the central region of the periodic table, as well as protoactinium, are deposited in the alveolar structures of the lung, as well as in the air-conditioning passages of the lungs containing ciliated epithelium. This fact is borne out by the radioautographic evidence presented, as well as by the different elimination rates of ciliated epithelium as compared with other structures of the lung, including the ductus alveolaris and beyond. Despite their different chemical and physical natures, the aerosols used in these studies were eliminated from the lung primarily via the bronchial tree at comparable rates. Although the mechanism by which these aerosols were eliminated from the lung was not the problem at hand in these studies, quantitative data were obtained demonstrating their removal and qualitative data indicating their areas of deposition. It would appear to us that the aerosols used, under the experimental conditions of these studies, are removed via the bronchial tree, which is one of the routes suggested by Carleton and others.

No evidence was obtained that any large percentage of the material used in these studies found its way to the lymphatic system of the lungs. In fact, this appears unlikely, since the particles inhaled were continuously removed via the bronchial tree as long as 8 months after exposure. This suggests that the particles remained on the air side of the alveolar structures. The mechanism of their removal appears to be


the same with respect to the aerosols studied here. This can be demonstrated by plotting all of the pulmonary elimination data on one curve. This is presented in figure 11. Any of the data presented in this report would fall on this curve despite the difference of the materials used in the production of the aerosols.

**SUMMARY**

The purpose of these experiments was to ascertain the possible hazard resulting from inhalation of fissionable materials and fission products. Aerosols of plutonium, uranium plus fission products, and protoactinium were administered to rats. A Zr⁹⁹ aerosol was administered to a human subject and to rats. Aerosols of the aforementioned elements were almost totally retained by the head and the lungs immediately after exposure. After four days the lungs contained the largest percentage of these elements. The elements deposited in the head and bronchial tree were quickly eliminated via the gastrointestinal tract. The same avenue of elimination was presumably used by the nonciliated portion of the lungs, but at a slower rate. The small percentage absorbed into the body was primarily deposited in the skeleton after conditions of equilibrium had been established. Radicautographic studies indicate that the pulmonary site of deposition of these materials is in the bronchial passages and the alveolar structures. The materials are rapidly removed from the bronchial tree, presumably by ciliary action, and are slowly released from the alveoli. No accumulation of any of the radicelements was observed in either blood vessels or lymph nodes.