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DISTRIBUTION OF POLONIUM^{210} IN PULMONARY TISSUES OF CIGARETTE SMOKERS*

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BOSTON

CIGARETTE smoke contains trace amounts of an alpha-particle-emitting radioactive element, polonium^{210} (Po^{210}),[1] a naturally occurring daughter isotope of radium^{226}. In establishing whether this source of radiation exposure may be involved in the initiation of bronchial cancer in smokers, an important step is to show that pulmonary tissues of smokers, particularly certain regions of the bronchial epithelium, contain more of this element than those of nonsmokers. Because polonium has the property of binding strongly to solids, it is a reasonable hypothesis that a major part of the inhaled Po^{210} may remain attached to smoke particles as they are excreted. On this basis analysis of pulmonary tissues for Po^{210} may also offer some information concerning the dynamics of smoke absorption and excretion in human lungs. Present knowledge of these turnover processes is largely based on animal experiments.

The present investigation was undertaken, therefore, to measure Po^{210} concentrations in various pulmonary tissues of smokers and nonsmokers. From such measurements estimates may be obtained of the radiation dose delivered to the lung and bronchial epithelium by this element. Equally important, however, these measurements offer an opportunity to evaluate the dynamics of pulmonary turnover of smoke itself.

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MATERIALS

This investigation is based on lung specimens from 40 different subjects, of whom 36 have been studied in detail. Of the latter, 31 were whole lungs obtained at autopsy, and 5 were surgical specimens from patients who underwent elective lobectomies or pneumonectomies. Among these patients 25 were currently cigarette smokers, 2 currently pipe smokers, and 1 formerly a cigarette smoker, as well as 8 who had never smoked.

The clinical data on each subject, including smoking histories, pertinent autopsy findings and causes of death are presented in Table 1. Histories were obtained from hospital records and the attending physician and in most cases by direct contact with the next of kin. All current smokers had smoked continuously for periods of at least twenty years, up until a maximum of ten days before death or surgery. The nonsmoking interval indicated in Table 1 represents the time elapsed between the moment cigarette smoking was stopped and death or surgical intervention.

METHODS

Autopsy Specimens

The average elapsed time between death and autopsy was ten hours. With the exception of Cases 1-13 whole lungs were obtained directly from the autopsy table and brought immediately to our laboratory. In Cases 1-13 an additional period up to twenty-four hours elapsed after autopsy; during this time the lungs were kept under refrigeration at 4°C. Lungs either were dissected immediately after they were obtained or were quick frozen and subsequently dissected after careful thawing within ten days. In most cases several tissue samples were obtained from various parts of the bronchial tree for histologic examination. These samples were taken either just

TABLE 1. *Clinical Data on Cases Studied in Detail.*

CASE NO.	SEX	AGE	SMOKING HISTORY			TREATMENT OF LUNGS AFTER AUTOPSY	COMMENT & CAUSE OF DEATH
			PACKAGES OF CIGARETTES/DAY	YR. SMOKED	NONSMOKING INTERVAL BEFORE DEATH		
		yr.					
1	M	63	1½	>30	10 days	Fresh lung*	Smoke inhalation, pulmonary emboli & edema
2	M	42	1½	±25	4 days	Fresh lung*	Alcoholic patient; skull fracture & subdural hematoma.
3	M	70	1-2	>20	7 days	Fresh lung*	Pulmonary emphysema, with coronary heart disease
4	M	55	1½	±35	5 days	Fresh lung*	Status asthmaticus
6	M	57	> ½	>20	3 days	Fresh lung*	Alcoholic patient found dead in bed; chronic pancreatitis.
7	M	68	2-3	±50	10 days	Fresh lung*	Bronchopneumonia, with abscess
8	M	41	1-2	±20	4 days	Fresh lung*	Ruptured carotid-bifurcation aneurysm
9	M	76	½-1	>20	± 2 days	Fresh lung*	Patient dead on arrival; coronary heart disease.
10	M	56	2	>30	± 2 days	Fresh lung*	Alcoholic patient; Friedländer's pneumonia.
12	M	52	1½	30	4 days	Fresh lung*	Subarachnoid hemorrhage
13	M	46	1¼-2	>20	4 hr.	Fresh lung*	Acute myocardial infarct
17	M	68	1-1½	>30	8 days	Fresh lung†	Carcinoma of right lung
18	M	51	1	30	2 days	Fresh lung‡	Acute myocardial infarct
19	M	56	2	25	3 days	Fresh lung‡	Acute myocardial infarct
21	F	75	1½-2	50	±10 days	Fresh lung‡	Carcinoma of lung — advanced
22	M	52	1-2	25	2 days	Fresh lung‡	Cirrhosis; heart failure, with acute pulmonary edema.
23	M	55	1¼	±25	0	Fresh lung‡	Acute myocardial infarct
24	M	76	1	60	6-12 hr.	Fresh lung†	Acute septicemia
25	M	56	>2	>20	7 days	Fresh lung†	Subdural hemorrhage
30	M	56	1½	30	2 days	Fresh lung†	Alcoholic patient; acute myocardial infarct.
31	M	42	1-2	20	7 days	Fresh lung†	? Dissecting aneurysm; death during elective surgery.
32	M	70	1½-2	>30	7 days	Fresh lung†	Carcinoma of lung, with metastases
33	M	57	½	30	1 day	Fresh lung‡	Surgical specimen: right lung after pneumonectomy; carcinoma.
36	M	40	1½	27	1 day	Fresh lung‡	Surgical specimen: left upper lobe after lobectomy; carcinoma.
37	M	55	>2	>30	12 hr.	Fresh lung‡	Surgical specimen: left upper lobe after pneumonectomy; carcinoma.
5	M	72	(Nonsmoker)			Fresh lung*	Acute pancreatitis; coronary heart disease; pulmonary edema.
11	F	15	(Nonsmoker)			Fresh lung*	Leukemia
14	M	87	(Nonsmoker)			Fresh lung‡	Cerebrovascular accident
16	M	87	(Nonsmoker)			Fresh lung†	Cerebrovascular accident; bronchopneumonia.
26	F	90	(Nonsmoker)			Fresh lung‡	Acute intestinal obstruction
28	F	64	(Nonsmoker)			Fresh lung†	Metastatic carcinoma from breast
34	F	38	(Nonsmoker)			Fresh lung‡	Surgical specimen: right middle lobe, after lobectomy; bronchiectasis.
35	F	49	(Nonsmoker)			Fresh lung‡	Surgical specimen: left lung after pneumonectomy; undifferentiated carcinoma.
15	M	78	(Pipe smoker until 2 days before death)			Fresh lung†	Acute myocardial infarct
20	M	74	(Stopped cigarettes 16 yr. before death)			Fresh lung‡	Acute myocardial infarct
29	M	66	(Pipe smoker until 1 day before death)			Fresh lung†	Acute myocardial infarct

*Dissection delayed 2-24 hr. after autopsy.
†Frozen immediately — dissected later (see text).
‡Dissected immediately.

before dissection or before the lung was frozen. Systematic microscopical and histochemical examinations were performed on multiple epithelial sections from 14 lungs; these findings will be described in detail in a future publication. The left lung was used uniformly in these studies, except in a few cases in which it was specifically diseased and the right lung only was available for analysis. With the exception of Cases 1-13, 17 and 28 analyses were performed on lungs in which the bronchial tree had not been opened at autopsy.

Surgical Specimens

Whole lungs or single lobes were obtained during elective surgery in Cases 32-36. To minimize postmortem changes, surgical specimens were dissected within twenty minutes after removal. The bronchial tree had not been opened, and samples were dissected for Po^{210} analysis before routine histologic sections were taken. In 2 of these specimens (Cases 33 and 34) relatively little normal bronchial tissue was available.

Dissection of Specimens

Peribronchial lymph nodes were removed from the region of the lower-lobe bronchus and, if necessary, the hilar area. Whenever possible, about 1 gm. of lymphoid tissue was obtained. Samples of lung parenchyma weighing about 5 gm. were dissected from areas as free as possible of bronchi. Parenchymal samples contained no bronchi larger than 1 mm. in exterior diameter and were taken from the periphery of the lower lobe and, in 16 cases, from the region of the lower-lobe primary segmental bifurcations. In 10 cases peripheral parenchymal samples from both the upper and the lower lobes were obtained. To study in greater detail the gross paren-

chymal distribution of Po^{210}, 4 to 7 contiguous parenchymal samples were dissected from 4 additional lungs, following the course of a bronchus from the perihilar region out to the lung periphery.

Samples of bronchial epithelium were obtained whenever possible from the main-stem bronchus, lower-lobe bronchus and lower-lobe segmental bronchi, as well as from primary and secondary segmental bifurcations in the upper and lower lobes. When the bronchial tree had been opened at autopsy areas were chosen that had been minimally traumatized and where the mucous sheet appeared intact grossly. The epithelium, along with overlying mucus, was gently scraped off with a dull scalpel and analyzed separately from the underlying wall and submucosa. Separate determinations were also performed on samples of superficial mucus obtained by careful lifting off of areas of the mucous sheet with curved forceps. Samples of bronchial epithelium were obtained from areas averaging 1 or 2 square centimeters except in bifurcations, where they were as small as 0.1 to 0.2 square centimeter. In very small samples epithelial tissue was usually dissected from the underlying bronchial wall and cartilage with iris scissors, and the mucosa and submucosa were analyzed together.

Since epithelial samples contained varying amounts of superficial mucus or submucosa the Po^{210} concentrations in bronchial epithelium were calculated from the surface areas of the samples. In each lung the concentrations in mucus and in specimens of bronchial wall and submucosa were separately determined; these concentrations were in general similar to those found in lung parenchyma, but much lower than in epithelium. The weight of the epithelium alone in a given sample was calculated from its surface area on the basis of an average epithelial thickness of 40 microns — a value derived from the study of histologic sections in the present series and from the figures reported by Altshuler et al.[3] This calculated epithelial weight was subtracted from the measured weight of the entire sample, yielding the weight component due to superficial mucus or submucosa or both. The Po^{210} content of this latter component was then calculated from the concentrations measured in mucus and submucosa obtained elsewhere in the same lung. By subtraction of this value from the total activity measured in the sample the Po^{210} content of the epithelium alone was obtained.

Polonium^{210} Analyses

The details of the radiochemical analysis and counting of radioactivity due to Po^{210} have previously been described.[3] Briefly, tissue samples were digested for an hour in hot concentrated hydrochloric acid, after which the solution was diluted to 100 ml. with 0.5-N hydrochloric acid and put into plating cells maintained at 90 to 95°C. This technic is specific for polonium isotopes, but, of the natural isotopes, only Po^{210} has a long enough half-life to be counted one or two hours after plating. Radioactivity was measured in gas-flow proportional counters, with background rates of 0.2 to 0.6 counts per hour, and efficiencies of 51 per cent for polonium alpha particles. Counters with backgrounds of 0.2 to 0.3 counts per hour were used for most epithelial samples; these samples were counted for periods of twenty-four or forty-eight hours in different counters for a total elapsed time of three to seven days, until a minimum of 15 to 20 counts above background had been obtained. For samples with minimally detectable activity the count rate ranged from 35 to 65 per cent above background, and the standard deviation of a particular measurement was roughly ±50 per cent. When the total net count was less than 15, and the count rate less than 35 per cent above background, the activity of the sample was considered not significantly different from zero. Determination of background count rates, as well as the counting of reagent blanks, was performed at regular intervals; these showed remarkably little variation over long periods.

Results

Lung Parenchyma

Polonium^{210} concentrations found in lung parenchyma, peribronchial lymph nodes and bronchial epithelium are listed for each subject in Table 2. These are expressed as picocuries (10^{-12} curies, or 2.2 disintegrations per minute) of Po^{210} per gram of wet tissue. The average concentration in peripheral parenchyma of current cigarette smokers was 0.0074 picocurie per gram (range, 0.002 to 0.023) as compared with 0.0016 (range, 0.001 to 0.002) for nonsmokers. These results are shown graphically in Figure 1, in which the difference between smokers and nonsmokers is clear. Parenchymal concentrations in the 2 patients currently smoking pipes were similar to those of nonsmokers (0.001 and 0.0015 picocuries per gram).

In 12 cigarette smokers samples of more centrally located parenchyma were also analyzed (Table 2). Po^{210} content in these samples was greater than in peripheral samples in 9 of the 12 subjects and less in only 1; the average concentration in central specimens was roughly twice that in peripheral samples from the same group. In 10 smokers' lungs in which peripheral parenchyma from both upper and lower lobes was analyzed the upper-lobe parenchyma showed greater activity in 9 of 10 cases though the differences were not large (average concentration in the upper-lobe peripheral parenchyma was 0.010 picocurie per gram as compared with 0.008 picocurie in lower-lobe parenchyma from these 10 patients). In the 4 additional lungs in which contiguous parenchymal specimens were taken along the course of a bronchus from the hilar region to the

TABLE 2. *Polonium*^{210} *Concentrations in Pulmonary Tissues.*

CASE NO.	CONCENTRATION IN PARENCHYMA		CONCENTRATION IN PERIBRONCHIAL LYMPH NODES	CONCENTRATION IN BRONCHIAL EPITHELIUM*				
	PERIPHERAL	CENTRAL†		MAIN-STEM BRONCHUS	LOBAR BRONCHUS	SEGMENTAL BRONCHUS	LEFT-UPPER-SEGMENT BIFURCATION‡	LEFT-LOWER-SEGMENT BIFURCATION‡
	picocuries/gm. of wet tissue	*picocuries/gm. of wet tissue*	*picocuries/gm. of wet tissue*	*picocuries/gm. of wet tissue*	*picocuries/gm. of wet tissue*	*picocuries/gm. of wet tissue*	*picocuries/gm. of wet tissue*	*picocuries/gm. of wet tissue*
1	0.013	—	0.007	—	0.7	—	1.0	0.3
2	0.018	0.025	0.007	0.1	<0.2	<0.3	1.3	<0.8
3	0.002	0.005	0.013	<0.2	0.1	<0.2	0.5	2.9
4	0.004	0.007	0.006	0.2	<0.2	<0.2	0.6	0.5
6	0.009	—	0.018	—	<0.2	0.4	0.8	0.6
7	0.004	—	0.010	0.2	0.2	0.2	<0.8	1.8
8	0.010	—	0.009	0.6	0.1	<0.2	<4.0	<1.5
9	0.006	—	0.010	—	0.1	0.2	0.8	3.8
10	0.007	0.012	0.014	—	0.3	0.1	<2.0	2.9
12	0.005	—	0.020	—	0.3	<0.2	<1.0	13.9
13	0.005	0.010	0.003	—	<0.2	<0.3	3.8	3.5
17	0.008	—	0.013	—	0.2	0.1	2.0	2.7
18	0.004	0.019	0.010	<0.2	<0.4	1.0	2.7	13.0
19	0.007	0.007	0.015	0.2	0.5	<0.5	4.2	6.7
21	0.003	—	0.008	0.1	0.3	0.3	—	4.9
22	0.004	—	0.020	<0.2	0.6	1.1	5.0	7.5
23	0.009	0.009	0.015	0.4	0.4	2.6	3.1	4.9
24	0.002	0.0025	<0.002	1.7	<0.3	0.4	<1.0	<1.0
25	0.018	—	0.006	—	<0.2	<0.2	5.0	5.0
30	0.007	0.005	0.010	—	0.2	<0.4	2.1	—
31	0.002	0.006	0.005	<0.2	<0.2	0.2	1.4	<2.5
32	0.002	0.0025	0.003	—	0.1	<0.4	1.4	0.7
33	0.006	—	—	—	—	2.5	7.8	—
36	0.017	—	0.034	—	<1.0	<1.2	1.5	—
37	0.023	—	0.010	0.1	—	—	—	12.8
5	0.0015	0.001	0.007	—	<0.2	<0.3	—	<0.2
11	0.002	—	0.017	<0.5	<0.2	<0.4	<2.0	4.5
14	—	—	0.009	—	<0.1	—	<0.7	<0.3
16	0.0015	—	0.004	<0.3	<0.5	<0.4	<1.0	<1.0
26	0.002	0.004	<0.0015	0.2	<0.2	<1.5	<1.5	1.6
28	0.001	0.0015	0.0035	<0.6	0.6	<0.6	<1.5	6.8
34	0.0015	—	—	—	—	<0.6	<1.3	—
35	0.0015	—	0.0025	<0.6	<0.2	<0.2	—	0.9
15	0.0015	—	0.007	0.3	0.9	<0.2	7.2	1.5
20	0.0015	—	0.006	—	0.5	<0.5	<1.5	1.5
29	0.001	0.001	0.002	0.5	0.3	<0.2	6.2	2.7

*Calculated from surface area (see text).
†Parenchyma from region of primary segmental bifurcations.
‡Values given for single bifurcation in each lobe with highest concentration.

periphery, the results varied slightly, depending on the lobe studied. In the lower lobes Po^{210} concentrations were greatest centrally, in the region of the lobar bronchi and major segmental bifurcations, and gradually decreased to a minimum in the most peripheral samples. In the right middle lobe (1 case) and the lingular segment of the left upper lobe (3 cases), concentrations reached a maximum near the tertiary segmental bifurcations, in 2 of the 4 cases being lower more centrally (though still higher than in the most peripheral samples).

We have attempted to correlate concentrations in the lung parenchyma with smoking history. There was no correlation with total cigarettes smoked expressed as pack years (packages per day times number of years smoked), or with the age of the individual at death. As shown in Figure 2, however, a trend toward higher Po^{210} levels is suggested in the persons whose daily cigarette consumption was higher. Correlation with daily cigarette consumption, but not with total cigarettes smoked, is not unexpected, considering the rapid clearance time for particulates by the lung, as well as the relatively short half-life of the polonium isotope. Such relations are difficult to establish, however, owing to the inaccuracies inherent in the next of kin's estimation of cigarette consumption and the lack of specific data in hospital records. When parenchymal Po^{210} was studied as a function of time (one to ten days) since cessation of smoking a significant trend toward higher levels was evident only in those who smoked up until twenty-four hours or less before death or surgery, but the scatter was great. The parenchymal Po^{210} concentration in the patient who had not smoked cigarettes for sixteen years (Case 20) was very low (0.0015 picocurie per gram).

Lymph Nodes

The concentrations of Po^{210} found in peribronchial lymph nodes of smokers and nonsmokers are

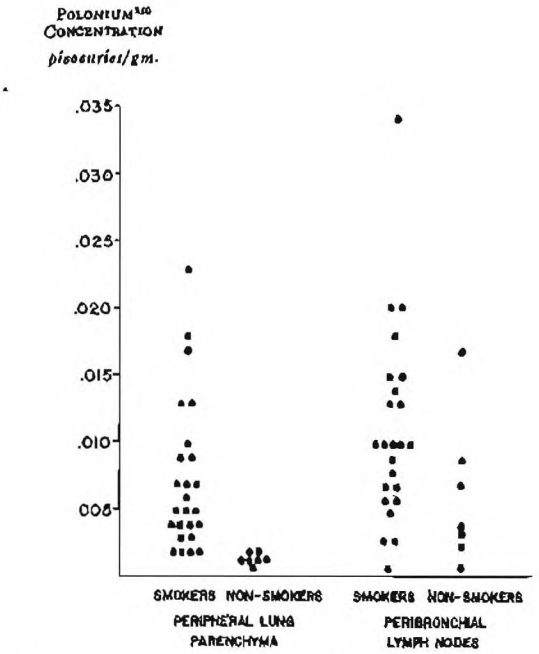

FIGURE 1. *Po^{210} Concentrations in Peripheral Lung Parenchyma and Peribronchial Lymph Nodes from 25 Patients Currently Smoking Cigarettes and from 8 Nonsmokers. Each point represents average findings in a single patient. No results were available in the lymph nodes from 2 lungs and in the parenchyma from 1 other lung.*

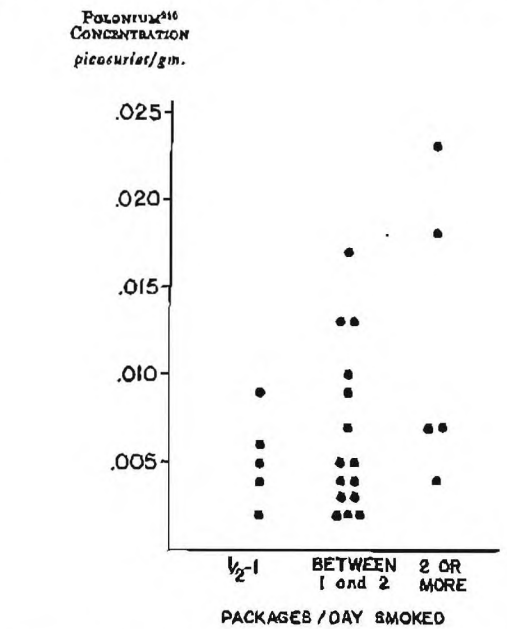

FIGURE 2. *Po^{210} Concentrations in Peripheral Lung Parenchyma as a Function of Daily Cigarette Consumption in 25 Patients Currently Smoking Who Smoked until Ten Days or Less before Death or Surgical Intervention.*

also shown in Figure 1. Again, considerable individual variation was evident. Though the average level in nonsmokers (0.0063 picocurie per gram) was somewhat below that found in those currently smoking (0.011 picocurie per gram) the difference was far less marked than in the lung parenchyma. There was no correlation with total cigarettes smoked, or number smoked per day, and little if any relation existed between Po^{210} concentrations in lung parenchyma and peribronchial lymph nodes in the same subject (for example, Cases 12, 22, 25 and 37).

Bronchial Epithelium

Though the Po^{210} concentration in bronchial wall was similar to that present in lung parenchyma, it was generally about two orders of magnitude greater in bronchial epithelium than in parenchyma or lymph nodes. The individual results in epithelium from 5 different sites are shown in Table 2. The concentrations indicated for bifurcations of the upper and lower lobes, where several similar specimens were frequently analyzed in each lung, were those found in the single bifurcation in each region containing the greatest measured activity. Since parenchymal and lymph-node samples weighed 1 to 5 gm. good accuracy could be achieved in measurement of Po^{210} activity in these specimens. Epithelial samples usually weighed less than 25 mg. and contained much less total activity. The accuracy of each determination was therefore considerably reduced, particularly in small bifurcations. When no activity was observed, Po^{210} was recorded in Table 2 as being less than the concentration that we should have been able to detect on the basis of the epithelial weight and total counting time of the sample.

Measurable Po^{210} was also present in superficial mucus from all smokers; the concentrations ranged from 0.002 to 0.044 picocurie per gram of mucus, with the exception of Case 36, in which the concentration was much higher (0.28 picocurie per gram). The latter result may have been due to an error in analysis. The results in mucus are probably the least representative of equilibrium conditions during life, owing to the rapid clearance characteristics of superficial mucus and the abnormally large quantities of mucus undoubtedly present in many of these patients at death.

When histologic sections were obtained at the time of dissection in the lungs in which dissection was delayed for two to twenty-four hours after autopsy they showed varying degrees of post-mortem changes, especially loss of areas of bronchial epithelium. We shall consider in detail, therefore, the results from the 14 smokers' lungs that were analyzed or frozen immediately. In these cases histologic sections revealed minimal post-mortem changes and generally intact bronchial epithelium. The anatomic locations of epithelial samples, as well as the averages and ranges of Po^{210} concentrations found in epithelium from this group of 14 smokers, are shown graphically in Figure 3. With the exception of Cases 33 and 36 lobar and segmental

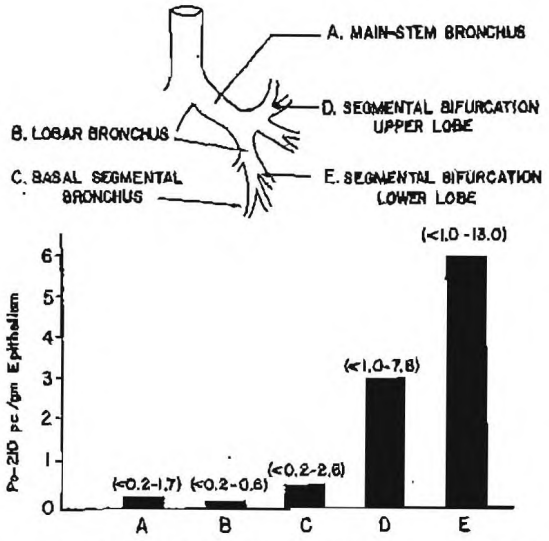

FIGURE 3. *Average Po^{210} Concentrations in Bronchial Epithelium from Various Regions of the Bronchial Tree of 14 Cigarette Smokers.*

The figures in parentheses are ranges. For the purpose of these averages, samples in which no activity could be measured (see Table 2) were considered as having zero activity. In bifurcations the averages are of concentrations found in the single bifurcation in each lobe with the highest measured activity.

bronchi analyzed were all from the lower lobes. Po^{210} activity was observed in epithelium from 5 of the 8 main-stem and 7 of the 12 lobar bronchi analyzed. With 1 exception the concentrations in these regions ranged from 0.1 to 0.6 picocurie per gram of epithelium. Activity was found in segmental bronchi from 8 of 13 lungs; epithelial concentrations were 1.0 picocurie per gram or greater in 4 of these bronchi, but were similar to those in lobar and main-stem bronchi in the other 4. The levels were considerably higher, however, in segmental bifurcations. Po^{210} was found in epithelium from upper-lobe bifurcations in 11 of the 12 lungs and in lower-lobe bifurcations in 9 of the 11 lungs in which they were analyzed. In 9 lungs in which bifurcations from both upper and lower lobes were analyzed 7 showed activity in both regions. In all 14 lungs the average Po^{210} concentration in segmental bifurcations from both lobes was 4.5 picocuries per gram. Po^{210} in epithelium from individual bifurcations, however, exceeded 10 picocuries per gram in 2 lungs, and ranged from 4.5 to 10 picocuries per gram in 7 of the remaining 12 specimens.

It is evident from Table 2 that considerable variation in epithelial Po^{210} concentration was present among smokers. In addition, however, considerable variation was found among different bifurcations in the same lung and lobe.

In the 11 additional lungs from cigarette smokers in which delayed dissections were performed (Cases 1 to 13) Po^{210} activity was found in segmental bifurcations from 10 of the 11 specimens, but the concentrations were generally lower than in the lungs that were frozen or dissected immediately after autopsy. We believe that even in the latter cases, polonium may have been lost from local "hot spots" because of the delay between death and autopsy.

No correlation existed between number of cigarettes smoked, or time since the last cigarette, and the Po^{210} levels in bronchial epithelium. Similarly, there was no correlation between parenchymal and epithelial concentrations. In the 2 pipe smokers epithelial Po^{210} content was similar to that of cigarette smokers though the parenchymal concentrations were very low. Significant, though low, levels of activity were found in the lobar bronchus and 1 bifurcation of the single past smoker (Case 20).

The difference between these results and those in bronchial epithelium from the lungs of the 8 nonsmokers is not as clear as the results in the lung parenchyma. Though in no nonsmoker was activity found in segmental bronchi or upper-lobe bifurcations, and in only 1 case each was there activity in main-stem or lobar bronchi, significant Po^{210} was found in epithelium from lower-lobe bifurcations in 4 of the 8 nonsmokers. In 2 of these the concentrations were similar to those found in many smokers, but in the remaining 2, only low Po^{210} levels were observed in 1 of 3 bifurcations analyzed in each case. Obviously, cigarette smoking may not be the only environmental source of Po^{210} for bronchial epithelium.

DISCUSSION

It is evident that human lung tissues contain measurable amounts of the radioactive isotope polonium^{210}. In general, this element may enter the body in two ways. In the first, "unsupported" Po^{210}, or polonium not present with its long-lived parent, lead^{210}, may be taken into the body directly. Because the half-life of Po^{210} is only a hundred and thirty-eight days, exposure to the isotope would have to be fairly continuous for a steady-state concentration to be reached in tissues. On the basis of preliminary measurements of lead^{210} we believe that most of the Po^{210} in smokers' lungs comes from such unsupported Po^{210} present in cigarette smoke. Secondly, when lead^{210} is present, Po^{210} may arise in the body from a decay of this element.* Lead^{210} is present in many foodstuffs, as well as in the air in low concentrations.[4] Its major route of entry is probably the gastrointestinal tract, from either ingested food or swallowed mucus from the lungs. We

*Po^{210} is the last in a series of radioactive elements derived from radium^{226}. If Po^{210} is present with its long-lived parent, lead^{210} (physical half-life, twenty years), it will be in equilibrium when the rate of Po^{210} decay to stable lead equals the rate of production of new Po^{210} from the decay of lead^{210}. Polonium^{210}, therefore, may be present for long periods despite its relatively short half-life (a hundred and thirty-eight days) if it is "supported" in this way by long-lived lead^{210}. For example, the Po^{210} in cigarettes depends on the presence of lead^{210} because of the long time between harvesting of tobacco and consumption of the cigarette. It is chiefly the Po^{210}, however, that is volatilized when the cigarette burns and is carried off in the smoke and inhaled.

believe that the Po^{210} activity in soft tissues other than the lung may arise principally from this source; Po^{210} levels in liver, spleen and kidneys, for example, are similar in smokers and nonsmokers.[6] Likewise, Po^{210} in nonsmokers' lungs may also arise from lead^{210}.

Though some pulmonary Po^{210} comes from normal environmental sources, such as ingested or inhaled lead^{210}, the present studies indicate that cigarette smoke is a significant additional source of this isotope in the lungs.

Polonium as a Tracer for Clearance of Smoke Particles in Human Lungs

If we assume that Po^{210} in cigarette smoke remains attached to the smoke particles, we may infer some of the characteristics of particle deposition and clearance in human lungs from the pattern of polonium distribution in pulmonary tissues of smokers. The relatively low Po^{210} concentration in lung parenchyma of cigarette smokers, for example, suggests that the majority of inhaled smoke particles is rapidly cleared from the lung. The average excess Po^{210} concentration in lung parenchyma of cigarette smokers as compared to nonsmokers was 0.010 picocurie per gram, on the basis of our findings in central and peripheral samples. This excess would represent about 10 picocuries of Po^{210} in both lungs at any given time, or the amount deposited from smoking of about 7 packages of cigarettes.[1,6] Turnover of polonium in the lungs is therefore a relatively rapid process. As discussed below, Po^{210} clearance appears to occur primarily by way of the mucous sheet. On the basis of our measurements in mucus from persons with no lung disease who smoked until less than forty-eight hours before death (excluding Case 36), and on the assumption that each lung contains less than 10 gm. of superficial mucus, the total Po^{210} in the mucus of both lungs at any given time would be less than 0.4 picocurie — a quantity that would be deposited from the smoking of 6 cigarettes. Though the findings relevant to superficial mucus in these specimens probably do not duplicate in vivo equilibrium conditions our results are consistent with the rapid mucus transit and clearance times calculated for human beings by Albert and Arnett.[7]

The distribution of polonium activity in the lung parenchyma of cigarette smokers suggests that either deposition or clearance of smoke is not uniform. Because deposition of cigarette smoke depends on diffusion it should be relatively uniform within the lung. The lower polonium content in peripheral parenchyma, therefore, probably reflects a more rapid clearance of smoke from peripheral lung tissue, into the bronchial tree, than from more central regions. Unexpectedly, the lymphatics apparently do not have an important role in clearance of smoke particles, or at least in clearance of the isotope itself. This conclusion is based on the observations that peribronchial lymph nodes in smokers contained relatively little Po^{210} and that the concentrations in smokers were little different from those found in persons who had never smoked. Finally, the observation that blood of cigarette smokers contains only about 0.0016 picocurie per gram of Po^{210} as compared with 0.0007 picocurie per gram in nonsmokers,[8] despite a low urinary clearance, indicates that only a very small fraction of inhaled Po^{210} in cigarette smoke is absorbed into the bloodstream. In summary, then, clearance of the majority of inhaled cigarette-smoke particles appears to be rapid and to occur primarily by way of the bronchi.

The epithelial measurements indicate that Po^{210} in cigarette smoke can be absorbed in measurable quantities into the bronchial epithelium. As previously pointed out,[1,6] high local concentrations within the epithelium would be by far the most important factor contributing to a significant radiation dose to bronchial tissues. It is logical that Po^{210} deposition from the mucous sheet should occur in epithelium from bifurcations, because at these points the flow must split and move laterally to the wall of the single bronchus.[10] In the region where the splitting takes place, a dead spot or eddy frequently occurs, and material contained in the mucus may more readily penetrate to the underlying epithelium. It is of interest that Auerbach et al.[11] found the highest incidence of premalignant changes in the bronchial epithelium to occur at bifurcations. The wide variation in Po^{210} concentrations in segmental bifurcations is not unexpected, considering the normal anatomic and physiologic variability and the varying degrees of pulmonary disease and post-mortem changes present in many of these lungs.

The observation that Po^{210} was also present in some epithelial samples from nonsmokers indicates that cigarette smoke is not the only environmental source of this isotope in bronchial epithelium. In general, however, the levels were much lower in epithelium from nonsmokers than in those currently smoking cigarettes; no activity was found in any epithelial sample from 4 of the 8 nonsmokers. The Po^{210} activity measured in bronchial epithelium of nonsmokers may arise from lead^{210}, and specific physiologic factors relevant to each subject may determine the accumulation of localized concentrations of Po^{210} or lead^{210} from sources other than cigarette smoke.

Radiation Dose from Po^{210} in Bronchial Epithelium

Although the epithelial concentrations measured may not represent equilibrium conditions during life, we may use them as a base line in calculating the radiation dose from Po^{210} to local areas of bronchial epithelium. Owing to post-mortem changes, primarily some loss of epithelium, one would ex-

pect that any errors in such a calculation would lead to a calculated dose lower than that actually received. If an equilibrium concentration of 10 picocuries per gram is distributed in a volume of bronchial epithelium (levels of 7.5-14 picocuries per gram were measured in bifurcations from 7 subjects in this series), and 80 per cent of the energy from the alpha radiation (5.3 Mev., with a range in tissue of about 40 microns) is absorbed in this volume, the total radiation dose to the tissue in twenty-five years will be about 20 rad, or 200 rem, on the basis of a relative biologic-effectiveness factor for alpha particles of 10. (Normal background-radiation exposure to the bronchial epithelium during this period would be in the order of 5 rem.[1]) This calculation is based on a homogeneous distribution of Po^{210} radioactivity within the small epithelial volume and must therefore be considered a minimum dose. It is possible that localized "hot spots" were present even within the small tissue samples that we have measured; in this case local radiation doses would be considerably higher. It should be pointed out, however, that the relative importance of localized irradiation in the production of bronchial cancer, as compared to irradiation of a large volume of tissue, is not yet well understood. Certainly, on the basis of our findings in lung parenchyma and superficial mucus of smokers, the radiation dose from Po^{210} to the lung or bronchial epithelium as a whole would be very small as compared to normal background radiation.

The best evidence available for the importance of alpha-emitting isotopes in the production of bronchial cancer in man comes from recent studies of underground mine workers exposed to moderately elevated radon concentrations in the air.[12,13] The latest report of the continuing evaluation of uranium miners in the Colorado Plateau[12] has permitted an estimation of the dose-response relation between exposure to alpha radiation and the mortality rate for bronchial cancer. Direct comparison of mortality rates between the general smoking population and these miners is not possible because the age distribution and smoking histories are not given. The best comparison is within the miner group itself. The radiation exposures have been given in "working-level months." Altshuler et al.[2] and Jacobi[13] have calculated in detail the radiation dose to the basal-cell layer at various sites of the bronchial epithelium arising from inspired radon daughters. Although their estimates depend on many assumptions they indicate that the highest radiation dose to localized areas of epithelium would be about 1 rad of alpha-radiation exposure per working-level month. This highest dose would apply only to small areas of the segmental bronchi where the epithelium is thin.

From the data of Wagoner et al.[12] the incidence of bronchial cancer in the lowest exposure group (less than 120 working-level months or less than 120 rad of added exposure) is found to be only half that observed in the second exposure group, who received local cumulative exposures of about 240 rad. It is clear, therefore, that relatively small increments in alpha-radiation exposure to a localized region of bronchial epithelium can significantly affect the incidence of cancer at that site.

A direct application of this dose-response relation to the doses arising from Po^{210} in the epithelium of smokers is not possible, however, for three main reasons: too much uncertainty about the degree of linearity of the dose-response curve at low dosage levels remains; there are differences in the latent period and types of tumors found in mine workers as compared to smokers, and longer-term follow-up in the miners may reveal a higher incidence of bronchial cancer; and, finally, in comparing nonsmokers with smokers, we are assessing differences not only in exposure to alpha radiation but also to all other components of cigarette smoke.

It is unlikely that alpha radiation is the sole factor responsible for bronchial tumors in smokers. Other agents in cigarette smoke may well contribute significantly as cocarcinogens, and the effect of a small radiation dose may be considerably magnified by the action of these agents. In this connection, the high incidence of bronchial cancer in Newfoundland fluorspar miners is of interest.[14] We estimate that this incidence has been about 1 per cent per year for men having a cumulative radiation exposure of approximately 1000 working-level months. If we assume that the age distribution and smoking histories are comparable, the incidence of bronchial cancer appears to be at least five times as high among the Newfoundland fluorspar miners as among the Colorado uranium miners for similar radiation exposures. Although radon and its daughters in the air are common to both, the dusts in the mines from the two areas are quite different; in the Newfoundland mines considerable fluorspar dust, but no arsenic or uranium compounds, was found in the air. The greater incidence in these miners than in the Colorado miners suggests that an additional factor or cocarcinogen is present, and the possibility that fluorspar itself is the cocarcinogen is under investigation.[15]

Because of the uncertainty associated with dose estimates to bronchial stem cells in both miners and cigarette smokers it is premature to assert that Po^{210} is or is not likely to be the *major* factor in induction of bronchial cancer in smokers. We should like to emphasize, however, the point that it is not particularly relevant to compare these localized radiation doses from alpha emitters to external x-ray or gamma-ray exposure to lungs. Since it is highly probable that the relative biologic effectiveness of alpha particles in producing long-term effects on cell populations is very great, at least ten to twenty times greater than external gamma radiation given

acutely or chronically,[16] small radiation doses from alpha particles will be considerably more effective than a comparison with the sparsely ionizing electromagnetic radiations would suggest. Furthermore, it is unlikely that there is a threshold dose below which no effect would be produced by alpha radiation; on this basis any dose, no matter how small, would have a certain probability for tumor induction. Finally, recent preliminary studies in animals indicate that alpha radiation may be a much more potent carcinogen in the production of certain skin cancers than more sparsely ionizing radiation (in this case, protons).[17]

As for the distribution of Po^{210} within the lung, the high levels found in segmental bifurcations are in regions where bronchial carcinomas frequently arise. The relatively low concentrations in lung parenchyma indicate that significant localization does not occur in the alveoli, and, indeed, parenchymal tumors are relatively uncommon in cigarette smokers. Lung cancer in males is reported to occur about twice as frequently in left-upper-lobe segmental and lobar bronchi as in similar areas of the left lower lobe.[18,19] Auerbach et al.,[11] however, found the incidence of premalignant changes to be only very slightly higher in the upper-lobe bronchi of cigarette smokers. These findings do not correlate with the Po^{210} levels that we have observed though the difference in Po^{210} concentrations in bifurcations of the upper and lower lobes is not as significant as it appears because of the wide individual variation. The values given in Table 2 are for the single segmental bifurcation in each lobe with the highest Po^{210} concentration; in most cases only 1 or 2 upper-lobe bifurcations were analyzed, whereas levels in 2 or more lower-lobe bifurcations were frequently measured.

It has been shown in animals that ionizing radiation may potentiate the effects of directly applied components of cigarette smoke in the experimental production of malignant skin tumors.[20] We conclude, on the basis of the available evidence, that radiation from Po^{210} may be an important factor in the initiation of bronchial cancer in cigarette smokers.

Summary and Conclusions

The alpha-emitting radioactive isotope polonium^{210} present in cigarette smoke was found in higher concentrations in lung parenchyma, peribronchial lymph nodes and bronchial epithelium of 25 persons currently smoking cigarettes than in those of 8 nonsmokers. From its distribution within the lung, certain characteristics of the pulmonary deposition and clearance of inhaled cigarette smoke may be determined. The clearance of the majority of smoke particles appears to be rapid and to occur primarily by way of the bronchi, but absorption of Po^{210} into bronchial epithelium does occur. By far the highest local concentrations of Po^{210} were found in bronchial epithelium from segmental bifurcations, and with continual exposure to the isotope, as experienced by cigarette smokers, the cumulative local radiation dose to these small regions of bronchial tissue may be quite high. On the basis of these results, we believe that Po^{210} may be an important factor in the initiation of bronchial carcinoma in man.

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