CANCER

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Lung Tumors of Primates and Rodents

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The materials reviewed include 269 industrially induced human lung cancers and 276 pulmonary neoplasmata, which developed In monkeys. rabbits, guinea pigs and rats after inhalation exposure or intratracheal injection of 266 chemical substances. The animal tumors developed in 10.768 experimental subjects, whereas 4,143 control animals, matched for sex, age and survival, showed no tumors. In addition to neoplasia, there were large numbers of lesions that were judged to be pre-neoplastic. The morphology of the animal tumors is compared with that of human tumors and some homologies were Identified, A tentative explanation of the histogenesis of morphological varieties of animal tumors is offered. [Ed. note: This is the first in a three-part series. This article will be of parnmount interest to all professions concerned with the association of the worker and his environment, but because of its length, we will present it in three installments.]

Two types of experiences arc reviewed in this paper. The first concerns a number of lung cancers seen in a variety of industrial and non-industrial workers. The second represents several series of experimental animals exposed by the tracheal injection and inhalation methods to a variety of chemical substances of special significance in industry.

HUMAN LUSC CASCER

That various environmental agents can induce lung cancer no longer is in doubt. The current list of acceptable environmental carcinogens is given in Tabla 1. Certain other agents have been suggested, but sincc there is residual doubt about these, they arc not included in the Table.

During three decades of preoccupation with industrial medicine, 330 lung cancers were personally studied (Table 2). These were found in a relatively defined working population group, so that approximate prevalence rates could be calculated. The 13.9/1000 rate for the 269 lung cancers seen among all worker groups appears to be appreciably higher than the 4-7/1000 rate for the 61 cancers observed among persons who had no industrial exposures. The two groups were approximately age, sex and race matched, so that the prevalence rates may be comparable.

The highest prevalence was clearly among persons exposed to asbestos dust. Factory workers showed higher prevalences than did asbestos miners. The rates for cod mincrs in this scries are nigher than are those reported for coal miners in general. This is perhaps due to the fact that the cases derive from special regions where lung cancer appears to occur more frequently than among coal mincrs in general. In the case of the gold miners, there appears to be a slight excess prevalence of lung canccr. Since Witwatersrand gold mine air yields about 600 microcuries of radon per cubic mrter and since the lungs of long-term gold mincrs are midly radioactive, as determined by autoradiography, ionizing radiation may be a carcinogenic factor. In hematite and magnetite mine air. radon gas also is demonstrable. bur in much lower concentrations (15-60 μci/M^3). The lung of hematite and magnetite miners contain relatively large quantities of mineral substances and this m3y influence lung cancer rates.

The inhalation csposurcs of the 13 chemical workers with lung cancer were so varied that no specific carcinogenic agent could bc incriminated. The rates for ceramic and glass workers appear to be lower than those for non-industrial workcrs. The foundry cases derived from iron, steel and brass foundries. No specific carcinogen has becn identified. Metal workers included grinders, polishers, press and cutting tool operators. The miscellaneous group includes carpenters, typesetters, ink makers. hose manufacturers, etc. Specific causes for the slightly enhanced prevalence of lung cancer have not becn identified.

TABLE 1. Environmentally Induced Lung Cancer*

Probable Carcinogens

Arsenic: As fumes, dusts or insecticides
Asbestos: As crocidolite and amosite†
Chromium: As monochromate dust, fume or mist
Ionizing Radiation: As alpha and beta particles and as gamma and x rays
Isopropyl Oil: As mists and vapors
Nickel: As particulate metallic nickel and as nickel carbonyl
Smoke: As cigarette smoke
Soot: As particulate matter and as coal gas

Suspected Carcinogens

Asbestos: † As chrysotile, anthophyllite, and as tremolite
Beryllium: As $BeZnMnSiO_4$, BeO, BeF_2, $BeSO_4$, $BeHPO_4$
Diepoxides: As general air pollutants
Engine Exhausts: As general air pollutants
Mineral Oil: Aromatic series — as mists and vapors
Mustard Gas: In mustard gas factories
Tar: As fume

*Report of Committee on Occupational Chest Disease, American College of Chest Physicians

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TABLE 2. Lung Tumors Environmental Factors: Human*

Industrial Workers	*Number*	*Prevalence/1000*
Miners	218	13.7
Asbestos	22	32.7
Coal—soft	9	7.1
Anthracite	5	13.4
Cold	176	7.3
Iron—hematite	4	6.8
.. magnetite	2	5.6
Manufacturing	51	14.3
Asbestos	17	51.3
Chemical	13	9.5
Ceramic and glass	5	3.2
Foundries	7	9.6
Metal	5	5.5
Miscellaneous	4	6.4
TOTAL Industrial	269	13.9
Non-Industrial	61	4.7

*Personally observed

ANIMAL TUMORS

These were all observed in animals experimentally exposed to a large variety of industrially significant substances. Over a cumulative period of three decades, 265 lung tumors were observed in 7,876 animals that had been exposed by the inhalation method to 136 aerosols (Table 3). None were observed in 3,167 animals used as age, sex and survival matched controls in these inhalation experiments. In addition, 2,862 animals received 130 substances (or combinations of substances) by the intratracheal route. Among these, 11 tumors were found, limited to two substances. The controls for these groups, comprising *976* animals, displayed no tumors.

TRACHEAL INJECTIONS

Tables 4, 5, 6, 7 and 8 summarize the 130 experiments performed on guinea pigs, and occasionally on rabbits, rats, swine and cats. The substances were tested to survey their biological actions because certain human subjects are occupationally exposed to them. No primates were used, since they are too expensive for this type of experiment.

Of these 130 experiments, 9 yielded negative biological results during the periods of observation. Apart from exonerating the nine substances as pulmonary pathogens, this confirms that intratracheal injection of a suspension or solution of any chemical substance is not necessarily pathogenic. It has often been argued that intratracheal injections create highly artifical local conditions that must necessarily induce pulmonary lesions. To a degree, the intratracheal method does exaggerate the biological effects of most substances. However, if the material is truly inert, this can be proven by the intratracheal method.

Reference is also made to the wide range of severity of the effects of the substances which did cause lesions. The latter ranged from slight to extreme. This suggests that the tracheal method can be quite discriminative of biological effects produced by chemically or physically different materials. The 11 tumors have already been mentioned.

The lesions induced in these 130 tracheal experiments also varied considerably in quality. Some materials

TABLE 3. Lung Tumors: Experimentally Induced: Animal

Species	*Chemical Exposure*			*Controls*		
	Animals	*Tumors No.*	*Tumors E*	*Animals*	*Tumors No.*	*Tumors %*
Primates	128	2	1.60	64	0	0
Rabbits	564	3	0.52	232	0	0
Guinea pigs	4294	11	0.26	1878	0	0
Rats	2486	244	10.62	763	0	0
Other	524	S	1.03	230	0	0
Totals	7306	265	3.59	3167	0	0

TABLE 4. Pulmonary Lesions: Experimentally Induced: Tracheal Route: 12 Months

Substance	Species	Lesions O	E	N
Aloxite	Rb	++		
Aluminum – Metal	GP	+		
– Al (OH)$_3$	GP			
Alundum	CP	+		
Anthophyllite – Short Fiber	GP	+	+	
Long Fiber 20-50µ	GP	++	++	
Amosite	CP	++	+	
Amphibole 20-60µ	GP	+		
Amphibole Alpine	CP	+		
Arizona Asbestos	GP	+		
Bagasse	GP	+		
Bakelite	CP	+		
Berlinite	CP	+		
Beryllium oxide	CP	+	++	
Beryllium slag	GP	+	+	
Beryllium stearate	CP	+	+	
Beryllium sulphate	GP, R		+++	6
Beryllium ZnMnSiO$_4$	GPRb, R, Sw	++	+++	3
Biotite	CP	+		
Brucite 20-50µ	CP	++	+	
Cadmium – borate	CP	+++	++	
Oxide	CP	++	+	
Selenite	CP	++++	++	
Carbon 2D	CP	+		
Carbon CLC	CP	+		
Carbon + Quartz	GP	+++		

Rb, Rabbit; GP, Guinea Pig; R. Rat; Sw, Swine
O, All other lesions; E, Epithelialization; N, Neoplasia
+, Slight reaction; ++, Moderate reaction: +++, Marked reaction;
++++, Extreme reaction

TABLE 5. Pulmonary Lesions: Experimentally Induced: Tracheal Route: 12 Months

Substance	Species	Lesions O	E	N
Carborundum	CP	+	+	
Carborundum + R$_1$	CP	++	+	
Cement	CP			
Cement + R$_1$	GP	+		
Clay – calcined	CY	++	+	
Coal – sea	GP	+		
Wattstown	GP	++	+	1
Wyco	CP	+		
Cobalt	CP	++	+	
Cobaltic oxide	CP	+	+	
Copper oxide	CP	+		
Chrysotile 20-50µ	GP, R,	C	++	
Chrysotile 65-200µ	D	+		
Chrysotile + Al (OH)$_3$	R	+		
Chrysotile + Serpentine	GP	++		
Crocidolite	CP	++	+	
Diatomite – raw	GP	+		
Diatomite – flux calcined	CP, R	[illegible]	+++	1
DFC + Aluminum	GP, R	++	+	
DFC + Al (OH)$_3$	GP, R	4		
Ether	GP			
Feldspar	CP	+		
Ferric oxide	CP	+		
Ferric oxide + quartz	CP	++		
Fluorspar	Rb	+	+	
Garnet	GP	+		
Garnet + R$_1$	GP	+		

Rb, Rabbit; GP, Guinea Pig; R, Rat; C, Cat; D, Dog
O, All other lesions; E, Epithelialization; N, Neoplasia
+, Slight Reaction; ++, Moderate Reaction; +++ Marked Reaction;
++++, Extreme Reaction
R$_1$, R$_1$ Rv Mycobacterial Infection; DFC, Flux Calcined Diatomaceous Earth

TABLE 6. Pulmonary Lesions: Experimentally Induced: Tracheal Route: 12 Months

Substance	*Species*	*Lesions* O	E	N
Glass – Fiberglass *20-Sop*	GP	+		
Vycor	R	+		
Wool – Ball Milled	GP			
Wool 20-50μ	GP	+	++	
Granite	GP	++		
Graphite	GP	+		
India ink	R			
India ink R$_1$	R			
Kaolin	GP	+		
Kaolin halloysite	GP	+		
Kaolin montmorillonite	GP	+		
K-Lo	GP	+	+	
K-Lo + Quartz	GP	++	+	
Magnesium metal	GP, C	+		
Magnetite	GP	++		
Manganese carbonate	GP	+	+	
Manganese tungstate	GP	+	++	
Marble	GP	+		
Metronite	GP	+		
Mica	GP	+	+	
Mica + Bakelite	GP	+	+	
Molybdenum	GP	++	+	
Muscovite	GP	+		
Olivine Norwegian	GP			
Olivine USA	GP			

GP, Guinea Pig; R, Ret; C, Cat
;O. All other lesions; E. Epithelialization; N, Neoplasia
+, Slight Reaction; ++, Moderate Reaction

TABLE 7. Pulmonary Lesions: Experimentally Induced: Tracheal Route: 12 Months

Substance	*Species*	*Lesions* O	E	N
Perlite	GP			
Phosphorus getter	GP	+	++	
Polyester resin	CP	+		
Potassium carbonate	GP			
Rare earth fluorides	GP	+	+	
Rare earth oxides	GP	+	+	
Rhodonite	CP	+		
Sericite	CP. RB	+		
Serpentine	GP	+		
Sillimanite	GP	+		
Talc – Georgia	GP			
Tremolite	GP	++	+	
Tantalum	GP	+		
Titanite (bar[illegible])	GP	+		
TNT	CP			
Thorium (GM)	GP	+	+	
Tungsten	GP	+	■	
Tungsten arhidr	CP	+	+	
Welding fume	GP	+		
Willemite	GP	+		
Zinc oxide	GP	+		
Zinc stearate	GP	+		
Zircon	GP			
Zircon oxide	GP			

GP; Guinea Pig; Rb, Rabbit
O. All other lesions: E. Epithelialization; N, Neoplasia
+, Slight Reaction; ++, Moderate Reaction
GM, CAS Mantel Dust

TABLE 8. Pulmonary Lesions: Experimentally Induced Tracheal Route: 12 Months

Substance	*Species*	*Lesions* O	E	N
Quartz – 2-5μ	GP, R	++		
1-3μ	GP	++		
>1μ	GP, Rb	+++		
Silex	GP	++		
Quartz + Aluminum	GP	+		
+ Al $(OH)_3$	G1			
Carbon	GP	+++		
+ CuO	GP	+++		
+ Fe_2O_3	GP	++		
+ KCO_3	GP			
Silica – amorphous				
Dow Corning K_3	GP, Rb, R	+		
DuPont hydrophobic	Rb, GP, R	++		
Salt free	Rb, CP, R	++		
Estersil	Rb, GP	++		
GE (ethyl silicate)	GP	++	+	
GE fume	GP	+++	++	
Goodrich AF_5	Rb, GP, R	+++	+	
Monsanto silica	GP	++		
PP CO. HiSil 101	GP, R	+		
HiSil C	GP	++	+ *	
HiSil 404	GP	++		
HiSil T	GP	+		
Syton	GP, Rb, R	+	++	
Silica – vitreous	GP, R			
Silicon – metal	Rb	+	4	
Sodium silicate	GP	+		
$NaSiO_4 + R_1$	GP	+		

GP, Guinea Pig; R, Rat; Rb, Rabbit
O, All other lesions; E, Epithelialization; N, Neoplasia
+, Slight reaction; ++, Moderate reaction; +++, Marked reaction

induced destructive changes; some caused cells to invade or multiply in the lungs; others resulted in focal or in diffuse fibrosis. In some experiments, the major lesion affected the bronchi and bronchioles. Other substances caused their greatest effects on the pulmonary parenchyma. Some substances selectively caused obliteration of blood vessels. Emphysema was observed in certain cases. Pleural lesions resulted in a minor proportion of cases. Some tracheal injections induced major effects in regional lymph nodes and even in extrathoracic organs.

Of specific relevance to the subject matter of this paper is the number of substances which, after tracheal administration, caused epithelialization of alveolar surfaces. The majority of the epithelializations were of slight degree only. In five cases the epithelialization was rated as moderate, and in two as marked, either by virtue of the number of animals affected, the multipliciiy of lesions per animal, or the local extent of the epithelial proliferation.

Two distinct varieties of epithelialization could be identified. The first affected alveoli immediate around bronchioles and alveolar ducts and the epithelial cells tended to be of the tall columnar variety among which goblet cells were observed (Fig. 1A). This epithelialization is designated bronchiologenic. The second variety may be called alveologenic (Fig. 1B). These lesions occurred on alveolar surfaces at some distance from the nearest bronchioles, or even in subpleural locations. The cells were of the low cuboidal or semi-flattened variety. No goblet cells were observed in these lesions. Sometimes these epithelializations lay opposite intra-alveolar collections of the injected material or near lymphoid foci. At other times they appear to be quite separate from any trapped extraneous matter. A little more than half of the lesions were of the bronchiologenic variety and these included those rated as of moderate severity. The rest were alveologenic epithelialization. In some instances, epithelialization was so extensive that differentiation from tumor was almost impossible.

Beryllium sulfate and zinc manganese beryllium silicate caused not only moderate to marked epithelializations, but nine animals developed neoplastic changes. One guinea pig also displsyed an osteogenic sarcoma. The histological and cytological features of the lung tumors varied considerably. Squamoid carcinoma predominated in animals that had been dosed with zinc

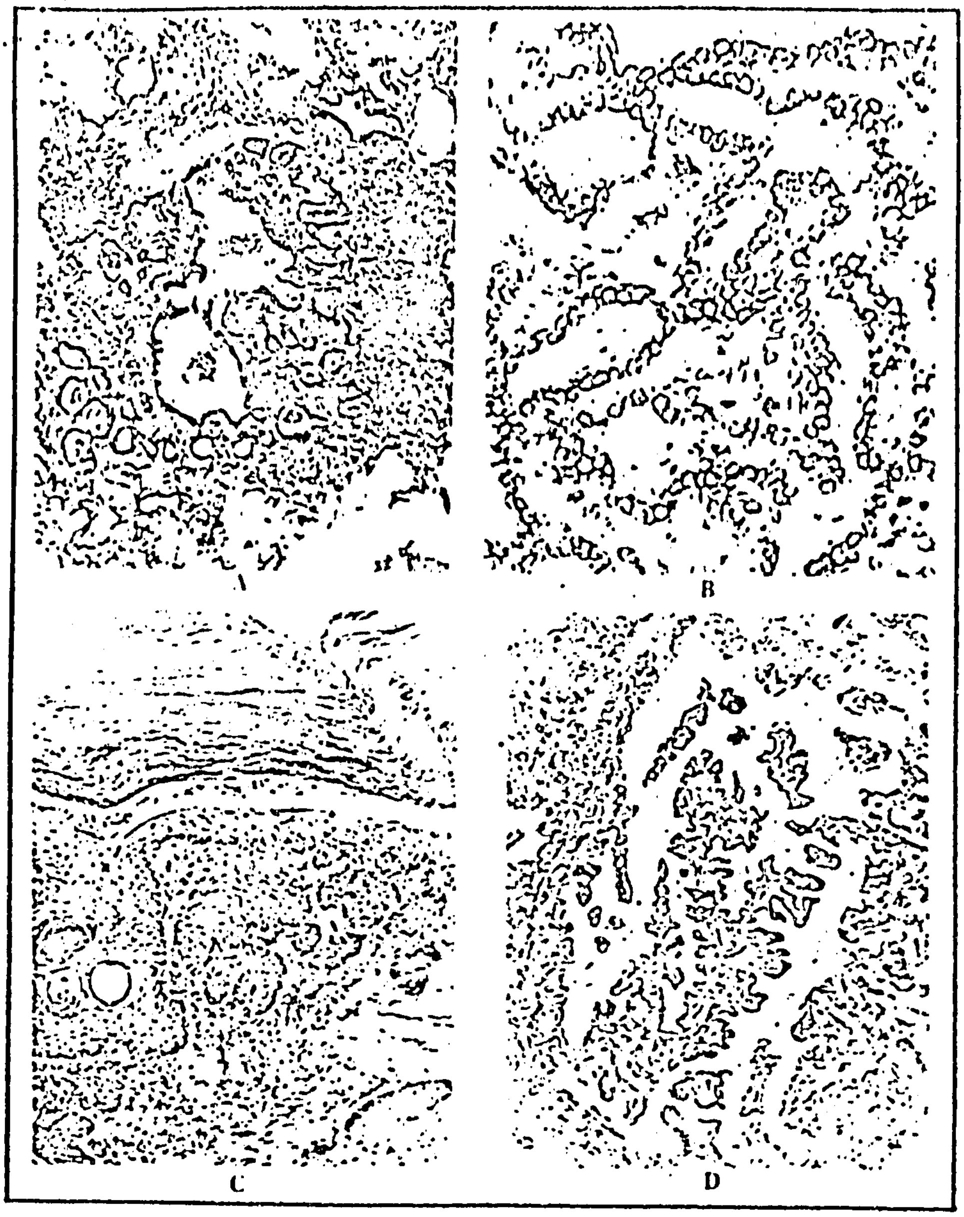

FIGURE 1. Pulmonary lesions induced by tracheal administration of chemical agents
A. Bronchogenic Epithelialization:
Rat Lung: 12 months after dosage with a suspension of mixed rare earth fluoride particulates (X 100);
B. Alveologenic Epithelialization:
Guinea Pig Lung: 16 months after dosage with flux calcined diatomite (X360);
C. Squamoid Carcinoma:
Rat Lung: 17 months after administration of beryllium sulfate (X 160);
D. Adenomatoid Carcinoma
Rabbit Lung: 14 months after injection of zinc manganese beryllium silicate (X 100).

manganese beryllium silicate (Fig. IC) and adenomatoid carcinoma was observed mainly after administration of beryllium sulfate (Fig. ID). The detailed features of these tumors will be further considered when those induced by inhalation techniques are reviewed.

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