

- ceedings of the 11th Aspen Emphysema Conference, Aspen, Colo. U.S. Department of Health, Education, and Welfare, Public Health Service Publication 1879, 1969. Pp. 159-181.
- S68. QUINLAN, M. F., SALMAN, S. D., SWIFT, D. L., WAGNER, H. N., Jr., PROCTOR, D. F. Measurement of mucociliary function in man. *American Review of Respiratory Diseases* 99(1) : 13-23, January 1969.
- S69. RAO, B. S., COHN, F. E., ELDRIDGE, F. E., HANCOCK, E. W. Left ventricular failure secondary to chronic pulmonary disease. *In: Current Research in Chronic Respiratory Diseases. Proceedings of the 11th Aspen Emphysema Conference, Aspen Colo., U.S. Department of Health, Education, and Welfare, Public Health Service Publication 1879, 1969. Pp. 129-134.*
- S70. RYDER, R. C., THURLBECK, W. M., GOUGH, J. A study of interobserver variation in the assessment of the amount of pulmonary emphysema in paper-mounted whole lung sections. *American Review of Respiratory Diseases* 99(3) : 354-364, March 1969.
- S71. RYLANDER, R. Alterations of lung defense mechanisms against airborne bacteria. *Archives of Environmental Health* 18(4) : 551-555, April 1969.
- S72. RYLANDER, R. Environmental air pollutants and lung defense to airborne bacteria. *In: Current Research in Chronic Respiratory Diseases. Proceedings of the 11th Aspen Emphysema Conference, Aspen, Colo. U.S. Department of Health, Education, and Welfare, Public Health Service Publication 1879, 1969. Pp. 297-304.*
- S73. SAINDELLE, A., RUFF, F., GUILLERM, R., PARROT, J.-L. Libération d'histamine par la fumée de cigarette et certains de ses constituants. *Revue Française D'Allergie* 8(3) : 137-144, July-September 1968.
- S74. SCHABORT, J. C. Lactic dehydrogenase from human lung inhibition by certain water-soluble ciliastatic components of tobacco smoke. *Journal of the South African Chemical Institute* 20 : 103-112, October 1967.
- S75. SPAIN, D. M. The distribution of tracheobronchial metaplasia (regenerative hyperplasia) (age, sex, cigarette smoking, and relation to Reid Index)—Preliminary report. *In: Current Research in Chronic Respiratory Diseases. Proceedings of the 11th Aspen Emphysema Conference, Aspen, Colo. U.S. Department of Health, Education, and Welfare, Public Health Service Publication 1879, 1969. Pp. 183-186.*
- S76. STANESCU, D. C., GAVRILESCU, N., TECULESCU, D. B. Effect of smoking on pulmonary mechanics and ventilation in young healthy males. *Respiration* 25(5) : 434-440, 1968.
- S77. STANESCU, D. C., TECULESCU, D. B., PACURARU, R., GAVRILESCU, N. Chronic effects of smoking upon pulmonary distribution of ventilation in healthy males. *Respiration* 25(6) : 497-504, 1968.
- S78. STONE, R. M., GINSBERG, R. J., COLAPENTO, R. F., PEARSON, F. G. Bronchial artery regeneration after radical hilar stripping. *Surgical Forum* 17 : 109-110, 1966.
- S79. TAKENOUCHI, S. Boji gyosho gyosha ni okeru mansei kokyuki shogai ni kansuru ekigakuteki kenk yu. (Epidemiological studies on chronic respiratory disturbances among employees in a certain organization's workshop.) *Nara Igaku Zasshi* 19(5-6) : 749-763, December 1968.
- S80. ULMER, W. T., REICHEL, G., WERNER, U. Die chronisch obstruktive Bronchitis des Bergmannes. Untersuchungen zur Häufigkeit bei der Normalbevölkerung und bei Bergleuten. Die Bedeutung der Staubbelastung und der Einfluss des Rauchens. *Internationales Archiv für Gewerbepathologie und Gewerbehygiene* 25(1) : 75-98, December 20, 1968.

- S81. WEISS, W. Cigarette smoke gas phase and paramecium survival. A method for intermittent exposure. Archives of Environmental Health 17(1) : 62-64, July 1968.
- S82. WEISSBECKER, L., CARPENTER, R. D., LUCHSINGER, P. C., OSDENE, T. S. *In vitro* alveolar macrophage viability. Effect of gases. Archives of Environmental Health 18(5) : 756-759, May 1969.
- S83. WENDEL, H. Zur Bedeutung des Rauschens für die chronische Bronchitis. Zeitschrift für die Gesamte Innere Medizin 23(5) : 147-151, March 1, 1968.
- S84. WEST, J. B., GLAZIER, J. B., HUGHES, J. M. B., MALONEY, J. E. Effect of gravity on the morphology of pulmonary capillaries and alveoli. *In*: Current Research in Chronic Respiratory Diseases. Proceedings of the 11th Aspen Emphysema Conference, Aspen, Colo. U.S. Department of Health, Education, and Welfare, Public Health Service Publication 1879, 1969. Pp. 135-137.
- S85. WINKELSTEIN, W., Jr., KANTOR, S. Respiratory symptoms and air pollution in an urban population of Northeastern United States. Archives of Environmental Health 18(5) : 760-767, May 1969.

CHAPTER 3

Smoking and Cancer

Contents

	Page
Summary	55
Epidemiological Studies	55
Lung Cancer	55
Oral Cancer	58
Laryngeal Cancer	58
Cancer of the Urinary Bladder and Kidney	60
Cancer of the Pancreas	60
General Aspects of Carcinogenicity	61
Tobacco Alkaloids	61
Nickel	62
Experimental Aspects of Carcinogenesis	62
Retention of Smoke Constituents	62
Changes in Cell Cultures Induced by Cigarette Smoke	62
Experimental Studies of Bronchogenic Carcinoma in Animals	63
Experimental Aspects of Cancer of the Bladder and Kidney	64
Cited References	65
Cancer Supplemental Bibliography	69

SMOKING AND CANCER

SUMMARY

Previous reports (59, 60, 61) have presented the evidence that cigarette smoking is a major cause of lung cancer and that cessation of cigarette smoking sharply reduces the risk of dying from lung cancer as compared to the risk taken by those who continue to smoke. Cigarette smoking was also shown to be a significant factor in the causation of cancer of the larynx. A strong association between various forms of smoking and cancers of the buccal cavity, pharynx, and esophagus was also shown. Data were presented which indicated that cigarette smoking was associated with cancer of the urinary bladder. Data were also presented which suggested that cancer of the kidney and pancreas may be related to cigarette smoking.

During the past year, both population studies and laboratory studies from various countries have added to the weight of the evidence linking smoking and cancer. A major study of histological changes in the larynx has demonstrated the higher risk of premalignant changes among smokers. More studies have been done to identify those substances in tobacco smoke which take part in carcinogenesis. New animal models for the experimental study of respiratory cancer, which may be helpful in elucidating the mechanisms of respiratory tract carcinogenesis, have been developed and refined.

EPIDEMIOLOGICAL STUDIES

It is interesting to note that epidemiological information on cigarette smoking and lung cancer, similar to that which has been collected in the United States and Western European countries, is now being reported from Eastern Europe and Africa as well.

Lung Cancer

In Norway, a study of histologically proven cases of lung cancer by Kreyberg demonstrated the low frequency of lung cancer among nonsmokers. The cases were collected between 1950 and 1964 from two hospitals and a diagnostic laboratory which service all parts of Norway. The author states that the population represented in this study is most probably geographically representative of the whole country. In comparing his results in Norway with those in other European

countries, Kreyberg stated that a nonsmoking Norwegian population today should present lung cancer cases in the same number, with the same sex ratio, and with the same representation of histological types as prevailed in Norway 40 years ago, and in Europe in general at the beginning of this century (24, 25). The risks of developing various histological types of lung cancers among smokers, as contrasted to nonsmokers, are presented in table 1. Two facts are strikingly apparent from the table. First, the preponderance of the higher risk of lung cancer in smokers lies in the categories of epidermoid carcinoma and anaplastic small cell carcinoma. Second, while female smokers have a higher risk of developing lung cancer than female nonsmokers, the relative risks are smaller than those for males. At least part of this difference may be accounted for by differences in smoking habits between men and women. Women tend to smoke fewer cigarettes, to smoke brands lower in tar and nicotine, inhale less and smoke less of each cigarette than do men; therefore, women have lower exposure to cigarette smoke.

TABLE 1.—*Tumor prevalence among males and females 35-69 years of age, by type of tumor and smoking category*

[Smokers constituted 85 percent of populations studied]

Sex and type of tumor	Smoking category			Expected number among smokers ¹	Risk ratio among smokers
	Total	Smoking all methods	Non-smokers		
Males:					
Epidermoid carcinoma.....	434	431	3	17.0	25.4
Small cell anaplastic carcinoma..	117	116	1	5.7	20.4
Adenocarcinoma.....	88	83	5	28.3	2.9
Bronchiolo-alveolar carcinoma...	---	---	---	---	---
Carcinoid.....	46	39	7	39.7	1.0
Bronchial gland tumor.....	---	---	---	---	---
Total.....	685	669	16	90.7	7.4
Females:					
Epidermoid carcinoma.....	12	9	3	.75	12.0
Small cell anaplastic carcinoma..	8	5	3	.75	6.6
Adenocarcinoma.....	56	14	42	10.5	1.3
Bronchiolo-alveolar carcinoma...	---	---	---	---	---
Carcinoid.....	32	7	25	6.3	1.1
Bronchial gland tumor.....	---	---	---	---	---
Total.....	108	35	73	18.3	1.9

¹ Number that would be expected if incidence rate among smokers was equal to that of nonsmokers.

Source: Kreyberg, L. (24).

Brett, et al. (8) found that the mortality rate for lung cancer in smokers in England was especially high for the smokers who "drooped" the cigarettes off the lip while they smoked, a habit which may result in the delivery of a greater dose of smoke from each cigarette.

Gelfand, et al. (19) in a study of lung cancer in Rhodesian Africans, reported a preponderance of smokers among the lung cancer patients as compared to a control group. The authors express the opinion that air pollution does not play a role in respiratory cancer in Rhodesia.

In the 1967 Health Consequences Report (59), it was pointed out that the lung cancer risk of ex-smokers declined, relative to those who continued to smoke. It equalled that of nonsmokers about 10 years after stopping smoking, and the rate of decline depended on the number of cigarettes previously smoked and the duration of smoking. Bross, et al. (10) reported that the risk of developing lung cancer is lower among filter cigarette smokers than nonfilter cigarette smokers. Since filter cigarettes are generally lower in tar content than nonfilter cigarettes, this study supports the inference that the tar content of cigarettes is a meaningful measure of exposure to risk.

In view of the fact that practically all lung cancer patients started to smoke nonfilter cigarettes and have smoked filter cigarettes only in recent years and for a variable length of time, a more exact comparison of the risks run by smokers of filter and nonfilter cigarettes must await further studies (67).

The relationship of smoking to lung cancer in women is an area of continuing concern, since we may expect a continued increase of lung cancer in women with the increase in cigarette smoking among them since World War II. Lombard, et al. (32) show a relationship of cigarette smoking to epidermoid lung cancer in women but not to adenocarcinoma. It is generally agreed that the contribution of cigarette smoking to the development of epidermoid and oat-cell lung cancer (Kreyberg Group I) in males is significantly greater than to the development of adenocarcinoma (Kreyberg Group II).

An association of other diseases to cancer of the lung is found in a report by Salzer, et al. (48). Salzer and his colleagues have reported in an autopsy study that lung cancer and scars from stomach ulcers are statistically associated and suggested that cigarette smoking may have contributed to both conditions. A study by Stamler, et al. (53) indicated that male cigarette smokers with elevated cholesterol levels had higher rates of lung cancer than those with lower cholesterol levels. Additional studies are needed to confirm and elucidate these observations.

Programs have been recently established to perform cytological examinations on the sputum of smokers, since they represent a population at a high risk for the development of carcinoma of

the lung. These programs have detected individuals with atypical or frankly malignant cells in their sputum before a shadow has appeared in the lung fields of x-ray (18, 62). Valaitis, et al. (62) reported that some degree of cytological abnormality was found in the sputum of 4.8 percent of the smokers and 0.9 percent of the nonsmokers.

Oral Cancer

In the Soviet Union, Orlovskiy has shown an association between cigarette smoking and lung cancer, as well as an association between the use of "nas" (a mixture of tobacco and ashes) and the development of cancer of the oral cavity (37). Other studies of interest from around the world include one by Pindborg, et al. (39) on the epidemiology and histology of oral leukoplakia and leukoedema among Papuans and New Guineans. They report that smoking may be more closely associated with these conditions than is the chewing of betel nut which previously was considered the obviously associated habit. A study by Wahi (64) reports on the relationship of tobacco chewing to oral and oropharyngeal cancer in a district in India. Pindborg also presents evidence from India indicating that oral submucous fibrosis (38) may be associated with tobacco use and may result in an oral epithelium more susceptible to the carcinogenic substances in tobacco. In a study of oral malignancies indexed in a large tumor registry in California, Chierici, et al. (13) found that 88 percent of the cancer patients were smokers. The proportion of smokers ranged from 81 to 83 percent for cancers of the gingival and alveolar mucosa, buccal mucosa, hard palate, and lip, to 94 percent or more for cancers of the floor of the mouth, soft palate, tonsil, or oropharynx. Unfortunately, comparable percentages of smokers in a control population are not presented. No new studies have appeared which clarify the relative contributions of other environmental risk factors for oral cancer, such as alcohol consumption, nutritional problems, and poor oral hygiene.

Laryngeal Cancer

Auerbach, et al. (1) studied the histology of the larynx of 942 men, aged 21 to 95, who were autopsied at a single hospital between 1964 and 1967. Cases of primary cancer of the larynx were excluded from the study. Smoking histories for all cases were obtained from family members of the deceased by trained interviewers. The numerous randomized histological sections were graded by one observer. Table 2 shows the percentage of cells with atypical nuclei found in the true vocal cord. Of the men who never smoked, 75 percent had no cells with atypical nuclei, only 4.5 percent had sections with areas containing 60 to 69 percent of cells with atypical nuclei, and none had a higher percentage.

TABLE 2.—Number and percent distribution by relative frequency of atypical nuclei among true vocal cord cells, of men classified by smoking category

[100 per cent atypical cells defined as carcinoma]

Percent atypical nuclei	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Less than 1 pack a day		1-2 packs a day		2 or more packs a day	
							Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
Total.....	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
None.....	66	75.0	86	74.1	1	1.1	1	.8	0	0
Less than 50....	8	9.1	14	12.1	4	4.3	25	20.0	4	1.2	0
50-59.....	10	11.4	13	11.2	50	53.0	54	43.2	87	26.4	29	15.3
60-69.....	4	4.5	1	.9	23	24.5	21	16.8	116	35.3	75	39.4
70-79.....	0	2	1.7	9	9.6	9	7.2	44	13.4	38	20.0
80-89.....	0	0	2	2.1	2	1.6	19	5.8	11	5.8
90-99.....	0	0	1	1.1	0	5	1.5	0
100:												
Carcinoma <i>in situ</i>	0	0	3	3.2	13	10.4	52	15.8	35	18.4
Invasive carcinoma.....	0	0	1	1.1	0	2	.6	2	1.1

SOURCE: Auerbach, O., et al. (1).

The 116 ex-smokers had laryngeal histology similar to that of the nonsmokers, as far as atypical nuclei were concerned. However, disintegrating nuclei were found in 40.5 percent of the ex-cigarette smokers and in only 0.4 percent of the remaining cases. Only one of the 94 cigar and/or pipe smokers had no atypical cells. Three had carcinoma *in situ* and one case had a section showing early invasive primary carcinoma. The highest percentage of atypical cells was found among the cigarette smokers. The proportion of cases with a high degree of cellular change increased with increased daily smoking. None of the pack-or-more-a-day smokers was free of atypical nuclei. Of those who smoked two or more packs per day, 85 percent had lesions with 60 percent or more atypical cells as compared to 4 percent of the nonsmokers. Between 10 and 18 percent of the cigarette smokers had areas of carcinoma *in situ*, and four of the 644 cases showed early microscopic invasion. The thickness of the basal level of the true vocal cord was also directly related to the amount smoked (table 3).

TABLE 3.—Number and percent distribution, by highest number of cell rows in the basal layer of the true vocal cord, of men classified by smoking category

Number of cell rows	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
							Less than 1 pack a day		1-2 packs a day		2 or more packs a day	
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
Total.....	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
Less than 5 cell rows.....	30	34.1	7	6.0	4	4.3	3	2.4	1	0.3	0
5 cell rows.....	29	33.0	27	23.3	20	21.3	27	21.6	38	11.6	20	10.5
6 cell rows.....	8	9.1	15	12.9	15	6.0	25	20.0	51	15.4	24	12.6
7 cell rows.....	6	6.8	12	10.3	18	19.1	12	9.6	38	11.6	19	10.0
8 cell rows.....	8	9.1	14	12.1	9	9.6	13	10.4	30	9.1	23	12.1
9 cell rows.....	1	1.1	7	6.0	7	7.4	6	4.8	26	7.9	14	7.4
10 or more cell rows.....	6	6.8	34	29.4	21	22.3	39	31.2	145	44.1	90	47.4

SOURCE: Auerbach, O., et al. (1).

Cancer of the Urinary Bladder and Kidney

Several studies have dealt with the relationship of smoking to cancer of the bladder and kidney. James, et al. (23) demonstrated that an association existed for cancer of the bladder. The study by Fraumeni (17) also showed epidemiological evidence for such a relationship for bladder and kidney cancers. Bennington, et al. (3, 4) indicated an association between all kinds of tobacco usage and adenocarcinoma of the kidney as well as adenoma of the kidney. However, on the basis of this study alone, the relationship between "all kinds of tobacco" and cancer of the kidney cannot be considered as established in view of the small number of cases involved. In a preliminary report of a study on the epidemiology of cancer of the kidney, Wynder, et al. (68) have shown a strong association between excessive cigarette smoking and adenocarcinoma of the kidney, and although the disease is not uncommon in non-smokers, they considered excessive cigarette smoking to be a contributory factor. This study found no relationship to pipe smoking, and only a very weak relationship to cigar smoking. A significant association was found between cigarette smoking and epidermoid cancer of the kidney, a relatively uncommon type of cancer. Further research on the strength and mechanisms of the association between smoking and cancers of the urinary tract is needed.

Cancer of the Pancreas

The previously suggested association between cigarette smoking and cancer of the pancreas was again noted in a Japanese study by Ishii, et

al. (22), in which the authors reported a higher relative risk for pancreatic cancer among smokers than among nonsmokers.

GENERAL ASPECTS OF CARCINOGENICITY

The majority of the tumorigenic agents in tobacco smoke are found in the particulate matter "tar." The well established carcinogenicity of tobacco "tar" in a variety of animal species and tissues (66) was reconfirmed recently (11, 35, 40, 52, 56). A small portion of the smoke particulates (0.03 percent) is made up of polynuclear aromatic hydrocarbons (PAH) with two or more rings. A concentrate containing polynuclear aromatic hydrocarbons and amounting to 0.6 percent of the whole "tar" was found to be the most carcinogenic fraction of tobacco smoke (66). Another preparation of a PAH concentrate induced significant cytologic changes in mouse trachea and human fetal lung when grown in organ culture (28, 29). Other applications of concentrations of selected polynuclear aromatic hydrocarbons have produced similar results (27).

Of the identified PAH, at least 12 are known tumor initiators. These particular compounds have been shown to be carcinogenic, even when applied in doses of a few micrograms (63, 66). Tumor initiators induce changes in the target cells, especially in DNA (9, 14). Tumor promoters are agents which promote the neoplastic transformation of initiated cells. Although the structures of most of these tumor promoters are still unknown, there appear to be several different types in tobacco smoke (5, 41, 59, 66). Recently, Bock, et al. (6) published data which confirmed earlier findings that whole cigarette tar, the neutral fraction, two neutral subfractions and the weak acidic (phenolic) fraction contain tumor promoters. One recent study indicated that "tar" obtained from tobacco stems only had essentially no tumor promoting activity (65).

During the last year, several studies have reconfirmed the finding that selection of tobacco and the use of tobacco sheets and filters can lead to a significant reduction of "tar" and PAH in cigarette smoke, as well as to a reduction of the tumorigenicity of tobacco "tars." Similar results have also been reported for commercial cigarettes (21, 34). Experimental studies demonstrated that with tobacco additives one can reduce "tar," nicotine, PAH and tumorigenicity of cigarette smoke (12, 21). In terms of selective reduction of tobacco smoke components, these investigations may be of practical value, as well as of academic interest (57).

Tobacco Alkaloids

Present evidence does not indicate that tobacco alkaloids are carcinogenic. A possible exception may be cotinine, which was reported to induce malignant tumors in rats [principally leukemias (58)] and

adenomas of the bladder in mice (7). Boyland recently suggested that one or more of the three possible nicotine-N-oxides may be present in tobacco smoke and may be carcinogenic (7).

Tobacco alkaloids could theoretically contribute to the overall carcinogenicity of tobacco smoke, based on the possibility that in tobacco smoke nornicotine and other secondary amines may react with nitrogen oxides to form the N-nitrosamines, of which several are known carcinogens, especially N-nitrosornicotine and N-nitrosoanabasine (36). So far, however, N-nitrosamines of nornicotine and other alkaloid N-nitrosamines have not been detected in tobacco smoke (36).

Nickel

The relationship of nickel compounds to the development of cancer has been discussed in a recent review by Sunderman (55), who suggests that there is a possibility that nickel carbonyl may be present in cigarette smoke and may act as a cocarcinogen by inhibiting the induction of pulmonary benzopyrene hydroxylase, an enzyme which converts 3,4-benzopyrene to noncarcinogenic hydroxylated derivatives.

EXPERIMENTAL ASPECTS OF CARCINOGENESIS

Retention of Smoke Constituents

Studies on human smokers by Dalhamn, et al. (15) demonstrated that about 60 percent of the volatile, water soluble compounds of cigarette smoke, 20 percent of the volatile, nonwater soluble compounds, and 16 percent of the particulate matter of cigarette smoke can be retained in the mouth when the smoke is held in the mouth for up to 2 seconds. Under conditions in which the smoke is immediately deeply inhaled, between 91 and 99 percent of the components of cigarette smoke investigated (particulate matter, toluene, acetonitrile, acetone, isoprene, acetaldehyde) were retained, with the exception of carbon monoxide, of which 50 to 60 percent was retained (16).

Changes in Cell Cultures Induced by Cigarette Smoke

Leuchtenberger, et al. (30) have reported that passing cigarette smoke through a charcoal filter prevented the damage caused by either whole smoke, or the isolated gas phase of cigarette smoke, to cultures of mouse kidney cells. In the same paper, they reported that the single exposure of tissue cultures to puffs of charcoal-filtered smoke produced a significant increase in the mitotic index of the kidney cells. In another study, Leuchtenberger, et al. (31) reported that single exposure to nine puffs of the gas phase from charcoal-filtered cigarette smoke quickly stimulated the synthesis of DNA and RNA by cultures of mouse fibroblasts. Repeated exposure of the cultures to the filtered gas phase resulted in morphological and cytochemical changes indicative

of abnormal proliferation. Since the same alterations were found to be present, to a much lesser extent, in some control cultures, the authors considered that the filtered gas phase enhanced characteristics already possessed by the cells. They concluded that the gas phase of unfiltered cigarette smoke contains not only substances which inhibit cellular metabolism, but also factors which stimulate cellular metabolism. These latter factors may be unmasked by passing the gas phase through a charcoal filter. The identities of the specific gases removed by the charcoal filter and the extent to which each was removed were not reported by the authors. Investigation of the relationship between the changes observed in the tissue cultures and *in vivo* metabolism is necessary for the interpretation of the results of these experiments.

Experimental Studies of Bronchogenic Carcinoma in Animals

Because of the technical problems involved in inhalation experiments in small animals (59, 61), various animal models have been developed which do not employ the inhalation of smoke. These models have been used to study the role played by carcinogenic substances found in tobacco smoke in the induction of bronchogenic carcinoma.

Saffiotti (43) in a recent review of experimental respiratory tract carcinogenesis described the development of experimental models for the induction of pulmonary tumors and discussed a method of inducing bronchogenic carcinomas in Syrian golden hamsters by intratracheal instillation of a finely particulated crystalline carcinogen (e.g., benzo(a)pyrene) attached to a suspension of fine particles of a carrier dust (e.g., ferric oxide). This method reproduces some of the conditions of human exposure to inhaled carcinogens and has resulted in incidences of up to 100 percent of respiratory tumors, mostly squamous cell and anaplastic carcinomas of the larger bronchi. These tumors have been found to be invasive, metastasizing, and transplantable. Saffiotti reported that the carrier dust particles play an essential role in transporting the carcinogens through the bronchiolar and alveolar wall into the lung tissues where they are phagocytized. The carcinogens are then eluted by the plasma and diffused into the lung tissue, reaching up to the mucosa of the larger bronchi (42, 44, 45, 46). Variations in particle size and distribution in the suspended particulate matter affect the retention rates of benzpyrene in the lungs (47). The development of this experimental model has led to the undertaking of new research in many laboratories attempting to define the factors responsible for carcinogenesis in the respiratory tract.

Two other techniques used to produce squamous cell carcinoma in small laboratory animals are the passage of threads impregnated with carcinogenic hydrocarbons into the lung and the implantation of wire

mesh pellets in the bronchus. The latter technique gives a dose-response relationship between carcinogenic hydrocarbons and squamous cell carcinoma of the lung in rats (27). In order to overcome the traumatic effects of the surgery involved in these procedures, two additional techniques have been utilized. In one method, the carcinogen is suspended in Freund's adjuvant and upon tracheal instillation can lead to bronchial cancer (69). In this experiment, even more cancers were found when the rats were pretreated with tubercle bacilli. Pretreatment of the animals with tubercle bacilli produced infarcts, as well as scarring of the lung. This finding is of interest because earlier studies showed that scarring of rat lung by the halogenated hydrocarbon hexachlorotetrafluorobutane increases their susceptibility to the development of squamous carcinoma when exposed to carcinogenic hydrocarbons (54). That scarring of the lung may increase the susceptibility of the lung to carcinogens is in line with some recent observations on humans by Bennett, et al. (2) who showed the frequent occurrence of pulmonary scars in males with adenocarcinoma of the lung.

Experimental Aspects of Cancer of the Bladder and Kidney

Tobacco smoke appears to contain traces of several aromatic amines which are established bladder carcinogens. Of these, however, only Betanaphthylamine has thus far been identified in tobacco smoke with 2.2×10^{-8} g. per cigarette (20). At concentrations such as this, it appears unlikely that such aromatic amines can account for the increased risk among cigarette smokers of developing kidney and bladder cancer. A more likely correlation may exist between these types of cancers in smokers and their elevated urinary excretion rate of carcinogenic metabolites of tryptophan, and their oxidation products (49, 50).

Recently, the tobacco alkaloid cotinine was reported to induce adenomas in the bladder of mice [16 percent (7)]. This observation needs further testing. Cotinine is one metabolic product of nicotine and is found in tobacco, cigarette smoke (26) and the urine of smokers (33).

A study by Schlegel, et al. (51) indicates an elevated concentration of certain o-aminophenols plus their phenoxazon-oxidation products in the urine of certain types of bladder cancer patients and cigarette smokers, when compared to the urine of nonsmokers. Further studies are needed on this problem.

CITED REFERENCES

- (1) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Personal Communication. April 1969.
- (2) BENNETT, D. E., SASSER, W. F., FERGUSON, T. B. Adenocarcinoma of the lung in man. A clinicopathologic study of 100 cases. *Cancer* 23(2) : 431-439, February 1969.
- (3) BENNINGTON, J. L., FERGUSON, B. R., CAMPBELL, P. B. Epidemiologic studies of carcinoma of the kidney. II. Association of renal adenoma with smoking. *Cancer* 22(4) : 821-823, October 1968.
- (4) BENNINGTON, J. L., LAUBSCHER, F. A. Epidemiologic studies on carcinoma of the kidney. I. Association of renal adenocarcinoma with smoking. *Cancer* 21(6) : 1069-1071, June 1968.
- (5) BOCK, F. G. The nature of tumor-promoting agents in tobacco products. *Cancer Research* 28(11) : 2362-2368, November 1968.
- (6) BOCK, F. G., SWAIN, A. P., STEDMAN, R. L. Bioassay of major fractions of cigarette smoke condensate by an accelerated technic. *Cancer Research* 29(3) : 584-587, March 1969.
- (7) BOYLAND, E. The possible carcinogenic action of alkaloids of tobacco and betel nut. *Planta Medica Supplement* 11(14) : 13-23, June 1968.
- (8) BRETT, G. Z., BENJAMIN, B. Smoking habits of men employed in industry, and mortality. *British Medical Journal* 3(5610) : 82-85, July 13, 1968.
- (9) BROOKES, P. Quantitative aspects of the reaction of some carcinogens with nucleic acids and the possible significance of such reactions in the process of carcinogenesis. *Cancer Research* 26 (9, Part 1) : 1994-2003, September 1966.
- (10) BROSS, I. D. J., GIBSON, R. Risks of lung cancer in smokers who switch to filter cigarettes. *American Journal of Public Health and the Nation's Health* 58(8) : 1396-1403, August 1968.
- (11) BRUNE, H. Experiments with cigarette smoke condensates and nitrosamines on mice. *In: Weber, K. H., editor. Alkylierend wirkende Verbindungen. Zweite Konferenz über aktuelle Probleme der Tabakforschung. Wissenschaftliche Forschungsstelle im Verband der Cigaretten industrie. Hamburg, 1968. Pp. 53-64.*
- (12) BURDICK, D., BENNER, J. F., BURTON, H. R. Apparent correlations between thermogravimetric data and certain constituents in smoke from treated tobaccos. 22d Tobacco Chemists Research Conference, Richmond, Va., October 19, 1968.
- (13) CHIERICI, G., SILVERMAN, S., Jr., FORSYTHE, B. A tumor registry study of oral squamous carcinoma. *Journal of Oral Medicine* 23(3) : 91-98, July 1968.
- (14) COLBURN, N. H., BOUTWELL, R. K. The binding of beta-propiolactone and some related alkylating agents to DNA, RNA, and protein of mouse skin; relation between tumor-initiating power of alkylating agents and their binding to DNA. *Cancer Research* 28: 653-660, 1968.
- (15) DALHAMN, T., EDFORS, M-L., RYLANDER, R. Mouth absorption of various compounds in cigarette smoke. *Archives of Environmental Health* 16(6) : 831-835, June 1968.
- (16) DALHAMN, T., EDFORS, M-L., RYLANDER, R. Retention of cigarette smoke components in human lungs. *Archives of Environmental Health* 17(5) : 746-748, November 1968.
- (17) FRAUMENI, J. F., Jr. Cigarette smoking and cancers of the urinary tract: Geographic variation in the United States. *Journal of the National Cancer Institute* 41(5) : 1205-1211, November 1968.

- (18) FULLMER, C. D. Microscopic observations of sputum of chronic cigarette smokers. A preliminary report. Rocky Mountain Medical Journal 65(8) : 13, August 1968.
- (19) GELFAND, M., GRAHAM, A. J. P., LIGHTMAN, S. Carcinoma of bronchus and the smoking habit in Rhodesian Africans. British Medical Journal 3(5616) : 468-469, August 24, 1968.
- (20) HOFFMAN, D., MASUDA, Y., WYNDER, E. L. Alpha-naphthylamine and beta-naphthylamine in cigarette smoke. Nature 221(5177) : 254-256, January 18, 1969.
- (21) HOFFMAN, D., WYNDER, E. L. Selective reduction of the tumorigenicity of tobacco smoke. Experimental approaches. In: Wynder, E. L., Hoffman, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 28, June 1968. Pp. 151-172.
- (22) ISHII, K., NAKAMURA, K., OZAKI, H., YAMADA, N., TAKEUCHI, T. Suizogan no ekigaku ni okeru mondaiten. (Some aspects of the epidemiology of cancer of the pancreas.) Nippon Rinsho 26(8) : 1839-1842, August 1968.
- (23) JAMES, A. F., BRITO, R., JACOBSON, M. E. Bladder carcinoma—Natural history and behavior in males in Kansas. Journal of the Kansas Medical Society 68(8) : 336-339, August 1967.
- (24) KREYBERG, L. Aetiology of lung cancer. A morphological epidemiological and experimental analysis. Oslo, Universitetsforlaget, 1969. 90 pp.
- (25) KREYBERG, L. Nonsmokers and the geographic pathology of lung cancer. Chapter 18. In: Liebow, A. A. Smith, D. E., editors. The Lung. International Academy of Pathology Monograph, 1968. Pp. 273-283.
- (26) KUHN, H. Tobacco alkaloids and their pyrolysis products in the smoke. In: Von Euler, U. S., editor. Tobacco Alkaloids and Related Compounds. New York, MacMillan, 1965. Pp. 37-51.
- (27) KUSCHNER, M. The J. Burns Amberson Lecture. The causes of lung cancer. American Review of Respiratory Diseases 98(4) : 573-590, October 1968.
- (28) LASNITZKI, I. The effect of a hydrocarbon-enriched fraction from cigarette smoke on mouse tracheas grown *in vitro*. British Journal of Cancer 22(1) : 105-109, March 1968.
- (29) LASNITZKI, I. The effect of hydrocarbon-enriched fraction of cigarette smoke condensate on human fetal lung grown *in vitro*. Cancer Research 28(3) : 510-513, March 1968.
- (30) LEUCHTENBERGER, C., LEUCHTENBERGER, R. Cytologic and cyto-chemical effects on primary mouse kidney tissue and lung organ cultures after exposure to whole, fresh smoke and its gas phase from unfiltered, charcoal-filtered, and cigar tobacco cigarettes. Cancer Research 29(4) : 862-872, April 1969.
- (31) LEUCHTENBERGER, C., LEUCHTENBERGER, R., BLANCHARD, J., DECKERT, M. Abnormal proliferative effects of the gas phase of charcoal filtered fresh cigarette smoke on 3T3 cells. Presented 53d Annual Meeting, Federation of American Societies for Experimental Biology, Atlantic City, April 17, 1969. 3 pp.
- (32) LOMBARD, H. L., HUYCK, E. P. An epidemiological study of lung cancer among females. Growth 32(1) : 41-56, March 1968.
- (33) McNIVEN, N. L., RAISINGHANI, K. H., PATASHNIK, S., DOBFMAN, R. I. Determination of nicotine in smokers' urine by gas chromatography. Nature 208(5012) : 788-789, November 20, 1965.

- (34) MOORE, G. E., BOCK, F. G. "Tar" and nicotine levels of American cigarettes. *In: Wynder, E. L. Hoffman, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 28, June 1968. Pp. 89-94.*
- (35) MUNOZ, N., CORREA, P., BOCK, F. G. Comparative carcinogenic effect of two types of tobacco. *Cancer* 21(3) : 376-389, March 1968.
- (36) NEURATH, G. On the occurrence of N-nitroso-compounds in tobacco smoke. *In: Weber, K. H., editor. Alkylierend wirkende Verbindungen. Zweite Konferenz über aktuelle Probleme der Tabakforschung. Wissenschaftliche Forschungsstelle im Verband der Cigarettenindustrie, Hamburg, 1968. Pp. 95-102.*
- (37) ORLOVSKIY, L. V. Znachenie sotsial'no-gigienicheskikh issledovaniy pri izyuchenii paka. (Significance of the social hygienic investigations in a study of cancer.) *Gigiena I Sanitariia* 33(6) : 71-73, 1968.
- (38) PINDBORG, J. J. Oral submucous fibrosis as a precancerous condition. *Journal of Dental Research* 45 (Supplement to No. 3) : 546-553, 1966.
- (39) PINDBORG, J. J., BARNES, O. D., ROED-PETERSEN, B. Epidemiology and histology of oral leukoplakia and leukoedema among Papuans and New Guineans. *Cancer* 22(2) : 379-384, August 1968.
- (40) ROE, F. J. C. Comparison of carcinogenicity of tobacco smoke condensate and particulate air pollutants and a demonstration that their effect may be additive. *In: Weber, K. H., editor. Alkylierend wirkende Verbindungen. Zweite Konferenz über aktuelle Probleme der Tabakforschung. Wissenschaftliche Forschungsstelle im Verband der Cigaretteindustrie, Hamburg, 1968. Pp. 110-111.*
- (41) ROE, F. J. C. Examination of the neutral fraction of tobacco smoke condensates for tumor promoting activity. *In: Weber, K. H., editor. Alkylierend wirkende Verbindungen. Zweite Konferenz über aktuelle Probleme der Tabakforschung. Wissenschaftliche Forschungsstelle im Verband der Cigarettenindustrie, Hamburg, 1968. Pp. 112-113.*
- (42) SAFFIOTTI, U. Lung cancer: An experimental approach. *Cancer Bulletin* 19(4) : 72-73, July-August 1967.
- (43) SAFFIOTTI, U. Experimental respiratory tract carcinogenesis. *Progress in Experimental Tumor Research* 11 : 302-333, 1969.
- (44) SAFFIOTTI, U., CEFIS, F., KOLB, L. H. A method for the experimental induction of bronchogenic carcinoma. *Cancer Research* 28(1) : 104-124, January 1968.
- (45) SAFFIOTTI, U., CEFIS, F., SHUBIK, P. Histopathology and histogenesis of lung cancer induced in hamsters by carcinogens carried by dust particles. *In: Severi, L., editor. Lung Tumors in Animals. Perugia, Division of Cancer Research, University of Perugia, June 1966. Pp. 537-546.*
- (46) SAFFIOTTI, U., MONTESANO, R., SELLA Kumar, A. R., BORG, S. A. Experimental cancer of the lung. Inhibition by vitamin A of the induction of tracheo-bronchial squamous metaplasia and squamous cell tumors. *Cancer* 20(5) : 857-864, May 1967.
- (47) SAFFIOTTI, U., MONTESANO, R., TOMPKINS, N. Benzo(a)pyrene retention in hamster lungs: Studies on particle size and on total dust load. *Proceedings of the American Association for Cancer Research* 8 : 57, March 1967.
- (48) SALZER, G. M., KUTSCHERA, H., DECRISTOFORO, A. Zur Frage einer Syntropie von Ulcus pepticum und Bronchuskarzinom. *Brunns' Beiträge zur Klinischen Chirurgie* 216(4) : 316-321, June 1968.
- (49) SCHIEVELBEIN, H., ZIEGKRAF, T. Tumoren der Harnblase. *In: Schievelbein, H., editor. Nikotin. Pharmakologie und Toxikologie des Tabakrauches. Stuttgart, Georg Thieme Verlag, 1968. Pp. 242-249.*

- (50) SCHIEVELBEIN, H., GRUMBACH, H. The influence of tobacco smoke components on the activity of kynureninase. Chapter 15. *In*: Deichmann, W. B., Lampe, K. L., editors. Bladder Cancer. Proceedings of the 5th Inter-American Conference on Toxicology and Occupational Medicine. Coral Gables, University of Miami, School of Medicine, 1967. Pp. 180-186.
- (51) SCHLEGEL, J. U., PIPKIN, G. E., NISHIMURA, R., DUKE, G. A. Studies in the etiology and prevention of bladder carcinoma. *Journal of Urology* 101(3) : 317-324, March 1969.
- (52) SCHMÄHL, D. Vergleichende Untersuchungen an Ratten über die carcinogene Wirksamkeit verschiedener Tabakextrakte und Tabakrauchkondensate. *Arzneimittel-Forschung* 18(7) : 814-817, July 1968.
- (53) STAMLER, J., BERKSON, D. M., LINDBERG, H. A., MILLER, W. A. SOYUGENC, R., TOKICH, T., WHIPPLE, T. Does hypercholesterolemia increase risk of lung cancer in cigarette smokers? *Circulation* 38 (4, Supplement 6) : 188, October 1968.
- (54) STANTON, M. F., BLACKWELL, R. Induction of epidermoid carcinoma in lungs of rats: A "new" method based upon deposition of methylcholanthrene in areas of pulmonary infarction. *Journal of the National Cancer Institute* 27(2) : 375-407, August 1961.
- (55) SUNDERMAN, F. W., JR. Nickel carcinogenesis. *Diseases of the Chest* 54(6) : 527-534, December 1968.
- (56) TAKAYAMA, S., SUGANO, H. Induction of malignant lymphomas in ICR mice treated with cigarette tar. *Gann* 59(4) : 363-365, August 1968.
- (57) TERRELL, J. H., SCHMELTZ, I. Cigarettes: Chemical effects of sodium nitrate content. *Science* 160(3835) : 1456, June 28, 1968.
- (58) TRUHAUT, R. DECLEREQ, M., LOISILLIER, F. Sur les toxicites aigue et chronique de la cotinine, et sur son effet cancerigene chez le rat. *Pathologie et Biologie* 12(1) : 39-42, January 1964.
- (59) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A public Health Service Review : 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.
- (60) U.S. PUBLIC HEALTH SERVICE. Smoking and health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.
- (61) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1968. 117 pp.
- (62) VALAITIS, J., MCGREW, E. A., CHOMET, B., CORRELL, N., HEAD, J. Bronchogenic carcinoma *in situ* in asymptomatic high-risk population of smokers. *Journal of Thoracic and Cardiovascular Surgery* 57(3) : 325-332, March 1969.
- (63) VAN DUUREN, B. L. Tobacco carcinogenesis. *Cancer Research* 28(11) : 2357-2362, November 1968.
- (64) WAHI, P. N. The epidemiology of oral and oropharyngeal cancer. A report of the study in Mainpuri District, Uttar Pradesh, India. *Bulletin of the World Health Organization* 38(4) : 495-521, 1968.
- (65) WYNDER, E. L., HOFFMANN, D. A study of tobacco carcinogenesis. X. Tumor promoting activity. (In press.) *Cancer* : 1969.
- (66) WYNDER, E. L., HOFFMANN, D. Experimental tobacco carcinogenesis. *Science* 162(3856) : 862-871, November 22, 1968.

- (67) WYNDER, E. L., MABUCHI, K., BEATTIE, E. J., Jr. The epidemiology of lung cancer. Some recent trends in hospital data. [Unpublished.]
- (68) WYNDER, E. L., MABUCHI, K., WHITMORE, W. F., Jr. The epidemiology of cancer of the kidney. [Unpublished.]
- (69) YASUHIRA, K. Experimental induction of lung cancer in rat and mouse with 20-methylcholanthrene in Freund's adjuvant. *Acta Pathologica Japonica* 17(4) : 475-493, 1967.

CANCER SUPPLEMENTAL BIBLIOGRAPHY

- S1. AHLSTROM, C. G., HEATON, J. Combined action of Rous sarcoma virus and chemical carcinogen in rats. *Experientia* 24(4) : 411-413, 1968.
- S2. ALFRED, L. J., DIPAOLO, J. A. Reversible inhibition of DNA synthesis in hamster embryo cells in culture: Action of 1,2-benzanthracene and 7,12-dimethylbenz (a) anthracene. *Cancer Research* 28(1) : 60-65, January 1968.
- S3. ATHERTON, J. G. Formation of tobacco mosaic virus in an animal cell culture. *Archiv für die Gesamte Virusforschung* 24 : 406-418, 1968.
- S4. BARON, F., JOINVILLE, R., KERNEIS, J. P., DE LAJABIRE, LENNE, BRUNEAU, Y. Tumeurs blanches du larynx et cancer. *Journal Francais d'Oto-Rhino-Laryngologie et Chirurgie Maxillo-Faciale* 16(3) : 181-188, March 1967.
- S5. BARONI, C., BERTOLI, G., FABRIS, N. Risposta immunitaria primaria in topi di ceppo albino iniettati alla nascita con un'unica dose di 7,12-dimetilbenz[a]anthracene. *Tumori* 54(2) : 117-126, March-April 1968.
- S6. BENAGIANO, A. Influenza del fumo sulla cavita orale. *Annali di Stomatologia* 12 : 575-578, 1963.
- S7. BENEDICT, R. C., STEDMAN, R. L. Complexity of enzymatic inhibition by cigarette smoke. *Experientia* 24(12) : 1205-1206, 1968.
- S8. BLACK, S. C. Polonium in tobacco and tobacco smoke. *Radiation Bio-Effects Summary Report* : 46, January-December 1967.
- S9. BLENKINSOPP, W. K. Particle accumulation in the lung as a possible factor in the aetiology of lung cancer. *Journal of Pathology and Bacteriology* 96(2) : 297-304, October 1968.
- S10. BROOKES, P., HEIDELBERGER, C. Isolation and degradation of DNA from cells treated with tritium-labeled 7,12-dimethylbenz(a)-anthracene: Studies on the nature of the binding of this carcinogen to DNA. *Cancer Research* 29(1) : 157-165, January 1969.
- S11. BUELL, P. E., MENEZ, W. M., DUNN, J. E., Jr. Cancer of the lung among Mexican immigrant women in California. *Cancer* 22(1) : 186-192, July 1968.
- S12. CADY, B., CATLIN, D. Epidermoid carcinoma of the gum. A 20-year survey. *Cancer* 23(3) : 551-569, March 1969.
- S13. CAVALLAZZI, G., BERGOMI, A. I carcinomi primitivi della ghiandola sottomascellare. *Archivio Italiano di Otologia, Laringologia e Patologia cervico-facciale* 78(6) : 835-846, November-December 1967.
- S14. CZARNIK, Z. Zmiany poziomu 5-HT w surowicy kobiet zwiazane z paleniem papierosów. (Changes in the serum 5-hydroxy-tryptamine level connected with cigarette smoking and women.) *Przeglad Lekarski* 24(6) : 561-563, 1968.
- S15. DALE, E., SCUTCHFIELD, F. D. Adrenal lipid and plasma corticosterone depletion after 7,12-dimethylbenz(a)anthracene administration to the albino rat. *Experientia* 24(7) : 723-724, 1968.

- S16. DE GROOT, M. J. W. Recente trends in de Kankersterfte bij mannen en vrouwen. *Tijdschrift voor Sociale Geneeskunde* 46(23): 824-827, November 15, 1968.
- S17. DEICHMANN, W. B. Introduction. *In*: Lampe, K. F., Penalver, R.A. Soto, A., editors. Bladder Cancer. A Symposium. Fifth Inter-American Conference on Toxicology and Occupational Medicine. Coral Gables, University of Miami, School of Medicine, 1967. Pp. 3-33.
- S18. DE MARIA, A., BERTINI, P., DE BELLA, E. Studio clinico su 1000 casi di cancro del polmone. *Archivio di Chirurgia del Torace* 21(3): 341-399, July-September 1964.
- S19. DIAMOND, L., SARDET, C., ROTHBLAT, G. H. The metabolism of 7,12-dimethylbenz(a)anthracene in cell cultures. *International Journal of Cancer* 3(6): 838-849, November 15, 1968.
- S20. DICKENS, F. Alkylating lactones and lactams. *In*: Alkylierend wirkende Verbindungen. Erste Konferenz über N-Nitroso-Verbindungen und Lactone. Hamburg, Wissenschaftliche Forschungsstelle in Verband der Cigarettenindustrie, 1964, Pp. 9-22.
- S21. DIPPLE, A., LAWLEY, P. D., BROOKS, P. Theory of tumour initiation by chemical carcinogens: Dependence of activity on structure of ultimate carcinogen. *European Journal of Cancer* 4(5): 493-506, October 1968.
- S22. DOLL, R. Carcinogens in the environment: Human evidence. *Tidsskrift for den Norske Laegeforening* 88(12b): 1187-1194, June 25, 1968.
- S23. DONTENWILL, W., ELMENHORST, H., RECKZEH, G., HARKE, H.-P., STADLER, L. Experimentelle Untersuchungen über Aufnahme, abtransport und Abbau cancerogener Kohlenwasserstoffe in Bereich des Respirationstraktes. *Zeitschrift für Krebsforschung* 71(3): 225-243, August 27, 1968.
- S24. DÖRKEN, H. Einige Daten bei 280 Patienten mit Pankreaskrebs. Häufigkeit, vor- und Begleitkrankheiten, exogene Faktoren. *Gastroenterologia* 102: 47-64, 1964.
- S25. DUNHAM, L. J., RABSON, A. S., STEWART, H. L., FRANK, A. S., YOUNG, J. L. Rates, interview and pathology study of cancer of the urinary bladder in New Orleans, Louisiana *Journal of the National Cancer Institute* 41(3): 683-709, September 1968.
- S26. DUBAN-REYNALS, M. L. Combined effects of chemical carcinogenic agents and viruses. *Progress in Experimental Tumor Research* 3: 148-185, 1963.
- S27. DURAN-REYNALS, M. L. Enhancing effect of chemical carcinogens on experimental viral infection: Its significance and probable mechanism. *In*: Rich, M. A., Moloney, J. B. editors. Conference on Murine Leukemia. National Cancer Institute Monograph No. 22, September 1966. Pp. 389-396.
- S28. ELGJO, K. Growth kinetics of the mouse epidermis after a single application of cigarette smoke condensates. *Acta Pathologica et Microbiologica Scandinavica* 73(3): 316-322, 1968.
- S29. ERICSSON, J., RINGERTZ, N., SJOSTROM, A., SWENSON, D. Svenska cancerregistret 10 ar. *Lakartidningen* 65(16): 1648-1653, April 17, 1968.
- S30. FARAGO, L. Bericht über oto-rhino-laryngologische Krebsreihenuntersuchungen. *Monatsschrift für Ohrenheilkunde und Laryngo-Rhinologie* 102(10): 588-601, 1968.
- S31. FIORENTINO, M. Lung cancer in the U.S.: Observations on the age at death. *Medical Record and Annals* 61(7): 228-230, July 1968.
- S32. FLAKS, A. The effect of 9,10-dimethyl-1,2,benzanthracene on young mice of low and high cancer strain. *British Journal of Cancer* 19: 547-550, 1965.

- S33. FRANCIS, C. W., CHESTERS, G., ERHARDT, W. H. 210-Polonium entry into plants. *Environmental Science and Technology* 2(9) : 690-695, September 1968.
- S34. FRANKE, R. Die hydrophobe Wechselwirkung von polycyclischen aromatischen Kohlenwasserstoffen mit Humanserumalbumin. *Biochimica et Biophysica Acta* 160(3) : 378-395, August 13, 1968.
- S35. FROST, J., SACKETT, W. M. Polonium radioisotopes in tobacco and the atmosphere. *Nuclear Science Abstracts* 22(6) : 1093, March 31, 1968.
- S36. GOFFIN, R., MUSIN, L. Fréquence et localisation du cancer parmi un groupe d'assurés sociaux. *Archives Belges de Médecine Sociale, Hygiène, Médecine du Travail et Médecine Légale* 26(4) : 279-295, 1968.
- S37. GOLUBTSOV, F. S. Khronicheskiy bronkhit i rak legkogo. (Chronic bronchitis and lung cancer.) *Sovetskaya Meditsina* (3) : 129-130, 1968.
- S38. GRÄF, W. Über natürliches Vorkommen und Bedeutung der kanzerogenen polyzyklischen, aromatischen Kohlenwasserstoffe. *Medizinische Klinik* 60(15) : 561-565, April 9, 1965.
- S39. GRAFFI, A., HORN, K.-H., PASTERNAK, G. Antigenic properties of tumors induced by different chemical and physical carcinogens. In: Harris, R. J. C., editor. *Specific Tumor Antigens. A Symposium. UICC Monograph Series 2* : 204-209, 1967.
- S40. GROUPE, L. Progression du cancer du poumon chez l'homme et les animaux. *Revue de Pathologie Comparée et d'Hygiène* T 2-7(770) : 405-410, 1965.
- S41. GSELL, O., REICH, T. Bronchialkarzinom: Bemerkungen zu einer Sektionsstatistik. *Medizinische Klinik* 60 (47) : 1886-1889, 1965.
- S42. HACKETT, R. L., SUNDERMAN, F. W., Jr. Pulmonary alveolar reaction to nickel carbonyl. Ultrastructural and histochemical studies. *Archives of Environmental Health* 16(3) : 349-362, March 1968.
- S43. HAENSZEL, W., KURIHARA, M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *Journal of the National Cancer Institute* 40(1) : 43-68, January 1968.
- S44. HAMAZAKI, Y. Tabako ha fumatsu kyunyu ni yotte hassei suru shoshu no shinseimotsu ni. Tsuite 2. (Development of various kinds of neoplasms through the inhalation of tobacco leaf dust 2.) *Transactiones Societatis Pathologicae Japonicae* 56 : 127-128, 1967.
- S45. HARBERS, E., LEDERER, B., SANDRITTER, W., SPAAR, U. Untersuchungen an Nucleohistonen. IV. "Heterochromatisierung" in der Rattenleber während der Carcinogenese. *Virchows Archiv Arbeiten B. Zellpathologies* 1(2) : 98-106, June 10, 1968.
- S46. HEMS, G. Factors associated with lung cancer. *British Journal of Cancer* 22(3) : 466-473, September 1968.
- S47. HENNINGS, H., BOUTWELL, R. K. The inhibition of DNA synthesis by initiators of mouse skin tumorigenesis. *Cancer Research* 29(3) : 510-514, March 1969.
- S48. HIRAO, F., FUJISAWA, T., TSUBURA, E., AKAMATSU, Y., YAMAMURA, Y. Experimental cancerous changes in the lung induced by chemical carcinogens in rabbits. *Gann* 58(5) : 427-434, October 1967.
- S49. HYDE, L., YEE, J., WILSON, R., PATNO, M. E. Cell type and the natural history of lung cancer. *Journal of the American Medical Association* 193(1) : 52-54, July 5, 1965.
- S50. KERN, W. H., JONES, J. C., CHAPMAN, N. D. Pathology of bronchogenic carcinoma in long-term survivors. *Cancer* 21(4) : 772-780, April 1968.
- S51. KIBIKAE, I. Koto gan no ekigaku ni okeru. Mondaiten. (Some aspects of the epidemiology of cancer of the larynx.) *Nippon Rinsho* 26(8) : 1808-1811, August 1968.

- S52. KOZHEVNIKOVA, E. P. O. Sensibilizatsii organizma k kanserobennomu veshchestvu. (Concerning sensibilization of the organism to a carcinogenic substance.) *Voprosy Onkologii* 14(4) : 57-60, 1968.
- S53. LEMOINE, J. M., FAUVET, J., VASSELIN, M. 194 tumeurs bronchiques malignes des femmes démontrées par biopsie bronchique. *Journal Francais de Medecine et Chirurgie Thoraciques* 20 : 329-345, 1966.
- S54. LINDNER, J., GRIES, G., FREYTAG, G., BRACK, W. J., HOLTZ, J. Morphologische und biochemische Untersuchungen zur Geschwulstbildung. *Gegenbaurs morphologisches Jahrbuch* 109(1) : 37-42, 1966.
- S55. LITTLE, J. B., MCGANDY, R. B. Systemic absorption of polonium-210 inhaled in cigarette smoke. *Archives of Environmental Health* 17(5) : 693-696, November 1968.
- S56. MADEY, J. Clinical evaluations of 745 cases of primary lung carcinoma. *Polish Medical Journal* 7(4) : 917-927, 1968.
- S57. MANHOLD, J. H., RUSTOGI, K. N., DOYLE, J. L., MANHOLD, B. S. Microscopic and microrespirometer (QO₂) study of the effect of cigarette smoking on human oral soft tissues. Preliminary report of an *in vivo* study. *Oral Surgery, Oral Medicine, Oral Pathology* 26(4) : 567-572, October 1968.
- S58. MARTINOTTI, G., FERRERO, L. Il cancro primitivo del polmone nella rilevazione dispensariale. (Risultanze clinico-statistiche dal 1947 al 1966). *Lotta Contro La Tubercolosi* 37(4) : 308-316, October-December 1967.
- S59. MASIN, F., MASIN, M. Alveolar cells of sputum in pulmonary carcinoma. 21(6) : 1042-1051, June 1968.
- S60. MEINSMMA, L. Longkankersterfte in Nederland. *Nederlands Tijdschrift voor Geneeskunde* 107(32) : 1432-1436, August 10, 1963.
- S61. MEINSMMA, L., VERSLUYS, J. J. De lon kankersterfte bij volwassenen stijgt niet meer. *Nederlands Tijdschrift Voor Geneeskunde* 112(19) : 891-895, May 11, 1968.
- S62. MILLER, J. A., MILLER, E. C. Metabolism of drugs in relation to carcinogenicity. *Annals of the New York Academy of Sciences* 123 : 125-140, 1965.
- S63. MONTGOMERY, P. O'B. Nucleolar studies. *Bulletin of Pathology* 7(3) : 66-67, March 1966.
- S64. MORREAL, C. E., DAO, T. L., ESKINS, K., KING, C. L., DIENSTAG, J. Peroxide induced binding of hydrocarbons to DNA. *Biochimica et Biophysica Acta* 169(1) : 224-229, November 20, 1968.
- S65. MUCKERMAN, C. Studies on the nature of the binding products of beta-propiolactone and mouse skin protein. M.S. Thesis, University of Wisconsin, 1968. 86 pp.
- S66. MUIR, C. S. The incidence of laryngeal cancer in Singapore. *Journal of Laryngology and Otology* 79(3) : 203-213, 1965.
- S67. NEIMAN, J. M. The sensitizing carcinogenic effect of small doses of carcinogen. *European Journal of Cancer* 4(5) : 537-545, October 1968.
- S68. Occupation, chemicals, and cancer. *British Medical Journal* 2(5553) : 649-650, June 10, 1967.
- S69. OTT, G., DAUM, R. Lungenkrebs bei Frauen. *Langenbecks Archiv für Klinische Chirurgie vereinigt mit Deutsche Zeitschrift für Chirurgie* 310(2) : 93-106, 1965.
- S70. OTTO, H., ELMENHORST, H. Experimentelle Untersuchungen zur Tumordinduktion mit der Gasphase des Zigarettenrauchs. *Zeitschrift für Krebsforschung* 70(1) : 45-47, 1967.

- S71. PARK, H-Y., KIPROWSKA, I. A comparative *in vitro* and *in vivo* study of induced cervical lesions of mice. *Cancer Research* 28(8) : 1478-1489, August 1968.
- S72. PILHEU, J. A., YERGA, M., CROXATTO, O. C. Cáncer broncopulmonar primitivo. Consideraciones sobre 522 casos. *Revista Asociacion Medica Argentina* 82(5) : 159-162, May 1968.
- S73. PINDBORG, J. J., KALAPESSI, H. K., KALE, S. A., SINGH, B., TALYERKHAN, B. N. Frequency of oral leukoplakias and related conditions among 10,000 Bombayites. *Journal of the All India Dental Association* 37: 1-2, July 1965.
- S74. PINDBORG, J. J., KLAER, J., GUPTA, P. C., CHAWLA, T. N. Studies in oral leukoplakias. Prevalence of leukoplakia among 10,000 persons in Lucknow, India, with special reference to use of tobacco and betel nut. *Bulletin of the World Health Organization* 37: 109-116, 1967.
- S75. POPOFF, N., SUTTON, C. H., ZIMMERMAN, H. M. Viruslike particles in reactive cells associated with crystals of implanted carcinogen. *Acta Neuropathologica* 10(4) : 308-323, June 7, 1968.
- S76. PUISEUX-DAO, S., IZARD, C. Les effets de l'acroléine et de la phase gazeuse de la fumée de cigarette, sur l'ultrastructure cellulaire du *Dunaliella bioculata*. *Comptes Rendus Hebdomadaires des Séances de l'Academie des Sciences; Series D-Sciences Naturelles* 267(1) : 74-75, July 1, 1968.
- S77. RIMINGTON, J. Smoking, sputum, and lung cancer. *British Medical Journal* 1(5594) : 732-734, March 23, 1968.
- S78. ROWE, N. H. Epidemiological concepts relative to cancer of the oral cavity. *Missouri Medicine* 65(8) : 660-664; 668; 679, August 1968.
- S79. SACHS, L. *In vitro* cell transformation by carcinogenic hydrocarbons: A system for the study of tumor specific antigens in the absence of immunological selection. In: Harris, R. J. C., editor. *Specific Tumor Antigens. A Symposium. UICC Monograph Series 2* : 361-366, 1967.
- S80. SEDA, H. J., SNOW, J. B., Jr. Carcinoma of the tonsil. *Archives of Otolaryngology* 89(5) : 756-761, May 1969.
- S81. SHABAD, L. M. On the distribution and the fate of the carcinogenic hydrocarbon benz(a)pyrene (3,4-benzpyrene) in the soil. *Zeitschrift für Krebsforschung* 70: 204-210, 1968.
- S82. SHEETS, T. J., SMITH, J. W., JACKSON, M.D. Insecticide residues in cigarettes. *Tobacco* 166(15) : 26-29, April 12, 1968.
- S83. SIMECKOVA, B. Plicní rakovina u žen. (Lung cancer in women.) *Rozhledy V Tuberkulose A V Nemochech Plicnich* 28(8) : 565-568, September 1968.
- S84. TAKANO, K., OSOGOSHI, K., KAMIMURA, N., KANDA, K., KANE, K., KAMIYAMA, R., SAKAMOTO, K., SATO, H., SHIRAI, Y., SEI, M., TANABE, T., HORINO, M., MINAMI, Y., MOTOJI, H., MORITA, R., ORIHATA, H., HIRAYAMA, T. Shokudogan no ekigaku, toku ni atsui inshokubutsu, inshu, kitsuen narabi ni eiyo ketsubo ni tsuite. (Epidemiology of cancer of the esophagus, with particular reference to the effect of hot food and drink, drinking, smoking, and nutritional deficiencies.) *Nippon Rinsho* 26(8) : 1823-1828, August 1968.
- S85. TAKAYAMA, S., SUGANO, H. Induction of malignant lymphomas in ICR mice treated with cigarette tar. *Gann* 59(4) : 363-365, August 1968.
- S86. TAPPAN, W. B., VAN MIDDELEM, C. H., MOYE, H. A., DDT, endosulfan, and parathion residues on cigar-wrapper tobacco. *Journal of Economic Entomology* 60(3) : 765-768, June 1967.

- S87. TREFNY, J. Rozsireni zhoubnych nadoru dychacihho ustroji v Ceskoslovensku a v jinych zemich. (Occurrence of malignant tumors of the respiratory system in Czechoslovakia and in other countries.) *Casopis Lekarů Ceských* 107(26) : 790-796, 1968.
- S88. VON ESSEN, C. F., SHEDD, D. P., CONNELLY, R. R., EISENBERG, H. Cancer of the larynx in Connecticut, 1935-1959. *Cancer* 22(6) : 1315-1322, December 1968.
- S89. WAHI, P. N., LAHIRI, B., KEHAR, U. Epidemiology of oral and oropharyngeal cancer. A study of regional factors in Uttar Pradesh. *Journal of the Indian Medical Association* 46(4) : 175-181, February 16, 1966.
- S90. WALLER, R. E., COMMINS, B. T. Studies of the smoke and polycyclic aromatic hydrocarbon content of the air in large urban areas. *Environmental Research* 1(4) : 295-306, December 1967.
- S91. WARD, N. O., GORE, W. A., ACQUARELLI, M. J. Carcinoma of the tonsil. *American Journal of Surgery* 116(4) : 487-490, October 1968.
- S92. WATTENBERG, L. W., LEONG, J. L., GALBRAITH, A. R. Induction of increased benzpyrene hydroxylase activity in pulmonary tissue *in vitro*. *Proceedings of the Society for Experimental Biology and Medicine* 127(2) : 467-469, February 1968.
- S93. WEISSMANN, G., TROLL, W., VAN DUUBEN, B. L., SESSA, G. Studies on lysosomes-X. Effects of tumor-promoting agents upon biological and artificial membrane systems. *Biochemical Pharmacology* 17(12) : 2421-2434, December 1968.
- S94. ZECHNER, G. Zum Begriff des Raucherkehlkopfes. Eine klinische und pathologisch-anatomische Untersuchung. *Monatsschrift für Ohrenheilkunde und Laryngo-Rhinologie* 102(4) : 250-259, 1968.

CHAPTER 4

Effects of Smoking on Pregnancy

Contents

	Page
Summary	77
Epidemiological Studies	77
Experimental Studies	80
Cited References	81