

E. Stevens
L. W. Bass
E. H. Hainer
J. R. Darkis

(Princeton Meeting)

Case: Date: February 8, 1955 Page: 1
Subject: American Cancer Society Sponsored Conference
on Lung Cancer and Heart Disease with Particular
Emphasis on Tobacco as a Potential Causative Agent
Program arranged by Dr. Harry Weaver of the
American Cancer Society

Friday, January 28, 1955 - A.M.

The morning session was devoted to consideration of the possible role played by air pollutants such as coal tar and soot, diepoxides, engine exhausts, ionizing radiation, etc. in the increased incidence of lung cancer. The general consensus of opinion was that in terms of the public at large, as opposed to certain specific occupational groups, that the coal tar and engine exhaust derivatives were the only ones which might have major significance. There was no unanimity of opinion as to what portion of the increase might be attributed to the action of these agents.

Friday, P.M. Afternoon session.

This session was devoted to a discussion of the chemical composition of smoke and a fractionation program with respect to 3,4-Benzpyrene. Dr. Fieser presented his work indicating that this compound was probably not present in the amounts which had been reported by the English group, if it was present at all. He reported that compounds giving similar fluorescent spectra, but partially different ultraviolet absorption spectra were present. Dr. Dickey of Tennessee-Eastman Co. and Dr. Wright of the University of Toronto concurred in this evaluation.

Dr. Fieser presented his work on the isolation of tobacerol from tobacco and suggested that it might be a precursor for the formation of aliphatic or aromatic carcinogens. Dr. Wright reported that he had isolated the amounts of 5 mgs. per 15 gms. of $C_{12}H_{12}O_5$ compound which was highly fluorescent, was an acid, and was sensitive to alkali in the presence of air.

Dr. Frankenburg of American Cigar Co. discussed the chemistry of cigar tobacco, stressing (a) the variation of alkaloid content from strain to strain and year to year, (b) some of the changes occurring in the composition of the tobacco leaf as a result of fermentation. He presented no evidence on the composition of cigar smoke.

Dr. Stephano presented some material which purported to show that if the temperature of the smoke hitting the tongue was 4-5 degrees above room temperature, that the smoker decreased the volume of the puff and usually shortly thereafter put out the cigarette. He claimed that all machines used to smoke cigarettes were grossly inadequate to give combustion conditions similar to those which hold in normal smoking. He felt that puffs every 20 seconds were too frequent. (Keith Cannan who sat next to Dr. Stephano the next morning, timed Stephano's smoking habits and found that he smoked a cigarette on the average of $5\frac{1}{2}$ minutes and that his puff averaged higher than two per minute).

Dr. Newman of Ohio State stated that he did not believe that the rate of puffing or volume of puff would alter the combustion process significantly and lead to changes in the composition of the smoke.

From Charles J. Kensler.....
/gm

MEMORANDUM

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Case: Date: February 8, 1955 Page: 2

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Friday Afternoon Session (cont'd)

Dr. Hammer, Research Director of American Tobacco Company reported some of their studies which indicated nicotine acids and aldehydes in the smoke, were very sensitive to the smoking conditions and did not increase or decrease uniformly (i.e. one component might increase 50% whereas another only 10% and vice versa).

Dr. Hobbs presented his data on the composition of the gas phase and reported that he could account for more than 95% (?) of its composition.

Dr. Wright who is preparing fractions for test by Wynder, is using Imperial Cigarette Company cigarettes which do not contain any flavoring materials. He is using "magneson" for a chromatographic fractionation. Dr. Shear mentioned the desirability determining the carcinogenic activity of cigarette smoke prepared in the absence of particulate matter in the air which is known to contain carcinogenic materials. Dr. Kensler stated that this was being done at Arthur D. Little, Inc.

Friday Evening - Bio Assay

Dr. Toolan presented her work on the cultivation of human embryonic lung tissue in the cheek pouch of the hamster and subcutaneously in the rat. Rats were irradiated and treated with cortisone; the hamsters treated with cortisone alone. Weanling females were used in both cases. The rats were employed as a reservoir host and the hamsters for experimental work. The embryonic material was obtained from Sweden. Usually 36 hours later, the tissue was implanted in the rat. The tissue was minced and approximately 3 mg. portions were implanted and left for 14 to 16 days. The tissue was then transferred to the hamster. It was found most effective to insert the tissue by the use of a needle to cut down on infection. Takes were of the order of 95% to 100%. The embryonic lung increased in mass by a factor of 20 in four months. The hamsters were treated with cortisone with an initial dose of 3 mgs. and subsequent doses of 1 mg. per week. The first human tissue was received on October 7th and has increased in amount from 25 to 500 mgs. In contrast to the behavior of the embryonic lung in the aqueous humor of the rabbit's eye, this material in the hamster's cheek pouch rapidly takes on adult morphology (3 to 4 days). The lobules are filled with a fluid of unknown composition. Tissue implants in the cheek pouch of the hamster can be inspected regularly and are accessible for local treatment with potential carcinogens. Problems which may arise in the future in terms of evaluating any response to these agents are: 1) The uncertainty of the effects of cortisone. 2) The abnormal stromal-parenchymal cell relationship. It does appear to be a promising technique to gain information on the susceptibility of human tissues to suspected carcinogenic agents. Other Bio assay procedures were discussed, but the consensus was that the production of neoplasia was still the only reliable guide for carcinogenicity. The possibility of using paramecium was discussed, as this organism had been reported some years ago by Mottram to be inhibited by photo-oxidation products of aromatic hydrocarbon carcinogens.

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Case:

Date: February 8, 1955 Page: 3

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Saturday morning: January 29

Hammond presented the results of his forward epidemiologic study in terms of smoking and lung cancer, coronary disease and longevity. The material was essentially that reported by him in San Francisco last June.

Wynder reported on the experimental approach to the problem of cigarettes and lung cancer, and stressed that he was using the skin of the mouse as a means of measuring carcinogenic activity of cigarette smoke and that he did not consider the production of cancer in this species to constitute proof that cigarette smoke was carcinogenic to man. He presented his fractionation scheme which did not differ from the slide presented to the Pharmaceutical Manufacturers Association in December.

Wynder reported that Swiss mice are more susceptible than C₅₇ and CAF₁. He mentioned that cigar tars appear to be less active than cigarette tars. He is making measurements of sebaceous gland activity and epidermal thickness in assaying his fractions. The acidic and basic fractions produced predominantly a hyperplasia and the neutral fractions predominantly decreased sebaceous gland activity. The neutral fraction appears to be less active than the total tar in long-term test for carcinogenicity. He reported that Dr. Sugiyama using cigarette tars obtained from Dr. Wynder, had produced 3 papillomas out of 60 mice, the time being around 9 months.

Dr. Kensler, at the request of Dr. Weaver, discussed some of the pharmacologic factors involved in the actions of tobacco smoking on the cardiovascular system, stressing the need for more information of the actions on coronary flow and the production of arteriosclerotic lesions following chronic exposure and pointing out that the available evidence in the latter situation is practically worthless.

Saturday afternoon: January 29

Dr. Nelson attempted to summarize the significant points that had been brought out in the discussion and it was his conclusion that cigarette smoking is a factor in the present increase of lung cancer, but how important a factor is not known. He pointed out the difficulty of resolving the interplay of other factors in the lung-cancer-smoking problem by epidemiologic methods, and suggested that a withdrawal-type experiment would be in order. He also stressed the differences between urban and rural areas and placed emphasis on the need for more information on coal tar and petroleum products as air pollutants. In the discussion which followed, Ancel Keys commented to the effect that he still questioned the significance of the epidemiologic findings in terms of coronary disease. He mentioned that in various countries, changes in coronary disease and lung cancer did not go in parallel. He also mentioned the difficulties of studying this problem experimentally.

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Case: Date: February 8, 1955 Page: 4

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Dr. Schrek reported on a study in progress which indicates the correlation between lung cancer and smoking, and reported a slight correlation for coronary disease. He stressed the point that of the various things they had studied, infectious diseases, etc., that everything correlated positively with smoking, with the exception of diabetes.

Mr. Lew, Actuarial of Metropolitan Life, commented on the fine job Hammond and Horn had done in their epidemiologic study, but pointed out: (a) the information obtained would be much more reliable if they had a longer period of observation, and (b) he thought that the study was biased in terms of favoring decreased correlation for the older age groups.

He stressed the probability that a significant proportion of the reported increase in lung cancer may be due to improved diagnosis and reporting. He also questioned the significance of any estimates as to the proportionate role that cigaret smoking might play in this process. He mentioned that he had recently surveyed 500 death claims of people who had taken out insurance in the 1920's and mentioned that in this limited series, only 4 diseases appeared to be correlated with smoking; these were lung cancer, cancer of the buccal cavity, coronary disease and duodenal ulcers.

Dr. Clemmensen from Copenhagen reported on the incidence of lung cancer in Denmark, and pointed out that the urban area curves were about ten (10) years ahead of the rural areas, and noted that the birth rate increases were relatively separated by the same period of time. In a study of the incidence of lung cancer as a function of the economic level, the conclusion was that the people who lived in the poorer neighborhoods had a higher incidence of lung cancer.

Dr. Rigdon from Texas pointed out the difficulty of determining whether lung cancer was squamous or adenocarcinomatous and stated that his experience, many lung tumors contained areas which resemble both types. Hence the smaller the area examined, the more certain the opinion of the pathologist.

Dr. Clemmensen agreed with Dr. Rigdon that this introduced a problem, particularly as the squamous type has been characterized as the "cigaret cancer".

Dr. Rigdon reported on a new study underway involving 12,000 cases. He presented tabular data showing variations of smoking habits with age and educational level.

Dr. Gilliam presented data to show that if there had been a 4% error in the diagnosis of lung cancer over the years which was gradually corrected, that the total reported increase in lung cancer could be explained by this degree of improvement in diagnosis.

Charles J. Kensler