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LABORATORY CONTRIBUTIONS TO THE TOBACCO-CANCER PROBLEM*

BY

ERNST L. WYNDER, M.D.

Head, Section of Epidemiology, Division of Preventive Medicine, Sloan-Kettering Institute, New York; Associate Professor of Preventive Medicine, Sloan-Kettering Division, Cornell University Medical College, New York

The sum total of evidence linking smoking to cancer of the respiratory tract is based upon different types of evidence: presumptive, epidemiological, pathological, animal, and chemical. All of the evidence so far established demonstrates smoking to be a carcinogenic factor. It is now our task to bring the problem posed by this association to a successful solution. The present report represents an evaluation of the contributions that laboratory research is making in this field.

The importance of laboratory work is not to prove that smoking is a cause of cancer in man. Such proof can only come from human epidemiological investigation. Laboratory research can, however, contribute to, and give a logical explanation for, the human findings. Just as an animal experiment cannot disprove that a given factor causes cancer in man because of possible species differences, so, by itself, an experiment cannot prove a given agent to be carcinogenic to man. It is primarily as a corollary to the human findings that the animal experiment has its significance. The basic tasks of laboratory research, which are of a biological and chemical nature, are to identify the specific agents in a given product that produces cancer and to devise ways and means whereby such agents can be reduced or removed. In so doing, we can only assume that the agents responsible for the activity in animals are also responsible for the human activity. In view of the many similarities established for tumour growth in animals and man, such an assumption, though it cannot be proved, stands on a firm foundation.

Most cancer researchers would surely agree that once a carcinogen has been identified in a given material suspected to be active for man and proved to be active for animal tissue, particularly when this is demonstrated for several species of animals, such an agent should, if at all possible, be reduced or eliminated from man's environment. It is along these lines that laboratory research, as it applies to the tobacco-cancer problem, has its greatest significance. It is now our purpose to review the methods followed in respect to this work and the results already achieved.

Methods of Study

Since the primary purpose of the biological study is to establish the activity of the agents suspected to be carcinogenic, the test site is perhaps less important than

is generally considered. In choosing the test site, one must be sure not only to use a site which is not too sensitive to tumour formation, but also to avoid one in which tumours cannot be produced even with very potent carcinogens. In general, it would be advantageous to use the type of tissue similar to the one involved in man. In view of these considerations, the subcutaneous tissue of mice would be a less useful site because it does not yield epithelial tumours and also because it has been shown to be quite sensitive to a large variety of substances. On the other hand, the lungs of mice would not represent a good test organ, since, even upon inhaling high doses of potent polynuclear hydrocarbons,^{8 35} it has been difficult to produce lesions in the bronchus in mice. The skin, on the other hand, is a satisfactory site not only because of ease of application, but also because it represents a type of tissue similar to the epithelial tissue of the respiratory tract.

An important factor when testing a product to which man is exposed is to test this product under a condition similar to that under which man is exposed. Thus we should smoke tobacco in a manner simulating human smoking habits, and should not distil the tobacco smoke in a closed container. Another important principle is that, when testing a substance suspected to be only weakly carcinogenic, the substance should be applied in maximum concentration over a maximum period of time. With these considerations on methodology we shall review the actual experiments already completed.

BIOLOGICAL DATA

Lung Studies

A number of experiments have been conducted exposing mice to cigarette smoke. As could be expected from similar experiments with pure carcinogens, it is most difficult to produce bronchiogenic lesions in this manner. The method is particularly difficult with tobacco smoke because if the concentration of the smoke is too high animal mortality is too great. Campbell, and later Essenberg, have succeeded in producing pulmonary adenomas in susceptible mice by exposing the animals to varying concentrations of cigarette smoke.^{7 16} Lorenz obtained negative results.³² In a more recent and detailed study, the Leuchtenbergers found that there is an increase in hyperplasia, metaplasia, dysplasia, and carcinoma *in situ* when mice are exposed to cigarette smoke for a relatively short period of time.³¹ These experiments are of interest because they show

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the same types of early bronchial changes as demonstrated by Auerbach and others^{1 12 22} in human lungs.²⁴ Using a more direct approach, Rockey applied condensed cigarette smoke to the trachea of dogs for about 11 months, noting severe metaplasia of the epithelium.⁴⁰ Blacklock, injecting tobacco smoke condensate together with tubercle bacilli into the hilum of rats, was able to produce two carcinomas in the eight rats treated in this way.⁴

Though inhalation studies, therefore, have so far not produced any actual bronchiogenic carcinomas in the experimental animal, a result which could not be expected because of the toxicity of high doses of tobacco smoke and in view of the fact that this has been difficult even with high concentrations of polycyclics, the available evidence has nevertheless indicated an abnormal reaction of the pulmonary and bronchial tissue to tobacco smoke and in one instance the production of carcinoma in this tissue when the smoke condensate was directly applied.

Skin Studies

There are surprisingly few experiments dealing with the production of skin cancer in animals upon application of tobacco smoke condensate in view of the attention given to the problem. In fact, until 1953 no study had been done with condensed tobacco smoke. At that time we published our first report showing the production of 44% cancers and 59% papillomas among CAF₁ mice which had been painted with a 50% tar-acetone solution three times a week.⁴⁶ In 1955 we reported⁴⁷ the production of cancers in two additional strains of mice, Swiss and C₅₇. Since this time we have reported positive results on yet another mouse strain.⁴⁸ In the meantime, Hammer and Woodhouse, as well as Passey, reported their inability to produce skin cancer in mice with tobacco tar.^{21 39} However, as will be shown subsequently, the negative results are not necessarily due to differences in British and American tobaccos but rather to the fact that the tar was applied at a subthreshold level. The fact that tobacco tar is carcinogenic to mouse skin has since been confirmed by Sugiura, by Bock, by Orris, and by Engelbreth-Holm.^{5 15 38 44} These studies leave no doubt that tobacco smoke condensate is carcinogenic to mouse epidermis. In more recent experiments we demonstrated that carcinogenic activity is also present in cigar and pipe smoke.¹⁴ In fact, we found a slightly greater activity in cigar and pipe smoke than in cigarette smoke.

Carcinomas have been produced not only in mice but also in rabbits. Roffo published a whole series of articles on the production of cancer in rabbit ears with a tobacco smoke distillate.⁴¹ However, it could be argued that this distillate represented a variance from the tobacco smoke condensate. We recently reported the production of carcinoma in rabbit ears after applying cigarette smoke condensate over a period of six years five times a week, 100 mg. per painting, in a 50% tar-acetone solution: 100% of the rabbits developed papillomas and 12.5% of 48 rabbits developed histologically proved cancers. Two of these cancers showed widespread metastases.²⁰

In summary, biological experiments to date have proved that tobacco smoke condensate is carcinogenic to at least two species of animals and several strains of mice.

Before the chemist could proceed to identify the active materials, biological study had to be conducted to determine the particular components of the total tar in which the majority of the activity is located. In a large-scale study, summarized in Fig. 1, we have shown

CIGARETTE TAR FRACTIONATION - RELATIVE BIOLOGICAL ACTIVITY

Fig. 1.—The plus sign indicates relative values of carcinogenic activity.

that the majority of the active fractions of tobacco smoke condensate are in the fraction which is eluted with carbon tetrachloride from the neutral tar.⁴⁹ This fraction, representing only 1.7% of the total tar, produces 100% cancer in animals when applied in 10% concentration. We did observe some activity in other fractions. However, it cannot be said whether this is a result of independent carcinogenic substances or whether it is the consequence of unsatisfactory chemical separation. Present data suggest that in the basic portion of the tar, where polynuclear substances are not thought to remain, there are at least cocarcinogenic elements.⁴⁹ This is believed to be the case not only because of the high hyperplastic reaction obtained with this material, but also because it increased the tumour yield when added to the neutral tar. However, we conclude at this time that the major carcinogens are in the carbon tetrachloride fraction of the neutral tar.

Chemical Data

The chemical studies have been directed toward identifying the agents in tobacco suspected to give rise to the carcinogenic activity of the total tar. The first suspicion obviously falls upon the higher aromatic polycyclics, since it is a well-established principle that the burning of any organic matter will give rise to these substances.^{2 19} A large number of investigators have now identified 3:4-benzpyrene in tobacco smoke condensate, ranging up to 2 µg. per 100 cigarettes.^{3 6 9 11 13 17 18 23 27 29 30 33 42 43} It is generally realized, of course, that this amount of benzpyrene is not sufficient to account by itself for the carcinogenic activity of the total tar. We have also reported the identification of 1:2:5:6-dibenzanthracene in cigarette smoke condensate again, though in minute amounts.²³ Tentative spectrographic identification has also indicated the presence of additional carcinogens such as 1:2-benzanthracene,^{23 33 37} 1:2-benzpyrene,^{11 23 33 38} 1:12-benzpyrene,^{13 23 38}

chrysene,^{33 38} 3:4:9:10-dibenzpyrene,³⁷ and 3:4:8:9-dibenzpyrene.^{33 34} The last-named has also been tested by Buu-Hoi, but has relatively little biological activity for the skin.²⁵ Recently, Hoffmann, and also Van Duuren, have identified 3:4-benzfluoranthene, which we have proved to be carcinogenic to mouse skin.^{23 38} Additional higher aromatic polycyclics identified but not yet tested for carcinogenic activity include benz(mno)-fluoranthene, 10:11-benzfluoranthene, and 11:12-benzfluoranthene.^{23 38}

Chemical work done at present in our laboratory is directed toward determining additional polycyclics in the various tobacco fractions found to be carcinogenic. In Table I, as most recently completed by Dr. Hoffmann,

TABLE I

Polycyclic Hydrocarbons	p.p.m. Fraction B	p.p.m. Fraction C
3:4-Benzpyrene	0.57 . 10 ²	1.14 . 10 ²
1:2:5:6-Dibenzanthracene	0.24 . 10 ²	0.01 . 10 ²
3:4-Benzfluoranthene	0.055 . 10 ²	0.73 . 10 ²
10:11-	0.18 . 10 ²	0.08 . 10 ²
1:2-Benzpyrene	0.055 . 10 ²	+
1:12-Benzperylene	0.08 . 10 ²	0.99 . 10 ²
1:2-Benzanthracene	+	—
Chrysene	1.1 . 10 ²	+
Alkylchrysene	0.55 . 10 ²	+
Fluoranthene	0.93 . 10 ²	—
Alkylfluoranthene	+	—
Pyrene	4.0 . 10 ²	—
Alkylpyrene	1.6 . 10 ²	—
Perylene	0.03 . 10 ²	—
11:12-Benzfluoranthene	0.1 . 10 ²	—
Benzo(mno)fluoranthene	+	0.1 . 10 ²
2:3-Benzfluorene	—	—
Anthracene	+	—
Phenanthrene	+	—

Fraction B is the carbon tetrachloride eluate of the neutral tar (see Fig. 1). Fraction C is biologically the most active fraction of the 880° C. pyrolysate of a hot hexane extract of cigarette tobacco.

we show the identification of higher aromatics present in the carbon tetrachloride fraction of the neutral tar. Even though at present we may still not have identified all of the polycyclics responsible for the total activity of this fraction, the activity of this fraction is largely due to polycyclics. There obviously remain other polycyclics still to be identified, a project which may be of greater academic than practical importance, since it may be assumed that polycyclics are produced in the same manner. These tables also show the identification of polycyclics in Fraction C, representing one of the ten subfractions of the 880° C. pyrolysate of hexane extracted tobacco which, in 0.01% concentration, proved to be biologically active.⁵⁵ It is of interest that, even though a whole range of polycyclics was identified in the 880° C. pyrolysate (Table II), only Fraction C in a 0.01% concentration proved to be biologically quite active, while Fraction B had very minor activity. This

TABLE II.—Polycyclic Composition of 880° C. Pyrolysate of Hot Hexane Extract of Cigarette Tobacco Determined Spectrophotometrically

Pyrolysate Fraction	
A	Mixture of aliphatic hydrocarbons, naphthalene, mono-substituted aromatics (yellow oil), phenanthrene, 4-methylpyrene, anthracene, pyrene, fluoranthene, and a mixture of unknowns.
B	Unknown (alkyl anthracene), 1:2-cyclopentanophenanthrene, 1:2-benzanthracene, chrysene, acenaphthylene (trace of 3:4-benzpyrene).
C	Perylene, 1:2-benzpyrene, 3:4-benzpyrene, 1:12-benzperylene (total in Fractions C and D), and other polycyclics (Table I).
D	1:12-Benzperylene and other polycyclics.
E	1:2:3:4-Dibenzpyrene, 3:4:8:9-dibenzpyrene, 3:4:9:10-dibenzpyrene, and other polycyclics.
F	1:2:7:8-Dibenznaphthalene, 2':3'-naphtho-3:4-pyrene, coronene, and other polycyclics.
G	Coronene, 1:2:5:6-dibenzanthracene, and other polycyclics.
H	Unknown, 3:4-benzpyrene derivative and other polycyclics.
I	A mixture of several unknown polycyclic compounds.

would suggest that the majority of the carcinogenic polycyclics present in tobacco tar chromatograph in the region of benzpyrene.

The identification of 3:4 benzfluoranthene as an active carcinogen represents a case in point. Additional work in which Dr. Hoffmann is engaged concerns studies with radioactive benzpyrene and 1:2:5:6-dibenzanthracene, and is designed to determine the effectiveness of our chemical separation schemes in removing the benzpyrene present in the total tar in the final solutions. Though the higher polynuclear substances are the only carcinogens present in tobacco, they are the major carcinogenic components, and may be regarded as a standard on which to predict the carcinogenic activity of any type of tobacco smoke condensate.

Preventive Approaches

Having determined the major tobacco carcinogens, it now remains to be considered how the carcinogenic activity of tobacco smoke could be most effectively reduced.

Dose-Response Studies

In view of the established principle of carcinogenesis that the higher the dose the greater, up to a given point, the tumour yield, it became pertinent to establish this factor for the experimental animal.⁵⁰ In Figs. 2 and 3 we summarize the data in this respect. They indicate that there is a minimum as well as an optimum level at which tobacco smoke condensate produces cancer in the experimental animal, and that the minimum level is about one-third of the optimum level.

FIG. 2.—Percentage of papillomas by 18 months.

FIG. 3.—Percentage of cancers by 18 months.

These studies are of academic importance in that they demonstrate the reasons why certain investigators may have been unable to produce tumours with tobacco products. More important, they are of practical significance in that they show that if tar exposure is reduced below a certain point the rate of tumour formation, at least in the experimental animal, is

greatly reduced. In this respect they are similar to the epidemiological studies which show the same relationship. In view of these conclusions it becomes of obvious practical importance to determine ways by which the tar content of the tobacco smoke condensate can be reduced.

Tobacco Types

Considering the possibility that various tobacco types might differ in the production of carcinogenic substances, we undertook a study of cigarettes made of pure Burley, Maryland, Turkish, and Virginia tobaccos.⁵² The results of these studies are summarized in Fig. 4, and indicate

FIG. 4.—Percentage of cancers at 18 months, with different types of tobacco.

no significant variation in carcinogenic activity, even though there are obvious variations in nicotine content and thus in the base-free fractions of these tars. These comparisons could be made only for the base-free portion of the tars, since the nicotine content of the Burley tobacco is too high for biological testing. We conclude at the present time that tobacco selection, though it can greatly influence the nicotine content and certainly can also influence the total tar content of the condensate, will not significantly influence the carcinogenic activity of the tar on a gramme-to-gramme basis.

Filter Cigarettes

In view of the points emphasized by the dose-response studies, we were interested in conducting studies with filter cigarettes. As summarized in Fig. 5,⁵¹ these studies

FIG. 5.—Percentage of cancers at 18 months, with different types of cigarette.

indicate that on a gramme-to-gramme basis the carcinogenic activity of tar obtained from filter cigarettes is similar to that of unfiltered cigarettes. Therefore it is established that a mechanical filter cannot selectively remove the carcinogenic materials from tobacco smoke, which, knowing the physical make-up of tobacco smoke, could have been predicted. A filter thus serves its purpose not because it removes certain components of tobacco tar selectively, but because it can lower the total tar content of the smoke. Any filter which does not fulfil this requirement is not useful. In the past some tobacco manufacturers, while employing a fairly efficient filter, used high tar-yielding tobaccos. Such smoking products are misleading to the consumer. Tar reduction can be most effectively achieved by a combination of efficient filtration and proper tobacco selection.

Data recently reported showing the tar content of filtered and unfiltered cigarettes as currently smoked in the United States indicate that to-day there is a cognizance of this principle by at least some of the tobacco manufacturers in this country.³⁶ As indicated

TABLE III

	1957	1958	Change
<i>Tar content in mg. of some 85-mm. filter cigarettes*</i>			
Filter A	32.6	29.1	-11%
" B	30.4	17.9	-41%
" C	30.2	27.7	-8%
" D	38.5	24.9	-35%
" E	36.3	17.7	-51%
" F (70 mm.) ..	25.6	15.1	-41%
<i>Tar content in mg. of some 70-mm. regular cigarettes</i>			
Brand A	31.0	28.7	-7%
" B	31.5	28.6	-9%
" C	32.7	30.6	-6%
" D	35.3	28.9	-18%
" E	30.9	22.4	-41%
" F (85 mm.) ..	38.6	37.1	-4%

* Foster D. Snell.³⁶

in Table III, a marked reduction in some of the major cigarette brands in the United States has taken place. This movement is to be encouraged, and it is hoped that before long all of the tobacco manufacturers in the United States and elsewhere will follow suit. While such a move will not prevent a smoker from developing lung cancer, present evidence indicates that it will reduce his chances of developing this disease.

Pyrolysis Studies

In biological experiments we have shown that an extract of tobacco is only weakly carcinogenic compared with tobacco smoke condensate.⁴⁹ There is present in unburned tobacco a very small amount of some higher aromatic polycyclics which are apparently formed during the curing process.^{10 17 18} However, it is clear that the majority of the higher polynuclear substances are formed during the combustion processes of tobacco.

We have set out to undertake a series of studies to determine the temperature ranges at which the majority of the carcinogens are formed. We have pyrolysed hot-hexane-extracted tobacco at temperatures ranging from 880° C. to 560° C. and found that the formation of carcinogens is related to the burning temperature. It does not appear to be so much related to the presence or absence of oxygen, since the activity of the 880° C. pyrolysate in nitrogen and with the addition of oxygen was similar. However, we found that when the temperature was reduced below 700° C. the biological activity was greatly reduced (Fig. 6).⁵³

FIG. 6.—Tumour formation in mice upon application of pyrolysis products of hexane extract of tobacco obtained at different temperatures.

We were interested in investigating this problem from a number of different aspects. We smoked cigarettes with a high and a low puff volume in an effort to determine whether this would alter the carcinogenic activity. In view of the fact that maximum temperatures reached in these cigarettes are quite similar, 884° C. $\pm$ 30° C., we did not expect a variation in activity, and, indeed, none was found.⁵³ It is of interest in this respect that the cigarettes smoked with a high puff volume yielded more tar. However, all our experiments are based upon a gramme-to-gramme comparison. We

also set out to test whether cigarettes smoked halfway or to the butt end would show different activity, since repyrolysis of condensed tar might produce more carcinogenic material. However, the results again showed a similarity in biological activity even though the tar yield of cigarettes smoked to the very butt end is obviously greater than of those smoked halfway down.⁵³

Finally, we have studied the comparative activity of cigar, pipe, and cigarette tars. We found cigar and pipe tar somewhat more active, which, we believe, is due to the fact that cigar and particularly pipe tobacco burns at a high level for a longer period of time than does cigarette tobacco, even though the maximum temperature of cigarettes is higher than that of pipes. These temperature studies have been reported in detail by Touey and Mumpower, and are summarized in Fig 7.^{26 45} In burning at a high temperature for a longer

FIG. 7.—Potentiometer graphs (Touey and Mumpower^{26 45}).

period of time the combustion may be more complete in cigars and pipes. Obviously the formation of the carcinogens from organic material is not only a consequence of maximum temperature, but also of the duration of contact with a given temperature level. Present evidence strongly suggests that modification of temperature levels, if achieved, could influence the formation of carcinogens in tobacco.

Study of Precursors

By studying precursors we planned to determine whether there were any components in tobacco smoke condensate which would be particularly susceptible to the formation of higher aromatic polycyclics. We washed tobacco with hot hexane and smoked the extracted tobacco. Of immediate interest is the fact that, though only 5.4% of the tobacco by weight was removed, the tar yield of this cigarette was 35% less than that of an ordinary cigarette.⁵⁴ However, on a gramme-to-gramme basis, one of the two experiments showed a somewhat decreased activity and the other showed no decrease in activity from regular tar. Therefore, at present we must conclude that this method cannot effectively reduce the carcinogenic activity of tobacco tar. Lindsey had previously shown some reduction in benzpyrene content of hexane-extracted tobacco.¹⁰ However, our studies do not show a reduction of benzpyrene in hexane-extracted tars.

Lindsey has shown that a large variety of agents present in tobacco can produce higher aromatic polycyclics when pyrolysed.¹⁹ Lam has pyrolysed some of the sterols present in tobacco and has identified higher aromatic polycyclics.²⁸ We have shown this pyrolysate to be biologically active on mouse skin.⁵³ In view of

these observations it would be most difficult to remove any given substance from tobacco in the absence of which no polycyclics could be formed. We believe, therefore, that even though the different components in tobacco may vary in their relative susceptibility to form higher aromatic polycyclics, a removal of certain substances from the tobacco itself would not be a practical way of reducing its carcinogenic activity upon being smoked.

Practical Preventive Measures

The practical preventive measures as derived from completed laboratory work fall into the following categories.

1. *Lowering of Tar Content in View of Studies on Dose-Response Levels.*—This can be attained through effective filtration and tobacco selection. The greater the decrease in tar content of a given cigarette the lower the liability to cancer development. This is a practical step which can be undertaken by the tobacco industry without delay.

2. *Temperature Reductants.*—We are currently engaged in a study of a number of substances, including aluminium products, to determine whether the temperature of the tobacco during smoking can be lowered sufficiently to influence the formation of polynuclear substances.⁵⁵ A number of suggestions have been made to cool the main stream of the smoke. However, since the carcinogens undoubtedly are formed in the burning process, it is here that we must concentrate our efforts.

3. *Modification of Pyrolysis.*—Through the use of a variety of catalysts we are currently engaged in determining whether the polynuclear content of tobacco smoke condensate can be reduced.⁵⁵ The idea of catalysts, which is useful in the petroleum industry, may be less applicable in the case of tobacco because of shorter contact time. However, work completed so far suggests that the polynuclear content can be altered. It also seems to affect the proportion of different polynuclear substances. These studies are still in the preliminary stage, and it remains to be determined through combined biological and chemical investigations whether there is a particular catalyst or group of catalysts which could reduce in a practical fashion the carcinogenic activity of the tobacco smoke condensate.

Conclusion

In summary, we have reviewed the work being conducted in various laboratories throughout the world, and particularly in our own laboratory, relating to the tobacco-cancer problem. We have stated the purpose of the laboratory experiment, the direction in which it must go, and have emphasized the relationship that it bears to the human epidemiological study. Like any other phase of scientific investigation, it is the co-operation in different areas of scientific activity which furthers the achievement of a solution to any given problem. While only the epidemiological study can give definite proof of the relationship of smoking and lung cancer, the studies in the laboratory are essential in providing a practical solution to this problem; short of abolishing the smoking habit. Knowing that man will continue to smoke regardless of the evidence, we must expand our laboratory work in order to provide a practical solution to the problem. The thousands of

lives lost in every country each year from cancer of the respiratory tract demands that we expedite our efforts. It is hoped that with the evidence already at hand a practical solution may be within our reach. It is toward this end that laboratory studies involving the smoking-cancer problem must now be directed.

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LUNG CANCER MORTALITY AND THE LENGTH OF CIGARETTE ENDS

AN INTERNATIONAL COMPARISON

BY

R. DOLL, M.D., D.Sc., F.R.C.P.

A. BRADFORD HILL, C.B.E., F.R.S.

Statistical Research Unit of the Medical Research Council

P. G. GRAY, B.Sc.

AND

E. A. PARR, B.A.

Social Survey Division of the Central Office of Information

Study of the recorded death rates from lung cancer in different parts of the world shows that there is a fairly close relationship between the present national mortality from the disease and the national consumption of cigarettes 20 to 25 years ago. Data for 16 countries are given in Table I and illustrated in the Chart, in which for each country the standardized mortality of men in 1952-4 is set against the consumption of cigarettes per adult (of both sexes) in 1930. The latter

TABLE I.—Mortality from Lung Cancer and the Consumption of Cigarettes in 16 Countries*

Standardized Mortality of Men from Cancer of Lung in Years 1952-4. Rate per Million			Cigarette Consumption in Year 1930 (per adult)	Mean Cigarette Consumption (Unweighted)
Mortality Group	Country	Rate		
Over 300	England and Wales	461	1,378	1,330
	Finland ..	433	1,662	
	Austria ..	380	960	
200-299	Netherlands ..	276	632	840
	Belgium ..	254†	1,066	
	Switzerland ..	236†	706	
	New Zealand ..	216	478	
	U.S.A. ..	202†	1,296	
100-199	Denmark ..	179	465	550
	Australia ..	177	504	
	Canada ..	176	760	
	France ..	140	585§	
	Italy ..	110†	455	
Under 100	Sweden ..	89†	388	490
	Norway ..	77	359	
	Japan ..	40	723	

* The standardized mortality rates were calculated by Segi (1957). Rate for cigarette consumption were given by Todd (1957) or were derived from data for Finland and Norway published by Nielsen and Clemmesen (1954), for Switzerland published by Gsell (1951), and for New Zealand kindly provided by the New Zealand Government, Department of Statistics.

† 1951-3. ‡ 1954. § 1951.

Relationship between lung cancer mortality and previous cigarette consumption in 16 countries. The regression line is given by $y = 0.24x + 28$; the correlation coefficient is 0.76.