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TOWARDS A SOLUTION OF THE TOBACCO-CANCER PROBLEM

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Human Evidence

Statistical and epidemiological evidence linking smoking to cancer of the lung and also to cancer of other sites of the upper respiratory tract is so extensive that it hardly needs to be recited for the physician and the scientist who have followed these data. Sixteen separate investigations from seven different countries, studying smoking habits of over 6,000 patients with lung cancer, are all in agreement that lung-cancer patients smoke significantly more than any group of controls and that the relative risk of developing lung cancer rises in proportion with the amount of tobacco and particularly of cigarettes consumed. Two prospective studies, carried out in England and in the United States, that followed population groups whose smoking habits were known, also showed that the heavy cigarette smoker has a far greater chance of developing lung cancer than the non-smoker. In fact, the study by Hammond and Horn (1954 and personal communication) indicated that for a person smoking 40 cigarettes a day this chance was 70 times greater than for a non-smoker. To account for such magnitude of difference on the basis of statistical errors would require errors of equal magnitude. Such errors have so far not been demonstrated.

The belief that smoking is a major cause of lung cancer is not only based upon statistical evidence but it also is supported by the general epidemiological pattern of lung cancer. In countries, such as Great Britain and the United States, with a high cigarette consumption already 30 years ago, the present lung-cancer rates are high, while in countries, such as Iceland, where the cigarette consumption was low, the current rate of lung cancer is low. Among males in every country lung cancer is more common than among women. This fact has always presented a particular challenge. Any factor found to be significant statistically has to account, at least in part, for this sex difference. In a recent study we have shown that the present sex ratio of lung cancer is quite consistent with the long-term smoking habits of the two sexes. For instance, while some 20% of American males over the age of 50 smoke in excess of one packet a day, only 2% of the women in this age group smoke this amount. This study also showed that, among women who had smoked, the risk of developing epidermoid cancer of the lung or its undifferentiated types is about the same as that for men (Wynder *et al.*, 1956).

To consider smoking as a major cause of lung cancer does not mean that it is the only cause of this disease. Obviously there is the factor of internal predisposition

which must exist, since not everyone who smokes develops lung cancer. Obviously, too, there are other exogenous factors that may produce cancer of the lung. Among these are a number of occupational exposures. There is also evidence that general air pollution and/or motor exhaust fumes may be a contributing factor (Stocks and Campbell, 1955; C. Mills, personal communication). However, with the possible exception of a few isolated cities, such as Liverpool, air pollution is at best only a secondary factor. This belief is based on the fact that among non-smokers lung cancer occurs but rarely, that the incidence of lung cancer among women, who are also exposed to city air, is low, and that the age distribution of epidermoid lung cancer with its peak in the fifth to sixth decade and its subsequent decline is more compatible with an exogenous factor to which only a certain population group was exposed some 30 to 40 years ago rather than with air pollution, which would expose an entire population group at the same time (Levin, 1953).

While most students of the problem of the aetiology of lung cancer admit to an association between smoking and lung cancer, some question whether this association also represents causation. Until proved otherwise, an association means at least a contribution toward if not a causation of a disease. For any given patient it matters little whether a factor has contributed to or caused a disease. In either case the elimination of this factor will lead to reduction of the disease. In this sense, smoking, and especially cigarette smoking, is to be regarded as an important factor in the development of lung cancer. In fact, among the exogenous factors that influence the development of this disease it represents the most important one. Present incidence data indicate that some 80% of all lung-cancer cases occurring in males to-day would not have occurred were it not for tobacco smoking, and that about 10% of males over the age of 25 who smoke in excess of 20 cigarettes daily will develop lung cancer by the age of 75.

In view of these data, which gain significance because lung cancer represents the most common cause of cancer death among males in many countries, it becomes paramount to ask what we can do about solving this problem. Ideally this problem could be largely overcome by abolishing the use of tobacco. It is evident, however, that because of economic factors and because of firmly entrenched habits such advice is not likely to be heeded, regardless of how strong the evidence. For this reason we became interested in experiments that might lead to a reduction of carcinogens in tobacco and its products.

Animal Evidence

Experimental work is not carried out to prove that smoking causes cancer in man. Such proof can come only from human statistical and epidemiological studies. The purpose of an animal experiment is to define the mechanism by which a given agent produces cancer and to determine the specific substances responsible for this activity. In a series of experiments with different strains of mice we have demonstrated that condensed cigarette tar obtained in a manner simulating human smoking habits will produce skin cancers in a significant number of animals, varying from 10 to 44%, depending upon the strain of mice used (Wynder, Graham, and Croninger, 1953, 1955; Wynder, Lupberger, and Grener, 1956). Preliminary data show that some 20% of rabbits whose ears have been painted with tobacco tar for more than five years also develop cancer (Graham, Croninger, and Wynder, unpublished data). Thus carcinogenic activity of cigarette tar has been demonstrated in two species of animal and in several strains of mice. By itself, this observation might be only of academic significance, but taken together with the human evidence already at hand it gains practical significance.

Among the well-established principles of carcinogenesis is the relationship of dose to the latent period and number of tumours that may be obtained. The fulfilment of this principle is one of the reasons smoking is regarded as a cause of lung cancer in man. The risk of developing lung cancer rises in proportion to the amount of tobacco smoked. It has been of interest to determine whether with tobacco this principle could also be established for the experimental animal. Preliminary work leaves no doubt that this is the case (Wynder, Kopf, and Ziegler, unpublished data). When tar was applied to the back of Swiss mice twice a week, instead of three times weekly as is standardly followed in our laboratory, only 10% of 40 mice developed papillomas and 3% cancers at the end of 17 months. Of the animals painted three times a week for the same interval, 58% had developed papillomas and 26% cancers. The first papilloma in the group painted twice a week occurred two months later than in the group of animals painted three times a week. 40 mice painted once a week for 17 months developed only one papilloma.

A comparable reduction in tumour formation and lengthening of latent periods is also noted when one decreases the amount of tar applied. A 33% solution produced about 20% fewer cancers and increased the latent period by three months over that obtained with a 50% solution.

In still another way we can demonstrate the dose-response principle by stopping the painting after a given period of months. Painting animals three times a week for only three months and then stopping produced no tumours after 16 months of observation; painting 50 mice for six months produced two papillomas which subsequently regressed; nine months' painting produced a significant number of papillomas and cancers, but this was exceeded if animals were painted for one year.

Thus, animal experimentation has demonstrated a definite relationship between the amount and duration of tar applied to an animal and the total number of tumours and the duration of the latent period observed. The importance of this demonstration serves not so much as an example for those investigators who report negative results after painting animals with insufficient amounts of tar or over a too short time period, but serves chiefly to re-emphasize the existence of a threshold value for tobacco tar below which tumours will not or but infrequently occur after a long latent period. Here again human and animal data confirm one another. The realization of this principle has practical aspects that are discussed below.

Tobacco Carcinogens

Having established the carcinogenic activity of cigarette tar, one needs to determine the nature of the carcinogens responsible for this activity. The benzpyrene content of

cigarette tar is not more than 2 p.p.m., which, according to our experiments, is not sufficient to produce the type of activity noted in our animals painted with tobacco tar (Wright and Wynder, 1955, 1956). The arsenic content of our tar sample is about 35 p.p.m. Again this is not sufficient to induce the number of skin cancers produced. Cooper and Lindsey (1955) have found traces of 1:2-benzpyrene, and G. L. Wright (unpublished data) observed spectrographic evidence of traces of 2 methyl,3:4-benzphenanthrene. At present there is no evidence of a known carcinogen in tobacco tar in quantities large enough to account for the observed animal activity. A summation effect of the substances just mentioned or perhaps a co-carcinogenic effect of other substances remains to be ruled out. It seems more likely, however, that there are carcinogenic substances in tobacco tar which are as yet unestablished.

Most, though not all, of the carcinogenic activity of the cigarette tar lies in the neutral fraction (Wynder and Wright, 1956). Within the neutral fraction the carcinogenic components are those that are eluted by hexane and particularly by carbon tetrachloride or solvents of similar polarity. Both of these fractions proved highly active for the rabbit, and the latter particularly potent for the mouse (Wynder and Wright, 1956). The benzpyrene content of both fractions is low. In the concentration as applied to the animals it was not more than 2 p.p.m. In these fractions there is spectrographic evidence of other higher aromatic hydrocarbons which are present in 50 times the concentration of benzpyrene. We are currently engaged in various separation schemes trying to isolate these substances.

Formation of the Tobacco Carcinogens

Present evidence suggests that the majority, though not all, of the carcinogens in tobacco are formed during pyrolysis. Human statistics comparing the risk of cancer among tobacco chewers with that of tobacco smokers, and our own experimental work comparing the activity of cigarette tar obtained by extracting cigarettes with methanol and hexane with that of condensed cigarette smoke, indicate far greater activity for the latter in each case (Wynder and Wright, 1956). Thus there is good reason to believe that the majority of the carcinogens are formed during combustion. In fact, ever since the classical work of Kennaway (1925) and his associates showing that under pyrolytic conditions by which they are formed the pyrolysis of isoprene and that of acetylene in turn form potent carcinogens, it has been apparent that higher aromatic hydrocarbons can be formed by the pyrolysis of saturated or terpinoid aliphatic hydrocarbons. Most recently this was again demonstrated by Lam (1956a, 1956b), who obtained such substances upon pyrolysis of dicetyl as well as of aliphatic tobacco hydrocarbons. In this respect one recalls Kennaway's recent remark (personal communication) that in view of the high temperatures associated with smoking he was surprised that tobacco smoke was not more carcinogenic than present evidence indicates.

It is our working hypothesis that a major proportion of the tobacco-tar carcinogens are formed through pyrolysis of substances naturally occurring in tobacco, which thus serve as precursors to tobacco-tar carcinogens. The practical aspects of research in this field must be directed towards reducing the exposure to and the formation of carcinogens in tobacco tar.

Practical Aspects

Practical aspects of solving the tobacco-cancer problem centre in the following suggestions and research programmes.

1. *Moderation of Smoking Habits.*—All a physician can do is to present the facts to the public. In general, of course, the public is unable to evaluate the present facts fully, in part because of the confusion that special interests in some countries have added to this situation. In the final instance it must become the function of the public health services of different countries to evaluate the data at hand, and, if convinced by the evidence that tobacco plays a part in the development of lung cancer, decide whether lives are more

important than economic considerations. In view of the apparent difficulty that may be foreseen in arriving at a decision on this issue, research must be carried forward that may give a practical solution to the problem at hand.

2. *Effective Filtration.*—During recent years filtered cigarettes have become increasingly popular, initially because of "supposed health protection" and to-day because of a combination of factors, which include large advertising campaigns, the perhaps more pleasant feeling of a filtered tip, and a somewhat "milder smoke." According to present knowledge, filtration to remove specific components from the particulate phase of the smoke seems not possible. Thus we must concentrate on mechanical filtration permitting a minimum of tobacco smoke to pass, a minimum compatible with a satisfactory pressure drop and tobacco taste. In the United States some tobacco companies have taken advantage of the public's desire for filtered cigarettes and its equal wish for good tobacco flavour by marketing increasingly ineffective filters. Since both human and animal evidence indicates that the risk of developing cancer is directly related to the amount of tar exposure, it stands to reason that a given filter which will permit x milligrams of tar to pass is more effective than one which will permit the passing of $3x$ milligrams of tar. Sooner or later, regulations must be passed that establish criteria for the amount of tar which may pass through a given filter and that will make it a requirement for the manufacturer to state the effectiveness of a given filter. Present work indicates that it is entirely possible to develop a filtered cigarette with a good pressure drop and satisfactory tobacco taste which will remove about 40% of nicotine and tar from a given cigarette. Uniform acceptance of a filter in this range will be a partial answer to the present problem, provided, of course, that the smoker does not decide to smoke twice as many cigarettes, and provided, too, that the tobacco selection, cut, or packing is not altered in such a way as to yield increasingly more tar.

3. *Removal of Precursors.* If the hydrocarbons naturally occurring in tobacco represent one of the major precursors of tobacco-tar carcinogens, a reduction of such substances may have a direct effect in reducing the carcinogens. Most of the aliphatic hydrocarbons are in the waxes that cover the tobacco leaf. Terpenes are also present. It may be practicable to remove all or part of these substances from tobacco by washing it with eluents such as hexane. Experiments testing this hypothesis are now in progress.

4. *Modification of Pyrolysis.*—Since pyrolysis plays an important part in the formation of carcinogens, modifications of pyrolysis may affect the formation of carcinogens. This problem can be studied from the point of view of all those factors that affect the process of pyrolysis of tobacco. This includes the amount of oxygen supply, the temperature levels reached and maintained, the catalysis available, the cut of the tobacco leaf as such, the length to which a cigarette is smoked, and even the cigarette paper used. Experiments are now in progress for studying the interrelation of these factors so as to determine how a modification of the factors might lead to a reduction of the carcinogens formed during pyrolysis.

In this respect recent work of Lam (1956a, 1956b) is of particular interest. Pyrolysing aliphatic tobacco hydrocarbons, he found smaller amounts of aromatic compounds formed at 700° C. than at 800° C. At the latter temperature Lam found 3,4-benzpyrene to account for 1.3% of the total aromatic compounds and at 700° C. for 0.5%. The respective figures in parts per million were 340 and 30. At 600° C. Lam was unable to find evidence of aromatic substances, but studies by Wright indicate that some polynuclear aromatics are found even at lower temperatures (G. Wright, unpublished data).

Conclusion

The practical aspects outlined above may not individually lead to a tobacco tar that will have less tumorigenic activity, but a combination of these factors may be effective.

This discussion has dealt only with the problem of carcinogens and not with the equally important problems of nicotine and its apparent effect on the cardiovascular system. Jointly with work carried out toward reducing the carcinogens in tobacco tar to a subthreshold level, work should also be carried out on nicotine effects to determine whether it can also be brought to a subthreshold level so far as its effects on man are concerned.

A final point concerns a comparison of human and animal data referred to in the beginning of this discussion. It was there stated that the proof that smoking is the cause of cancer in man rests entirely upon human statistical and epidemiological data. Animal data chiefly serve to indicate the nature of the carcinogens in tobacco tar. Obviously they can only indicate the nature of a carcinogen to a specific animal strain, species, and tissue. This truism applies not only to this specific instance but to all phases of cancer research. In cancer chemotherapy, as in carcinogenesis, many similarities and also many differences are known to exist between human and animal data. On having identified the specific carcinogens in tobacco tar as they apply to the experimental animal, one can only assume that these carcinogens are also responsible for the human cancer problem. If an agent has been found to be carcinogenic to a variety of animals, and human epidemiological data are not inconsistent with this finding, then the burden of proof lies upon those who claim that these substances are not carcinogenic to man. For that reason we should try to establish measures, if at all practicable, that can reduce established carcinogens from tobacco tar and apply these to the manufacturing of smoking products and the smoking habits of the population. This problem, as any other problem in life, cannot be solved by ignoring its existence or depreciating its importance. It can only be solved by facing it directly. In view of the work already completed and the investigations in progress now, a satisfactory solution should be attainable. The lives of people everywhere who will in years to come die from cancer of the lung and cancer of the upper respiratory tract demand that we give this problem our fullest attention.

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Reporting to the Waikato Hospital Board, Hamilton, North Island, on the shortage of house-surgeons in New Zealand, the medical superintendent of the Waikato Hospital, Mr. R. S. A. GRAHAM, said that early marriage or projected marriage was one of the three predominant causes of the early loss of senior house-surgeons from the hospital service to better-paid positions in private practice. Mr. Graham said he understood that the marriage rate among medical students was increasing rather than diminishing. In 1956 nearly 30% of final-year students at the University of Otago would have married by the end of the year, as against 10 to 12% in previous years. Of the two other main causes for the loss of senior house-surgeons, one was the desire to get overseas—or at least to take a locum to accumulate funds for overseas work, he said.