TOBACCO AND HEALTH RESEARCH - WHERE SHALL WE GO FROM HERE?

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It is a pleasure to be here with you tonight where I can see again a number of old friends and have an opportunity to make some new ones. Despite that pleasure, what I have to say is not in the nature of entertainment. I know that you all must be rather weary of the subject of tobacco and health research, and wish that it could be ignored or forgotten, with its reminders of difficult and unpalatable problems. I sometimes feel this way myself, especially when confusions, misapprehensions, contradictions and misunderstandings seem to be in possession of the field. But these problems cannot be ignored and they are not likely to evaporate in any near future. Whether we like it or not, we must grapple with them. Facing this fact, as we must, we come to the question I have put before you tonight. "Where do we go from here in tobacco and health research? I will try to give you a few answers to this question, as I see them, and some reasons for these answers.

Within the last few weeks we have witnessed two events that illustrate the kinds of confusions, misapprehensions and contradictions that I have mentioned. The first of these events was a series of hearings during the week of August 24th before the Consumer Subcommittee of the Senate Commerce Committee on the general subject of "making cigarettes safer." The other event was the World Conference on Smoking and Health during the week of September 11th. No doubt you have seen a number of reports from both.

In the hearings on "making cigarettes safer" some extremely divergent points of view were expressed. It was noteworthy that a good part of the testimony was based upon acceptance of the concept that the goal to be sought in producing "safer cigarettes" is simply reduction in the amounts of "tar" and nicotine received by the consumer while enough flavor is preserved to make the product acceptable. Most of the inventions described were aimed at this goal and claims of the inventors were stated in terms of nicotine and "tar" delivery without biological tests to provide any direct basis for claims of greater safety.

For example, one witness advocated a "cigarette" made from treated lettuce leaves on the ground that its smoke is entirely free of nicotine. Such lettuce cigarettes do, however, produce smoke and this smoke, like others produced in a similar manner from plant material, consists in part of particulate matter. This can be condensed into the same kind of dark liquid that has come rather generally, though erroneously, to be called "tar" in the case of tobacco. Another witness at the same hearing reported experiments showing that such smoke condensates from burning dried lettuce have exactly the same kind of action when painted on the skins of mice as the smoke condensates from ordinary commercial tobacco cigarettes. Smoke from dried cabbage leaves was also reported to have a similar but higher activity.

I shall comment later upon my dissatisfaction with mouse skin painting as a test method. At this point I will only say that these mouse-skin tests with lettuce and cabbage smoke condensates turned out just as any chemist or biologist would have expected. It is well-known that there is nothing unique in this respect about the leaves of the tobacco plant. The mouse-skin activity of condensed smoke from other plant material does, of course, show that nicotine is of no significance in this connection.

A few witnesses showed a broader grasp of the problems involved and described more sophisticated long-range programs. We applaud such constructive plans. But overall, my impression was that a number of well-meaning inventors have been concentrating entirely upon the reduction of "tar" and nicotine delivery because they have interpreted the various releases from the U.S. Public Health Service as authority for the assumption that a blueprint for the "safer" cigarette has already been established in these terms.

This brings us to the World Conference on Smoking and Health. Its whole plan was based upon the assumption that the use of cigarettes has already been established as a major health hazard. Hence the scientific evidence bearing

on this point was not a topic for discussion. Instead the emphasis was placed upon methods for dissuading people from starting to smoke or of persuading them to stop. Some relatively minor attention was given to the question of how cigarettes might be made "safe" or "safer." In this latter discussion, again, the basic assumption was that the desired goal is maximum reduction of "tar" and nicotine while still producing a product that confirmed smokers might accept.

In his keynote address, Surgeon General William H. Stewart did state however that "the door to cooperation has always been open. It remains open."

Dr. Daniel Horn, Director of the U.S. Public Health Service National Clearinghouse for Smoking and Health, in leading a panel discussion, took a rather philosophical view toward smoking. He devoted much of his talk to a review of man's search for stimulants and tranquilizers. He said in part:

> "Throughout history people everywhere have searched for natural products in their environment which would provide them not only with sustenance and shelter but certain pleasureable effects as well. In his search for gratification man has experimented with things to drink, sniff, smoke, chew or swallow. . . . We must face up to the fact that the cigarette caught hold because it fulfilled certain functions that needed to be fulfilled for a great many people. The cigarette offered an accessible, inexpensive way to deal with a variety of problems. . . . if there were no harmful consequences, it would have served mankind well."

He then went on to assert however:

> "We simply had the rotten luck to have discovered after all these years that the harmful effects are overwhelming. . ."

The Council for Tobacco Research did not participate as such in this World Conference because the conference had no primary concern with the type of fundamental medical research with which The Council is engaged. Grantees of The Council were perfectly free to participate if they saw fit to do so and several did. But The Council, as such, does not take any position as to whether people should or should not smoke and it does not participate in advocacy. Vast numbers of persons have been smoking cigarettes in this country since the turn of the century. Vast numbers of persons are smoking them at the present time. The indications are that vast numbers will continue to do so for a long time to come.

Hence our task of seeking the reasons why people need or want to smoke and of observing and describing the effects of smoking, good or bad, continues to be relevant and important.

We have never assumed or asserted that cigarette smoking is free from hazards. If we were sure of this, there would be little need for a research program. Dr. Horn has acknowledged the benefits, though a full account of these has certainly not yet been rendered. Is he right in his conclusion that "the harmful effects are overwhelming"? This is still the key question and we do not think that it has yet been answered for reasons that I will explain.

The industry long ago undertook not only cooperation but leadership in seeking reliable answers. They did so first by setting up and financing The Council for Tobacco Research* as an independent commission of scientific and medical men to conduct investigations into any and all aspects of tobacco use and human health. Later they made a very substantial contribution, without strings attached, to the American Medical Association for a similar but separate program.

It was certainly their hope and expectation that these programs would in time determine whether there are in fact health hazards in cigarette smoking and, if there are, define and measure them and elucidate their mechanisms by laboratory and clinical studies. Meanwhile, in their own company laboratories they continued the highly intricate work of identifying and determining quantitatively as many individual smoke components as possible, whether condensable or non-condensable. The industry also made available a variety of relatively low "tar" and nicotine cigarettes to meet the public demand.

I think there has been no lack of very realistic and constructive cooperation. If, however, the present plea for cooperation implies acceptance of all the current doctrines, viewpoints and dogmas of the U.S. Public Health Service,

*-First called the Tobacco Industry Research Committee

there must be reservations. We of The Council are eager to cooperate energetically and effectively toward attainment of the ultimate objective. This, we conceive to be to find the real cause or causes of such constitutional diseases as cancer, cardiovascular ailments and chronic lung diseases.

We feel that our cooperation toward this end will be most effective in the long run if we maintain and exercise our independent judgment rather than adopt any "party line" imposed by others.

There is time this evening for only a few examples and illustrations of what I mean.

First, let us take Dr. Horn's statement that the harmful effects of cigarettes are "overwhelming." On what evidence, actually, do he and his colleagues base any such statement? Their method basically is this. The death rates of cigarette smokers and of non-smokers are compared and found to be higher for the smokers. A figure ~~of~~ for the "excess deaths" among smokers is then obtained, as they say, "by subtracting from the number of deaths occurring in a group of smokers, the number of deaths which would have occurred if that group of smokers had experienced the same mortality rates as a comparable group of nonsmokers." The resulting figure is that which they advance in their publicity as the "excess deaths associated with cigarette smoking." They do not speak of these "excess deaths" as caused by cigarette smoke, but a careless reader is likely to assume that this is what is meant. It seems to be what Dr. Horn wants the public to believe when he speaks of the harmful effects of cigarettes as "overwhelming."

The fallacy in concluding that these "excess deaths" are caused by smoking is obvious to any thoughtful man in the street and to many a bright high school student, as I have discovered by actual test. It has been pointed out by every one of the two dozen or so statisticians with whom I have discussed the matter. The fallacy is simply this: if we knew that the cigarette smokers were alike in all other respects and that the only difference was in their smoking or

non-smoking, we might be able to conclude that the difference in mortality was caused by the smoking. But we know just the opposite from such relatively meager studies as have been made so far. And as more studies of this kind are accomplished, the evidence increases that different physical and emotional characteristics and habits of life are associated with cigarette smoking and non-smoking. Cigarette smoking may well be an evidence or reflection of some combination of such characteristics and habits. The needs which Dr. Horn pointed out as being met by smoking certainly vary in degree and intensity from person to person and the heavy smoking population would be expected to include a group whose life expectancy is relatively low because of the intensity of their physical and mental maladjustments. This situation might be reflected in increased death rates among the whole group of smokers even if their smoking helped in some degree to relieve these maladjustments.

I recall a study which showed that people who use tranquilizers have much higher death rates than those who do not. The author did not conclude that tranquilizers kill people but rather that some of the people who need tranquilizers are sick enough to affect the statistical picture of the group by dying relatively early.

Similarly, it was shown that people who regularly spend ten hours a night in bed have higher death rates than those who average only seven hours of sleep. It was not concluded that excessive sleep will kill people, but rather that among the long sleepers there are enough people whose excessive requirements are due to life-shortening illness to affect the mortality statistics of the whole group. We would not expect the longevity of such people to be improved by restricting them to seven hours a night.

So far as the epidemiological method of approach to these problems is concerned, I cannot see any difference between the cases of sleeping habits, use of tranquilizers and of cigarette smoking. I am not denying the possibility that cigarette smoking may actually cause some excess deaths. I am only saying that

this kind of study does not tell us whether or not this is the case or give us any idea whatever of how many so-called "excess deaths," if any, are attributable to smoking. That is why The Council constantly stresses the need for new studies of quite a different character and is trying to lead the way by demonstration projects. We are giving assistance to a very ambitious study of human factors associated with relatively long life and with relatively early death. A tremendous number and variety of observations are being made upon the subjects of this study. Smoking habits are only one. We are trying to find out how other characteristics and life habits tend to be grouped with smoking or non-smoking.

The handling of such numerous pieces of data requires the development of new computer programs capable of doing more quickly the kind of statistical weighting of factors that used to be done by laborious multiple regression analysis or discriminant function analysis. We have therefore undertaken also to support the development and application of new, better and faster computer programs for such purposes. The methodology developed in these studies will be available for use by the various government and other agencies concerned with similar problems. Already it can be said that cigarette smoking or non-smoking by groups of subjects seems to "summarize" groups of other characteristics and habits which can serve statistically as "predictors" of relatively long or short life without inclusion of smoking. Among these other factors are many candidates for exploration of possible causal effects. We regard these pioneering studies as intelligent cooperation.

So far we have been discussing overall mortality rates in smokers and non-smokers of cigarettes. I want to say a few words more specifically about coronary heart disease. This, as you know, is one of the prime causes of death among American males. The so-called "excess deaths" from this disease among cigarette smokers, calculated as described before, constitute a large fraction of the total "excess deaths" reported for the cigarette smoking group. All the comments we have made before about attributing such "excess deaths" causally to

cigarette smoking are applicable here as well. This was recognized by the committee that reported to the Surgeon General in 1964. They said at that time, "Male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance." You will understand that I agree with this conclusion for reasons that have been explained. Moreover, I cannot find in the data provided by continuation of the epidemiological studies any justification for a change in this conclusion. On the other hand, there are several recent studies that tend to reduce the likelihood that this is a causal relation. I can think offhand of two in which a number of factors other than smoking were tested for their ability to contribute to a profile description capable of serving as a valid "predicter" of coronary artery disease. In these cases, cigarette smoking did not contribute to the predictive power of the profile and was discarded.

But probably the most significant new contribution is the recent Swedish twin study. Identical twins are the nearest thing we have in the human species to the litter mates of dogs, cats, mice, rats, etc. Their genes are the same so that they have the same hereditary predispositions and tend to be much more nearly alike even in life habits than fraternal twins or ordinary brothers and sisters. They even tend to be very much alike in smoking habits, which fact is one of the good evidences for the belief that constitutional makeup has an important effect in determining whether and how people smoke. Nevertheless, the Swedish twin registry turned up a considerable number of pairs of identical twins one of whom had smoked cigarettes for a substantial period while the other had not. Extensive study of the cardiovascular function of these twin pairs showed no significant difference between the smokers and non-smokers. This finding might have been even more significant if the number of twin pairs had been a little larger and if the study had been continued over a period of years. It is expected that there will be follow-up at intervals. A similar study of a larger number of

twin pairs is urgently to be desired and I recommend to our U.S. Public Health Service that this be given a high priority in their plans. It well might provide some very helpful information on the kind of difficult questions we have been discussing.

Meanwhile properly designed studies with animal models should be considered as another way of obtaining valuable information, since it is possible to use litter mates (that is, twins) in such studies and to make sure that all environmental factors are kept the same except for the one whose effect is to be assessed. The Council is planning further work along such lines.

In the recent Public Health Service Review, entitled The Health Consequences of Smoking, considerable attention is also given to the analysis of laboratory and clinical studies of the effects of nicotine, smoking or of smoke constituents on the heart and arteries. This discussion was quite properly hedged with many "possiblys," "perhapses," and "conceivablys." Many of the studies reviewed were sponsored by The Council. They include investigations of coronary blood flow, thrombus formation, serum cholesterol, free fatty acids in the serum, and the amount of arteriosclerosis found post mortem. This was, in effect, a search for effects and mechanisms that might plausibly explain how and why smokers show a higher mortality from coronary artery disease. In my opinion, none of these mechanisms or effects so far described offers any convincing explanation of the statistical picture. I will mention just one by way of illustration. Council studies have shown that nicotine, directly or indirectly, tends to increase blood flow in the small arteries that supply the heart muscle itself with oxygen. The alkaloid also has a stimulating effect on the heart muscle much like that of mild exercise. This is accompanied by a moderate increase in heart rate, systemic arterial pressure, cardiac output, stroke volume and muscular contraction.

There are many types of things in life -- like taking a stroll or even smoking a cigarette -- which may have an effect on people who are very, very ill that they would not have on people who are well. As we all know, people do in fact experience fatal heart attacks when engaging in these very activities. We do not conclude from this fact however, that exercise is a basic cause of coronary heart disease. There is evidence rather that exercise, if regular and not too strenuous, will help delay or compensate for arteriosclerosis. I fail to see any significant difference between mild exercise and cigarette smoking insofar as this particular set of mechanisms is concerned.

To summarize then, it seems to me that this very large portion of Dr. Horn's so-called "excess deaths" among cigarette smokers (the ones from coronary heart disease) is very doubtful with respect to any causal implications. They may well be removed from suspicion altogether. This event would greatly reduce the appearance of "overwhelming harmfulness" he mentions. To a greater or lesser degree this is true of other diseases included in the statistics. The evidence needs to be thoroughly analyzed in each and every case.

Since we have brought up the subject of nicotine, I want to mention again the 1964 report to the Surgeon General which made a review of nicotine pharmacology and drew the following conclusion:

> "The rapidity of degradation to non-toxic metabolites, the results from chronic studies on animals and the low mortality ratios of pipe and cigar smokers when compared with non-smokers indicate that the chronic toxicity of nicotine in quantities absorbed from smoking and other methods of tobacco use is very low and probably does not represent a significant health problem."

I have seen no research reports since 1964 that would justify any change in this conclusion.

This brings me to the last question that I shall try to discuss tonight. On what evidence are people basing their doctrine that the claimed hazards of cigarette smoking are related to the "tar" output of cigarettes? Attempting to analyze the thinking of the proponents of this doctrine, I find

three kinds on which it seems to me that they mainly depend. The first is the kind of evidence provided by epidemiological studies in which they try to relate disease incidence to the level of exposure to total smoke, that is, to the number of cigarettes smoked per day. We have already discussed the difficulties in interpreting such studies. In the present context I want to add the point that the exposures they are talking about are exposures to whole smoke with all its ingredients. Whatever conclusions may be justified from such studies, any effects claimed cannot be attributed specifically to "tar" any more than they can be attributed to nicotine. If they are effects attributable to the inhaled smoke at all, they cannot be assigned to any smoke fraction or ingredient unless or until there is some evidence to justify such assignment.

The second kind of evidence on which the "tar" dogma apparently rests is the cellular abnormalities sometimes seen in the lungs of chronic smokers. But the same abnormalities also occur in the lungs of non-smokers. The point here is that there is no evidence that the changes mentioned are caused by smoking, much less by a particular component of smoke such as "tar."

The third and chief kind of evidence these proponents of the "tar" dogma are relying upon is the mouse-skin painting work. As I have said before, the trouble with this method is that it applies the wrong material, in the wrong form, in the wrong concentration, to the wrong tissue of the wrong animal to have any clear or simple relation to the human lung cancer problem. The condensates used in such studies do not contain all the ingredients of fresh, normal smoke. The physical form is entirely different from that of smoke. The skin is a very different kind of tissue from the lung, as shown by extensive studies sponsored by The Council. And Council-sponsored studies have shown that pipe tobacco and cigar tobacco smoke condensates are as active in producing tumors on the skins of mice as cigarette smoke condensates, even though human pipe and cigar smokers rarely get lung cancer.

Unfortunately mice are also quite different from men or monkeys in their susceptibilities to cancer-producing chemicals.

We think that we will learn much more about any effects tobacco smoke may have on lung tissue by making small animals inhale whole, fresh, normal smokes repeatedly over long periods, than by skin painting with condensates. It has been a difficult task to design mechanical devices for bringing about smoke inhalation and to measure the actual dosage received by animal lungs. Our aim is to bring the right material, in the right form and the right concentration to the right tissue, even though we still must use the wrong animal, and even though we cannot expect ever to duplicate human smoking conditions perfectly. In the past ten years, chronic exposures of this kind with earlier and cruder devices, have not been followed by appearance of human type lung cancers. It remains to be seen what will happen with use of the improved equipment. If no cancers are obtained with a wide variety of animal species, and with various kinds of conditionings to increase susceptibility, we will become increasingly doubtful whether tobacco smoke can act on lung tissues as a direct contact carcinogen. But this will not end the search. There are several methods by which lung cancers resembling the human type can be produced in animals. Using such models, a great variety of possibly relevant factors and influences can be screened. Among these factors and influences, tobacco smoke can be studied in context to see whether it could play some kind of an indirect contributory role and, if so, what and how. And whether or not any contribution by tobacco is found, such studies may well turn up clues to the prevention of human lung cancer.

It is a fortunate fact in scientific work that a variety of different working hypotheses and contrasting viewpoints can all engender good research. The results of good research can be expected eventually to intermingle, interrelate and provide illumination as well as to suggest new and better hypotheses. We hope

to continue and intensify our work along such lines as have been illustrated here tonight.

Hence, I would say that the door has always been open to cooperation. It remains open!