MEMORANDUM ON A PROPOSED INVESTIGATION BEARING ON THE POTENTIAL HAZARD OF THE INDUCTION OF CANCER OF THE LUNGS OF HUMAN BEINGS THROUGH EXPOSURE TO THE COMBUSTION PRODUCTS OF PETROLEUM HYDROCARBONS DISCHARGED IN THE ATMOSPHERE FROM THE EXHAUSTS OF AUTOMOBILES

I.

Statements made in various articles in the public press and in popular magazines, as well as in medical and scientific publications, have emphasized the importance of cancer of the lung as an increasingly frequent cause of human disability and death, especially in the male segment of the American population. The increasing frequency of the occurrence of this disease has led to the strong suspicion that relatively recent changes in the human environment, and especially in the part of the environment that has direct access to the human respiratory apparatus - namely the environmental atmosphere - play a significant part in the primary causation of lung cancer, or perhaps act as contributory factors in its induction.

Without entering into a lengthy discussion of this subject, in which a large number of considerations would require detailed examination, suffice it here to call attention to a few facts which may be assembled in such a manner as to create, in insufficiently objective and incautious minds, logical inferences concerning cause and effect relationships.

1. There are certain chemical substances or types of energy which have been proved to be capable of inducing malignant tumors in the skin, the urinary bladder, the blood-forming

tissues, or the bones of experimental animals and of man. Epidemiological information also indicates that exposure to certain substances (certain compounds of nickel and chromium), and certain occupational conditions which are not defined fully, are associated with an increased incidence of cancer of the upper respiratory tract or lungs of man.

2. Among the substances that induce cancer of the skin, are certain complex polycyclic hydrocarbons derived from petroleum or coal.

3. Certain of these "carcinogens" have been found in minute concentrations in the exhaust "gas" of automobiles, in cigarette smoke, and in the atmosphere of "smoke"-laden areas.

It should be reemphasized xxxxxxxx that these are by no means all of the matters that need to be considered in arriving at a reasonably sound conclusion concerning the problem of human lung cancer. These, however, plus the results of certain collections and analyses of statistics, are sufficient to account for the conflicting published opinions to the effect that lung cancer is the result of excessive smoking, on the one hand, and that it is certainly due to our inhalation of air polluted with petroleum hydrocarbons and/or their combustion products, on the other. They are also sufficient to bring about a very considerable amount of public apprehension, and there is little doubt that this apprehension is mounting.

Experimental work on this problem is being undertaken by a number of persons and groups under a variety of auspices, and financial sponsorships. A serious difficulty in such work lies in our inability, up to the present time, to reproduce in

experimental animals the disease with which we are here concerned - that of cancer arising in the epithelium (the cellular lining) of the bronchi (the secondary air-ways into the lungs). Until the disease can be reproduced through the use of specific chemical agents and investigated under carefully controlled conditions, we shall continue to be at a great disadvantage in arriving at conclusions that can be acted upon.

Despite what has been said above about the insufficiently critical expression of strong opinions on this subject, there is enough reason for concern about the problem of lung cancer, in relation to the environment, to justify careful investigation. Moreover, the matter would appear to be of considerable consequence to the automobile industry. Indeed, it is entirely possible that it is the most important hygienic problem that faces the automobile industry at this time, not excluding that of highway accidents. The latter is a fairly straightforward problem, with no mysterious overtones; the former, by reason of its insidious character, is prone, it seems, to invite a semi-hysterical approach which might well be manifested in troublesome legislation or regulations. For these reasons ~~xxxx~~ it seems advantageous to describe an experimental approach to the problem which seems to offer considerable promise, as a basis for seeking the financial support needed to follow it to its logical conclusions. The policies, functions and professional relationships of this laboratory are such that it turns first to industry for financial support for the investigation of hygienic problems that relate to industrial activities.

II.

The only method whereby bronchogenic cancer has been induced in the mouse, has consisted in the direct implantation (by surgical means) of solid carcinogenic substances (polycyclic, aromatic hydrocarbons) in the bronchial epithelium. Under these artificial circumstances, involving prolonged contact of these cells with a high concentration of the substance, animals that died before developing tumors were found to have certain microscopic changes in the local cell structure and arrangement. These changes are believed to be pointed in the direction of those which characterize malignant overgrowth. Such changes have failed to develop when animals have been subjected to the inhalation of air containing the finely divided solid carcinogenic material, methyl cholanthrene, or to the intratracheal injection of this material, and moreover no tumors have been induced by these experimental procedures. Other experiments have demonstrated that the type of changes in the bronchial epithelium of experimental animals referred to above can be induced in a number of ways, and there is evidence to suggest that this type of change may be in the nature of a conditioning factor for the induction of cancer.

Our initial approach to the investigation of this phenomenon was made by way of the human lung at necropsy, and without going into details, the observations have demonstrated a strong positive correlation between the occurrence and the extent of these changes in human bronchi and the history of long-term moderate to heavy smoking of cigarettes. As indicated above we do not regard these as necessarily specific in either

the sense of being initiated by tobacco smoke or in that of being of a malignant or cancerous or even precancerous type. We do suspect that they may be a conditioning factor. We have been able to demonstrate the occurrence of such conditioning in the skin of the mouse by contact with certain long-chain hydrocarbons such as cetane, which, of themselves, do not induce skin cancer but greatly enhance the ability of certain petroleum carcinogens to induce such tumors. The analogous process may not be involved in lung cancer, but considering the general character of malignant proliferation, it seems quite possible, even likely, that it may be influenced in much the same manner.

In any case, we propose to investigate this phenomenon further, and to attempt to translate it into a reproducible experimental technique. Experimental animals (mice, rats and dogs) will be subjected to respiratory exposure to specific components of the exhaust gases, beginning with certain aldehydes - acrolein or formaldehyde - in an attempt to induce regular and irreversible changes, of the type referred to above, in the bronchial epithelium. Such animals will then be subjected to exposure to air containing a carcinogenic hydrocarbon in known concentration.

III.

This work is being initiated. Funds are available for preliminary work during the current calendar year on an estimated budget of $25,000.00. Our intention, if funds can be obtained, is to extend this work in 1957 to a level that will require expenditures of the order of $60,000.00. This will require approximately $35,000.00 in new funds, since the funds now available cannot be continued at the level of more than $15,000.00 in each

of 1957 and 1958. If this work is to be really productive, it should be continued over a period of years, since time (involving the greater part of the life span of animals) is one of the most significant experimental variables in the whole problem of cancer. Accordingly, we anticipate that the full complement of work that can be undertaken by the experimental team developed for this purpose (out of the background of some ten years of productive work on skin cancer), will require an annual budget of about $80,000.00 over the period from 1958 through 1962. It is not anticipated that our present source of funds for this work will continue beyond 1958. Our requirements, therefore, in additional funds are estimated to be $45,000.00 in 1957, $65,000.00 in 1958, and $80,000.00 annually, thereafter, for several years until the productivity of the project can be gauged properly.

Attached hereto are certain reprints and manuscripts which may serve to demonstrate the progress of our investigations of this type, insofar as it has been reported.

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