TRANSLATION

Vigorous Research Activity in the German Cigarette Industry: On The Road to Removing Hazards From a Cigarette. No Evidence That Non-Smokers Are Endangered by Passive Smoking.

W. Dontenwill

Prof. Dr. W. Dontenwill has in Hamburg given an account of new and informative research results obtained in the "Research Institute of the (German) Cigarette Industry", of which he is the Director.

The main significance attaches to experimental evidence obtained by Prof. Dontenwill and his colleagues from two large scale series of experiments on animals, involving a total of 13,000 animals. The biological activity of smoke condensates was tested in a drop subjection test on the skin of 8,775 white mice, and that of the total smoke from standardised test cigarettes and from modified cigarettes was investigated by a smoke subjection test on the respiratory tract of 4,440 Syrian hamsters.

The scientific evaluation of these two experiments, each of which had lasted for more than three years, has recently been concluded and has not only provided valuable evidence in respect of the methods for the reduction in the content and for the "decontamination" of the smoke condensate, some of which have already been adopted in practice during the manufacture of cigarettes, but has also indicated new procedures for a further reduction in the biological activity of cigarette smoke. The results of the investigation have recently been communicated to the National Cancer Institute of Washington.

In the opinion of Prof. Dontenwill, the evidence collated can be regarded as a successful step in the direction of a "hazard-free" cigarette, this being the objective of his research project. In this respect, it should be remembered that prominent scientists such as Dr. Wynder, Dr. Boss and others have already established by means of epidemiological experiments that cigarettes currently on the market are 40% less biologically active than cigarettes as little as 15 years ago, which then led to the conclusions in the well-known Terry report.

During other investigations, the scientists in the Institute have again dealt with the problem known as "passive smoking". As a result of experiments from two extensive series of investigations, one of which has been conducted in conjunction with Prof. A. Bleichert of Hamburg University, it was impossible to confirm the assertion made by some authors that non-smokers are at risk.

The Skin-Drop Subjection Experiment

In continuation of a first series of experiments concluded in the year 1969, a second large-scale experiment has now been completed by the Hamburg Research Institute, involving drop subjection tests on the skin of 8,775 female white mice in 39 comparative groups. During this investigation, carried out in accordance with the traditional methods of cancer research, different smoke condensates and a certain condensate fraction were tested for their biological activity on the skin of the mouse. For this purpose, experiments were conducted on the condonsates of:

- Standard test cigarettes without filter tips, with a tobacco blend corresponding to the average contents of German cigarettes, but with a size and weight adjusted to the experiment so as to provide a higher content of condensate and of nicotine.
- Cigarettes from the same tobacco blend which had been powdered prior to the manufacture of the cigarettes and processed to form sheet tobacco.
- Cigarettes from the same tobacco blend which had been modified by means of additives.

For the first time, a fraction of the volatile components of tobacco smoke (gas/vapour phase) had also been dissolved into the condensates during these experiments.

By the use of experimental animals exhibiting a high resistance towards nicotine, but readily susceptible to the formation of skin tumours, and by the administration of extreme amounts of smoke condensate (sometimes as much as the body weight of a mouse during the duration of the experiment), it proved possible to induce a sufficiently high percentage of skin tumours which imparts high significance to the results of the experiments in

view of the large number of animals involved.

The main results provided by the experiment were as follows:

- It was impossible to establish a relation between the benzpyrene content of the different condensates and their tumour initiating activity. The experimental results indicate that the biologically active smoke constituents are to be found in a fraction containing the major part of the aromatic hydrocarbons.
- After an initial treatment with the compound dimethylbenzanthracene known to be a strong cancer inducer, the condensate applied in droplet form exhibited a significantly stronger activity.
- Cigarettes from sheet tobaccos differed in their biological activity, in accordance with the method of production of the sheet, but some of them provided a 50% reduction.
- An addition of sodium nitrate to the tobacco of the standard test cigarette reduced its biological activity by two-thirds.
- The gas/vapour phase proved to be biologically inactive.

The Smoke Subjection Experiment

Following tests which lasted for years, Prof. Dontenwill became the first scientist to develop a useful method which allows us to induce carcinomas in the respiratory tract by the chronic smoke subjection of experimental animals. Whereas only condensed smoke can be tested in drop subjection tests onto the skin of an animal, smoke subjection experiments allow for an investigation of the fresh total smoke in the respiratory tract of the animals. A first large-scale smoke subjection experiment on 4,440 Syrian hamsters, subdivided into 18 comparative groups each containing equal numbers of males and females and made up of 160 to 600 (control group) experimental animals, and on 840 hamsters for haematological and biochemical parallel investigations, has now also been completed at the Hamburg research institute. This large-scale experiment investigated the different biological activity of smoke from standard test cigarettes with and without filter tips, from cigarettes produced with tobacco sheet and with

black tobacco, and from cigarettes wherein the tobacco had been modified by means of additives.

The Syrian hamsters selected for the experiment exhibited an extremely high tolerance towards nicotine and made possible a long-term smoke subjection throughout their entire lives by means of amounts of fresh smoke which approached the threshold of a carbon monoxide intoxication. The animals in most of the experimental groups were "offered" the smoke from 30 cigarettes for inhalation twice daily in the smoke subjection appliances on five days per week.

The following results were arrived at from this smoke subjection experiment:

(Smoke subjection with different dosage rates (number of cigarettes) with the same quality of smoke):

- In the group of animals subjected to the higher dosage rate of smoke from standard test cigarettes, carcinomas of the larynx were found in 10.6% of the experimental animals. At half of this dosage rate, the proportion of carcinomas of the larynx was only 0.6%.
- Despite the extreme experimental conditions, lung cancer could not be induced by the inhalation of cigarette smoke.

(Smoke subjection at the same dosage rate (higher dose of the standard test cigarette) with additional treatment of the experimental animals):

- Following a single initial treatment of one experimental group with the strong carcinogen dimethyl-benzanthracene, the frequency of incidence of carcinomas in the larynx rose to a 20% percentage after smoke subjection from the standard test cigarette.
- No increase in the carcinomas of the larynx initiated by smoke subjection could be established by the additional treatment with diethyl-nitrosamine though this compound also exhibits a high carcinogenic activity.

(Smoke subjection at the same dosage rate (modified cigarettes) with qualitative and quantitative variations in the smoke):

- The number of animals with carcinomas in the experimental group dropped to 2.5% when they inhaled the smoke from standard test cigarettes with added sodium nitrate.
- Test cigarettes without filters from a blend providing a low amount of condensate, which was selected for the experiment from a special black tobacco, initiated carcinomas of the larynx among 1.3% of the respective group of animals.
- The incidence of carcinomas of this type was particularly low, at 0.6%. in the group of animals which had inhaled the smoke from standard test cigarettes with acetate filters. Other types of filters proved to be less effective, in view of a percentage of 2.5%.
- Sheet cigarettes of a certain type admittedly produced changes in the respiratory tract, but in none of the experimental animals in this group did they cause carcinomas of the larynx.
- No reactions were observed in the respiratory tract of the animals in the experimental group only subjected to smoke with the gas/vapour phase.
- It was impossible to establish any kinds of correlation between the inhalation of cigarette smoke and other diseases, such as gastritis, gastric ulcers, bronchitis, lung emphysemas, defects of the circulation and heart, formation of thromboses in the heart or lung, and tumours in the connective and supporting tissues. No effect on blood coagulation and fat metabolism could be established during the biochemical investigations.

Evidence From the Results of the Two Animal Experiments.

It is admittedly impossible to draw direct inferences from the results of animal experiments on the effect on human beings, because "it is practically impossible to establish an exact dosage comparison between man and animals", as Prof. Dontenwill states in the report on his investigations. Nevertheless, these experiments still provide reliable information in terms of comparative investigations with regard to the various dosage effects of certain materials and substances. This applies in particular to the two large-scale experiments, since despite the different

procedures adopted their results are largely in agreement with each other.

In detail, the findings allow us to make the following deductions, which serve as the points of departure for further investigations within the scope of the industrial research programme, some of which have already been instituted:

- On comparison with other carcinogenic materials, the carcinogenic effect of cigarette smoke in these two experiments must be regarded as weak, and this agrees with results by Prof. Schmähl of the German Cancer Research Centre and by other scientists. A dosage/effect relation can only be clearly established at the highest dosage rates.

- The significantly stronger activity of the smoke condensate on the skin of animals, and of the total smoke on the respiratory tract, after a preliminary treatment with the cancer initiator dimethyl-benzanthracene suggests a possible cocarcinogenic property of cigarette smoke.

- The markedly lower biological activity of the filter-tipped cigarettes, especially for the acetate filters employed on German cigarettes, indicated during the smoke subjection experiment that a quantitative reduction in the total condensate from the same starting blend leads to a significant reduction in the biological activity. This indicates that the different effects are largely determined by the content of condensate, but that there is also some effect of qualitative changes in the smoke, as also shown by the results of the skin drop tests.

- Cigarettes from certain sheet tobaccos exhibited the strongest reduction in biological activity during the two experiments on modified cigarettes.

- The stronger biological activity of some condensate fractions established during the skin drop experiment calls for further experiments on animals, in order to allow for the elimination of active components wherever possible.

- The experimental results gave no indication about any action of the nitrosamines detected or suspected to be present in smoke by some scientists.
- The lack of activity of the gas phase and of the gas/vapour phase in the two experiments allows us to draw the reliable conclusion that the biological activity of cigarette smoke will be found in the particle phase precipitated as the condensate rather than in the volatile constituents of cigarette smoke.

Overall, the results of the investigation have provided clear evidence that the biological activity of tobacco smoke can be influenced by a modification of the product, and clear indications have been given for methods to effect a further reduction in the risks due to cigarette smoking, in terms of a quantitative reduction as well as a qualitative change in the available smoke constituents.

Investigations on the Problem of "Passive Smoking"

The continued public discussion on the phenomenon known as "passive smoking" has prompted scientists in the Research Institute of the (German) Cigarette Industry to complement their proper research projects by new investigations so as to contribute to a solution of this problem. During a first series experiment carried out in 1970, it had already proved impossible to arrive at scientific evidence pointing to the debated risks said to be incurred by non-smokers.

A series of experiments conducted by Dr. H-P. Harke of the Hamburg Research Institute in collaboration with Prof. Bleichert of the Hamburg University was planned to answer the previously unsolved problem as to whether passively taken up amounts of smoke would be capable of causing any biologically recognisable effects among non-smokers. For this purpose, readings were taken of skin temperature reactions, pulse frequency, ECG and blood pressure.

The experiments carried out under extreme conditions which are not experienced in practice provided the following results:

Readings on actively smoking test personnel indicated a distinct and immediately discernible drop in skin temperature.

By contrast, no change in skin temperature was observed among non-smokers present in strongly smoke-laden rooms (150 cigarettes were smoked during 30 minutes in an unventilated room of capacity 170 m^3). When the non-smoking test personnel was induced to smoke a cigarette actively, an immediate strong drop in skin temperature was established. Readings of ECG's, blood pressure and pulse frequency have shown that these factors again do not change under conditions of passive smoking.

During a further series of experiments, Dr. Harke and his colleagues repeated the room concentration measurements carried out during the 1970 investigation with an extended research programme and method. Seven experimental series with different conditions were conducted, in order to investigate the content of carbon monoxide, nicotine, and other smoke constituents of well-known pharmacological activity in the air, as well as the changes in the concentration of these compounds throughout given periods of time.

The new experiments were again carried out under conditions which cannot be achieved in practice. Thus, by way of example of a single experimental result, the concentrations of the compounds of investigation achieved during the smoking of 108 cigarettes by 11 smokers during 2 hours in an unventilated room of capacity 170 m^3 were far below the MAK values (maximum concentrations at a place of work) specified as the limits which do not present health hazards by the German Research Association; for instance, the carbon monoxide concentration did not even reach half this value during this experiment, and the nicotine content only some 20% of the safety standards specified. The investigations have also shown that ventilation of the room caused a significant decrease in the concentration of all the compounds. It was unexpectedly found that the nicotine content is rapidly decreased even in unventilated rooms, so that as a consequence this content only exhibits an insignificant increase even when smoke subjection continues for a long time.

The experimental results obtained in 1970, which had inter alia shown that a "passive smoker" absorbs less than one hundredth part of the amount of nicotine taken up by a smoker, are therefore fully confirmed by the new experimental series.

.....