

TOBACCO TAR: AN EXPERIMENTAL INVESTIGATION OF ITS ALLEGED CARCINOGENIC ACTION

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Previous studies (1) have shown that, although nicotine is the most potent and dangerous component of tobacco, the products of combustion, particularly the irritant aldehydes, ammonia and carbon monoxide, may not be entirely ignored in assaying the possible harmful effects of smoking. Recently aggressive advertising (2) has appeared for a particular form of cigarette holder which, upon examination, is found to have little effect on the nicotine or gaseous products of combustion, but which does remove the greater part of the tarry, less volatile constituents of the smoke. It is implied that this so-called "tobacco tar" or "tobacco yellow" is really harmful, and that its removal is of real hygienic value. In view of the dearth of scientific information as to any deleterious effects of this substance, an inquiry into this point was undertaken.

The main charge made against tobacco tar, so far as can be determined, lies in the implication that, like mineral tars, it may act as a carcinogenic agent, and that, since it comes in close contact with the tissues of the mouth, pharynx, and lungs, it may be held responsible for cancers developing in these tissues. The clinical relationship between smoking and the presence of cancers of the lips, tongue, and buccal surfaces has been often noted (3, 4). More recently, the increasing incidence of cancer of the lung has been blamed on tobacco (5). It may be of interest in this connection to note that the only woman with this condition autopsied at the Olive View Sanatorium gave a history of more than fifteen years' excessive smoking of cigarettes.

The few experimental investigations of the alleged carcinogenic action of tobacco so far reported (6, 7, 8, 9, 10) have been made, for the most part, with extracts of the unburned leaf, rather than with the tar derived from its combustion, which, according to our analyses, is not present in appreciable amounts in the raw material. The very excellent studies of Haworth and his associates (11, 12) form a striking exception, but are also inconclusive.

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Tobacco "tar" is the name applied to the black or blackish brown viscous material with a "tarry" odor which settles out from the smoke or distillate of tobacco. It may be separated from the nicotine, creosotes, and other substances in the smoke, by extracting with hot dilute acid and then dissolving in fat solvents such as ether or alcohol. It is then slightly bitter to taste, and does not react readily with acids or alkalis, but is a strong reducing agent as tested with potassium permanganate. The material used in this investigation was obtained by the destructive distillation of Kentucky Burley tobacco in a current of carbon dioxide and was purified by repeated extractions with sulphuric acid, alcohol, and ether.

White mice used in the study were all the descendants of a single pair which had been used to start the colony here and had been bred without external admixture for over a year. They were of the same age, sex, and size, and showed no sign of difference at the beginning of the experiment. Spontaneous tumors have developed in less than one per cent of this strain during the past two years. These were all mammary adenocarcinomas which did not grow on transplantation to other mice.

Twelve mice were selected for this experiment in August 1931, and tobacco tar was applied to the back of the neck twice a week thereafter. The tar was diluted with equal parts of glycerine, as suggested by Woglom and Herly (13), and painted on an area about a centimeter in diameter, with a small applicator. Twelve additional mice were taken as controls, and similarly treated with a gas-house tar of known carcinogenic properties obtained through the kindness of the Crocker Institute.

The applications of tar in both groups produced little general toxic effect. The mice did not appear to lick off the tar very vigorously, and their general health was not noticeably impaired. Loss of hair appeared in a few animals of each set, over the entire back. Hair soon reappeared, however, except over the painted areas in the mice treated with the gas-house tar.

In the mice treated with the tobacco tar, no marked changes in the skin were observed. The area treated remained soft, thin, and smooth, the hair either did not fall out, or, if it did, rapidly grew again, and the skin remained pliable, warm and humid. There was no thickening of the skin and no sign of the formation of cutaneous horns, warts, or other epidermal proliferations.

In the control mice treated with the gas-house tar, however, the



skin showed marked changes within a few days. These changes continued progressively, with epilation, thickening, roughening, and dryness being the rule. Within a few months small warty growths or papillae appeared in almost every instance, and by the end of four months every one of these mice had a number of such protuberances in the region treated. As the treatments were continued, the growths became more extensive and invasive, leading eventually to metastases. Transplants of these invading tissues into other mice gave a high incidence of takes. This is the common type of tar tumor and need receive no more attention, except that it demonstrates that the mice used were of a highly susceptible strain, the method of application such as would, with a carcinogenic tar, produce tumors in all instances, and the time of application, now over a year, more than twice that required to produce such tumors with an active tar.

Sections taken from the skin of the mice treated with tobacco tar showed a thin, adherent cornified layer, the rete Malpighii only a few cells thick and showing the usual gradation of cell types down to the continuous parallel basal-cell layer, penetrated in places by hair follicles and glands, and with the corium and subcutis free from pathological infiltrations.

Sections taken soon after the application of the gas-house tar showed only a thickening in the corneum and rete Malpighii with increased activity of the germinal layer. Later the dermis becomes pushed out in the form of verrucoid protrusions of both hyperkeratotic and acanthotic proliferations, with increased depth and complexity of the interpapillary processes. Inclusions of cornified material appear in the rete masses, and give the appearance, in places, of epithelial "pearls." The basal layer may become irregular, processes may extend down deep into the subcutis, and masses of epithelial cells may appear separated from the continuous derma. With further invasion the cells become less and less differentiated, and the metastatic growths and transplants may appear as undifferentiated epithelial cells of various sizes and shapes, with prominent nuclei and nucleoli and abundant mitotic figures.

A similar experiment was performed, using the rabbit as the experimental animal, instead of the mouse, as originally recommended by Ishikawa. The left ears of two rabbits were painted with tobacco tar, gas-house tar being applied to the right ears of the same animals as a control. The ear treated with the tobacco tar is still smooth, soft, and pliable, and shows no evidence of epithelial



proliferation. On the ears treated with the gas-house tar the changes were slower to appear than in the mice, but after six months of treatment small papillomata were observed in both rabbits in the area treated. These are becoming larger and more irregular, but have not yet manifested definitely malignant characteristics.

From these experiments we may conclude that the cutaneous application of tar derived from the destructive distillation of tobacco does not possess the irritating and epithelial-stimulating properties that lead to the production of neoplastic growths, as tested upon the skin of mice and rabbits. That man is similarly



FIG. 1

These mice received repeated applications of a carcinogenic tar obtained from coal.



FIG. 2

These mice received repeated applications of an inactive tar obtained from tobacco.

unaffected is not proved, but is probable, since, although different species show marked differences in their susceptibility to carcinogenic agents, these appear to be quantitative rather than qualitative and a special species susceptibility to particular agents is not yet established. At any rate, in the light of these findings, it appears highly improbable that the tar obtained during the act of smoking is an important factor in the development of cancer of the oral cavity of man.

The prevailing, though not quite unanimous (14), clinical observation that cancer of the mouth is unduly prevalent among those accustomed to the use of tobacco is by no means controverted by these findings. Even though the gummy substance settling out from tobacco smoke may fail to show any appreciable carcinogenic properties, there are many other factors involved in



the smoking of tobacco which may prove to be potent agents in the production of malignant changes.

The mechanical irritation from the presence of a solid object in the mouth may deserve further attention in this connection. The frequent thickening of the lips under the place often occupied by a pipe or cigarette holder, the development of leukoplakia or smokers' patches on the adjacent mucous membranes, and similar lesions may well be early manifestations of reaction to repeated physical trauma which, if continued, will lead to malignant changes.

The temperature of the smoke, and more particularly that of the tobacco holder, may be an important factor in producing imperceptible repeated burns of the lips and tip of the tongue or buccal surface. As shown in a previous study, the temperature of tobacco smoke drops rapidly from about 400° C. at the burning point to only about 60° after passing through a half inch of tobacco in a cigarette, and drops rapidly thereafter. The temperature of the tobacco holder, on the other hand, depends mainly on its composition and length, the bowl of a clay pipe reaching above 100 degrees when vigorously smoked, while the mouthpiece of a long meerschaum may remain quite cool even after vigorous puffing.

The influence of the other substances in the smoke and tobacco extracts must also be considered, although there is no evidence, as yet, that any of them are actually carcinogenic.

The physiological effects of the use of tobacco have been considered more from the point of view of propaganda for or against it than in a dispassionate effort to learn the real facts and their practical significance. Any substance so widely and commonly used as the cigarette with so little obvious effects cannot be as dangerous and deleterious as the propaganda of the more fanatical "no-tobacco" advocates might lead one to infer. It may readily be recognized that, as has been said (1), a sound individual may bear what are for him moderate doses without visible injury. The significance of the modifying adjectives, however, should not be overlooked, and it is equally well demonstrated that an unsound individual, whether with thrombo-angiitis obliterans, angina pectoris, or optic neuritis, can indulge in this practice only at a very serious and appreciable risk. Moreover, although a few cigarettes or a cigar after meals may have no appreciable effect on a healthy man, there are few who can continue the excessive consumption of many packages of cigarettes daily over any length of time without

very noticeable symptoms developing. And even though moderate doses may, in the sound individual, fail to produce visible injury, the possibility of subclinical damage, not perceptible on casual observation but disclosed by more intensive examination of the pharyngeal mucosa, by the cardiometer or electrocardiograph, and by microscopic examination of the tissues, cannot yet be ruled out.

Measures to mitigate the harmful effects of tobacco smoking in the host of individuals who find it difficult or impossible to cease the habit, especially in the face of symptoms making this desirable, are obviously to be recommended from the point of view of the medical practitioner. Unfortunately, the commercial claims of interested parties forms no safe guide in this attempt. The blatant claims of "denicotinized" tobacco vendors, whose own advertisements disclose an amount of nicotine remaining in the tobacco as great or greater than that naturally encountered in some tobaccos not so treated, the unfounded appeals for various other brands, and more recently the exploitation of proprietary solutions alleged to "detoxify" the nicotine in a cigarette, which on investigation have been found to be completely without value, emphasize the necessity for caution in accepting information from interested commercial sources.

The use of a mechanical device which removes a large part of the tobacco tar, but little of the other, more active agents in cigarette smoke should receive favorable consideration from medical men only in the event that such tar may be demonstrated to be in itself a source of danger. The results of this investigation indicate that, whatever carcinogenic properties may inhere in the use of tobacco, they cannot well be ascribed to the chemical effect of the tar derived from distillation of the tobacco, and that the patient with leukoplakia or other reasons for fearing susceptibility to cancer of the mouth or lungs would do well not to rely upon such a device for his protection.

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