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This article has been revised in the light of constructive criticisms from a referee, but seems not to meet the following cogent criticisms: "From the average age of the subjects in the study, the workers were approaching a survivor population. If long term smoking does affect the mucociliary mechanism of a human lung it is likely that this occurs in the cohort of smokers who develop smoking related lung disease. By late middle age these subjects will either have died or will at least show evidence of lung disease. The source of the subjects (the staff of the school and volunteers from old people's homes) could not be representative of a survivor population. Those with most severe lung disease will have already been excluded. The paper states that, of the sixty-one subjects examined, twenty-two were then rejected because of lung disease. I feel this is an error of study design such that the findings cannot be interpreted with reference to long term effects of cigarette smoking."—Editor.

Absorption of Nicotine in Cigarette and Cigar Smoke through the Oral Mucosa

by

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Nicotine in cigar smoke (*p*H 8·5) is much more readily absorbed through the mucous membranes of the mouth than is nicotine in cigarette smoke (*p*H 5·3) because there is a higher concentration of unionized nicotine in the relatively alkaline cigar smoke.

A CIGARETTE smoker who inhales will obtain a dose of nicotine, during the five or ten minutes he is smoking his cigarette, equivalent to a series of intravenous injections between 1 and 2 μg/kg[1]. Such a dose of nicotine may well result in increased alertness[2]. It is usually believed that the majority of cigarette smokers inhale to varying degrees the smoke which they take into their mouths, whereas the majority of cigar smokers do not. The question then arises, does a cigar smoker who does not inhale get a similar dose of nicotine to a cigarette smoker who inhales? Kershbaum *et al.*[3] concluded that he does not, because they found that cigarette smokers excreted more nicotine in the urine during a 4 h period of smoking than did cigar smokers. The object of the experiments described here was to ascertain more directly the degree, and particularly the rate, of absorption of nicotine in cigarette and cigar smoke through the oral mucosa.

Cats, anaesthetized with chloralose, had the trachea and oesophagus tied high in the neck. Breathing occurred through a tube inserted in the trachea. 25 ml. of tobacco smoke was introduced into the mouth every 30 s from a smoking simulator[4] through a thin rubber dam held firmly in position over the mouth by artery clips. After 10 s the smoke was blown out. The changes in blood pressure and movements of the cat's ears caused by tobacco smoke or by buffered solutions of nicotine introduced into the mouth were recorded. Twitching of the ears is an action which is highly specific for nicotine and compounds with nicotine-like actions, and is an indication that nicotine has reached the brain[5].

Blood Pressure and Ear Twitching

It was necessary to administer between twenty and thirty puffs of tobacco smoke in order to elicit a measurable pharmacological response, and this was the quantity of smoke used in all eight experiments. In four experiments, cigarette smoke had no effect on blood pressure; in the other four, there was a rise in blood pressure varying from 8 to 35 mm Hg. In only one of the eight experiments did cigarette smoke cause twitching of the ears. Cigar smoke, on the other hand, caused a rise in blood pressure in all experiments, the smallest recorded rise being 20 and the largest 125 mm Hg. Ear twitching occurred in five of the experiments with cigar smoke; it began towards the end of the smoke administration period and persisted for approximately ten minutes. These observations indicate that there was a gradual accumulation of nicotine in the brain followed by gradual decline. Fig. 1*b* shows the slow rise in blood pressure caused by thirty 25 ml. puffs of cigar smoke introduced into the mouth during 14·5 min. A similar quantity of cigarette smoke, however, had no effect on blood pressure (Fig. 1*a*).

Standard cigarettes manufactured from a flue-cured blend of tobacco (T 29), and standard cigars (C 1), were smoked in the simulator at a rate of one puff every 30 s. The whole of each 25 ml. puff was collected on a Cambridge glass-fibre filter disk and the filters were analysed for nicotine by a method based on that of Willits *et al.*[6]. The average nicotine content of twenty puffs of cigarette smoke was 3·33 mg, and of thirty puffs 4·44 mg, and was in fact greater than that of the same number of puffs of cigar smoke (2·32 and 4·00 mg respectively). Yet the cigar smoke invariably caused a bigger pharmacological response. What is the explanation of this apparent anomaly?

One of the most striking differences between cigarette and cigar smoke is the *p*H of the smoke. The *p*H of T 29 cigarettes determined by the method of Grob[7] was 5·35, whereas the *p*H of the C 1 cigars was 8·5. The buffer capacity of the two smokes was about the same. The percentage nicotine present as free base in aqueous solution, calculated from the Henderson equation, is 0·40 at *p*H 5·35, 1·7 at *p*H 6, 15 at *p*H 7, 64 at *p*H 8 and 85 at *p*H 8·5. Although tobacco smoke is an aerosol and not an aqueous solution, the percentage nicotine as free base at the different *p*Hs will probably differ only proportionately. The uncharged nicotine base will clearly diffuse into the bloodstream more readily than the nicotine ion[8,9].

*p*H and Nicotine Absorption

Fig. 1 (*a'* and *b'*) shows part of an experiment in which solutions of nicotine in 0·1 M phosphate buffer in a concentration range of 0·2–2·0 mg/ml. were put in the mouth for 10 min. The rise in blood pressure caused by

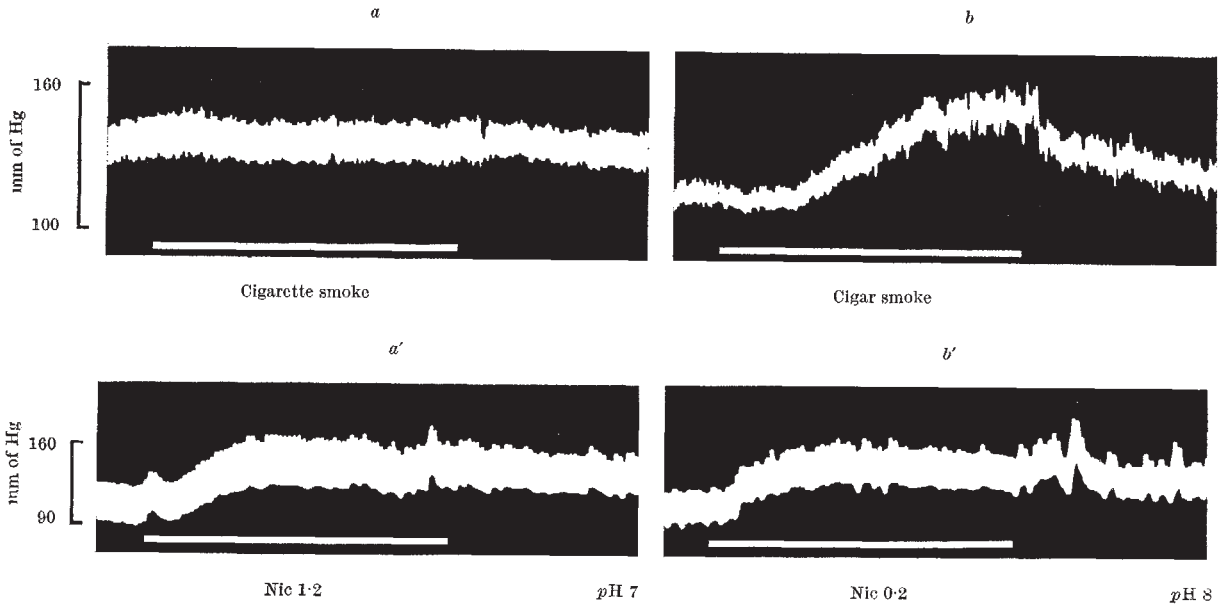

Fig. 1. Records of femoral blood pressure. Thirty puffs of cigar smoke introduced into the mouth of an anaesthetized cat during 14·5 min caused a slow rise in blood pressure (*b*) whereas a similar quantity of cigarette smoke had very little effect (*a*). In another experiment, *a′* and *b′* show the effects of buffered solutions of nicotine containing 1·2 mg/ml. nicotine base at *p*H 7 and 0·2 mg/ml. base at *p*H 8, when put into the mouth and left there for 10 min.

1·2 mg/ml. nicotine at *p*H 7 was closely matched by 0·2 mg/ml. at *p*H 8. The concentration of nicotine as free base was 0·18 mg/ml. at *p*H 7 and 0·13 mg/ml. at *p*H 8, showing that the pharmacological response is clearly dependent on the amount of nicotine in the mouth as free base.

Fig. 2 shows the mean carotid blood levels of nicotine in ng/ml. after the introduction into the mouth for 10 min of solutions of nicotine at *p*H 6, 7 and 8 each of which contained 0·8 mg/ml. (1·3 μCi/ml.) (2′-^{14}C)-nicotine. Nicotine concentrations in blood (2 ml. samples) were determined by the method described by Turner[10]. The graphs were drawn from data obtained in nine experiments. Whether nicotine exerts a pharmacological response depends on the rate at which it appears in the blood and on the peak concentration attained[11]. The peak concentration of nicotine at *p*H 8 was approximately 2·5 times that at *p*H 7 and four times that at *p*H 6. The rate at which the concentration of nicotine in the blood increased in the first 2·5 min at *p*H 8 was about 3·5 times the rate at *p*H 7 and eight times that at *p*H 6. These striking differences are consistent with the differences in the pharmacological effects of the relatively large amounts of cigarette and cigar smoke used in the present experiments.

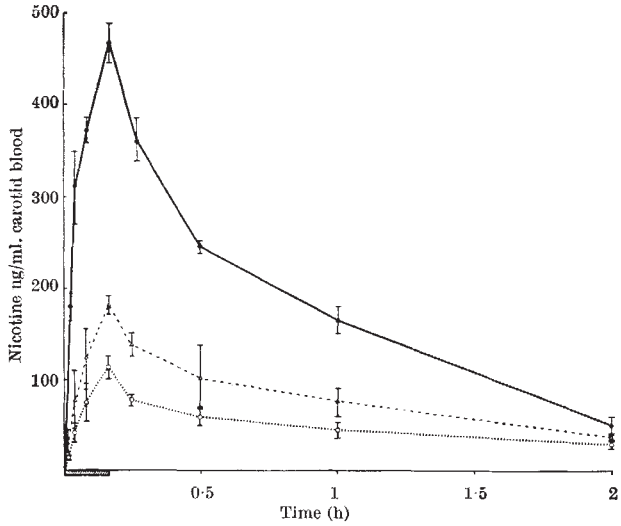

Fig. 2. Carotid blood levels of nicotine in ng/ml. after the presence in the mouth for 10 min of buffered solutions of nicotine at *p*H 6 (○ · · · ○), *p*H 7 (△ - - - △) and *p*H 8 (●—●). Each graph is the mean of three experiments: the bars show standard error of the mean.

We have recently shown that twenty intravenous injections of nicotine (4 μg/kg), given rapidly at minute intervals for 20 min, caused during the first 2·5 min a 15 ng/ml./min rise in the concentration of nicotine in carotid blood and a peak concentration of 100 ng/ml. at 20 min. This is probably the sort of blood concentration pattern that must be achieved to elicit a stimulant response. The data illustrated in Fig. 2 show that such blood levels are achieved (but only just at *p*H 6) when nicotine is present in the mouth continuously for 10 min at the relatively high concentration of 0·8 mg/ml. During the smoking of a cigarette or cigar, however, smoke is taken into the mouth intermittently and held there for only a few seconds. The concentration of nicotine bathing the mucous membranes of the mouth is not known, but clearly the conditions are less favourable for absorption than in the experiments of Fig. 2. The present evidence indicates that cigarette smokers who do not inhale may not obtain a "stimulant" dose of nicotine from relatively acidic cigarette smoke. It may, however, be possible for a cigar smoker to obtain such a dose without inhaling.

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