

Fig. 1. Changes in smoke preference on non-drug days induced by mecamylamine.

the large variability from subject to subject inherent in free puffing.

A smoking apparatus was attached to a 'Plexiglas' panel covering a 14 inch square opening in the door of each monkey's home cage. Two tubes, one delivering cigarette smoke and a "dummy" tube with access only to air, were also mounted on the panel. A water solenoid was mounted between the smoke and air tubes. A puff on either the smoke or air tubes preset the solenoid and would release a small amount of water when the monkey touched the solenoid spout. A light mounted above the solenoid signalled the availability of water. A fixed ratio (FR) contingency was added, so that a monkey could be required to puff a specific number of times to obtain water.

The monkeys received all their water during a daily 4 h puffing session. Thirty cigarettes were loaded into the smoking apparatus each morning and the test was started at 1030 h. A new cigarette was automatically lit every 7.5 min. The positions of the smoke and air tubes were interchanged each morning so that side preferences would not develop. Initially, water could be won with a single puff on either the smoke or air tube. The number of puffs for a reward of water was then increased to five, ten, twenty and finally to thirty. The FR 30 schedule was then maintained. Puffs were recorded on Sodeco counters and on an Esterline Angus recorder.

All four monkeys preferred smoke to air; that is, although they could get water by puffing on either the smoke or the air tubes, they reliably made more puffs on the smoke tube than on the air tube. When puffing rates on the FR 30 schedule stabilized, drug administration began.

The first drug was mecamylamine which is known to block both the peripheral and central effects of nicotine. Mecamylamine, in doses ranging from 0.4 to 3.2 mg/kg, was given intramuscularly 15 min before the beginning of a puffing session. Each dose was repeated two to five times, with at least 3 days between successive injections.

The results obtained from mecamylamine administration are shown in Table 1. The data on days immediately

Inhibition by Drugs of Smoking Behaviour in Monkeys

There have been several analyses of the role of nicotine in smoking. Johnston¹ found that heavy smokers reported a pleasurable sensation when given nicotine, whereas non-smokers reported an unpleasant effect. Lucchesi *et al.*² showed that intravenous administration of nicotine diminished the number of cigarettes smoked by heavy smokers. Jarvik *et al.*³ recently obtained a similar result with nicotine taken orally. If, as these studies suggest, nicotine is an incentive in smoking, then drugs which block the action(s) of nicotine should influence smoking.

Because of the relative ease of controlling environmental contingencies, an animal paradigm of smoking behaviour has been developed in this laboratory^{4,5}. In an attempt to modify smoking behaviour, various drugs have been given to four mature rhesus monkeys trained to puff cigarette smoke.

Puffing behaviour was initially instilled by making the monkeys suck on a tube in order to drink. The mouthpiece of a cigarette smoking apparatus⁵ was then substituted for the water tube. The smoking apparatus allowed a monkey to smoke lit cigarettes by automatically lighting each cigarette, spacing the cigarettes over time and sensing changes in pressure as the monkey puffed. When the monkeys had learned to puff, they were so trained that they had to puff but were allowed to choose between smoke and air⁶. This procedure was developed to reduce

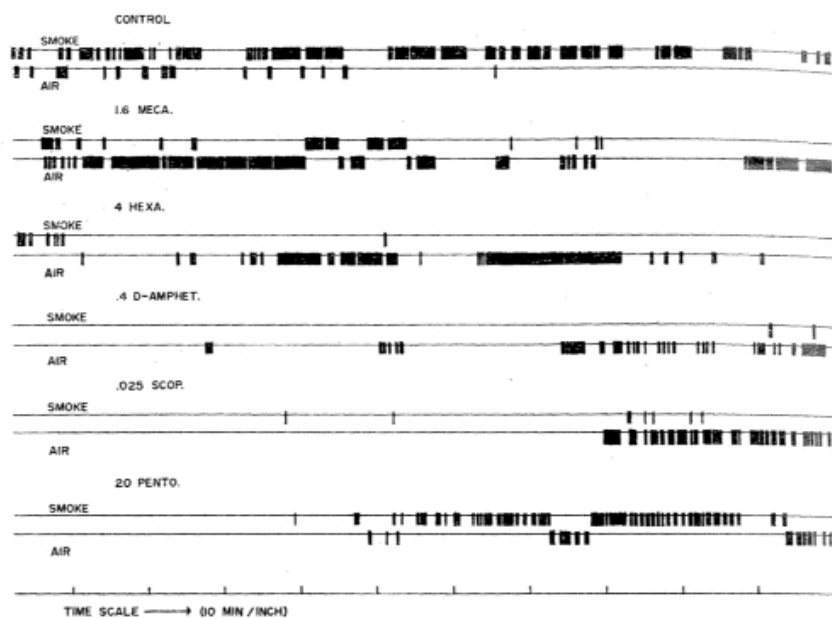


Fig. 2. Typical Esterline Angus puffing records.

preceding injections were used as control data in paired *t* tests. For each monkey, a dose of mecamlamine was found which reversed the smoke-air preference while producing a small decrease in the overall puffing rate.

We had not expected that mecamlamine would make smoke less desirable than air. If mecamlamine blocks the incentive effect of nicotine, then one might reason that smoke and air should be equally rewarding or that smoking should increase in order to get more nicotine and overcome the block. The reversal suggests that nicotine is the rewarding component in cigarette smoke and that smoke without nicotine is aversive. Mecamlamine, by blocking nicotine, may leave only the aversiveness of smoke itself.

It took approximately a month with two injections a week to complete the course of mecamlamine administration summarized in Table 1. During this time a gradual and consistent change in the smoke-air preferences under non-drug conditions was noted. The smoke preferences of the monkeys decreased and, after the last injection of mecamlamine, two of the monkeys still preferred air to smoke. Fig. 1 shows this progression for each of the monkeys, two of which recovered their preference for smoke. The other two monkeys, whose initial preferences were lower than those of the first two, did not recover within a 1 month period of observation. This long term after-effect of mecamlamine administration could be ascribed to negative conditioning; that is, repeated experience with smoke as an aversive stimulus precluded the rewarding effect of nicotine.

Table 1. CHANGES IN SMOKE PREFERENCE INDUCED BY MECAMLAMINE IN MONKEYS

Dose (mg/kg)	Dot		Randi		Phoebe		Freida	
	Total puffs	Per-centage smoke pref.	Total puffs	Per-centage smoke pref.	Total puffs	Per-centage smoke pref.	Total puffs	Per-centage smoke pref.
Control	4,461	64.6	4,274	82.5	4,515	76.7	2,821	70.8
0.8			3,658	84.3	4,834	67.7		
1.2			3,953	64.4*	3,437	35.7*		
1.6	3,795	70.3	3,757	1.7*	3,327*	12.3*	2,955	71.7
2.4	3,602	69.3					1,907	69.1
3.2	2,867*	39.3*					1,765*	33.5*

* Significantly less than control at $P < 0.05$.

Table 2. DRUG-INDUCED CHANGES IN SMOKE PREFERENCE IN MONKEYS

Drug	Dose (mg/kg)	Randi		Phoebe	
		Total puffs	Percentage smoke pref.	Total puffs	Percentage smoke pref.
Control		4,618	82.7	4,537	74.6
Pentobarbital	10	4,496	87.1	2,822*	78.6
	20	3,514*	68.8	2,635*	77.4
	30	2,028*	71.6	1,347*	78.7
Hexamethonium	1	4,491	80.0	4,016	80.6
	2	4,402	78.8	3,821	75.7
	4	4,243	37.4*	4,092	80.5
	8	2,084*	1.0*	4,008	69.6
	12			3,013*	39.4*
Scopolamine	0.025	2,043*	19.6*	2,902*	65.3
	0.05	741*	38.6*	3,136*	76.5
	0.1			2,530*	55.6*
	0.2			1,554*	44.7*
D-Amphetamine	0.2	1,614*	71.3	3,813	66.6
	0.4	114*	24.2*	1,143*	14.8*
Mecamlamine	1.6	3,844	14.1*	4,553	15.2*

* Significantly less than control at $P < 0.05$.

When the smoking preferences of the two recovered monkeys stabilized, the drug experiment was continued with them. Doses of pentobarbital, hexamethonium, scopolamine and D-amphetamine were given, in that order. One final dose of mecamlamine was also given. The results obtained from this series of injections are shown in Table 2. Pentobarbital, a barbiturate anaesthetic, decreased the overall puffing rate but did not change the smoke-air preferences. Hexamethonium, a nicotinic-blocker in the periphery which does not readily enter the brain⁷, reversed the smoke-air preference with large doses while decreasing the overall puffing rate. Scopolamine, a cholinergic blocking agent, and D-amphetamine, an adrenergic agonist, also reversed the smoke-air preferences and overall puffing rates were greatly decreased. Mecamlamine, again, reversed the smoke-air preferences with a small decrease in overall puffing rates.

The pentobarbital results indicate that a preference reversal is not just an artefact caused by decreased overall puffing. The hexamethonium results suggest that a peripheral action of nicotine may be part of the smoking incentive. Alternatively, in view of the much lesser potency of hexamethonium as compared with mecaml-

amine, perhaps a small amount of hexamethonium entered the brain.

A comparison of the patterns of puffing with the various drugs suggests that the scopolamine and D-amphetamine results may have been an artefact of decreased overall puffing. Fig. 2 shows sample patterns of smoke and air puffing under each of the drugs. Puffs are distributed fairly evenly in non-drug conditions and with mecamylamine, hexamethonium and pentobarbital. In contrast, puffing with scopolamine and D-amphetamine was completely suppressed for at least the first hour of the test session. Puffing on the air tube with these two drugs may have been a rebound after-effect caused by increased thirst when the drugs had been physiologically eliminated. To confirm this interpretation, we ran a deprivation test. A daily puffing period without drugs was started 2 h later than usual. Both monkeys had reversed smoke-air preferences at the beginning of the test sessions. Increased thirst may thus make smoke more aversive.

The results of this experiment must be qualified because of their questionable correspondence to human smoking. The forced and restricted nature of the monkeys' puffing certainly bears little resemblance to the free and intermittent smoking by humans. The ultimate importance of the present results will depend on their therapeutic significance. If, as these data suggest, nicotinic-blocking drugs will inhibit smoking by humans, then the animal paradigm will have been a most useful one.

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