THE ANTIDIURETIC ACTION OF NICOTINE AND OF SMOKING

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Nicotine has been well known since the time of Langley as a substance which stimulates the ganglia of the sympathetic system. Langley painted a solution of nicotine on a ganglion to determine what effects followed the stimulation of the cells present in it. He was thus able to locate the synaptic connexions of the sympathetic system. When nicotine is injected intravenously the stimulation of the ganglia results in a rise of blood pressure and a raised pulse rate. Nicotine also stimulates the carotid body, and so increases respiration. Finally, nicotine in sufficient doses produces convulsions. The experiments to be described show that, in addition to these properties, nicotine has an antidiuretic action, probably due to stimulation of the hypothalamus, and that man is so sensitive that the action can readily be demonstrated in some subjects after one cigarette.

In 1939 Dr. Mary Pickford demonstrated that when a diuresis is produced in a dog by giving it water, the diuresis is promptly inhibited by the intravenous injection of acetylcholine. To observe the effect a large dose—1 mg.—was used, and to exclude the action on the heart, on the blood vessels, and on the intestines atropine was given to the dog beforehand. The antidiuretic effect was shown to be due to the liberation of the hormone of the posterior lobe of the pituitary gland, because when the posterior lobe was removed the injection of acetylcholine no longer inhibited a diuresis.

Since this effect of acetylcholine was exhibited in the presence of atropine, it seemed likely to belong to those effects of acetylcholine which Dale (1914) called nicotine-like. If so, it was to be expected that nicotine itself would exert a similar action.

Observations on Rats

Experiments were therefore performed with groups of 16 rats to which water was given by stomach-tube to produce a diuresis (Burn, 1931); the antidiuretic action of acetylcholine

FIG. 1.—The broken line shows course of excretion of water given by stomach-tube to 16 rats at zero. The solid line shows course of excretion when each rat received 0.25 mg. nicotine (base) by subcutaneous injection 30 min. after it received water. Note period of inhibition between the two peaks of excretion.

was confirmed, and it was then found that the intravenous injection of 0.1 mg. of nicotine acid tartrate, given 45 minutes after the water, inhibited the diuresis during 45 minutes. The least dose of nicotine which, given subcutaneously, would exert

an antidiuretic action was next found. In Fig. 1 is shown a composite record of two experiments on 16 rats. They were males, about 190 g. in weight; after being kept without food overnight they were each given warm water by stomach-tube (5 c.cm. per 100 g.) and put in four cages for urine collection. The urine was recorded every 15 minutes. After 30 minutes from giving the water, 8 of the rats were injected with nicotine acid tartrate, 0.5 mg. per 100 g. The other 8 were injected with saline. The experiment was repeated on another day, when the rats previously injected with nicotine were injected with saline, and vice versa. Fig. 1 shows that rats when injected with nicotine had a larger diuresis than the controls during the next 15 minutes, but the diuresis was then inhibited for about 45 minutes. Thus the curve showing the diuresis when the control injection of saline was given is a curve with a single peak 75 minutes after the water was given; the curve when nicotine was injected is a curve with two peaks, in between which is the inhibition due to the injection of nicotine. When the experiment was repeated with half the dose of nicotine no inhibition was seen.

It is very probable that the increased excretion seen as the first peak in Fig. 1 immediately after the nicotine is explained by a rise of blood pressure due to the nicotine. This rise would increase the rate of diuresis. In support of this explanation is the observation that when a similar experiment to that shown in Fig. 1 was performed using tyramine instead of nicotine, the peak of the diuresis occurred earlier than in the controls, though when tyramine was injected there was no period of inhibition and therefore no second peak. Tyramine causes a rise of blood pressure as does nicotine, but by a purely peripheral action on heart and vessels.

Effect of Pituitary Removal

The main point of interest, however, was the inhibition of diuresis between the two peaks in Fig. 1. It was next shown that no such inhibition occurred when rats from which the pituitary gland was removed were used instead of normal rats. We are indebted to Dr. Edith Büllbring for preparing hypophysectomized rats for this work. These rats were injected daily with anterior pituitary extract kindly sent to us by Dr. I. W. Rowlands of the National Institute for Medical Research. They were given water by mouth (6 c.cm. per rat) in the morning of each day, and observations on water diuresis were then made in the afternoon after giving more water (6 c.cm. per rat). The graph in Fig. 2 shows that the injection of nicotine in the same dose and at the same time as in Fig. 1 failed to produce any inhibition of diuresis. When the experi-

FIG. 2.—A similar experiment to that in Fig. 1, carried out on 10 rats from which the pituitary body had been removed. The broken line represents the control experiment, the solid line the experiment in which nicotine was injected. There is no phase of inhibition.

ments were complete the rats were killed and the pituitary fossa of each was examined for remnants of gland. None were found. This result made it clear that the action of nicotine in exerting the antidiuretic effect depended on the presence of the pituitary gland, and probably on the posterior lobe.

Nicotine is not the only alkaloid which exerts this antidiuretic action, for de Bodo (1944) has found that morphine has a similar action in the dog, exerted through the neurohypophysis.

Observations on Man

The least dose of nicotine which, given subcutaneously, produced an antidiuretic effect in rats was 0.5 mg. of the acid tartrate per 100 g.: this corresponds to 0.25 mg. of nicotine base per 100 g. If man were equally sensitive per unit of body weight, 150 mg. of nicotine base would be required to exert an effect on a man of 60 kg. Despite the unlikelihood of observing a positive result in man, it seemed worth while to determine whether the smoking of cigarettes had an antidiuretic effect. In performing the experiment the subject, when his stomach was empty, passed water every 15 minutes and recorded the volume. When this was reasonably uniform he drank one litre of warm water and continued to pass water every 15 minutes. The excretion rose to a peak usually about 75 or 90 minutes after drinking the water and then fell to the original rate of excretion in about 2½ hours from the time of drinking. In Fig. 3, curve A shows the normal diuresis thus obtained in E. M. V. W. Curve B shows the course of the diuresis in E. M. V. W. when he smoked three cigarettes in succession, beginning 45 minutes after drinking

FIG. 3.—Subject E. M. V. W. drank 1 litre of water at zero. The broken line shows excretion of water in c.cm. per 15 min. The solid line shows excretion in a second experiment when he smoked 3 cigarettes, beginning 45 min. after drinking the water. Note the long period of inhibition.

the water. The diuresis had already begun when smoking started, but inhibition occurred after 15 minutes, and the effect of the three cigarettes was to produce complete inhibition during 2.5 hours; after which the diuresis began again to reach a peak 4.5 hours after drinking the water. E. M. V. W. is a healthy male of 26 years. In smoking the three cigarettes, he did so as rapidly as possible and inhaled deeply. He smoked them in 20 minutes. He suffered from vertigo and felt very sick; 5 minutes after finishing smoking he vomited, and continued to feel sick for one hour. The inhibition of the diuresis outlasted these symptoms, and in several other observations an inhibition was observed without the production of any appreciable symptoms at all. Thus in Fig. 5 an observation on the same subject—E. M. V. W.—is recorded, in which inhibition was produced by one cigarette; he noted "slight dizziness" while he smoked, but nothing more.

Variation among Subjects

This antidiuretic effect of smoking varied a good deal in different subjects. Subject E. M. V. W. was unusually sensitive, for, as seen in Fig. 5, the smoking of one cigarette produced an effect on him. Subject L. H. T., observations on whom are shown in Fig. 4, was less sensitive than E. M. V. W., for the smoking of one cigarette had no effect. In another subject, G. B. P., who was a fairly heavy smoker, the smoking of three cigarettes had only a very slight effect. However, out of seven subjects, six of whom were males between 20 and 26, one cigarette had an inhibitory effect on diuresis in three, two cigarettes had an inhibitory effect in two others, and three cigarettes had an inhibitory effect in a sixth. Only G. B. P. can be considered as scarcely affected by three cigarettes. He

smoked about 20 cigarettes a day in addition to two or three pipes. Another subject who was a regular pipe smoker observed no inhibitory effect from smoking a pipe; on the contrary, he observed an increased rate of excretion, probably due to the rise of blood pressure which the smoking caused. A positive effect was recorded only when as a result of smoking there were two peaks of diuresis as shown in Figs. 3, 4, and 5, and the time interval between these peaks is expressed as "delay" in the accompanying Table.

Table showing Experimental Results

Subject	Age	No. of Cigarettes	Delay (hours)
L. H. T.	21	3	3.5
"	"	3	2.0
"	"	1	Nil
E. M. V. W.	26	3	3.5
"	"	1	1.75
J. H. B.	51	1	3.25
T. H. C. L.	21	2	3.0
J. R. W. G.	19	3	3.25
G. B. P.	19	3	Nil

FIG. 4.—Similar experiments to that in Fig. 3, on subject L. H. T. The solid line is an experiment carried out smoking 3 cigarettes when L. H. T. was not otherwise smoking. The broken line is an experiment carried out also with 3 cigarettes when he was smoking 12 to 15 a day.

FIG. 5.—Similar experiments to those in Figs. 3 and 4. The broken line is an experiment in which 0.5 mg. nicotine (base) was injected intravenously at the arrow 60 min. after drinking the water. The solid line shows the effect of smoking one cigarette in the same subject.

Two experiments on L. H. T. afford further evidence that the antidiuretic effect is less when tolerance is established. These experiments are shown in Fig. 4. The first was done when L. H. T. had just finished a period of training for rowing, and had not been smoking; the delay was 3.5 hours. The second experiment was done seven months later, when L. H. T. was smoking 12 to 15 cigarettes a day; the delay was only 2 hours.

Intravenous Injection of Nicotine

In view of the large dose of nicotine required to produce the antidiuretic effect in the rat, it was surprising that smoking should exert an antidiuretic effect if this was due to the nicotine, as the amount of nicotine in the smoke seemed far too small. Some experiments were then carried out to determine whether small doses of nicotine would exert an antidiuretic action in human subjects. The nicotine was injected intravenously as acid tartrate when a diuresis was beginning. The effect of 1 mg. nicotine (base) in R. P. M. is shown in Fig. 6; the period of inhibition between the two peaks was 2.75 hours. In R. P. M. the injection of 0.5 mg. nicotine (base) had no antidiuretic effect. In E. M. V. W., however, the injection of 0.5 mg. nicotine (base) had an antidiuretic action such that the period between the two peaks was 2.75 hours (see Fig. 5). Now, as Fig. 5 shows, in this subject the smoking of one cigarette produced an antidiuretic action lasting 1.75 hours, so that the effect of one cigarette was rather less than that of 0.5 mg. nicotine (base).

Amount of Nicotine in Cigarette Smoke

Is there so much nicotine as this in the smoke of one cigarette? Schnedorf and Ivy (1939) have stated that one cigarette of the type they used yielded, in smoke taken in, about 0.2 mg. With the help of Mr. H. W. Ling we have determined the amount of nicotine which a smoker receives from British cigarettes. We connected a glass cigarette-holder to a long U-tube immersed in cold water. The other end of the U-tube was connected to a filter pump by a T-piece with one limb open to the air. When the filter pump was turned on gently, air was sucked in through the open limb of the T-piece. When this limb was closed, the air was sucked in through the cigarette-holder. We put a cigarette in the holder, lighted it, and, by alternately closing and opening the side limb of the T-piece, sucked some of the smoke into the U-tube and allowed part of it to escape into the air, imitating as closely as possible the ordinary smoking of a cigarette. The nicotine in the smoke was condensed in the U-tube. As a rule we "smoked" 10 cigarettes in the apparatus in succession. We then washed out the U-tube with ether, evaporated off the ether, and dissolved the residue with a little alcohol and 1% tartaric acid. As a rule the residue from 10 cigarettes (about 60 mg.) was collected in 10 c.cm. This solution was then estimated by comparing it with a known solution of nicotine acid tartrate for its pressor effect on the blood pressure of a spinal cat prepared by Dale's method (Burn, 1928). One estimation on 10 cigarettes gave the result that the smoke of one cigarette contained more than 0.66 mg. but less than 0.75 mg. nicotine (base). Estimations made on different batches of Gold Flake and Player's cigarettes gave figures varying between 0.6 mg. and 0.75 mg. nicotine (base) in the smoke of one cigarette. We observed no difference between the brands.

Now if 0.6 to 0.7 mg. nicotine enters the mouth of a smoker, not all of it will enter the blood. A certain proportion will do so, however, depending for its amount on how much the smoker inhales. When the smoker inhales, probably about 0.3 to 0.4 mg. reaches the alveoli of the lungs, from which it must be rapidly absorbed. This conclusion accounts very well for the observation on R. P. M. and E. M. V. W. In R. P. M. neither the intravenous injection of 0.5 mg. nicotine (base) nor the smoking of one cigarette had any antidiuretic effect. In E. M. V. W. the intravenous injection of 0.5 mg. nicotine (base) had an antidiuretic effect lasting 2.75 hours, and the smoking of one cigarette an effect lasting 1.75 hours.

Amount of Posterior Lobe Hormone Liberated

The antidiuretic action of nicotine depends on the pituitary body, and almost certainly, as Mary Pickford proved for acetylcholine, on the posterior lobe. Presumably the nicotine stimulates the supra-optic nucleus and adjacent nuclei, which, like it, send nerve fibres to the posterior lobe. When impulses arrive in the posterior lobe the antidiuretic hormone is released. What amount of hormone, in terms of the ordinary pituitary (posterior lobe) extract, is released when nicotine is injected? The ordinary posterior lobe extract is measured in units, the

official strength being 10 units per c.cm. An attempt was made in subject R. P. M. to imitate the effect of 1 mg. nicotine (base) injected intravenously, as shown in Fig. 6, by injecting posterior lobe extract also by the intravenous route.

Posterior lobe extract was first injected in a dose of 0.05 unit. The antidiuretic effect, shown at B in Fig. 6, was shorter than that of 1 mg. nicotine (base) by 30 to 45 minutes. In the next experiment twice this dose was used—0.1 unit—but it produced the same effect. These results indicated that when posterior lobe extract was given intravenously the duration of the effect was not proportional to the size of the dose, but probably depended on the rate of destruction of the hormone. This was supported by the fact that when two doses, each of 0.05 unit, were given at an interval of 45 minutes the antidiuretic effect was much more like the nicotine effect, being in fact slightly greater. Thus the results indicated that an intravenous dose of nicotine does not exert a single momentary stimulus to the posterior lobe, but rather a stimulus which persists for 30 to 45 minutes.

FIG. 6.—The solid line is an experiment in which 1 mg. nicotine (base) was injected intravenously into R. P. M. at arrow N. The broken line A is an experiment in which 0.05 unit posterior lobe extract was injected twice at an interval of 45 min. at arrows P.L. The lines at B are experiments in which (a) 0.05 unit and (b) 0.1 unit were each injected once.

Discussion

Although the effect of smoking in causing a rise of blood pressure has been known since 1907 (Hesse), that it does so cannot yet be said to be a matter of common knowledge. Recent observations by Roth, McDonald, and Sheard (1944) provide fresh evidence on the point, and also demonstrate the fall of skin temperature due to the vasoconstriction of the skin which occurs. The rise of blood pressure, of pulse rate, and of vasoconstriction in the skin are all the result of the stimulation by nicotine of sympathetic ganglion cells. The observations recorded in this paper indicate that it is not only the nerve cells of the sympathetic ganglia which are stimulated by nicotine but that nuclei in the hypothalamus are also stimulated, as a result of which the hormone of the posterior lobe of the pituitary is liberated in the blood. The effect was accompanied in several of the observations by symptoms regarded as toxic effects of nicotine, such as vertigo, nausea, and even vomiting. These effects were not always present, and there is no doubt that the antidiuretic action is observed in their absence.

If smoking causes secretion of the antidiuretic hormone it seems reasonable to suppose that the other hormones of the posterior lobe, such as the oxytocic hormone, are also liberated. If this occurs, smoking should accelerate labour.

Many believe that there is a connexion between smoking and gastric ulcer, and since Dodds *et al.* (1934) have shown that the injection of posterior lobe extract into rabbits causes gastric ulcer, it might appear that our experiments suggest the mechanism of the connexion. This is very doubtful; large amounts of posterior lobe extract are needed to produce ulcers, and the effect of pharmacopoeial doses of posterior lobe extract

in man is to diminish gastric acidity, not to increase it. This we have observed here, in confirmation of other workers. Our experiments do, however, raise the question whether those with impaired kidney function should be allowed to smoke.

Summary

Nicotine exerts an antidiuretic effect in the rat. This effect does not occur if the pituitary body is removed.

Smoking exerts an antidiuretic effect in man. In a sensitive subject one cigarette will inhibit diuresis for 2 to 3 hours.

The same antidiuretic effect is produced in man by the injection of nicotine intravenously in an amount approximately equal to the amount absorbed from one cigarette.

It is probable that the nicotine absorbed from cigarette smoke stimulates the supra-optic nucleus of the hypothalamus and causes a discharge of the hormone from the posterior lobe of the pituitary gland.

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ENFORCED LEISURE

A STUDY OF THE ACTIVITIES OF OFFICER PRISONERS OF WAR

BY

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Recent articles and correspondence in the medical press on prisoner-of-war mentality have naturally caused considerable discussion in P.O.W. camps. Whether rehabilitation on a large scale will be necessary or not is difficult for the individual to say. Nevertheless some observations on how the P.O.W. spends his time may be of general interest. In this paper an attempt is made not to produce an average individual but to assess what contribution the average prisoner makes to the life of the camp.

Ofag VII/B was originally formed as a camp for young officers. Its strength varies, but in the period under review is about 1,700, of whom 110 are Canadians, 117 are Australians, 87 are New Zealanders, and the rest are from the British Isles. There is a sprinkling of officers from other parts of the Empire. One is justified in regarding it as presenting a fair cross-section of the educated classes of the Empire. The living conditions, as regards accommodation, are fairly similar, while the food is completely standardized. Facilities for recreation, study, sport, etc., are available in exactly the same measure to everybody. The extent to which these facilities are exploited naturally depends on the individual.

Despite the limitations of the questionnaire form of investigation, it was chosen as being the only one practicable in the peculiar circumstances of captivity. A questionnaire covering all possible forms of camp activity was drawn up. This was issued to a number of patients in hospital, who were asked to allocate times on the basis of an average day to the various activities. The data thus collected proved interesting, and it was decided to extend the investigation to get a fair sample of the camp as a whole. The questionnaire was issued to various people, with a request that in each case every member of the mess or room should answer it. In some cases the return was 100%, in others there were one or two men who, for various reasons, refused to co-operate. Nevertheless I think that the return represents a fair cross-section of the camp.

It will be observed that no name is asked for; nevertheless, by inquiry it was generally possible to trace individuals when any point required clarifying. One objection raised was, What

Form of Questionnaire

Country (or Dominion) of Origin :	Age :
Previous Occupation :	Educational Standard :
Length of Captivity :	
Average Day :	
I. Camp official (administrative, parcel, education, medical, sports, etc.)	 hrs.
II. Activity for benefit of community (non-official): e.g., work on wood pile, gardening, tutoring, block cooks, T.O.C. nursing, voluntary massage, or any other altruistic activity	 hrs.
III. Study: (a) Prescribed course for examination	 hrs.
(b) Language—which?	 hrs.
(c) General study	 hrs.
IV. Handicrafts: Model-making, woodwork, tinsmithing, knitting, etc.	 hrs.
V. Art: Painting, drawing, sketching, modelling, etc.	 hrs.
VI. Music: (a) As performer. What type of instrument?	 hrs.
(b) Listening	 hrs.
VII. Writing: (a) Books or articles for possible publication	 hrs.
(b) Diary or scrapbook for own amusement	 hrs.
VIII. Dramatics: (a) Actor	 hrs.
(b) Producer, stage hand, scenery designer, etc.	 hrs.
IX. Reading: (a) Serious	 hrs.
(b) Light	 hrs.
X. Sport or exercise: (a) Active	 hrs.
(b) Spectator	 hrs.
XI. Indoor games, chess, or cards for amusement or nominal stakes	 hrs.
XII. Gambling	 hrs.
XIII. Serious discussion	 hrs.
XIV. Aimless gossip (war, reminiscences, local gossip)	 hrs.
XV. Sleeping and eating	 hrs.
XVI. Time spent on household fatigues	 hrs.
XVII. Hobbies: bird-watching, flowers, collecting (types of cigarettes, etc.)	 hrs.
XVIII. Do you attend general interest lectures?	
XIX. Do you work to a time-table?	
XX. Have you improved, or not, physically? How? Since when?	
XXI. Have you improved, or not, mentally, especially with regard to interest, concentration, and memory?	

is the difference between "study" and "serious reading" or between "light" and "serious" reading? To me it seems purely an individual distinction. Most people know what they are trying to study and they also have their own standards of serious and light reading, and I have accepted these standards.

Results

TABLE I.—Returns Collected from 300 Officers

Average age: 29.8 years.	
Educational standard: High, in that 97—i.e., 32.3%—were either University graduates or undergraduates; 16—i.e., 5%—had various professional qualifications.	
I. Official duties	35 mins.
II. Altruistic activities	46 "
III. Study: (a) Course for exam.	1 hr. 5 mins.
(b) Languages	29 "
(c) General	55 "
IV. Handicrafts	14 "
V. Art	6 "
VI. Music: (a) Performer	9 mins.
(b) Listener	14 "
VII. Writing: (a) For public	4 "
(b) Diary, etc.	3 "
VIII. Dramatics: Actors and stage assistants	3 "
IX. Reading: (a) Serious	1 hr. 1 min.
(b) Light	1 " 5 "
X. Sport: (a) Active	1 " 1 "
(b) Spectator	23 "
XI. Cards	20 "
XII. Gambling	11 "
XIII. Serious discussion	24 "
XIV. Aimless gossip	1 hr. 16 "
XV. Sleeping and eating	10 hrs. 37 "
XVI. Household fatigues	1 hr. 3 "
XVII. Hobbies	6 "
Unaccounted time	1 " 50 "
	24 hrs. 00 mins.
XVIII. General interest lectures	Yes = 57.3%; No = 42.7%
XIX. Work to time-table	" = 29.0%; " = 71.0%
XX. Feeling physically impaired	" = 33.7%; " = 66.3%
XXI. Feeling psychologically impaired	" = 40.0%; " = 60.0%

Discussion of Table I

The first two groups cover most of the actual work required for the running of the camp. The average time of 35 minutes per head for camp administration may appear high to an efficiency expert. 100 forms recorded some kind of activity. Three claimed to work 7 hours and one 6 hours a day, but the majority worked 1/2 to 1 hour a day. (Frequency Diagram 1.)