The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid

The effect of intravenously administered nicotine upon smoking behavior was studied in smokers who were unaware of the nature of the administered drug and the true purpose of the study. Smoking behavior was not altered significantly when nicotine was administered in a dose of 1 mg. per hour for 6 hours. A significant decrease in smoking frequency was obtained when nicotine was administered at the rate of 2 to 4 mg. per hour. Recordings of systolic blood pressure, heart rate, and the electrocardiogram indicate that the physiological alterations in these parameters produced by smoking can be reproduced by parenteral nicotine.

B. R. Lucchesi, Ph.D., M.D., C. R. Schuster, Ph.D., and G. S. Emley, A.B.
Ann Arbor, Mich.
Department of Pharmacology, University of Michigan Medical School

Larson, Haag, and Silvette[6] have summarized the literature concerning tobacco habituation and have listed the possible reasons for smoking in five main categories: (1) for the pharmacological effects of nicotine; (2) for stimulation of special senses by other constituents of tobacco smoke; (3) for psychological, psychic, or psychoanalytic reasons; (4) for social and cultural reasons; and (5) for economic reasons. Lewin[7] has stated, "the decisive factor in the effects of tobacco, desired or undesired, is nicotine and it matters little whether it passes directly into the organism or is smoked."

Of the many chemical substances present in tobacco smoke, nicotine is the only substance known to produce acute pharmacological effects. Johnston[5] first administered nicotine parenterally to smokers in an effort to satisfy their craving for tobacco and reported that his patients were disinclined to smoke for a time following the administration of the alkaloid. Similarly, Ejrup and Wikander[2] reported that some heavy smokers, receiving increasing dosages of nicotine, 6 to 18 mg., for 10 days, felt satisfied and saturated and could only take a few puffs on a cigarette or stopped entirely. Finnegan, Larson, and Haag[3] reported that inveterate smokers experienced different reactions to smoking low-nicotine cigarettes, but they became adapted to the change in 1 to 2 weeks. The authors concluded that with many smokers nicotine became a major factor in the cigarette habit, but in others nicotine was not of the same importance. More recently, Ejrup,[1]

This study was supported by a research grant from the American Medical Association Research and Education Foundation, Committee for Research on Tobacco and Health.

Received for publication June 12, 1967.

in discussing the role of nicotine in smoking pleasure and ways of breaking the cigarette habit, has suggested that injections of nicotine or a nicotine derivative such as lobeline be employed to reduce or eliminate the physiological part of the withdrawal symptoms experienced when smokers are denied the use of tobacco.

The limited number of studies on the role of nicotine in the smoking habit tend to suggest that it has an influence on an individual's desire for tobacco. The available studies, however, suffer from the fact that both subject and investigator were aware of the objectives of the study, and in many instances the subjects had expressed a desire to be assisted in their efforts to break the smoking habit. The present investigation was undertaken to evaluate the role of nicotine upon the smoking behavior in human volunteers who were unaware of the true objectives of the study. The subjects employed in this study were in excellent physical health as determined by medical examination and were not contemplating breaking their smoking habit.

Method

The studies were done on volunteers, man and women ranging in age between 21 and 30 years. Candidates for the study were selected after having passed a complete medical and psychiatric examination. Each subject was studied for fifteen consecutive days; each experimental session lasted exactly 6 hours.

The subjects were instructed to abstain from food, beverages, and tobacco from midnight of the day preceding the experimental session. The subjects arrived at the laboratory at 7:30 A.M. and were permitted to rest in the reclining position for 30 minutes before having their blood pressure and heart rate recorded in both the supine and sitting positions. The subjects were then put in a sound-proof, air-conditioned isolation booth. Electrodes for recording the electrocardiogram or heart rate were attached, as was a Beckman pulse pickup and blood pressure cuff for registration of the blood pressure. A 23 gauge scalp-vein hypodermic needle was inserted into a suitable forearm vein and fixed in place. The intravenous needle was connected to a Y-adapter and two sterile extension tubes that were led to the outside of the cubicle. Each tube was connected to a Holter Micro Bilateral Roller pump; the flow in each of the tubes could be varied independently. One pump delivered 0.9 per cent sodium chloride continuously throughout the 6 hour session. The other pump was used for the administration of nicotine or saline solution. Drug administration could thus be carried out without the subject being aware. The cardiac rate was recorded continuously; the blood pressure and electrocardiogram were recorded every 15 minutes on a Beckman-Offner Dynograph located outside the isolation cubicle.

During their period of confinement in the cubicle, the subjects were permitted to have a standardized breakfast and lunch and were allowed to smoke at any time.

Throughout the 6 hour experimental session the volunteers were assigned a variety of psychological testing procedures—time estimation, reaction time, and hand steadiness tests. The daily schedule was repeated in an identical manner on each of the fifteen experimental days. The number of cigarettes consumed during each of the sessions was recorded. In addition, the remaining portions of the cigarettes were collected and weighed at the end of each day.

Each subject received a trial intravenous infusion of nicotine bitartrate in which the dosage of nicotine ranged from 0.5 to 4 mg. per hour. These preliminary studies were carried out with the subjects in the supine position after an 8 hour fast. The subjects were unaware of the drug being administered and were instructed to report all subjective responses. The studies reported here were performed on subjects capable of tolerating the 4 mg. per hour dose of nicotine without subjective responses.

The experiments were designed so that

each subject had experimental sessions in which he received an intravenous infusion of 0.9 per cent sodium chloride (control sessions) and sessions in which nicotine bitartrate was administered (drug sessions). The sequence of control and nicotine administration sessions was selected randomly.

Results

Effects of intravenous nicotine on smoking frequency. Each of 4 men received nicotine bitartrate in a dose of 1 mg. over a 20 minute period which was repeated after 40 minutes. Thus, a total of 6 mg. of nicotine was administered by intermittent intravenous infusion in the course of 6 hours. Control sessions of equal duration were conducted in which the subjects received 0.9 per cent sodium chloride throughout the course of the experimental session. No statistically significant difference could be demonstrated between the number of cigarettes smoked during the control sessions versus the drug-administration sessions.

The mode of drug administration was altered in 5 additional subjects; they received 2 mg. of nicotine in the first hour and 4 mg. per hour for each of the next 5 hours. Thus, in the course of 6 hours each subject received a total of 22 mg. of nicotine intravenously. The results are summarized in Table I which shows the average number of cigarettes consumed during the saline-control and drug-administration sessions in each of 5 volunteers. There was a significant decrease in the average number of cigarettes smoked by each of the subjects receiving 22 mg. of nicotine over a 6 hour period. The average decrease in the number of cigarettes smoked per subject was 2.7 ± 0.4.

In addition to a reduction in the total number of cigarettes smoked by each subject receiving intravenous nicotine, there was a decrease in the amount of each cigarette smoked. The data in Table II show the residual weights of the cigarettes for each volunteer during saline control and drug infusion sessions. The residual weights of the cigarettes smoked during the nicotine administration sessions were greater than the residual weights of the cigarettes smoked during the saline control sessions. The differences were statistically significant and further suggest that the intravenous administration of nicotine decreases the motivation to smoke.

The act of smoking is associated with periodic inhalations of nicotine-containing smoke which results in phasic increases in nicotine absorption from the oral and pulmonary membranes. An attempt was made to infuse nicotine in a manner which would deliver 1 mg. of the alkaloid periodically over a duration of 14 minutes. The procedure was stopped for 32 minutes and repeated again for an additional 14 minutes and continued in this manner for the 6 hour session. Thus, the subjects received a total of 8 mg. per day of nicotine on this regimen. A significant decrease in the number of cigarettes smoked was obtained in 3 of 4 subjects. The data are summarized in Fig. 1. Subject 7 failed to demonstrate

Table I. *Comparison of average number of cigarettes consumed per six hour session under saline control and drug conditions*

	Saline control			*Drug*			
Subject	*No. of sessions*	*Mean*	*± S.E.*	*No. of sessions*	*Mean*	*± S.E.*	*Level of significance*
1	7	17.9	± 0.72	7	14.4	± 0.58	<0.005
2	4	7.0	± 0	5	4.4	± 0.24	<0.0005
3	6	7.3	± 0.40	6	4.8	± 0.48	<0.005
4	7	11.4	± 0.52	5	8.2	± 0.32	<0.005
5	5	6.7	± 0.25	4	4.7	± 0.25	<0.005

Table II. *Comparison of residual weights of cigarettes consumed under saline control and drug conditions*

Subject	Mean weight (Gm.)		Level of significance
	Saline control	Drug	
1	0.4196	0.4671	<0.025
2	0.6165	0.7430	<0.005
4	0.5100	0.5669	<0.05
5	0.5448	0.6292	<0.005

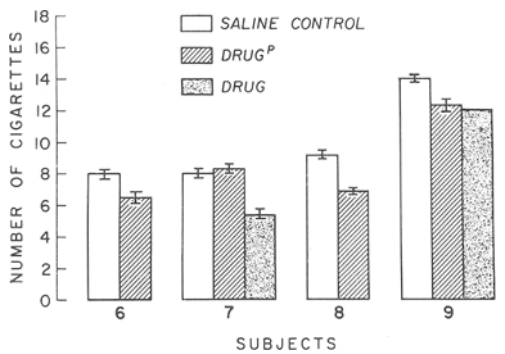

Fig. 1. Average number of cigarettes consumed per 6 hour session under saline control and two nicotine administration conditions. Drug^P condition represents the periodic infusion of 8 mg. per day. Drug condition represents the continuous infusion of 12 mg. per day. Brackets represent the standard error of the mean.

a change in smoking frequency when given 8 mg. of nicotine per day, but showed a significant decrease when the administered dose was increased to 12 mg. per day on the continuous regimen. Subject 9, however, showed the same decrease in smoking frequency on either the periodic schedule of 8 mg. per day or the continuous administration of 12 mg. per day.

Cardiovascular effects associated with smoking and/or the intravenous administration of nicotine. The heart-rate changes produced by smoking or by smoking plus the intravenous administration of nicotine (22 mg. in 6 hours) are presented in Fig. 2. The mean cardiac rate in 5 subjects, taken with the subjects at rest seated in the isolation cubicle, was 72 ± 3.3 beats

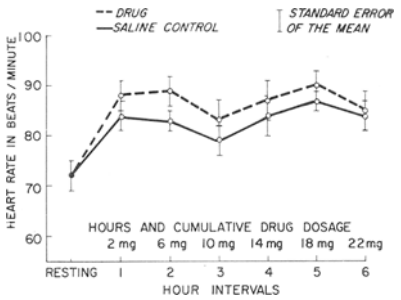

Fig. 2. Mean heart rate per hour interval for 5 subjects under saline control and nicotine administration conditions.

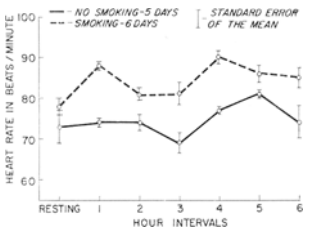

Fig. 3. Mean heart rate per hour interval for one subject under smoking and no smoking conditions.

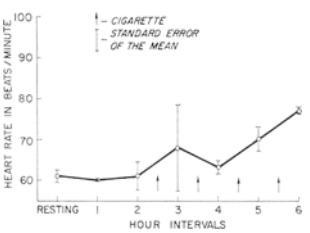

Fig. 4. Mean heart rate per hour interval for one subject smoking one cigarette per hour for 3.5 hours. Each point represents 3 determinations.

per minute. One hour after the start of the experimental session in which the subjects received only saline intravenously, the mean heart rate was 84 ± 2.8 beats per minute. The increase in rate was associated with the smoking of the first cigarette in each of the 5 subjects. At the end of 6 hours the mean heart rate obtained during saline control sessions was 84 ± 2.9 beats per minute. There was no difference in the magnitude of the heart rate increase in the same 5 subjects when they were given nicotine (22 mg.) during the 6 hour experi-

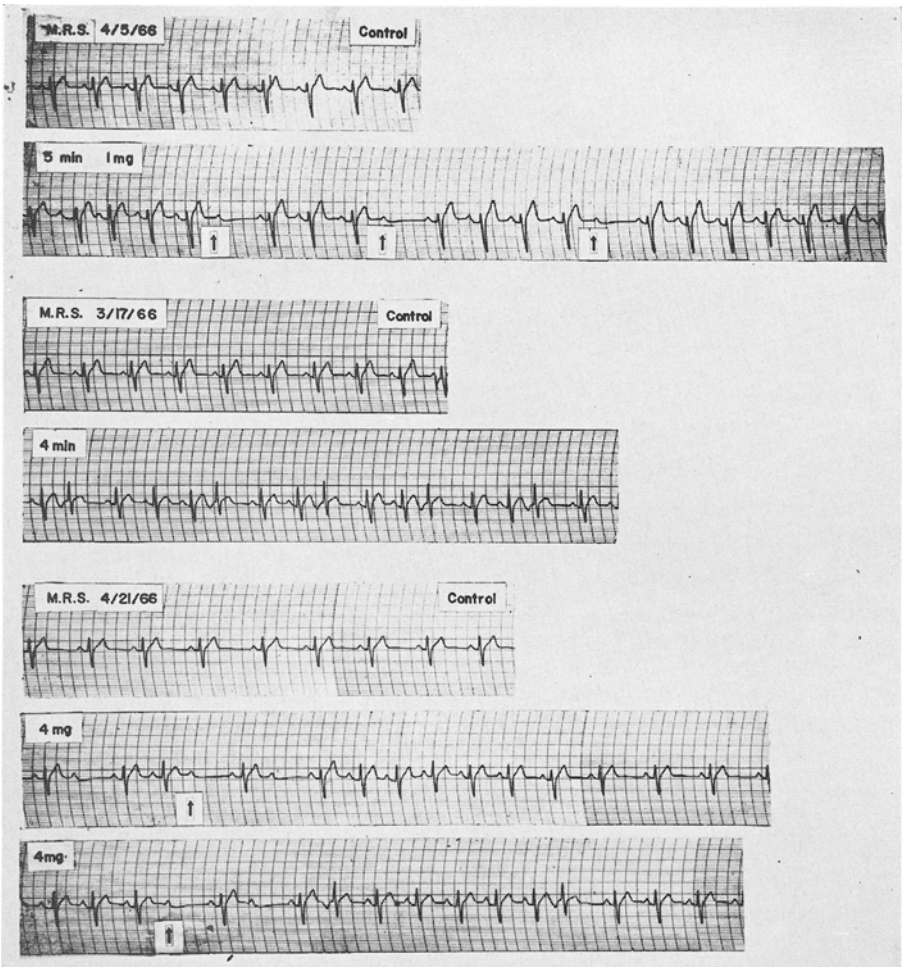

Fig. 5. Changes in cardiac rhythm induced by the infusion of 1 mg. (upper tracing) and 4 mg. (lower tracing) of nicotine. The middle tracing shows cardiac rhythm changes elicited by smoking the first cigarette of the day.

mental session. After the first hour, with the subjects smoking and having received 2 mg. of nicotine, the average heart rate was 88 ± 2.6 beats per minute, which was not significantly different from that seen when the subjects smoked during periods of saline administration. Similarly, at the end of 6 hours after a cumulative dose of 22 mg. of nicotine, the mean heart rate was 85 ± 3.7 beats per minute.

That the increase in heart rate was due to smoking was demonstrated by comparing the heart rate of one subject during five experimental sessions when smoking was permitted with identical experimental sessions when smoking was not permitted. The data are illustrated in Fig. 3. There is a significant elevation in heart rate associated with smoking. Likewise, Fig. 4 shows the effect obtained when an experimental subject was permitted to smoke after the first 2.5 hours of the experimental session. There is an abrupt increase in heart rate associated with the smoking of the first cigarette.

The results indicate that the heart-rate changes observed in these studies were associated with the act of smoking and not related to the activities of the subject during confinement in the isolation cubicle.

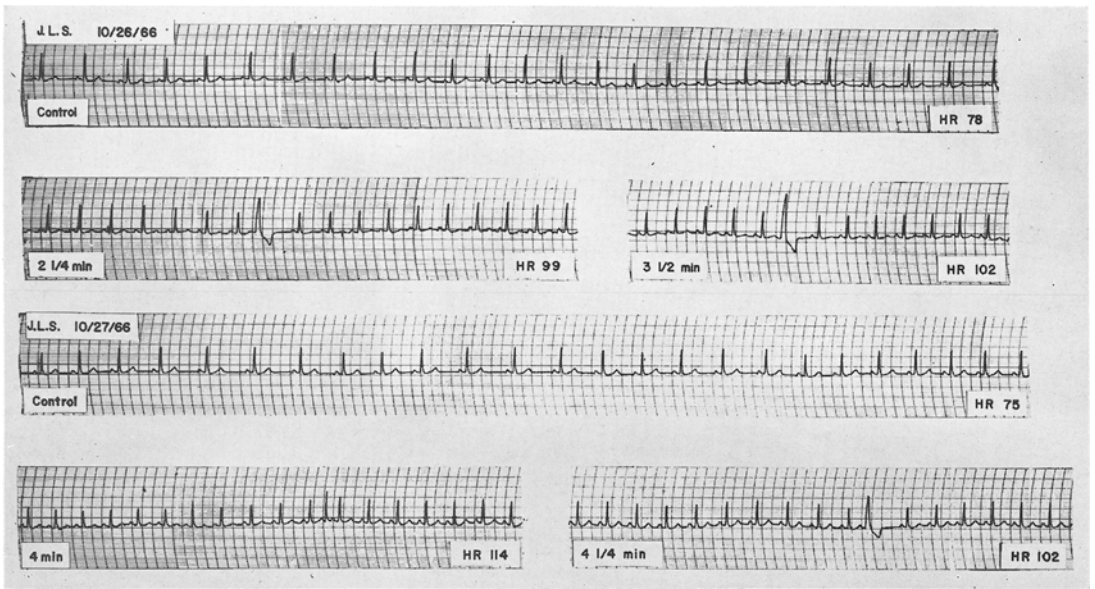

Fig. 6. Control electrocardiogram from a nonsmoker subject. The second set of tracings for each experimental day show changes in cardiac rhythm associated with smoking one cigarette. The time indicates the number of minutes from the onset of smoking. HR represents heart rate in beats per minute.

The increase in heart rate occurs after the first cigarette of the day and remains elevated as long as the individual continues to smoke. The administration of nicotine (22 mg. in 6 hours) did not increase the heart rate above that produced by smoking alone.

The changes in blood pressure were also associated with the use of tobacco. Systolic blood pressure increased significantly after the initial cigarette regardless of whether saline or nicotine was being administered. The diastolic pressure showed less of a tendency to increase. The end result was an increased pulse pressure. The average resting systolic pressure in 5 subjects was 110 mm. Hg at the start of the experimental session, whereas after smoking for 6 hours or smoking plus intravenous nicotine the average systolic pressure was 130 mm. Hg.

Electrocardiographic changes associated with smoking or the intravenous administration of nicotine were observed in 2 volunteers. Fig. 5 shows the EKG recordings from the same subject on three separate days. The rhythm changes illustrated in the upper and lower tracings were associated with the intravenous administration of nicotine, 1 and 4 mg. respectively. The bigeminy seen in the second set of tracings occurred 4 minutes after the subject had started to smoke the first cigarette of the day. It was of interest to note that subsequent cigarettes or continued intravenous administration of nicotine did not cause alterations in cardiac rhythm. Repeated twelve-lead electrocardiographic tracings showed the individual to be free of disturbances of cardiac rhythm or conduction.

The ECG tracings in Fig. 6 were obtained from a nonsmoker who volunteered to smoke one cigarette while resting in the supine position. The control tracings were obtained after the subject had rested for 30 minutes. The lower tracings of each pair were obtained while the subject smoked a cigarette. On each of two days smoking was associated with the development of coupled beats which subsided within 30 minutes after smoking was discontinued. Fig. 6 also illustrates the marked

increase in heart rate produced by one cigarette.

Discussion

The habitual use of tobacco is related primarily to psychological and social drives, reinforced and perpetuated by the pharmacological actions of nicotine on the central nervous system, the latter being interpreted subjectively either as stimulating or tranquilizing dependent upon the individual response.[11] The importance of nicotine in the cigarette habit has been suspected and subjected to study by a number of investigators. As demonstrated by Johnston,[5] it is possible to mimic the subjective effects of smoking by the parenteral or oral administration of nicotine. These experiments, although lacking in suitable experimental design and experimental controls, suggested that the motivation to smoke was reduced during the administration of nicotine. The study by Finnegan, Larson, and Haag[3] further emphasized the role of nicotine by demonstrating that smokers can detect a reduction in nicotine content of cigarettes and that in some individuals a cigarette containing no nicotine would be grudgingly accepted as better than no cigarette at all. The latter observation is supported by the fact that denicotinized tobacco has not found general public acceptance as a substitute.[6]

The present investigation attempted to determine if the smoking habit was related to a general craving for the pharmacological effects of nicotine in subjects who were unaware of the nature of the administered drug or the true purpose of the studies. The doses of nicotine used were in the range which did not produce subjective effects; this made it possible to randomly alternate between nicotine and saline infusions in the same subject. The results obtained suggest that nicotine plays a small but significant role in the smoking habit and that part of the craving for a cigarette can be satisfied by the intravenous administration of the alkaloid. This was manifested by a reduction in the number of cigarettes consumed and by a reduction in the amount of each cigarette smoked by subjects receiving intravenous nicotine.

Smoking is a form of dry distillation, during which the nicotine is partially destroyed by the heat of combustion. Part of the vapor is condensed in the cooler regions of the cigarette. The smoke which is inhaled is referred to as the mainstream smoke and that which is given off to the environment is called the sidestream smoke. The standard cigarette with a weight of 1 Gm. contains approximately 20 mg. of nicotine. The data of Pierce[10] and that of Harlan and Mosekey[4] indicate that the mainstream smoke from one cigarette contains from 1.2 to 3 mg. of nicotine. Therefore, the dose of nicotine of 4 mg. per hour intravenously would be equivalent to the amount of the alkaloid absorbed systemically during the smoking of one or two standard cigarettes per hour. Thus, if the pleasure of smoking or craving for tobacco were due to the general effects of the alkaloid we should have observed a much greater reduction in the smoking frequency. As suggested by Ejrup,[1] the physiological effect of nicotine may be general or local. The experimental design used in this study did not permit an evaluation of the importance of the local effects of nicotine in the smoking habit.

The results of the psychological testing procedures, while not presented in this publication, are of significance. The parenteral administration of nicotine did not alter the performances of the subjects in any of the testing procedures. This would suggest that the ability of nicotine to depress cigarette-smoking frequency is a specific effect and not a generalized behavioral action of the alkaloid.

The effects of smoking and nicotine upon the cardiovascular system have been covered in many excellent studies and have been summarized by Larson, Haag, and Silvette.[6] The effects of cigarette smoking upon the heart rate and blood pressure

were of interest in that increases in both parameters occurred immediately with the first cigarette of the day and were maintained throughout the day as long as the subject continued to smoke. The electrocardiographic changes noted in subject M. R. S. (Fig. 5) occurred during the smoking of the first one or two cigarettes or during the initial administration of intravenous nicotine. The electrocardiographic alterations were less prominent and absent as subsequent cigarettes were consumed. It is important to stress that in each instance the subjects had abstained from smoking for a minimum of 8 hours. Therefore, we were in a position to observe the acute effects of smoking or nicotine upon the cardiovascular system. In the majority of healthy subjects neither smoking nor the intravenous injection of nicotine produces any pathological electrocardiographic changes.[9] At times extrasystoles, occasionally coupled, can occur as a result of nicotine in healthy subjects as well as in the presence of cardiac pathology.[8, 9] The subjects showing electrocardiographic changes in heart rhythm were considered to be in good health and had electrocardiographic examinations which were considered to be within normal limits.

The authors are indebted to Dr. Merle Lawrence of the Kresge Hearing Research Institute for providing the laboratory facilities required for this study.

References

1. Ejrup, B.: The role of nicotine in smoking pleasure, nicotinism, treatment, *in* Von Euler, U. S., editor: Tobacco alkaloids and related compounds, New York, 1965, The Macmillan Company.
2. Ejrup, B., and Wikander, P. A.: Forsok med. nicotin, lobelin och placebo, Svenska läk-sällsk. forhandl. **56**: N. 32, 1959.
3. Finnegan, J. K., Larson, P. S., and Haag, H. B.: The role of nicotine in the cigarette habit, Science **102**:94-96, 1945.
4. Harlan, W. R., and Mosekey, J. M.: Tobacco, Encyclopedia Chem. Technology **14**:242, 1955.
5. Johnston, L.: Tobacco smoking and nicotine, Lancet **2**:742, 1942.
6. Larson, P. S., Haag, H. B., and Silvette, H.: Tobacco: Experimental and clinical studies, Baltimore, 1961, The Williams & Wilkins Company.
7. Lewin, L.: Phantastica: Narcotic and stimulating drugs: Their use and abuse, London, 1931, Kegan Paul, Trench, & Co.
8. Mattioli, M.: Observazioni e richerche cliniche sul cuore da tabacco, Cuore e circolaz. **26**: 257-269, 1942.
9. Oram, S., and Sowton, E.: Tobacco angina, Quart. J. Med. **32**:115-143, 1963.
10. Pierce, I. H.: Absorption of nicotine from cigarette smoke, J. Lab. & Clin. Med. **26**: 1322-1325, 1941.
11. Smoking and Health—Report of the Advisory Committee to the Surgeon General of the Public Health Service. U. S. Department of Health, Education and Welfare. Public Health Service Publication No. 1103, Washington, D. C., 1964.