CLINICAL PROGRESS

Effect of Smoking on the Cardiovascular System of Man

By Grace M. Roth and Richard M. Shick

The smoking of tobacco is a truly American custom, first discovered by Columbus in 1492 when he found the Indians of San Salvador smoking tobacco rolled in maize husks. These primitive cigarettes most likely were the precursor of the modern cigarette. From America the smoking of tobacco was spread quickly by the sailors and merchants to Europe and later to Asia.

After the beginning of colonization of North America by the English, the cultivation and smoking of tobacco by the white man returned to this country from Europe. In the early colonies tobacco was chewed, sniffed, and smoked in pipes. The cigar was not made in North America until 1801, although cigars had been made earlier in Cuba and the first cigar factory had been erected in Hamburg in 1788. With the introduction of the cigar, the tobacco habit changed considerably and cigar smoking became popular. The cigar became the symbol of wealth, substance, and solidity.

The introduction of cigarettes was a slower process; it started in France, proceeded to England and then to the United States by about 1850.

The merits and demerits of tobacco have been the subject of much controversy. Hundreds of books, pamphlets, and poems have portrayed the joys and glory of tobacco and the way to health by its use, while equally as many publications have satirized and virulently condemned the bewitching leaf. Physicians, scientists, philosophers, and men of the world have supported both sides, but sharp differences of opinion still remain.

During the century from 1848 through 1947, the effects of long-continued use of tobacco on the heart and peripheral blood vessels of man were investigated widely. A few of these investigations will be mentioned to show the trends. Graves,1 in England, as early as 1848 published observations of disturbed heart action produced by heavy smoking. Beau,2 in 1862, stated that tobacco smoking could initiate angina pectoris under certain conditions. Favarger,3 in 1887, suggested that nicotine was the most important of the poisons in tobacco smoke. He described chronic tobacco poisoning in detail and stated that the continued use of nicotine initiated coronary spasm by constriction of the coronary arteries. Thus, chronic tobacco poisoning was given as the true cause of heart disease. Even then some doubt arose because some persons 70 to 80 years of age did not have any evidence of chronic tobacco poisoning in spite of heavy smoking for many years. Huchard,4 another incriminator of tobacco as a cause of heart disease, introduced the term "tobacco angina" in 1899. Plesch5 disagreed with Favarger and reported that chronic excessive use of tobacco was not the chief cause of heart disease. Still other investigators6-10 stated that heavy smoking predisposed to arteriosclerosis.

More evidence of the causal role of tobacco in peripheral vascular disease was available, particularly in thromboangiitis obliterans. Although thromboangiitis obliterans and to a less degree coronary heart disease seem to have some statistical relationship to the smoking of tobacco, experimental and clinical evidence indicated that smoking probably was only a contributory factor and not an etiologic one.

Today one of the major medical questions is, "Does smoking really have an effect on the cardiovascular system of man?" It seemed

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wise to review the evidence presented on this question during the last decade and to refer briefly to earlier work whenever necessary.

**Substances in Tobacco Smoke and Their Absorption**

The 2 substances absorbed in any appreciable amounts from tobacco smoke are carbon monoxide and nicotine. Previously many of the effects of smoking were attributed to carbon monoxide. Now acceptable evidence indicates that carbon monoxide plays little, if any, role in producing the cardiovascular effects, and this leaves nicotine as the most important agent.

The first question that might be asked is how much nicotine is absorbed when a cigarette is smoked? The standard cigarette weighs 1 Gm. and contains 20 mg. of nicotine. According to Baumberger,\(^1\) when a cigarette is smoked, 35 per cent of the nicotine is destroyed at the burning tip, 35 per cent is lost in the side stream and much of this is given off to the environment, 22 per cent enters the mouth through the main stream of the smoke, and the remaining 8 per cent remains in the unsmoked portion of the cigarette. It is estimated that 3 to 4 mg. of nicotine enters the respiratory passages while from 2.5 to 3 mg. is absorbed by the lungs. When the smoke is held in the mouth for 2 seconds and then released, 66 to 77 per cent of the nicotine is absorbed, and when smoke is inhaled, 88 to 98 per cent of the nicotine is absorbed. Thus the amount of nicotine absorbed is dependent on how long the smoke remains in the mouth, whether the smoke is inhaled or not, and the frequency and depth of inhalation.

Weatherby\(^1^2\) found that vasoconstriction took place after smoking standard brands of cigarettes but that when such cigarettes were denicotinized and smoked, the vasoconstriction was abolished almost completely. Other investigators\(^1^3-1^7\) found that vascular effects produced by smoking were similar whether standard cigarettes or commercially denicotinized cigarettes were smoked.

**Effect of the Filter.** McDonald, Sheard, and Roth\(^1^8\) reported that the physiologic effects of smoking a cigarette with a filter were not different from those of smoking an ordinary cigarette and smoking a denicotinized cigarette.

Haag, Finnegan, and Larson\(^1^9\) studied the efficiency of filters in reducing the effects of irritants of the edema-producing type in cigarette smoke. They found that the edema-producing properties of the second and third puffs of smoke from an unfiltered cigarette were significantly less than those of the fifth and sixth or the eighth and ninth puffs. Also, when used the first time, cartridge filters significantly reduced the irritants of edema-producing type contained in cigarette smoke. However, with continued use, their effectiveness was reduced. The investigators stated, therefore, that the development of increasingly efficient filters would have as its culminating achievement a filter that would pass no smoke at all. It is exceedingly doubtful that the average smoker would take kindly to this.

Because of the controversy concerning the production of cancer of the lung by smoking, additional filters have been produced as a measure of protection in removing both nicotine and tars from cigarette smoke. From a survey made by the Chemical Laboratory of the American Medical Association,\(^2^0\) the following results were found. In all cases the fraction of nicotine removed from the main stream of smoke by the filter is small. The amounts of nicotine and tars assimilated by the smoker are proportional to the amounts that reach a smoker’s mouth from the main stream of the smoke. The amounts assimilated cannot be determined easily because of the variations among individuals and the differences in their smoking habits.

**Effects of Central Origin on Smoker and Nonsmoker**

The nausea and vomiting that may occur when tobacco is first smoked by a nonsmoker are mainly central in origin. Tolerance to nicotine indicated by cessation of these symptoms does take place after repeated smoking. This is evidenced by the absence of
these effects in habitual smokers. Therefore the actual effect of smoking can be determined better in a habitual smoker than in a nonsmoker.

**Effects of Smoking on the Peripheral Circulation**

That smoking causes constriction of the peripheral blood vessels, both in normal subjects and more conspicuously in those with peripheral vascular disease, is rather generally agreed. To have a subject smoke and then to determine the effects of the smoking on the peripheral blood flow seem simple. However, all methods of measuring blood flow in man are indirect, and each has its own inherent error. Furthermore, irrespective of the method used, certain fundamental factors concerned with the status of the individual bear directly on the measurement of the blood flow in the extremities. These appear to be the environmental temperature, the position of the subject, particularly of his extremities, the taking of food and the basal metabolic rate.

To determine changes in blood flow, one of us (Roth) and co-workers used the thermocouple method of Sheard, which measures small changes in the skin temperature electrically. This method was chosen because previous work had demonstrated that the skin temperature of the fingers and toes is the most sensitive indicator of the vasomotor tone of the superficial blood vessels of the extremities. Thermocouples were attached to the fingers and toes to determine any changes before and after smoking. All the factors previously mentioned concerned with the status of the individual were considered in these studies.

At a constant room temperature of 25.5°C (78°F.) normally the fingers are warmer than the toes, and the temperature of the toes will depend on the initial basal heat, or the basal metabolic rate. As figure 1 indicates, the skin temperature of the fingers and toes of a man with rather high basal metabolic rate increases rapidly after a meal. This demonstrates vasodilatation. The skin temperature of the toes particularly of the subject with low basal metabolic rate will increase to the same height after a meal, but it will take longer. For the man with the low basal metabolic rate whose skin temperatures are shown in figure 1, it took 2½ hours to produce the same degree of vasodilatation. The pattern will be the same whatever vasodilating agent is used. If the basal metabolic rate of these 2 individuals were not known, the effects of food would be confusing.

The Smoking Test. Smoking tests were carried out in a constant-temperature room at 25.5°C (78°F.) and relative humidity of 40 per cent. The subjects fasted for 15 hours before the test. During the tests they wore light-weight, short pajamas and were in a supine position on comfortable beds. Basal metabolic rates were determined before most tests.

At intervals of 10 minutes the temperatures of the plantar surfaces of both first and third toes and the volar sides of the distal phalanges of both first and third fingers were measured by copper constantan thermocouples. The blood pressure, pulse rates, and the basal metabolic rate were determined during the control period. When fairly constant readings of skin temperature, blood pressure, and pulse rate were obtained, smoking was begun. Cigarettes of different brands bought on the open market were used. Two cigarettes were smoked in succession until two thirds of each had been smoked. Simultaneous determinations of blood pressure, pulse rate, and skin temperature were obtained at intervals of 1 minute during the smoking period, which generally lasted 12 to 16 minutes. Observations were continued for 30 minutes after smoking had ceased.

All the subjects were habitual smokers and inhaled the tobacco smoke with the depth and frequency to which they were accustomed, usually about once per minute. All unnecessary noise and other undesirable stimuli that might cause vasocostriction were excluded.

Sixty-six standard smoking tests were carried out on 6 normal subjects, 4 physicians and 2 women technicians whose basal metabolic rates ranged from −17 to +1 per cent. These studies showed that the responses to smoking, of the skin temperature of the same individual, varied from day to day according to the basal metabolic rate, but the increase of the blood pressure and pulse rate during smoking varied little from day to day. Thus it was necessary to determine the basal meta-
bolic rate and skin temperatures for each study. On smoking, the skin temperature of the toes of all the subjects decreased an average of 2.5 C. (4.5 F.) with a range from 1 to 4 C. (1.8 to 7.2 F.). For the fingers the average decrease was 3.2 C. (5.8 F.). The average increase of blood pressure during smoking was 20 mm. Hg systolic and 14 mm. diastolic. The pulse rate increased an average of 36 beats per minute, ranging from 20 to 52 beats. The electrocardiographic changes consisted of increased heart rate and decreased amplitude of T waves with inverted T waves in one instance.

Habitual smokers did not show tolerance to the vascular effects of smoking as the skin temperatures of the extremities decreased and the blood pressure and pulse rate increased. The decrease of the skin temperature was not related to the length of time the subject had been a smoker or the number of cigarettes smoked a day.

Two groups of tests were made to determine whether the vascular changes were due to nicotine: 1. Normal subjects received a solution of sodium chloride intravenously as a control and then 2 mg. of nicotine was added to the solution without the subject's knowledge. The skin temperatures decreased rapidly and definitely, the heart rate increased, and the amplitude of the T waves decreased. 2. Thirty smoking tests were carried out on additional subjects with various commercially available denicotinized cigarettes. The vascular effects were similar to those obtained from standard cigarettes.

To determine how much the content of nicotine in a cigarette should be decreased to banish the vascular effects, 192 standard smoking tests were done on 29 normal subjects who were between the ages of 20 and 36 years. The main stream of smoke from 1 cigarette from each of the 6 batches used contained respectively an average of 0.23, 0.55, 1.28, 1.83, 2.47, and 3 mg. of nicotine. As the concentration of nicotine in the main stream of

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**Fig. 1.** The increase of the skin temperatures of the toes as well as the metabolic rate after the ingestion of a substantial meal in two normal individuals. **Left.** The subject with high basal heat production. **Right.** A subject with low basal heat production. The curves show a delay in the rise in the skin temperatures of the toes in the subject with the lower basal metabolic rate. (Reprinted from Roth, G. M. and Sheard, C.: Relation of basal metabolic rate to vasodilatation and vasoconstriction of the extremities of normal subjects as measured by skin temperatures. Circulation 1: 1142, 1950.)
the smoke increased, the skin temperatures of both the fingers and toes decreased until the effects were the same as those from standard cigarettes. The lower the concentration of nicotine in the smoke the less the blood pressure and pulse rate increased from the basal level and vice versa. The increase was sharp when the concentration of nicotine was raised from 0.55 to 1.28 mg. Apparently then, the content of nicotine in a cigarette must be decreased more than 60 per cent from that in a standard cigarette before smoking produces only slight or no vascular effects. The habitual smoker finds the smoking of cigarettes containing so little nicotine unsatisfactory.

Since alcohol\textsuperscript{27} taken by mouth will dilate the blood vessels of the extremities in contrast to the constriction from smoking, smoking tests were made on normal subjects and the next day 87 smoking tests were made on the same subjects after ingestion of alcohol. The blood pressure and pulse rate rose definitely on smoking after the ingestion of alcohol in all the subjects. In 72 per cent the skin temperatures of the fingers and toes decreased below the basal level on smoking during the vasodilatation from alcohol (fig. 2). This seems to indicate that the alcohol did not prevent vasoconstriction from smoking.

From 425 smoking tests with tobacco or corn silk\textsuperscript{28} on 100 normal subjects who were habitual smokers, the following observations were made: 1. No tolerance develops to tobacco with respect to the vascular effects. 2. An elevation of the blood pressure and pulse rate and a decrease of the skin temperature of the extremities occur only on smoking tobacco. 3. Nicotine appears to be the most important factor in producing the vascular effects. 4. Alcohol does not nullify the effect of smoking.

Recently another investigation by Eckstein, Wood, and Wilkins\textsuperscript{28} demonstrated that vaso-
constriction could occur during vasodilatation. These authors reported that smoking 2 cigarettes reduced the blood flow in the foot in 28 of 31 tests. Reductions ranged from 9 to 55 per cent and averaged 22.3 per cent. Smoking in a normal temperature room, a warm room, and also in a cool room caused average reductions in blood flow of 21.7, 23.0, and 20.6 per cent respectively. This striking similarity of response suggests that these different control levels of vasomotor activity do not alter significantly the vasoconstrictor effects of smoking cigarettes. Under the conditions of this study smoking was a less intense vasoconstricting stimulus than cooling the environment from 83 to 68 F.

Returning to the depth and frequency of inhalation of tobacco smoke, Shepherd\(^29\) reported on the effects of cigarette smoking on blood flow through the hand as determined by the plethysmograph. In his opinion the frequency of inhalation of tobacco smoke was most important and has not received enough attention. He chose an inhalation rate of 1 a minute. In studies by one of us (Roth) on the variation in individuals, inhalations were not more rapid than 1 a minute. Shepherd previously had not obtained as great an increase in blood pressure and pulse rate during smoking as our group had, but when 2 of his subjects inhaled at this rate following 15 hours without food and cigarettes, the increases in pulse rate and blood pressure were similar to those obtained by us. The influence of food seems important in all studies concerned with peripheral circulation.

**Effect on Peripheral Vascular Disease.** The evidence that smoking plays a role in the progression of peripheral vascular disease is no longer controversial. Although it may not be the etiologic factor, it is certainly the most prominent contributing factor. In the series of patients seen at the Mayo Clinic thromboangiitis obliterans rarely if ever was seen in a nonsmoker. Gifford and Hines\(^30\) reported a case of thromboangiitis obliterans in which a 12-year clinical cure was obtained after complete cessation of smoking. Whether the beneficial effect of abstinence from tobacco in thromboangiitis obliterans accrues primarily from arresting the disease process in the arteries and veins, or whether circulation is improved merely by relaxation of unaffected arteries is hypothetical. That abstinence from tobacco is beneficial and should form the primary basis for all treatment in these cases is not hypothetical but is a well-established fact.

Although we discussed filters earlier, we think it important to report further that Friedell\(^31\) has found that men and women are not equally sensitive to tobacco and that the principle of filtration of tobacco smoke is probably a good one and should be used by both men and women. Women evidently need it more than men.

In regard to the new filters, Wright\(^32\) has stated:

Since at least one of the manufacturers of filtered cigarettes used the results of tests of the laboratory of the American Medical Association in advertising, implying that there is a definite added safety factor, I believe that the following information should be available. During the past years, we have tested a variety of filtered cigarettes as well as the so-called denicotinized cigarettes and have yet to find any that contain tobaccos that do not produce a response in the vascular system as measured by drops in temperature of the finger tips and other determinations. In addition, we have repeatedly observed that relapse in thromboangiitis obliterans may occur when patients smoke the filtered cigarettes. Two days ago, we admitted a patient to the New York Hospital who presents a perfect example of this. This patient first had active thromboangiitis obliterans in 1940. In 1941, he stopped smoking and his symptoms remained quiescent until 1949 when he started to smoke. Within six months gangrene of three toes developed. Once more, on abstinence from smoking and with other therapy, the disease became quiescent, and the man was free from symptoms. About four months ago, impressed by the advertising of filtered cigarettes, he started to smoke filtered cigarettes. Again, his disease has been reactivated, and he has early signs of pregangrenous involvement of the tips of two toes.

In 1950 Rapaport, Frank, and Massell\(^33\) reported that lumbar sympathectomy abolished the peripheral vasoconstriction produced by smoking in the lower extremities of 19 patients. They concluded that the vasoconstriction, therefore, is mediated by sym-
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same agents such as epinephrine or posterior pituitary hormone. The response was the same whether sympathectomy was performed for thromboangiitis obliterans, arteriosclerosis, or severe vasospasm. One of us (Roth) has likewise found no vasoconstriction as indicated by the skin temperature of the toes during smoking if lumbar sympathectomy was complete, but a considerable fall in the skin temperatures of the fingers occurs during smoking. Thus after lumbar sympathectomy the remainder of the sympathetic nervous system seems to function in a more than adequate manner. This effect can also be seen in the graphs of Rapaport, Frank, and Massell.

EFFECTS OF TOBACCO ON THE HEART

Most investigators agree that the effects of smoking tobacco or the intravenous injection of nicotine on the heart are an increase in the pulse rate, an elevation of the arterial blood pressure, and some flattening of the T waves in the electrocardiogram. Two conflicting opinions had developed about 20 years ago: (1) that the changes are due solely to the increased work of the heart and (2) that the changes are due to spasm or constriction of the coronary arteries. In regard to the first, Graybiel, Starr, and White44 reported in 1938 that undoubtedly a few individuals are susceptible to small amounts of nicotine absorbed during smoking. They suggested that the occasional attacks of angina pectoris precipitated by smoking (tobacco angina) are not the result of coronary vasoconstriction but of a sudden increase in the work of the heart as shown by the increase in blood pressure or heart rate or both.

In the present year further work has substantiated this opinion in regard to the increased work of the heart. Kien, Lasker, and Sherrod25 determined the effect of cigarette smoke on the open chests of dogs during pentobarbital anesthesia by measuring blood pressure, cardiac output, coronary blood flow, cardiac oxygen consumption, cardiac work, and the electrocardiographic effects. Immediately after the administration, by a specially calibrated smoking device, of 1,200 to 1,500 ml. of cigarette smoke from a standard “king-sized” nonfiltered cigarette, the heart slowed briefly but markedly, and a sustained pressor response followed. These effects were attributed to autonomic ganglionic stimulation by the nicotine absorbed from the cigarette smoke. The “time course” of the hemodynamic responses indicated an early increase in cardiac work that extended for 3 minutes. The coronary blood flow was increased in relation to the rises in both blood pressure and cardiac output. No independent action of cigarette smoke on the coronary vessels was observed. The coronary arteriovenous oxygen difference decreased markedly at first and then increased for a long time. As a consequence, the cardiac oxygen utilization was reduced initially during the period of greatly increased cardiac work and then increased and remained high. These alterations were explained on the basis of metabolic changes in the myocardium. In addition there were extreme electrocardiographic alterations with the changes in oxygen utilization during the period of increased cardiac work.

Until recently it has not been possible to measure the effect of nicotine on the coronary blood flow in man, but it has been shown that nicotine decreases the blood flow in the coronary arteries of the dog. Bellet, Kirshbaum, Meade, and Schwartz26 administered nicotine to dogs before and after ligation of a coronary artery. After the ligation only a fourth as much nicotine as before operation was required to produce marked electrocardiographic changes.

Travell, Karp, and Rinzler37 recently studied the electrocardiographic effects of nicotine on 12 normal rabbits and 16 cholesterol-fed rabbits with coronary artery disease. Nicotine caused sagging depression of the S-T segment in about 10 per cent of the rabbits with coronary artery disease. Occasionally lowering of the T waves occurred, but this may occur spontaneously in rabbits. Perfusion of the isolated hearts of rabbits with atherosclerosis showed a higher coronary flow, slower heart rate, and lower amplitude of contraction than in normal hearts. Nicotine in graded doses
injected directly into the perfusion system produced a diminution in coronary blood flow in the perfused hearts that previously had been made atherosclerotic.

In contrast West, Guzman, and Bellet\textsuperscript{88} working on dogs catheterized the circumflex or anterior descending branch of the left coronary artery via one carotid artery and cannulated the coronary sinus via one external jugular vein. From 0.25 to 0.5 mg. of nicotine per Kg. of body weight was injected into the coronary arteries. Small doses of nicotine produced a definite decrease in myocardial contractility but no other discernible effects. Larger doses increased coronary flow and myocardial contractility without any change in systemic blood pressure and heart rate. These effects were completely blocked by tetraethylammonium bromide. Still larger doses of nicotine elicited the coronary chemoreflex (Bezold-Jarish) accompanied by decrease in coronary blood flow. These effects were abolished by bilateral vagotomY. West, Guzman, and Bellet concluded that there was no evidence of coronary constriction following administration of nicotine and that the explanation of the effects was the presence in the heart of parasympathetic and sympathetic ganglia and chemoreceptors influenced by nicotine.

In 1957 the first studies using direct catheterization of the coronary sinus and a needle in the femoral artery were carried out on human beings by Bargeron and co-workers.\textsuperscript{38} From studies on 30 adults they found that smoking a cigarette caused a significant rise in coronary blood flow and heart rate, a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose. In normal subjects smoking did not produce constriction of the coronary blood vessels. As yet the various investigators do not agree completely.

The work of Burn and his co-workers\textsuperscript{40-42} on man presents an entirely different view in regard to coronary vasoconstriction. They\textsuperscript{40} and Walker\textsuperscript{41} found that smoking 1 or 2 cigarettes had an antidiuretic effect for 1 to 3 hours in man. An injection of nicotine (0.33 to 1 mg.) had a similar antidiuretic effect. According to them the inhibitory effects of both smoking and nicotine were accompanied by a rise in the total excretion of chloride, an effect characteristic of the action of the posterior pituitary hormone. In 1951 Burn and Grewal\textsuperscript{42} stated that the posterior pituitary hormone is excreted in the urine after 1 or 2 cigarettes are smoked. Thus Burn and Grewal concluded that smoking may produce coronary constriction in man as a result of the release of posterior pituitary hormone.

In the present decade, the electrocardiograph or the ballistocardiograph, or in a few instances, both have been employed in the study of the effects of smoking on the heart of man.

Electrocardiographic Findings. To determine whether smoking of tobacco produced a spasm of the coronary arteries as a result of transient myocardial impairment, von Ahn\textsuperscript{43} produced hypoxia in the myocardium and in turn coronary insufficiency by the inspiration of oxygen-poor gases. He found that tobacco smoking or injection of nicotine during hypoxia increased the heart rate and the amplitude of the P waves, flattened the T waves, and caused slight depression of the S-T segments. These electrocardiographic changes were due chiefly to increased sympathetic tone. In studying the origin of these changes, he found that dihydroergotamine counteracted the effect of nicotine on the electrocardiogram, whereas atropine led to approximately the same degree of flattening of the T waves as nicotine. There was practically no flattening of T waves or depression of S-T segments after elimination of the increased heart rate due to smoking or injection of nicotine. Physical work during hypoxia led to more marked flattening of the T waves and depression of the S-T segments than did nicotine under the same condition. In certain cases heavy smoking or injection of nicotine resulted in flattening of the T waves without simultaneous increase in heart rate. This was probably due to increased adrenal secretion. Von Ahn concluded that it is unlikely that the electrocardiographic changes provoked by
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smoking or injection of nicotine during hypoxia in persons with clinically healthy hearts were of coronary origin, but that they were probably secondary to increased heart rate.

Ballistocardiographic Findings. The ballistocardiograph records the stroke volume of the heart as a means of determining the cardiac output. Starr\textsuperscript{44} almost 20 years ago set up the normal standards and various modifications of ballistocardiograms. Ten to 14 years later Starr and Hildreth\textsuperscript{45} tested 67 of the same individuals and determined the effect of aging hearts and of the development of disease in these previously healthy persons. They conceived the idea that the weakening heart has a recourse open to it that has not been realized. By changing the manner of systolic ejection of blood so that acceleration is kept at a minimum, the load of the heart is lifted more slowly, and by this means a heart lacking in strength can maintain its cardiac output unimpaired. It is this change in cardiac function that can be detected from the change in the form of the ballistocardiogram seen so clearly as age advances. And since this adaptation will leave the heart's main function, that of pumping blood essentially unimpaired, it provides an explanation for the observation that the ballistocardiogram will indicate an abnormality early in the course of disease before the development of symptoms or other evidence of cardiac dysfunction.

Dock,\textsuperscript{46} in discussing Starr's paper, pointed out that smoking in some persons can change the ballistocardiogram and the changes produced may be identical to those seen after coronary accidents and in older people who are aware of heart trouble. He emphasized, therefore, that tracings must be taken under basal conditions.

The introduction of the ballistocardiograph stimulated various workers to further study of the effect of smoking on the heart. In 1947, Boyle and co-workers\textsuperscript{47} used the ballistocardiograph in order to determine the effects of nicotine on the heart in normal persons and in patients with cardiovascular disease. The variations in responses were similar; severe reactions depended on individual susceptibility rather than on the presence of disease. In some patients with heart disease injection of nicotine induced coronary insufficiency that could be the result of constriction of the coronary arteries or of increased work of the heart or of both.

Levy and associates\textsuperscript{17} studied the effects of smoking of regular and commercially denicotinized cigarettes on a normal group and a cardiac group. In both groups the systolic and diastolic blood pressures as well as the heart rate increased slightly, but the average cardiac output did not change. The form of the electrocardiogram changed in less than half of the subjects in each group.

Dock and co-workers\textsuperscript{48} commented that pathologic patterns were rarely encountered when ballistocardiographic tracings were made with the breath held as was usual with the Nickerson table used by Levy and his group.

Mandelbaum and Mandelbaum,\textsuperscript{49} in 1951, used a high-frequency recording ballistocardiograph during normal breathing on 100 consecutive subjects without heart disease. Only 3 ballistocardiograms from the subjects less than 50 years of age were abnormal after smoking, while approximately 43 per cent of those from older persons showed some abnormalities. Among patients with coronary heart disease and hypertension, the incidence of abnormal ballistocardiograms on smoking was much greater. In 1952, the Mandelbaums\textsuperscript{50} again reported that 28 per cent of 50 normal subjects less than age 40 responded abnormally to smoking as indicated by the ballistocardiogram. In persons with heart disease the incidence of abnormality after smoking was more than twice this number. The Mandelbaums regarded as significant the fact that of 35 patients with heart disease whom they induced to abstain from smoking, 30 obtained symptomatic relief.

Capecse and Schrager\textsuperscript{51} found that the high frequency recording of the ballistocardiograph was much more sensitive than the electrocardiogram to the effect of nicotine on the
heart. Smoking produced mild alterations in the ballistocardiograms of 18 of 31 subjects (23 normal) and great changes in 7 (4 normal).

Scarborough and associates did not consider the ballistocardiogram a good diagnostic test for use on resting persons suspected of having coronary disease because the same abnormalities were found in about 75 per cent of patients given a clinical diagnosis of coronary disease and in 25 per cent of a normal control group of corresponding age.

Henderson in England reported that after smoking all 50 healthy young persons studied had normal ballistocardiograms in spite of an increase in average pulse rate, whereas 10.3 per cent of 30 older persons believed to be healthy had temporarily abnormal ballistocardiograms. In 38 per cent of 40 patients with coronary heart disease and in 4 patients without coronary heart disease but suffering from diseases in which coronary heart disease is a frequent complication, ballistocardiograms became abnormal or more abnormal in form on smoking. Henderson concluded that unusual cardiac sensitivity to nicotine can readily be detected from the ballistocardiogram, particularly in cardiac patients, and that pre-existing coronary artery disease enhances the deleterious effects of smoking on cardiac contraction. He said too that increased work of the heart might often have been a factor in producing relative ischemia, but he suggested, as Burn did, that an outpouring of pituitary hormones is the most likely explanation.

Davis and co-workers reported in 1953 that the high incidence of abnormal ballistocardiograms among older persons limits the value of this method in persons more than 50 years of age. The relative frequency of normal records from those less than 50 years old who have clinical evidence of coronary disease likewise impairs the diagnostic usefulness of this instrument.

After they studied the effects of smoking on 200 subjects, 118 controls and 82 patients with coronary heart disease, by means of the ballistocardiograph, they concluded, however, that the method had diagnostic value as only 6.8 per cent of the normal controls had abnormal ballistocardiograms in contrast to 58.6 per cent of the patients with diseased coronary arteries. This differential margin of 9.1:1 was more discriminating than that of any other objective method in separating patients with coronary disease from normal controls. In an extension of their previous work in 1956, they reported the effects of smoking on the ballistocardiograms of 252 normal subjects and 190 patients with coronary artery disease. Changes occurred on smoking in 7.5 per cent of the control subjects in contrast to 48.9 per cent of the coronary group. No abnormality occurred in any control subject who was less than age 40 while abnormalities occurred in only 3 of 89 normal subjects in the fifth decade. Although these figures have a discriminatory ratio of 6.5:1, which is less than the 9.1:1 ratio of the earlier series, Clough considered them highly significant.

Kelly and co-workers found no abnormalities in the ballistocardiograms in 100 healthy high school lads made during rest and no real ones after smoking. They assumed that the abnormal tracings seen occasionally after smoking represented poor habituation to tobacco.

Simon, Iglauer, and Braunstein reported that the gross changes in the ballistocardiograms of many coronary patients and of some normal subjects more than 30 years of age make it impossible to measure and compare the overall changes in stroke volume and cardiac output that occur after smoking. They found no significant change in cardiac output and in the form of the ballistocardiograms of 17 normal young men following smoking.

In contrast, Buff reported abnormalities in 42 (10 per cent) of 400 ballistocardiograms made after smoking on 250 men and 150 women. All were less than 40 years of age.

In 1956, Strober studied the effect of smoking on the ballistocardiograms of 2,736 male subjects at an air force base. The vast majority of the subjects had normal ballisto-
cardiograms after smoking. Of the 120 smokers in the obese group, 45 per cent had abnormal tracings after smoking, whereas in the nonobese group, 3.6 per cent had abnormal tracings. In regard to obesity Brozek and Keys noted no significant differences in relative weight, arm diameter corrected for subcutaneous fat (as a measure of musculature), or body density in a group of middle-aged business and professional men who never smoked from those in a group who were heavy smokers. They considered use of either cigarettes alone or all forms of tobacco smoking. However, in a study carried out for 5 years on 17 men who stopped smoking without a superimposed reducing diet the mean weights for 2 years prior to stopping smoking were 75.3 and 75.8 Kg. respectively and increased to 78.4 and 79.3 Kg. in the next 2 years. The increase was statistically highly significant.

Master, Donoso, Pordy, and Chesky carried out studies with the ballistocardiogram on 36 patients less than 50 years of age with uncomplicated peripheral arteriosclerosis or uncomplicated thromboangiitis obliterans; 28 had abnormal ballistocardiograms. Peripheral vascular disease per se, therefore, may produce an abnormal ballistocardiogram at rest in the absence of cardiac disease. When cardiac disease was evident together with peripheral vascular disease in 29 patients at rest, all the ballistocardiograms were abnormal.

Russek and co-workers studied 65 subjects; 28 normal persons who were habitual smokers, and 37 patients with coronary disease. They observed that on smoking, 16 of 28 normal subjects had significant changes in the electrocardiogram and ballistocardiogram, and 2 showed changes closely simulating those of patients with coronary artery insufficiency. No significant improvement in the electrocardiogram or ballistocardiogram was observed in any of these normal subjects as a result of the administration of glyceryl trinitrate. They concluded then that tobacco heart or tobacco angina is not due to underlying cardiac disease but is a definite clinical entity representing functional derangement of this organ due to nicotine. Total abstinence from tobacco was followed by disappearance of all symptoms and electrocardiographic and ballistocardiographic abnormalities.

They also stated that the main effects of tobacco on the cardiovascular system of hypersensitive normal subjects are not due to coronary vasoconstriction but appear more likely to be due to direct myocardial action, or to the effect of nicotine on the cardiac ganglion, or to both. In patients with coronary heart disease glyceryl trinitrate failed to modify or prevent ballistocardiographic changes induced by smoking, while whisky significantly decreased the ballistocardiographic abnormalities after smoking. Because alcohol did not prevent the electrocardiographic changes induced in such patients by a standard exercise test, they concluded that the nicotine response was based primarily on peripheral vascular constriction and not on alterations in coronary blood flow. They were of the opinion that the ballistocardiogram unlike the electrocardiogram was influenced not only by abnormalities in the heart itself but also to an equal or greater degree by changes in the vascular tree. In a strict sense the deterioration of the ballistocardiogram seen in patients with coronary disease after smoking did not seem to be due to hypersensitivity but rather to latent or overt inadequacies in myocardial function brought to light by peripheral vasoconstriction.

A digression will be made to include at this point some earlier work carried out in 1938 by Hines and one of us (Roth) on the effect of smoking on the blood pressure in order to supplement the work of Thomas and her associates soon to be considered. Our study was on 30 normal reactors and hyperreactors and 56 patients with hypertension, as determined by the cold pressor test. In the normal subjects with normal reactions to the cold pressor test the rise in the blood pressure during smoking was 17/8 mm. Hg while in those with hyperreactions it was 30/17. In the patients with hypertension the rise in the blood pressure was 41/23 and in the non-
smokers only 26/9. In the 10 patients with hypertension who had the greatest rise in blood pressure during smoking, the average rise was 47/32. In a more recent group of 40 normal subjects the rise during smoking was from 105/72 to 124/83. In 60 subjects who were hyperreactors to the cold pressor test the rise was 32/21, while in the 10 patients with hypertension the rise was 39/24 or from a basal pressure of 198/130 to 237/154. The conclusion from this study was that the effect of smoking tobacco on the blood pressure of the subjects or patients with inherently hyperreactive vascular systems as measured by the cold pressor test is not due to a nonspecific stimulus acting on a hyperreactive vascular system but is the result, at least in part, of the nicotine in the tobacco, which produces vasoconstriction.

Thomas, Bateman, Lindberg, and Bornholdt studied the ballistocardiographic effects of smoking on 113 healthy medical students, 103 men and 10 women, who were 21 to 35 years of age. In both smokers and nonsmokers the systolic and diastolic pressure, pulse pressure, heart rate, stroke volume, cardiac output, and cardiac index showed statistically significant changes on smoking 1 cigarette. The direction and degree of change after smoking varied greatly from subject to subject, so that striking individual differences in circulatory patterns were found.

Subjects whose cardiac output and cardiac index were large to begin with and whose parents had hypertension showed more than twice as great an increase in cardiac output and cardiac index on smoking 1 cigarette as did subjects whose parents did not have hypertension. No such relationship between familial hypertension and hyperreactivity to smoking has previously been described. The studies indicating that hyperreactivity to smoking is related to hyperreactivity to the cold pressor test, and that hypertensive patients react more strongly to smoking than do normotensive subjects are in harmony with the hypothesis that hyperreactivity appears particularly frequently in individuals who are the offspring of hypertensive parents and may be a precursor of hypertension in a given individual. Likewise, subjects with a parental history of coronary disease showed little increase in cardiac output and cardiac index in contrast to subjects with healthy parents.

Statistical Studies. Not many statistical surveys have been made in the past 10 years. Hammond and Horn in 1954 found that in the age group 60 to 65 years the death rates for coronary disease for men who smoked a pack or more of cigarettes a day were twice as high as the rates for men who had never smoked. This was a confirmation of the earlier figures of Pearl.

Doll and Hill in 1956 reported that the mortality rate among British doctors with coronary disease increased progressively with the amount of tobacco smoked. For the group who were more than 35 years of age, the mortality rate was 42 per cent higher in heavy smokers than in nonsmokers.

Sigler reviewed the records of 1,520 patients with demonstrable coronary disease and the anginal syndrome; more than two thirds of them had had at least 1 attack of coronary occlusion. Of this number 985 were living, and 535 dead. Of the 1,186 males in the group, 519 were nonsmokers and 667 smokers. Of the 334 females, 292 were nonsmokers and 42 smokers. Clinical manifestations of coronary disease developed before 50 years of age in 29.2 per cent of the nonsmokers and 44.8 per cent of the smokers among the males, and in only 19.1 per cent of nonsmokers and 50.2 per cent of smokers among the females. The higher the degree of smoking the earlier was the onset of the clinical manifestations of coronary disease. The age at death was also less for smokers than for nonsmokers. Of the males, 20.2 per cent of the smokers and 6.4 per cent of the nonsmokers died before the age of 50 years. Likewise of the females, 46.5 per cent of the smokers and only 5.6 per cent of the nonsmokers died before that age.

Sigler stated that although tobacco may expedite somewhat the development of coronary disease in a small proportion of the population, it is not the sole cause of coronary disease.
Dolgoff and associates\textsuperscript{70} studied the smoking habits of 551 men with coronary disease without hypertension and 328 men with hypertension but without coronary disease. These were compared with the smoking habits of 2 matched control groups. No correlation was found between smoking and hypertension. The relative incidence of coronary disease in heavy cigarette smokers was 1.5 times as frequent as in nonsmokers and other types of smokers.

**Comment**

In normal subjects smoking produces a transient increase in the blood pressure and pulse rate, a decrease in the skin temperature of the fingers and toes, and some flattening of the T waves in the electrocardiogram. The values may return to normal in 10 to 15 minutes. Habitual smokers do not show tolerance to smoking by a decrease in these effects. The effect of smoking is not related to the length of time the subject has smoked or to the number of cigarettes smoked.

Since Huchard introduced the term, "tobacco angina" in 1899, some normal subjects have been observed who have been hypersensitive to tobacco, as manifested by changes in the electrocardiogram and ballistocardiogram.\textsuperscript{71-73} Some normal subjects even have symptoms on smoking similar to those of coronary insufficiency. Cessation of smoking completely eliminates these symptoms and the changes in the electrocardiogram and ballistocardiogram. Thus tobacco angina or tobacco heart is a definite clinical entity.

For the most part, persons less than 40 years of age rarely have abnormal ballistocardiograms but older persons have abnormal tracings rather frequently. Some young normal subjects with abnormal ballistocardiographic tracings before and after smoking may be the offspring of parents with hypertension or coronary heart disease. Normal subjects who are hyperreactors show greater increase in the blood pressure on smoking than normal reactors do.

In patients with peripheral vascular disease smoking is not the etiologic factor but a most aggravating one. Cessation of smoking for a long time may produce great improvement, but return to smoking can reactivate the disease.

Considerable controversy has existed in regard to the effects of smoking on the heart. These effects are indicated by an increased pulse rate and blood pressure and some flattening of the T waves. Extensive studies have been carried out to determine whether they are due to sudden increased work of the heart or to coronary constriction. The early work on animals was not conclusive. Some workers have suggested that the increase of blood pressure or heart rate or of both reflects increased work of the heart. Confirmation of this has been given by other workers who showed that oxygen utilization by the heart was reduced initially during the period of greatly increased cardiac work and then increased and remained high. The alterations were explained on the basis of metabolic changes in the myocardium. It has been suggested too that constriction of the coronary arteries resulted from the release of posterior pituitary hormone after smoking. Also blood flow in the coronary arteries decreased in arteriosclerotic rabbits after injection of nicotine. In contrast one investigator concluded that the effects of smoking particularly during hypoxia were not due to constriction of the coronary arteries but were secondary to increased heart rate. Another group concluded that injection of nicotine produced no coronary constriction but influenced the parasympathetic and sympathetic ganglia and chemoreceptors in the heart. The first investigators to catheterize the coronary sinus in man concluded that nicotine did not cause coronary constriction but decreased resistance of the coronary vessels and decreased myocardial extraction of oxygen and glucose. Further work with direct catheterization may be expected.

The introduction of the ballistocardiograph added a new approach for study of the effect of smoking. While this instrument is not considered by some workers as being ready for use in diagnosis,\textsuperscript{74, 75} it has provided an interesting method for investigation and with
further refinements of the instrument the method may become more critical and practical. Abnormalities may be noted in the ballistocardiograms of patients with peripheral vascular disease without evidence of cardiac disease. Because the ballistocardiogram may be influenced by the entire vascular tree, it is more sensitive than the electrocardiogram to the effects of smoking. It has provided evidence that smoking may not exert its effect on the myocardium or the coronary arteries but mainly on the peripheral blood vessels. In some instances the constriction of peripheral vessels by smoking may point to latent disease of the coronary arteries.

It has been shown too that the cardiac output and cardiac index of normal subjects with hypertensive parents are large before smoking as compared with the controls. On smoking they increased twice as much in normal subjects with hypertensive parents as in the controls, and they increased less in normal subjects whose parents had coronary disease than in the controls.

From the various findings coronary disease seems to occur more frequently and at an earlier age in the heavy smoker than in the nonsmoker.

**Summary**

In normal subjects smoking or the injection of nicotine produces transient vascular effects on the heart and blood vessels. Apparently tobacco angina or tobacco heart is a clinical entity. Abnormal vascular responses after smoking in normal subjects may be due to hypersensitivity to nicotine, such as occurs in tobacco heart, or to the effect of nicotine on a vascular system demonstrated to be hyperreactive by the cold pressor test.

Tobacco is one of the most prominent contributing factors in thromboangiitis obliterans, as thromboangiitis is rarely found in nonsmokers.

The question as to whether the effects of smoking are due to sudden increased work of the heart or constriction of the coronary artery has stimulated a great amount of research. There is evidence to support both theories.

The findings of abnormal ballistocardiograms before and after smoking in the offspring of hypertensive parents and after smoking in the offspring of parents with coronary heart disease are highly important.

Statistically coronary artery disease seems to occur more frequently and at an earlier age in the person who smokes much than in the nonsmoker. Likewise, the mortality rate is higher among younger persons with coronary disease who are smokers than among those who are nonsmokers.

**Summario in Iterlingua**

In subjectos normal, fumar o injection de nicotina produce transient efectos vascular in corde e vasos de sanguine. Apparentemente, "angina a tabaco" o "corde a tabaco" es un entitate clinic. Anormal responsas vascular a fumar occurrente in subjectos normal pote esser le consequentia de hypersensibilitate a nicotina (del genere occurrente in "corde a tabaco") o del efecto de nicotina super un sistema vascular que se mostra hyperreactive in le test pressori a frigido.

Tabaco es un del plus important factores contributori in le causation de thromboangiitis obliterante, visite que thromboangiitis se trova ramente in non-fumatores.

Le question de saper si le efectos del fumar es le consequentia de un subite augmento del labor del corde o del constriction del arteria coronari ha stimulato numerosissime investigationes. Il existe datos in supporto del un e in supporto del altere theoria.

Le observationes facite ante e post fumar in le ballistocardiogrammas anormal del progenia de parentes hypertensive e post fumar in illos del progenia de parentes con morbo cardiac coronari possede un alte grado de signification.

Le statisticas pare monstrare que morbo de arteria coronari occurre plus frequentemente e a etates plus juvene in personas qui fuma que in non-fumatores. In plus, le mortalitate inter juvene individuos con morbo coronari qui es fumatores es plus alte que inter tal individuos qui es non-fumatores.
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EFFECT OF SMOKING ON THE CARDIOVASCULAR SYSTEM


Effect of Smoking on the Cardiovascular System of Man
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