1948

Effect of tobacco on the cardiovascular system

George L. Scholnick
University of Nebraska Medical Center

THE EFFECT OF TOBACCO
ON THE CARDIOVASCULAR SYSTEM

by

George L. Scholnick

SENIOR THESIS

PRESENTED TO THE COLLEGE OF MEDICINE

UNIVERSITY OF NEBRASKA

OMAHA, 1948

TABLE OF CONTENTS

INTRODUCTION

The common use of tobacco in every day life renders knowledge of its action on the cardiovascular system of practical importance.

While it is interesting to know how poisonous a drop of nicotine may be if given hypodermically or by mouth, such reports have little influence on the millions of smokers using tons of tobacco daily without noticeable effects. Furthermore, nicotine itself does not account for all the physiologic effects of smoking. Consequently, I shall endeavor to dwell only on the effects of tobacco as used in ordinary smoking.

One occasionally wonders whether the pleasurable habit of smoking may have a deleterious effect upon the cardiovascular system, but, as with all minor vices, one is inclined to favor moderate indulgence--a socially wise though hardly a scientific attitude. Perhaps a more authoritative and scientific answer to this question may be obtained by reviewing available literature on the subject.

TEMPORARY PHARMACOLOGICAL EFFECTS

The pharmacological action of tobacco upon the blood pressure, the pulse rate, and the peripheral vessels has interested many investigators. Erb, in 1904, was the first to report that tobacco smoking was a contributing factor to the production of peripheral vascular deficiencies. In 1907, Hesse observed that both the blood pressure and pulse rate usually increased upon smoking. Two years later Bruce, Miller, and Hooker (15) confirmed Hesse's work, and, by using a plethysmograph, demonstrated vasoconstriction in the hand.

Effect on pulse rate and blood pressure

After 1930 the literature became proliferate with articles concerning the effect of tobacco upon the vascular system. Almost all investigators agree that smoking usually causes an increase in the pulse rate (4, 16, 25, 30, 42, 49, 51, 52, 53, 57, 63, 65, 66, 69, 83) and an increase in the blood pressure (25, 30, 43, 49, 51, 52, 53, 57, 63, 65, 66, 69, 79, 83) for a period of about 10 to 45 minutes (25, 42, 51, 53, 66). The pulse usually increases 5 to 30 beats (16, 30, 53, 63, 65, 66, 83). The systolic blood pressure increases about 10 te 30 mm. Hg., and the diastolic about 5 to 25 mm. Hg. (30, 51, 53, 63, 79, 83).

There are only two contradictory reports. Dixion, in 1927, reported that the blood pressure of hardened smokers was scarcely altered by smoking and hence concluded they had developed a tolerance. In 1930 Grollman reported that subjects indulging moderately in the form of tobacco to which they were accustomed showed no demonstrable change in the blood pressure with only slight or no increase in the pulse rate.

Several investigators noted the increase in blood pressure and pulse were more marked when the smoke was inhaled than when it was puffed (42, 43, 53).

The effect of smoking upon the moderate and upon the novice smoker has been found to differ somewhat. Lee in 1908 (later confirmed by Dixion in 1927) observed that smoking in moderate smokers produced a slow and gradual rise in the blood pressure, usually associated with some acceleration of the pulse, until the smoking stopped. In novices, smoking caused a rapid rise in the blood pressure, and, as the smoking continued for about thirty minutes, there was a dramatic fall in the blood pressure, which fell as much as 25 to 50 mm. Hg. in 5 to 30 minutes. This fall in the blood pressure was associated with the symptoms of collapse.

Effect on Vasomotor Status

The effect of smoking upon the vasomoter status of the upper and lower extremities has been studied in considerable

detail. Bruce, Miller, and Hooker in 1909 were the first to demonstrate that smoking caused vasoconstriction in the hand. Subsequently this was confirmed by many investigators using various techniques.

The skin temperature of normal individuals lying quietly, unclothed, on a stretcher in a room of constant temperature reaches a reliable constancy at a given body point in about one hour. Thereafter any variations in skin temperature are due to changes in vasoconstrictor tone. Almost all the observers (4, 25, 48, 49, 52, 53, 54, 57, 59, 65, 66, 69, 79, 93) have reported a decrease in the skin temperature of the fingers and toes upon smoking, which indicates peripheral vasoconstriction. The skin temperature usually returns to normal in about 5 to 60 minutes (25, 48, 49, 53, 57, 59, 66).

However, it is interesting to note the variability of the responses which the different men reported. Wright and Moffat (93) reported that the drop in temperature varied in different individuals with the same tobacco, and in the same individuals at different times. They also stated that the degree of temperature drop which occurred bore no relation to the length of time a subject had been a smoker or the number of cigarettes he habitually smoked.

Other men studied the vasomotor effect by using the plethysmograph (1, 15, 49, 59). Their conclusions are in agreement with the results of digital skin temperature variations.

Some observers noted that the vasoconstriction was most pronounced in subjects who inhaled (48, 49, 59, 83).

The vasoconstrictor effect of tobacco was still further studied by Wright (92, 93) who observed the capillary tufts at the nail fold through a microscope. In certain individuals he noted marked slowing and often stasis in capillary circulation at the nail fold during the smoking of a single cigarette. The flow would slow perceptibly and often stop for varying lengths of time up to 15 seconds or occasionally longer. It would then regain its former rate, but another puff would cause a repetition of the cycle.

Weatherby (83) reported that mild physical activity inhibited the fall in skin temperatures of the extremities when smoking. This has not been confirmed, for Roth and her associates (65) found the same degree of vasoconstriction in their subjects while sitting or walking slowly as well as when they were at rest under basal conditions.

Is Vasomotor Effect Generalized or Localized?

Herrell and Cusick (19, 40) selected eight individuals who were known to manifest a marked increase in blood pressure and peripheral vasospasm upon smoking. They then photographed the retinal arterioles of these individuals before and during inhalation of tobacco smoke, measuring them with a modified Morgan graticule in the Keeler ophthalmoscope. The vessels showed a reduction in caliber which varied between 18 per cent and 26 per cent, and averaged 21 per cent.

It is quite generally accepted that arteriolar changes in the retinal vessels represent an accurate index of generalized vasomotor reactions. Hence, on the basis of Herrell's and Cusick's work (19, 40), it would seem that the vasoconstrictor response to tobacco is in the nature of a generalized rather than a localized vasospasm. Abramson and his associates (1), however, stated that this is not the case.

Using the plethysmograph, Abramson and his associates (1) noted that smoking decreased the volume of the hand (made up largely of skin) but had no effect upon the volume of the forearm alone (made up largely of muscle). Thus it appeared that smoking caused constriction of the arteries in the skin, but apparently had little, if any, effect upon those in the voluntary muscle. Therefore, he concluded that the vasoconstrictor response to smoking, observed in the skin vessels of the hand, could not be considered typical of reactions of blood vessels elsewhere in the body.

Up to the present date, vasoconstriction due to smoking has been demonstrated in only the hands and feet, and the retinal arterioles.

MECHANISM OF TOBACCO'S TEMPORARY PHARMACOLOGICAL EFFECTS

The mechanism by means of which smoking produces temporary pharmacologic changes in the cardiovascular system is quite controversial. I shall attempt to touch only upon the high points.

There are many observations indicating that nicotine alone is capable of producing the same cardiovascular changes as tobacco. Intravenous injections of nicotine can produce the same effects on the blood pressure, the pulse rate, and the skin temperature as smoking (53, 66)--probably by stimulating the adrenals to secrete epinephrine (69).

Weatherby (83) found that a thoroughly denicotinized cigarette produced no change in the blood pressure and pulse rate and only a very small drop in skin temperature. Roth and her associates (65) report that corn silk cigarettes (which contain no nicotine) cause little or no change. Moyer and Maddock in 1940 found that the simulation of smoking with small paper tubes or empty pipes resulted in neglibible cardiovascular effects. When Maddock and Coller (52) substituted cubebs for cigarets, or passed the smoke through ferric chloride solution, no drop in skin temperature occurred.

Many observers have noted that denicotinized as well as standard cigarettes can cause an elevation in the blood pressure, acceleration of the pulse, and peripheral vasoconstriction (25, 41, 49, 51, 83, 93). However, this is accounted for by the fact that the average commercially denicotinized cigarette still contains approximately 1 per cent nicotine. The average standard cigarette contains 2 per cent nicotine (8, 17).

All the preceding references would indicate that it is the nicotine which produces the peripheral vascular response noted in smoking. The evidence to the contrary is as follows:

Evans and Stewart (25) reported that regardless of whether regular, commercially denicotinized, or corn silk cigarettes were smoked, an increase in the pulse rate and blood pressure and a decrease in the peripheral blood flow of essentially the same magnitude and duration occurred in each instance. They postulated that the response was due to irritants in the smoke acting upon the respiratory tract to cause reflex vasoconstriction.

Bolton and Sturrup in 1936, and Mulinos and Shulman in 1939 have demonstrated that the deep inhalation of air alone can produce peripheral vasoconstriction.

Mulinos and Shulman (58, 59) demonstrated a decrease in hand volume following a deep breath. They also reported that deep inspiration produced a drop in the finger skin temperature of 0.15° to 2.27°C. Using regular cigarettes, other investigators

had found that the temperature dropped about 1.2° to 6.5°C. (48, 52, 53, 54, 65, 66, 83, 93). In 83 per cent of Mulinos' and Shulman's subjects a deep breath was followed by a complete standstill of the blood in the capillary tufts of the nail fold for 3 to 5 seconds. Wright (92), however, was not able to demonstrate this capillary phenomenon merely by deep breathing.

It seems clear that the act of smoking is probably associated with three factors each of which may independently produce peripheral vasoconstriction. These are (1) the pharmacological activity of the nicotine, (2) the irritant properties of the smoke, and (3) the deep inhalation. The combination of all three factors probably results in a greater effect than does any one factor alone.

CHRONIC CIRCULATORY EFFECTS

Chronic Effect upon Pulse Rate and Blood Pressure

It is quite essential to know whether or not habitual smoking has a chronic, prolonged effect upon the pulse rate or the blood pressure. This problem has been studied by Brigham (12), Earp (22), Johnson (46), and Hadley (34) who found no significant difference in blood pressure between smokers and nonsmokers. The pulse was very slightly increased in smokers.

Brigham in 1920 took records on 132 young men of the ages from 20 to 25. The men were divided into four classes, namely, nonsmokers, light smokers, moderate smokers, and heavy smokers. The blood pressure averaged approximately the same in all classes. The average pulse rate increased gradually from 82 in nonsmokers to 90 in the heavy smokers. Earp had similar findings in 1925 when he reported that in 304 male students (172 nonsmokers and 132 smokers) the blood pressures ran about the same in both groups before and after exercise.

In 1929 Johnson studied a series of 150 adult male smokers and 150 nonsmokers. The average age, weight, and height of the two groups were almost identical. In the smokers the systolic blood pressure averaged 128.2, the diastolic 78.9. In the controls the systolic averaged 129.6, and the diastolic 79.2.

Hadley in 1941 analyzed 7,000 office patients. The smokers had an average pulse rate of 78.4, and the nonsmokers of 77.3. In smokers the systolic blood pressure averaged 130.0, the diastolic 82.6. In nonsmokers the systolic averaged 133.1, the diastolic 84.0.

Thus it would appear that smoking has no significant chronic effect upon either the pulse rate or the blood pressure. Evidence to the contrary is quite meager.

In 1907 Stachelin (61) experimented upon himself. For six months he smoked 6 to 8 cigars daily; then abstained from smoking for six months. The pulse rate was a mean of 82 during the smoking period, and 75 during the period of abstinence. Similarly the pulse rate after a standard exertion was 157 compared with 124 per minute.

Fisk in 1935 analyzed 15,000 smokers' and monsmokers' life insurance records. Among the smokers there were 15 per cent more individuals with over-rapid pulses.

Sanguinette in 1930 reported one case were a blood pressure of 235/125 fell to 175/85 upon cessation of smoking; later, when smoking was resumed, the blood pressure returned to its previous high level.

Relationship to Arteriosclerosis

That smoking itself is an etiological agent of arteriosclerosis has never been proved or disproved. However, that smoking actually produces vasoconstriction and slowing of

capillary circulation of the extremities in the human has been amply demonstrated. Assuming an existing vascular disorder such as thromboangiitis obliterans or diabetic sclerosis with the tissues on the verge of gangrene, it is logical to suppose that a vasoconstriction due to tobacco may further decrease the nutrition of the tissue to the point where gangrene would result.

Perhaps this accounts for the findings of Weinroth and Herzstein in 1946. In a group of 301 male diabetic patients they found a significantly higher incidence of thrombosed peripheral arteries in smokers than in nonsmokers. The condition existed in those who had diabetes for less than 5 years as well as in those with diabetes of longer duration. Regardless of such factors as severity of illness, adequacy of control, presence of obesity, or hypertension, a lower frequency of arteriosclerosis obliterans prevailed in general among nonsmokers.

To cite a few animal experiments: Thienes and Butt (80), after giving daily injections of nicotine to rats and rabbits for three to six months, found no evidence of chronic vascular degeneration. Boylston (11) confirmed the experiments of Thienes and Butt in rats. However, in analyzing such results one must remember that species differences in reaction to drugs and poisons may be quite marked.

It has been shown that smoking as such does influence the peripheral vascular system. However, I do not believe that the present evidence is sufficient to lend much support to the theory that tobacco is an etiological factor in arteriosclerosis.

RELATIONSHIP TO HYPERTENSION

Smoking usually causes an elevation in the blood pressure, an acceleration of the pulse, and a peripheral vasoconstriction in hypertensive individuals just as in normal individuals (43, 76). However, there are considerable variations in the results, not only in different patients having the same initial pressures, but in the same patients when tested again after intervals of from one to three years (81). Thompson and Sheldon (81) observed 59 patients with high blood pressure and advanced arteriosclerosis while smoking; there was a rise in the pressure in 35 per cent of the cases, a fall in 45 per cent, and no change in 20 per cent. These variations emphasize the importance of studying each case of hypertension individually before imposing restrictions upon smoking.

It is interesting to note that Roth and her associates in 1938 (43) found a marked parallelism between hyperreaction to the cold pressor test and hypersensitiveness to tobacco. Then, in another experiment (65) in 1944, they found no similarity in these responses.

RELATIONSHIP TO THROMBOANGIITIS OBLITERANS

Clinical Relationship to Tobacco

Among the numerous etiological factors of thromboangiitis obliterans suggested since 1908, when Buerger first described that clinical and pathological entity, tobacco has been recognized as one of the important excitants. The way smoking acts as a contributing or exciting cause of thromboangiitis obliterans is not known.

Incidence of smokers among thromboangiitis obliterans sufferers: The association of tobacco smoking with thromboangiitis obliterans is an established medical fact. In 1916 Weber stated that he had never come across a case of thromboangiitis obliterans in a man or woman who was not, or had not been, a free cigarette smoker. Barker reported in 1931 that of 350 patients with the disease, only 5 or 1.4 per cent did not smoke. Trasoff, Blumstein, and Marks (82) reported 31 cases, only three of which were nonsmokers. Horton (13) reported 948 cases of which 93 per cent smoked.

The most prominent protagonist of the theory that tobacco is an etiological agent in thromboangiitis obliterans is S. Silbert (71, 72, 73, 74). In the 1,400 cases of the disease

he has seen (74), all were, without exception, smokers of tobacco. In response to the reports of those who claim to have seen instances of the disease in nonsmokers, he states that one can only be skeptical of the accuracy of the diagnosis. It is easy to confuse peripheral vascular disease due to thromboangiitis obliterans with that due to presenile arteriosclerosis, an entirely different disease. This is particularly true in the age group between 40 and 55. In both conditions the symptoms and local signs may be the same. A clinical differentiation rests on the recognition that when an individual shows signs of arteriosclerosis in other parts of his body, the disease process in his legs is due to the same cause and not to thromboangiitis obliterans.

Therapeutic response to abstinence from tobacco:

Silbert's wide experience with the treatment of thromboangiitis obliterans has convinced him that smoking is the most important contributing factor in producing the disease, and that cessation of smoking is an essential therapeutic measure (72). Repeatedly failure to improve under treatment was noted in men who continued to smoke, and prompt improvement began when they were finally induced to stop smoking (71).

On the basis of 289 cases, Silbert stated in 1930 that 50 per cent of the patients requiring amputation continued to smoke in spite of repeated warnings, and the recurrence of symptoms after the individual had been restored to good condition

was almost invariably traceable to a resumption of smoking. In only two of his cases had a progression of the disease taken place when the patient was not using tobacco.

Barker (3) and Horton (44) also stated that the incidence of amputations was greater in the heavier smokers than in the lighter smokers.

In 1945 Silbert reported that he had followed, for 10 years, 100 patients with thromboangiitis obliterans who had stopped smoking at the beginning of treatment and had not resumed since. In all of them the disease remained completely arrested.

Although I realize that clinical experience unsupported by experimental demonstration is unsatisfactory as valid proof, Silbert's careful clinical observation of 1,400 cases of thromboangiitis obliterans does bear considerable weight.

The evidence showing the very high incidence of smoking in thromboangiitis obliterans is very striking. In this disease it is difficult to believe that smoking is not a predisposing factor, though smoking obviously cannot be considered to be the only etiological factor. The well established peripheral vasoconstrictor effect of smoking constitutes supporting circumstantial evidence.

Hypersensitivity to Tobacco as a Factor

While it is a fact that patients suffering from thromboangiitis obliterans are almost universally excessive smokers, it is also true that many equally excessive users of tobacco never

develop thromboangiitis obliterans. If, therefore, tobacco does play an etiological role, the question arises why this agent should affect one group of individuals and not all others. The only apparent answer is "allergy".

Proponents of sensitivity: Much work has been done on tobacco sensitization to solve the problem. Harkavy and Sulzberger have gone into the problem extensively. They concluded that a large percentage of persons suffering from Buerger's disease belongs to the category of allergic persons, and that the allergy is manifest to tobacco.

Harkavy (37) using 87 cases of thromboangiitis obliterans, Sulzberger (77, 78) with 24 cases, and Green (31) with 44 cases found that 87 per cent, 78 per cent, and 66 per cent, respectively, of their cases had positive skin reactions to tobacco extracts. Only 16 per cent of Harkavy's 262 male smoker controls, 36 per cent of Sulzberger's controls, and 15 per cent of Green's controls reacted to tobacco.

Then in 1939 Harkavy reported the results on sensitivity in 140 cases of thromboangiitis obliterans; 68 per cent gave positive skin tests to tobacco only, and 10 per cent were polyvalent. Of 400 adult smokers, 9 per cent reacted to tobacco only; 32 per cent were polyvalent.

In addition to the skin tests, Harkavy (37, 38) demonstrated the presence of reagins to tobacco in the sera in 44 per cent of his thromboangiitis obliterans patients who had

positive skin tests. This was demonstrated by means of the passive transference method of Prausnitz and Kustner. It consists of withdrawing ten cc. of blood from the arm vein of a patient with thromboangiitis obliterans, clotting it and injecting 0.15 cc. of serum intradermally into various sites of the forearm of normal individuals who did not react to tobacco on preliminary testing. Three days later these sites are reinjected with the tobacco to which the patient had originally reacted. In the presence of reagins, an urticarial wheal will appear in the sensitized skin area of the normal individual similar to that obtained in the thromboangiitis patient.

Harkavy's work with reagins has never been confirmed. Sulzberger (78) reports that in spite of repeated and persistent experiments, reagins could be found in only one of his 24 cases. He stated, however, that hypersensitivities with immediate wheal reactions of the skin, without reagins, are well known in other sensitizations of human beings; urticarial and asthmatic reactions to drugs frequently fall in that group.

In 1933 Sulzberger started investigating to see whether nicotine or some other constituent or constituents of tobacco caused the skin reactions in his cases. In 1934, after testing many cases with denicotinized tobacco and with the nicotine, he stated that he had seen hundreds of positive reactions to tobacco, but only 2 cases in which there were slight to moderate reactions

to nicotine. Harkavy's skin tests (37, 38) with nicotine tartrate solution were also negative. This indicates that the sensitization in thromboangiitis obliterans, if there is any, is due to some constituent of tobacco other than the nicotine.

Harkavy (35, 37) and Sulzberger (78) state that multiple sensitization to other proteins characteristically prevalent in allergic individuals was also found in a high percentage of thromboangiitis obliterans patients, but that no other antigen seemed as dominant as tobacco. This polyvalent sensitization may explain why typical thromboangiitis obliterans can occur in nonsmokers.

Opponents of hypersensitivity: All investigators have not found such significant variations in skin sensitivity to tobacco between normal individuals and those with thromboangiitis. In 1935 Chobot reported that of 53 unselected asthmatic children, ages 3 to 12, who had never smoked, 89 per cent had positive skin reactions to tobacco. The striking disparity between these figures and those of Harkavy and Sulzberger must make us wonder whether or not the reaction has any great significance or value.

In 1936 Trasoff, Blumstein, and Marks reported that only 16 per cent of 31 cases of thromboangiitis obliterans (3 cases in nonsmokers) had positive skin tests to tobacco; no reagins were demonstrated. In 52 normal nonsmokers, 21 per cent had positive skin tests. In 40 normal smokers, 17 per cent had positive skin tests.

Westcott and Wright in 1938 reported that in 35 cases of thromboangiitis obliterans, 14 per cent of whom were allergic, only 43 per cent were sensitive to tobacco. In 35 controls, 27 per cent of whom were allergic, 48 per cent were sensitive to tobacco.

Along another line, Maddock, Malcolm, and Coller in 1936 found no relationship between skin sensitivity to tobacco and its temporary cardiovascular effect upon smoking. Similarly, Theis and Freeland in 1941 state that hypersensitivity to tobacco was not a factor since the effect of tobacco upon the blood pressure, pulse rate, and skin temperature has demonstrated the same response in patients with thromboangiitis obliterans as in normal controls.

EFFECT OF TOBACCO UPON THE HEART

Effect upon Longevity

The results of a study by Pearl (62) in 1938 clearly indicated that the average longevity of nonsmokers exceeded that of smokers. Among the smokers longevity decreased as the degree of smoking increased. This, of course, does not prove that smoking per se shortens the life of a smokers. For example, smoking may be associated with some factor such as a type of temperament, or other habits, which predisposes to a shorter life. However, Pearl's work cannot be passed over lightly. The significance of his report, if found to be accurate, would be most profound. It is to be hoped that other investigators will make similar studies and either confirm or deny Pearl's results.

Quite recently Haag and his associates (33) found that the exposure of rats to tobacco smoke, for one-half hour periods fourteen times daily from the age of weaning, did not decrease their average life span as compared to controls. This could mean either that the rat is less susceptible to tobacco smoke than man, of that the smoker's shorter life span (Pearl) is due to other factors.

Temporary Pharmacological Effects

The relationship of the use of tobacco to cardiac disturbances is a matter of widespread interest and great importance. It has been amply demonstrated that smoking accelerates the heart rate and elevates the blood pressure. Grollman (32) and Levy and his associates (51) found no significant change in the average cardiac output after smoking.

Smoker's heart: Bosworth (10) in 1889 was the first to coin the expression "smoker's heart". His cases were characterized by an arrhythmia and the clinical history of occasional attacks of palpitation brought on by overexertion. Other men also report clinical experience with the "smoker's heart" characterized by palpitation (14, 88) and arrhythmias (7, 13, 29, 88). In 1916 Neuhof (60) reported one case of sino-auricular block which was cured by the patient's abstaining from tobacco. The "smoker's heart" apparently is a rare clinical entity.

Relationship to Coronary Artery Disease

Tobacco angina: Since Huchard (45) first used the term "tobacco angina" in 1899, there has been much discussion of the relation which it suggests. Subsequently, several men reported patients who suffered angina pectoris only during periods of smoking, with cessation of attacks on omitting tobacco (13, 14). Such cases have generally been few in number, when specifically mentioned, as in an article published in 1928 by Moschocowitz (56) who reported four cases.

Huchard (45) cited four cases observed by himself; other cases of the sort he borrowed from various authors. The impression is, therefore, confirmed that no one observer has encountered personally many such individuals. Gallavardini (27) in nearly 800 personal observations found only two cases of tobacco angina.

Berk and Huber in 1939 reported three cases of angina pectoris caused by tobacco smoking. The electrocardiograms prior to cessation of smoking showed inverted T-waves; depressed ST segment in one patient; depressed Q_3 and T_3 in another--all these abnormal waves returned to normal when smoking was stopped.

However, these cases of tobacco angina seem to be rare, for the majority of men have not seen any (51, 63).

Clinical relationship to angina pectoris: Instances have been reported in which patients subject to typical anginal paroxysms could induce an attack by smoking (16, 30, 63, 64, 91).

There is a difference of opinion concerning the mechanism through which smoking precipitated these paroxysms of angina pectoris. Some observers (30, 63) feel that the attacks are not the result of coronary vasoconstriction, but the result of a sudden increase in the work of the heart as shown by an increase in heart rate or blood pressure or both. Only one case has been reported in which there was no such increase in heart work (16).

The other possibility is that tobacco may cause coronary spasm. Ralli and Oppenheimer (64) noted that the attacks of anginal pain induced by smoking were relieved by administering a nitroglycerin tablet under the tongue, but were not relieved by a tablet similar in appearance but not containing nitroglycerin. The relief of pain, therefore, was not due to a psychic factor.

Statistical relationship to coronary artery disease: Other investigators have attempted to determine the relationship of tobacco to angina pectoris by analyzing statistics regarding the incidence of coronary disease in smokers and nonsmokers.

Johnson (35) reported that of 60 fatal cases of angina pectoris is males, 70 per cent were smokers. A control series of 1000 men, whose names were taken from telephone directories in five cities, gave the incidence of smokers as 81.8 per cent.

White and Sharber (89) made an analysis of 750 patients with angina pectoris and 750 controls of the same sex and age and from the same walks of life. The comparison revealed that 54 per cent of the angina pectoris patients smoked, and that 24 per cent used tobacco in excess. Of the controls 63 per cent smoked, 33.5 per cent smoked excessively. Patients occasionally stated that omission or reduction of tobacco decreased the frequency of attacks of angina.

These figures would indicate that smoking was only an incidental factor of no etiological importance. However, according to the statistics of other men, coronary artery disease was found to be of a slightly higher incidence in smokers.

English, Willius, and Berkson (23) and Glendy, Levine, and White (28) report there is a greater incidence of coronary disease among smokers than among nonsmokers--this being most evident in the younger age groups. Of 100 patients who developed coronary thrombosis under forty years of age, 93 per cent smoked (28). This percentage far exceeds the high incidence in the general population. In the age group from forty to forty-nine years, the incidence of coronary disease among smokers was 4.8 per cent and among nonsmokers 1 per cent (23). In the age group from fifty to fifty-nine years, the incidence among smokers was 6.2 per cent and in nonsmokers 2.6 per cent (23). The percentages became about the same in the older age groups.

Short, Johnson, and Ley (70) reported on 2,031 cases. They found that dyspnea on exertion occurred in 4.8 per cent of nonsmokers and in 11.5 per cent of smokers--an increase of 140 per cent. Precordial pain occurred in 5.6 per cent of nonsmokers and in 9.7 per cent of smokers--an increase of 73 per cent. These findings indicate a trend in accordance with the report of Pearl (62) who found mortality markedly increased among heavy smokers.

Effect following coronary occlusion: In 1941 Bellet, Kershbaum, Meade, and Schwartz reported that after coronary ligation in dogs there was a pronounced increase in the sensitivity to tobacco smoke and nicotine. Following coronary ligation,

marked electrocardiographic changes were obtained with an amount of tobacco smoke, or nicotine, which was one-fourth of that required to produce only slight changes in the normal animal. These changes became less marked in the subacute stage and still less in the chronic stage of infarction, yet it was still greater than in the normal control dogs.

Sensitivity to tobacco as a factor: Several men have measured skin sensitivity to tobacco in coronary artery disease in the attempt to ascertain whether this group of individuals has a more than usual sensitivity to tobacco. Harkavy (36, 38) reported that of 110 patients with coronary artery disease, 44 per cent gave positive skin tests to tobacco. Trasoff, Blumstein, and Marks (82) reported only a 13 per cent incidence of positive skin tests in 25 patients. Green (31) reported skin sensitivity in 72 per cent of 18 patients with coronary disease, and in his controls sensitivity ran 52 per cent.

The incidence of positive tests is by no means as high in coronary artery disease as in thromboangiitis obliterans, and the clinical evidence incriminating tobacco is not as conclusive. Hence one is not justified in making any positive statement respecting the allergic relationship of tobacco to coronary artery disease.

Effect on the Electrocardiogram

Temporary effects on the electrocardiogram: Ssalischtschiff and Tschernogoroff (75) in 1929 were the first two men to study the

effect of inhalation of tobacco smoke on the human electrocardiogram. They noted no effect, except in two instances where there was a slight lowering of the T-waves. Subsequently many men have made similar studies.

There are no consistent changes in the electrocardiogram of the normal individual during or following smoking. Changes in the PR interval, the QRS complex, or the T-wave may be found (34, 47). However, there is no change whatsoever in the electrocardiogram after smoking in from 30 to 90 per cent of normal subjects (16, 25, 30, 47, 51, 66, 68).

The most frequently observed change in the electrocardiogram after smoking has been a reduction in the amplitude of the T-wave in one or more leads (16, 25, 30, 47, 51, 56, 65, 66, 68). The decrease has ranged from 0.5 to 4 mm., averaging from 1 to 2 mm. in different studies. On occasion an increase in the amplitude of the T-wave has occurred. A lowering of the T-wave may occur in patients with coronary artery disease (16, 30, 51) as well as in normal subjects without being associated with angina pain. Amyl nitrite fails to influence the T-wave changes (30).

The significance of the lowered T-wave is difficult to interpret. Minor changes in the T-wave induced by smoking usually represent a physiologic response to an increase in the heart rate and not to myocardial ischemia. It has been demonstrated in the case of normal subjects, and in the case of the majority of patients

with heart disease, that the changes in the T-wave induced by smoking and those induced by other agents which elevate the resting heart rate to a similar level are alike in kind and magnitude (2, 39). The administration of drugs which slow the heart is accompanied by an increase in the height of the T-wave, and the administration of those drugs which accelerate the rate is accompanied by a decrease in the height of the T-waves (20, 30).

Many investigators have observed that the change in the T-wave after smoking was associated with an acceleration of the heart rate (16, 25, 30, 65, 66, 68, 87). Segal (68) reported that in the age group from seventeen to fifty years, individuals responded to smoking with an increased heart rate and a lowering of the T-wave more frequently than did individuals over fifty years of age. Graybiel, Starr, and White (30) also noted that the greatest lowering or inversion of the T-wave, after smoking, occurred in the young, more emotionally labile individual than in the more stolid individual.

Permanent effects on the electrocardiogram: Two men, Hadley (34) and Johnson (47), have compared the electrocardiograms of smokers with those of nonsmokers to ascertain whether smoking has any chronic effect upon the heart. Johnson, studying over 2000 cases, found that 11 per cent of the smokers showed some abnormality in the electrocardiogram as compared to 7.4 per cent of nonsmokers. The abnormalities noted were inverted or

diphasic T_1 and T_2, and QRS over 0.10 seconds. This latter abnormality constituted the greatest discrepancy between the two groups--the smokers an incidence of 2.5 per cent and the nonsmokers 0.6 per cent.

Hadley (34), studying over 2,200 cases, noted a slight increase in the QRS amplitude, and a slight shortening of PR interval plus an increased heart rate among smokers as compared to nonsmokers.

SUMMARY

1. It has been quite definitely shown that smoking usually accelerates the pulse 5 to 30 beats, elevates the blood pressure 10 to 30 mm. Hg., and causes peripheral vasoconstriction for a period of 10 to 60 minutes. These reactions are more pronounced in individuals who inhale.

2. The temporary cardiovascular effects of smoking tobacco are due to three factors: The pharmacological activity of the nicotine, the irritant properties of the smoke, and deep inhalation.

3. There is no permanent hypertension resulting from the tobacco habit, but a tendency to a slight tackycardia exists as long as the habit is continued.

4. That smoking itself is an etiological agent of arteriosclerosis has never been proved nor disproved. Present evidence would seem to indicate that it is not such an etiologic agent.

5. The association of tobacco with thromboangiitis obliterans is an established medical fact. Thromboangiitis obliterans is less severe and more amenable to therapy in those patients who give up smoking early and completely. Proof of a cause and effect relationship is lacking, although several investigators

have shown a high incidence of skin sensitivity to tobacco in this disease.

6. Statistical studies by Pearl would indicate that smokers have a shorter life span than nonsmokers; such a study has not been repeated by other investigators. Pearl's study has not been borne out by animal experimentation.

7. Smoking does not alter the cardiac output. There is a rare clinical entity known as "smoker's heart" which is characterized by arrhythmias and palpitation.

8. Rare cases of "tobacco angina" have been reported in which individuals suffer from angina pectoris only during periods of smoking with cessation of attacks upon abstaining from tobacco.

9. In some individuals with angina pectoris, smoking may induce an anginal attack or decrease the amount of exertion needed to produce an attack. Whether such an attack is due to a sudden increase in the heart work or to coronary vasospasm has not been determined.

10. The statistical relationship of smoking to coronary artery disease is very controversial--some finding no increase, and others finding a definite increase in the incidence of the disease among smokers.

11. Following coronary occlusion the electrocardiogram reveals a pronounced increase in sensitivity to tobacco smoke.

12. Smoking causes a 1 to 2 mm. temporary lowering of the T-wave in 30 to 90 per cent of individuals. This probably represents a physiological response to an increase in the heart rate and not to myocardial ischemia.

CONCLUSIONS

1. The effect of tobacco smoking upon the life-span of the average healthy individual has not yet been ascertained. The majority of evidence, though admittedly circumstantial, would indicate that smoking has no permanent effect upon the cardiovascular system and hence no deleterious effect on the life-span. However, such a conclusion cannot be honestly reached until Pearl's work to the contrary (page 21) has been repeated and revaluated.

2. There is a very small group of individuals, of uncertain number, who are hypersensitive to tobacco and may manifest hypertension, smoker's heart, or tobacco angina upon smoking.

3. Usually smoking is harmful only in those disease conditions which are aggravated by its temporary cardiovascular effects of accelerating the heart rate, elevating the blood pressure, and peripheral vasoconstriction. Hence, hypertensive individuals would best avoid smoking. Diabetics with impaired peripheral circulation should not smoke.

4. Tobacco is definitely contra-indicated in thromboangiitis obliterans. The clinical observations, accumulated through out years and incriminating tobacco, combined with the evidence of the positive skin tests to tobacco in thromboangiitis

obliterans constitute strong, but not conclusive, evidence that thromboangiitis obliterans is, in most cases, due to localized hypersensitivity to tobacco.

5. Smoking is contra-indicated in those cases of angina pectoris where it has been shown to induce an attack or decrease the amount of exertion needed to produce an attack.

6. Smoking is contra-indicated in acute coronary occlusion.

** BIBLIOGRAPHY **

1. Abramson, D.I., Zaseela, H., Oppenheimer, B.S., 1939: Plethysmographic studies of peripheral blood flow in man. III Effect of smoking upon the vascular beds in the hand, forearm, and foot. Am. Heart J. 18:290-302.

2. Ashman, R., Byer, E., 1943: The normal human ventricular gradient. II Factors which affect its relationship to the manifest area of the QRS complex. Am. Heart J. 25:36-57.

3. Barker, N.W., 1931: Tobacco factor in thromboangiitis obliterans. Mayo Clin., Proc. Staff Meet. 6:65-68.

4. Barker, N.W., 1933: Vasoconstrictor effects of smoking. Mayo Clin., Proc. Staff Meet. 8:284-287.

5. Bellet, S., Kershbaum, A., Meade Jr., R.H., & Schwartz, L., 1941: Effects of tobacco smoke and nicotine on normal heart and in presence of myocardial damage produced by coronary ligation. Am. J. M. Sc. 201:40-51.

6. Birk, B.J., Huber, H.H., 1939: Angina pectoris and tobacco smoking; presentation of three cases with electrocardiographic records. Wisconsin M. J. 38:733-735.

7. Boas, E.P., Levy, H., 1936: Extrasystoles of clinical significance. Am. Heart J. 11:264-272.

8. Bogen, E., 1929: The composition of cigarets and cigaret smoke. J. A. M. A. 93:1110-1114.

9. Bolton, E.A.C., Sturup, G., 1936: Vaso-constriction following deep inspiration. J. Physiol. 86:83-94.

10. Bosworth, M.D., 1889: On the use of tobacco. Med. Rec. 35:318-320.

11. Boylston, G.A. as cited by Ross, P.H., Ivy, A.C., 1946: Tobacco smoking and coronary artery disease; an analytical review of the literature. Q. Bull. Northwest. Univ. M. School 20:435.

12. Brigham, R.O., 1921: Heart failure and tobacco as an etiological factor. Ohio M. J. 17:226-228.

13. Brooks, H., 1915: The tobacco heart. N. York M. J. 101:830-837.

14. Bruce, J.M., 1901: Diseases and disorders of the heart and arteries in middle and advanced life. Brit. Med. J. 1901 1:701

15. Bruce, J.M., Miller, J.R., Hooker, D.R., 1909: The effect of smoking upon the blood pressures and upon the volume of the hand. Am. J. Physiol. 24:104-116.

16. Bryant, J.M., Wood, J.E., 1947: Tobacco angina. Am. Heart J. 34:20-34.

17. Bureau of Investigation of the A. M. A., 1933: The nicotine content of tobacco. J. A. M. A. 101:385.

18. Chobot, R., 1935: The significance of tobacco reactions in children. J. Allergy 6:383-386.

19. Cusick, P.L., Herrell, W.E., 1939: Retinal arteriolar changes as part of induced general vasospastic reaction; effect of tobacco. Arch. Ophth. 21:111-117.

20. Dameshek, W., Loman, J., Myerson, A., 1938: Human autonomic pharmacology. VII The effect on the normal cardiovascular system of acetyl-beta-methylcholine chloride, atropine, prostigmine, benzedrine--with especial reference to the electrocardiogram. Am. J. M. Sc. 195:88-103.

21. Dixon, W.E., 1927: The physiological effects of smoking. Practicioner 118:20-28.

22. Earp, J.R., 1925: Tobacco, health, and efficiency. Lancet 1925 1:213.

23. English, J.P., Willius, F.A., Berkson, J., 1940: Tobacco and coronary disease. J. A. M. A. 115:1327-1329.

24. Erb, W., 1904: as cited by Maddock, W.G., Coller, F.A., 1933: Peripheral vasoconstriction by tobacco; relation to thromboangiitis obliterans. Ann. Surg. 98:70.

25. Evans, W.F., Stewart, H.J., 1943: Effect of smoking cigarets on peripheral blood flow. Am. Heart J. 26:78-91.

26. Fisk, E.F., as cited by Bastedo, 1935: What the physician should know about tobacco. Med. Record 141:509.

27. Gallavardin, L., 1924: as cited by White, P.D., Sharber, T., 1934: Tobacco, alcohol and angina pectoris. J. A. M. A. 102:655-657.

28. Glendy, R.E., Levine, S.A., White, P.D., 1938: Coronary disease in youth: comparison of 100 patients under 40 with 300 persons past 80. J. A. M. A. 109:1775-1781.

29. Goodman, L., Gilman, A., 1941: The pharmacological basis of therapeutics. ed. 1, New York 1941, The MacMillan Co. page 493.

30. Graybiel, A., Starr, R.S., White, P.D., 1938: Electrocardiographic changes following inhalation of smoke. Am. Heart J. 15:89-99.

31. Green, M.A., 1942: Tobacco skin reactions in peripheral vascular diseases and coronary artery disease. J. Invest. Dermat. 5:179-186.

32. Grollman, A., 1930: Action of alcohol, caffeine, and tobacco on cardiac output (and its related functions) of normal man. J. Pharmacol. & Exper. Therap. 39:313-327.

33. Haag, H.B., Weatherby, J.H., Fordham, D., Larson, P.S., 1946: The effect on rats of daily-life span exposure to cigaret smoke. Federation Proc. 5:181 as cited by Ross, P.H., Ivy, A.C., 1946: Tobacco smoking and coronary artery disease; an analytical review of the literature. Q. Bull. Northwest. Univ. M. School 20:435.

34. Hadley, H.G., 1941: Effect on circulatory system; study of chronic effect of tobacco. M. Rec. 153:267-269.

35. Harkavy, J., Hebald, S., Silbert, S., 1932: Tobacco sensitiveness in thrombo-angiitis obliterans. Proc. Soc. Exper. Biol. & Med. 30:104-107.

36. Harkavy, J., 1933: Tobacco sensitiveness in angina pectoris and coronary artery disease. Proc. Soc. Exper. Biol. & Med. 30:683-684.

37. Harkavy, J., 1933: Tobacco sensitiveness in thromboangiitis obliterans, migrating phlebitis, and coronary artery disease. Bull. New York Acad. Med. 9:318-322.

38. Harkavy, J., 1939: Tobacco skin reactions and their clinical significance. J. Invest. Dermat. 2:259-279.

39. Hartwell, A.S., Burrett, J.B., Graybiel, A., White, P.D., 1942: The effect of exercise and of four commonly used drugs on the normal human electrocardiogram with particular references to T-wave changes. J. Clin. Investigation 21:409-417.

40. Herrell, W.E., Cusick, P.L., 1938: Vascular and retinal abnormalities following inhalation of smoke; preliminary report. Proc. Staff Meet. Mayo Clin. 13:273-279.

41. Hesse, E., 1907: as cited by Bruce, J.M., Miller, J.R., Hooker, D.R., 1909: The effect of smoking upon the blood pressures and upon the volume of the hand. Am. J. Physiol. 24:106-107.

42. Hiestand, W.A., Ramsey, H.J., Dale, D.M., 1940: Effect of cigaret smoking on metabolic rate, heart rate, oxygen pulse, and breathing rate. J. of Lab. & Clin. Med. 25:1013-1017.

43. Hines, E.A.Jr., Roth, G.M., 1938: Effect on blood pressure as measured by standard smoking test. Proc. Staff Meet. Mayo Clin. 13:524-526.

44. Horton, B.T., 1938: The outlook in thromboangiitis obliterans J. A. M. A. 111:2184-2189.

45. Huchard, H., 1899: as cited by White, P.D., Sharber, T., 1934: Tobacco, alcohol, and angina pectoris. J. A. M. A. 102:655.

46. Johnson, W.M., 1929: Tobacco smoking: A clinical study. J. A. M. A. 93:665-667.

47. Johnson, H.J., 1940: Study of 2,400 electrocardiograms of apparently healthy males including comparison of smokers and nonsmokers. J. A. M. A. 114:561-563.

48. Johnson, H.J., Short, J.J., 1934: Effect of smoking on skin temperature. J. Lab. & Clin. Med. 19:962-966.

49. Lampson, R.S., 1935: Quantitative study of vaseconstriction induced by smoking. J. A. M. A. 104:1963-1966.

50. Lee, W.E., 1908: The action of tobacco smoke, with especial reference to arterial pressure and degeneration. Quart. J. Exper. Physiol. 1908 1:335-358, 1 pl.

51. Levy, R.L., Mathers, J.A.L., Mueller, A.A., Nickerson, J.L., 1947: Effects of smoking cigarets on the heart. J. A. M. A. 135:417-421.

52. Maddock, W.G., Coller, F.A., 1932: Peripheral vasoconstriction by tobacco demonstrated by skin temperature changes. Proc. Soc. Exper. Biol. & Med. 29:487-488.

53. Maddock, W.G., Coller, F.A., 1933: Peripheral vasoconstriction by tobacco; relation to thrombo-angiitis obliterans. Ann. Surg. 98:70-81.

54. Maddock, W.G., Malcolm, R.L., Coller, F.A., 1936: Thrombo-angiitis obliterans and tobacco; influence of sex, race, and skin sensitivity to tobacco on cardiovascular responses to smoking. Am. Heart J. 12:46-52.

55. Main, R.J., 1941: Acute effects of smoking on respiration and circulation. Proc. Soc. Exper. Biol. & Med. 48:495-500.

56. Moschcowitz, E., 1928: Tobacco angina pectoris. J. A. M. A. 90:733-737.

57. Meyer, C.A., Maddock, W.G., 1940: Peripheral vasospasm from tobacco. Arch. Surg. 40:277-285.

58. Mulinos, M.G., Shulman, I., 1939: Vasoconstriction in the hand from deep inspiration. Am. J. Physiol. 125:310-322.

59. Mulinos, M.G., Shulman, I., 1940: Effects of cigaret smoking and deep breathing on peripheral vascular system studied by five methods. Am. J. M. Sc. 199:708-720.

60. Neuhof, S., 1916: Sino-auricular block, due to tobacco poisoning. Arch. Int. Med. 17:659-662.

61. Ni, T.G., 1920:citing Stachelin 1907 in: The effect of tobacco on the vascular wall. J. Lab. & Clin. M. 5:534-537.

62. Pearl, R., 1938: Tobacco smoking and longevity. Science 87:216-217.

63. Pickering, G.W., Sanderson, P.H., 1945: Angina pectoris and tobacco. Clin. Sc. 5:275-288.

64. Ralli, E.P., Oppenheimer, B.S., 1928: Changes in the peripheral circulation accompanying tobacco angina. Proc. Soc. Exper. Biol. & Med. 26:9-11.

65. Roth, G.M., McDonald, J.B., Sheard, C., 1944: Effect of smoking cigarets and of intravenous administration of nicotine on electrocardiogram, basal metabolic rate, cutaneous temperature, blood pressure, and pulse rate of normal persons. J. A. M. A. 125:761-767.

66. Roth, G.M., McDonald, J.B., Sheard, C., 1945: Effect of smoking cigarets and intravenous administration of nicotine on heart and peripheral blood vessels. M. Clin. North America 29:949-957.

67. Sanguinette, H.H., 1930: Smoking and high blood pressure. Lancet 2:1290-1291 Dec. 13, 1930.

68. Segal, H.L., 1938: Cigarette smoking as cause of fatigue; effect on electrocardiogram with and without use of filters. Am. J. M. Sc. 196:851-861.

69. Short, J.J., Johnson, H.J., 1939: Direct comparison of reactions of human system to tobacco smoke and adrenalin. J. Lab. & Clin. Med. 24:590-593.

70. Short, J.J., Johnson, H.J., Ley Jr., H.A., 1939: Effects of smoking on health; study of 2031 medical records. J. Lab. & Clin. Med. 24:586-589.

71. Silbert, S., 1927: Studies on thromboangiitis obliterans. J. A. M. A. 89:964-966.

72. Silbert, S., 1930: Thrombo-angiitis obliterans. J. A. M. A. 94:1730-1733.

73. Silbert, S., 1935: Thrombo-angiitis obliterans (Buerger) Treatment of 524 cases by repeated intravenous injections of hypertonic salt solution; experience of ten years. Surg. Gynec. & Obst. 61:214-222.

74. Silbert, S., 1945: Etiology of thromboangiitis obliterans. J. A. M. A. 129:5-9.

75. Ssalischtschiff, A.S., Tschernogoroff, J.A., 1929: as cited by Graybiel, A., Starr, R.S., White, P.D., 1938: Electrocardiographic changes following inhalation of smoke. Am. Heart J. 15:89-99.

76. Steward, H.J., Haskell, H.S., Brown, H., 1945: Effect of smoking cigarets on peripheral blood flow in subjects in older age groups with coronary arteriosclerosis and hypertension. Am. Heart J. 30:541-550.

77. Sulzberger, M.B., 1933: Recent immunologic experiments in tobacco hypersensitivity. Bull. New York Acad. Med. 9:294-317.

78. Sulzberger, M.B., 1934: Recent immunologic studies in hypersensitivity to tobacco (in relation to thromboangiitis obliterans.) J. A. M. A. 102:11-17.

79. Theis, F.V., Freeland, M.R., 1941: Smoking and thrombo-angiitis obliterans. Ann. Surg. 113:411-423.

80. Thienes, C.H., Butt, E.M., 1938: Chronic circulatory effects of tobacco and nicotine. Am. J. M. Sc. 195:522-529.

81. Thompson, W.G., Sheldon, W.H., 1916: Tobacco smoking and blood pressure. Med. Rec. 89:1018

82. Trasoff, A., Blumstein, G., Marks, M., 1936: Immunologic aspect in thrombo-angiitis obliterans and coronary artery disease. J. Allergy 7:250-253.

83. Weatherby, J.H., 1942: Skin temperature changes caused by smoking and other sympathomimetic stimuli. Am. Heart J. 24:17

84. Weber, F.P., 1916: Thrombo-angiitis obliterans. Quart. J. Med. 9:289-300.

85. Weinroth, L.A., Herzstein, J., 1946: Relation of tobacco smoking to arteriosclerosis obliterans to diabetes mellitus. J. A. M. A. 131:205-209.

86. Westcott, F.H., Wright, I.S., 1938: Tobacco allergy and thrombo-angiitis obliterans. J. Allergy 9:555-564.

87. White, P.D., 1939: Discussion of Wilson and Johnston's paper (91). Tr. A. Am. Physicians 54:223.

88. White, P.D., 1944: Heart Disease 3 ed. MacMillan Co.

89. White, P.D., Sharber, T., 1934: Tobacco, alcohol, and angina pectoris. J. A. M. A. 102:655-657.

90. Willson, R. N., 1915: The effect of tobacco and alcohol upon the cardiovascular system. New York M. J. 102:541-549.

91. Wilson, F.N., Johnston, F.D., 1939: The occurrence in angina pectoris of electrocardiographic changes similar in magnitude and in kind to those produced by myocardial infarction. Tr. A. Am. Physicians 54:210

92. Wright, I.S., 1933: The clinical value of human capillary studies in fever, mental deficiency, nephritis, vascular diseases, clubbed fingers, arthritis, tobacco smoking, and argyria. J. A. M. A. 101:439-

93. Wright, I.S., Moffat, D., 1934: Effects on peripheral vascular system; further studies. J. A. M. A. 103:318-323.