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Effects of tobacco upon the cardiovascular system

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THE EFFECTS OF TOBACCO
UPON THE CARDIOVASCULAR SYSTEM

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INTRODUCTION

The use of tobacco has become an almost universal habit and as a result it is important to the physician to understand the various effects that this habit can have upon the human body. Abstinance from tobacco can be correctly prescribed only after its pharmacological activity with its possible end results are known. That the use of tobacco can aggravate and possibly be an etiological factor in certain diseases is known, but in what diseases it should be proscribed is not always d finite. That this question is worthy of consideration is beyond doubt.

Pearl (73) in 1938 found that smoking of tobacco was statistically associated with an impairment of life duration and the amount or degree of this impairment increased as the habitual amount of smoking increased. Moreover, tobacco has its most serious effects during the earlier period of life. Pearl noted that the differences in specific mortality rates between the various groups of smokers and non-smokers practically disappears from the age of seventy years on. Those who survive to the age of seventy years are tough and resistant specimens. Thereafter tobacco does them no further measurable harm as a group.

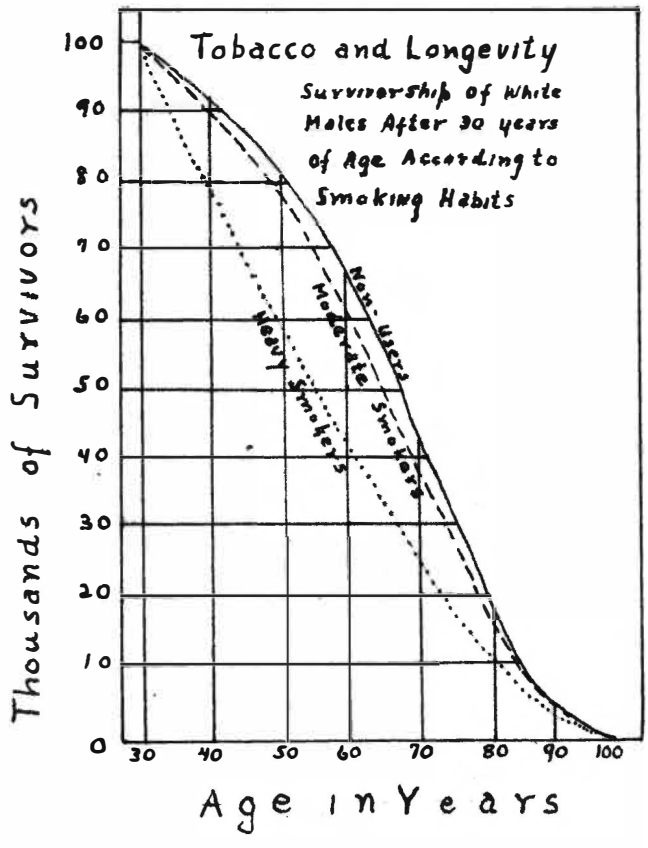

Fig. 1. The survivorship lines of life tables for white males falling into three categories relative to the usage of tobacco. A. Non-users: (solid line); B. Moderate smokers (dash line); C. Heavy smokers (dot line). (From: Pearl, 73)

(Of 100,000 non smokers age thirty, 66,564 will reach age sixty.
Of 100,000 moderate smoders age thirty, 61,911 will reach age sixty.
Of 100,000 heavy smokers age thirty, 46,266 will reach age sixty.)

No mention was made of the cause of death in the study by Pearl, but presumably a fair percentage were cardio-vascular in nature. Within the past forty-five years the use of tobacco has increased one hundred per cent in the United States and, during this period, the incidence of heart disease, apoplexy, Bright's Disease, and other diseases of cardio-vascular nature has also markedly increased. Holmes (50) also reported cardio-vascular disease to be much more prevalent among American men than women up to and including the year of 1921. Since that time more tobacco is being used by women and it will be interesting to note if the incidence of cardio-vascular deaths increases among them. In a series of two thousand thirty one cases by Short (79) in 1939 of individuals securing life insurance policies, it was found that symptoms of palpitation, precordial pain or stress, and dyspnea upon exertion increased from fifty per cent to one hundred and forty per cent in smokers, as compared to the same number of non-smokers of approximately the same age group.

THE PHARMACOLOGICAL ACTION OF TOBACCO IN THE NORMAL INDIVIDUAL

A considerable amount of work has been done in the attempt to learn the effects that tobacco has upon the human body. It has long been suspected of being harmful. In 1845 Brodie's experiments demonstrated that the action of an infusion of tobacco, when injected into the intestine of an animal, was to disrupt the action of the heart, stop the circulation, and thus produce syncope and death. (Allwatt-3) A short time later Claude Bernard showed by experimentation on mammalian animals that the effects of nicotine were the same whether applied to the alimentary canal, a wound of the skin, the mucous membrane, or the conjunctivae. He concluded that the arterial-capillary system was especially affected by nicotine through the medium of the sympathetic nervous system. (Taylor-90)

Most smokers perhaps have noted palpitation and a drop of temperature in the extremities following smoking, which brings up the question of the pharmacological action of tobacco.

There has been considerable controversy over the effect tobacco has upon the blood pressure. Lee (59) in 1908 found smoking raised the blood pressure and was of

the opinion that the rise was more in the novice smokers than in the habitual smoker. He believed that nicotine was the important poison in the smoke and that the pyridine bases present were not of sufficient amount to be injurious. Excessive smoking caused, according to Lee, a depression of the vasomotor center and lowered the blood presseure even to the extent that collapse occurred. Hesse (45) observed that both blood pressure and pulse pressure, as a rule, went up after smoking and then dropped below normal after about twenty minutes. He obtained the same results with denicotinized tobacco and concluded that the effects were of psychic origin and not due to the tobacco smoke. At the same time Hesse did his work it was not known that "denicotinized tobacco" contained 1.1% nicotine, whereas regular tobacco contained approximately only twice as much of the nicotine. Bogen (9). This fact causes Hesse's facts to be of little value.

Bruce et al (14) through experiments upon twenty-one year old males found the diastolic pressure was raised slightly, whereas the systolic pressure was increased to a more marked degree. This agress with the findings of Hesse that the pulse pressure is raised.

Aikmann (2) in 1915 reported as many or more

subjects exhibited a fall of blood pressure as responded to smoking with an increased vascular tension. He found that the results were not constant even in the same individual and out of twenty-seven subjects more experienced a drop of blood pressure than a rise after smoking one cigarette. Two years later in 1917, Thompson et al (93) obtained evidence that was in harmony with the results of Aikmann. In fifty-eight patients there was a rise of sytolic pressure in 35% and a fall in 45%, the remaining 20% being unaffected. They also found that the same patient sometimes exhibited a rise and less often a fall in systolic pressure. Since the time of Thompson's work, many men have taken up the study of tobacco and its effects on blood pressure. The results are similar and such that tobacco can be considered to cause a temporary elevation of the blood pressure. (28), (37), (43), (44), (49), (63), (64), (65), (78).

There is little evidence that tobacco causes any permanent hypertension in the average individual. Dixon (24) was of the opinion that chronic smokers exhibited a hypertension, but was immediately challenged. Even before Dixon, Brigham (12) observed one hundred thirty two smokers and non-smokers and found no appreciable difference between their blood pressures. The same

observations were made by Earp (25) in a series of two hundred subjects. Johnson (53), studying one hundred and fifty smokers and non-smokers of the same age group, found the average systolic blood pressure of smokers to be more than a millimeter of mercury lower than in the non-smokers. The diastolic was also slightly lower in the smokers. Hadley (34), working with seven thousand office patients, found the average systolic pressure in smokers nearly three millimeters of mercury lower and diastolic approximately one and one half millimeters lower than in the group of non-smokers.

The logical conclusions to be drawn from above are that tobacco smoking causes an initial temporary rise in blood pressure, but has little if any permanent effects. There is little doubt that in some individuals it causes a temporary lowering of the pressure, but this is more than likely due to nervous tension exhibited by many habitual smokers before they have their customary cigarette.

Another well known pharmacological reaction to smoking is peripheral vaso-constriction. This reaction is so closely related to the rise in blood pressure that it cannot be separated from it. Lee (59) realized that smoking raised the blood pressure by vaso-constriction. The methods of determining vaso-constriction have been

varied, but the results are approximately the same. The conclusion, that tobacco smoke causes vaso-constriction in the average normal individual is well accepted. An occasional individual will show vaso-dilatation.

Bruce et al (14) measured the size of the extremities before, during, and after smoking by a plethysmograph and thus determined the amount of peripheral vaso-constriction. Other workers demonstrated the vaso-constriction by the lowering of the skin temperature in the extremities. (5), (8), (54), (63), (64), (70), (78), (80). Evans and Stewart (28) measured the same by decrease in the skin temperature and rise in the rectal temperature. Friedländer et al (29) observed gangrene develop in the toes of a rat due to prolonged vaso-constriction following repeated injections of nicotine. Other men have directly observed the constriction of the arterioles of the nail folds and retina by the use of the microscope and ophthalmoscope. Photographs have been made of the retinal arterioles before, during, and following smoking. These also demonstrated the constriction. (42), (43), (44), (98). Wright (97) noted that the blooddflow decreased and even stopped in the capillaries of the nail fold during the smoking

of one cigarette.

Some very interesting observations were made by various men while studying vaso-constriction due to tobacco. Barker (5) found that in general the hypersensitive nervous type of individual was more subject to vaso-constriction from smoking. It would seem logical that a tolerance could be developed to tobacco against vaso-constriction, but Wright and Moffat (98) reported that the length of time a person had been smoking or the number of habitual daily cigarettes had no correlation with the degree of reaction. Their observations have been corroborated by Johnson and Short (54). Maddock et al (64) stated they found Jewish people more sensitive and responded with a greater degree of vaso-constriction than Gentiles. Blotner (8) found arteriosclerosis reduces very little the amount of active constriction of the arterioles. However, arteriosclerosis does decrease vaso-constriction. Herrell and Cusick (43) also noted that the increase in blood pressure approximates the amount of constriction of retinal arterioles on a percentile basis.

Much attention has been focused upon the possible activity of tobacco upon the coronary vessels. Most clinicians favored the view that it caused constriction presumably because smoking may precipitate anginal

attacks and perhaps coronary accidents in certain instances. (13), (65), (16), (20), (26), (30), (69), (75). Other authors question the possible fact that angina is due to the vaso-constriction of the coronaries, but think it is probably the result of other factors to be discus ed later in this paper. (33), (48), (53), (91), (95). Mansfeld and Hecht (67) introduced tobacco smoke into the lungs of the heart-lung preparation of dogs and found only coronary dilatation and increased coronary circulation with infusion of tobacco and with nicotine in all but excessive doses in isolated rabbit hearts. The controversy of coronary constriction versus coronary dilatation is not decided and more work will have to be done.

Tobacco also affects the pulse rate and at times the heart rhythm. Slight tachycardia, an increase of from four to fifteen beats per minute, is a temporary result of tobacco smoking that has been verified by numerous men. (2), (11), (14), (28), (35), (37), (42), (46), (59), (63), (64), (65), (70), (78), (84), (85), (91), (93), (94). Smith (84) found that phlegmatic individuals showed a more marked increase in the pulse rate than in the more sensitive individuals. Other authors disagree with his conclusions. The amount of tachycardia seems to be variable and the same subject

responds to a different degree at different times. (Thompson and Sheldon (93). Sontag and Wallace (85) observed an increase in the fetal heart rate after the mother smoked.

There is evidence that the tobacco habit causes a slight permanently increased pulse rate as long as the habit is continued. Hadley (34) studied seven thousand cases and found the average pulse rate of smokers to be 78.31 beats per minute and of non-smokers 77.30 per minute. Brigham (12), in one hundred thirty two young male smokers and non-smokers, found the average pulse rate to be 82 beats per minute in non-smokers, 83 in light smokers, 86 in moderate smokers, and 90 in heavy smokers. Other authors, Short et al (79) and Earp and Camb (25), believe there is no significant difference between the pulse rate of smokers and non-smokers. However, tobacco smokers as a whole seem to have a higher pulse rate than non-smokers.

THE AGENT IN TOBACCO SMOKE RESPONSIBLE FOR THE REACTIONS

The agent in tobacco smoke which causes the various reactions so far discussed has not definitely been isolated although much suspicion has been directed toward the nicotine content.

Maddock and Coller (63) reported the usual effects in subjects after smoking cigarettes regularly, but found no effect from merely puffing or fake smoking. Upon injecting the same amount of nicotine intraveinously as is inhaled, analogous results were obtained. Schulman and Mulinos (80) were interested in the causative factors of vaso-constriction from smoking cigarettes, and they found little difference in the degree of vaso-constriction between ten deep breaths of air and the same number of smoke inhalations. No blood pressures or pulse rates were recorded, but it is reasonable to assume that the effects were the same upon the blood pressure and pulse. It is well to keep in mind, that if their subjects took a full inspiration each time, their inhalations would be exaggerated in comparison to the normal smoking and hyperventilation would result. However, it is possible that the inhalation alone in smoking may result in increased blood pressure to a certain extent. Shulman and Mulinos further found the effects of denicotinized and regular cigarettes to

be the same, but also reported the effects to be more prolonged and to a greater degree from inhaling cigarette smoke than from simple deep breathing. Moyer and Maddock (70) have stated that in their series of subjects only a slight effect was obtained from inhaling smoke from cubeb cigarettes. The statement concerning the lack of effects from cubeb cigarettes are often used for symptomatic relief of asthmatic attacks, and cubeb probably has pharmacological properties that may nullify the results. Main (65), by carefully controlled experiments where the inhalations were of the same depth and frequency, found that nicotine free cigarettes produce very much less pressor action than regular cigarettes. Working with ten normal males, Evans (28) in 1943 reported an increase in blood pressure of essentially the same magnitude from smoking regular, commercially denicotinized, fully denicotinized, and cornsilk cigarettes. There were also the same results from smoke drawn through a water pipe. Evans also found no increase in blood pressure from breathing pure oxygen or hot air. He suggested that smoke of any kind is irritating to the respiratory tract and that sympathetic stimulation was responsible for the changes observed. On the other hand Barker (5) in 1933 noted

in his experiments more effect from smoking tobacco without paper than from smoking paper and tobacco together.

More experimental work will have to be done before definite conclusions can be made, but it is reasonable to assume that nicotine is not the only factor causing thevarious reactions. Nicotine, in conjunction with the act of inhaling and the irritating effects of smoke upon the respiratory tract, is probably responsible.

THE MANNER OF ACTION OF TOBACCO UPON THE CARDIOVASCULAR SYSTEM

It is necessary to have an understanding of how tobacco works upon the cardiovascular system in healthy individuals before its effects in disease can be discussed.

Traube (94) in 1862, while studying the action of nicotine upon the dog's heart, observed that there is at first a slowing or even temporary cardiac arrest followed by tachycardia with reinforced contractions.

Langley (56) in 1901 found that nicotine stimulates sympathetic nerve cells. The stimulation was shown to be direct by applying dilute nicotine to a ganglion after degeneration of its preganglionic fibers. By animal experimentation, comparing the intact kidney with a denervated kidney, Bariety and Kohler (4) found that nicotine produced a definite hypertension with a diminution in the volume of the kidney which was intact and and an augmentation of the volume in the one without nerve supply, thereby concluding that the effects of nicotine were upon and through the nervous system. Heyman's (46) by experimentation found nicotine acted reflexly on the carotid sinus producing tachycardia and vaso-constriction. Brunton (15) observed that nicotine stimulates the vagus center in small doses

and in larger doses paralyzes the vagal action resulting in tachycardia. Haskins and Rausom (52) in 1915 state that the pressor effect of nicotine is due in part to a stimulation of the vaso-constrictor center proper and half to a stimulation of the ganglion cells. They believe that occasionally spinal cord stimulation also contributes slightly to the reaction. Upon experimentation with dogs, they found that cutting the spinal cord at the eighth cervical level typically reduces the pressor reaction to nicotine about fifty per cent. The amount of nicotine necessary to produce an initial rise is approximately doubled. The rise in pressure upon injection of adrenalin is not significantly decreased. Further destruction of the cord through the dorsal and lumbar regions only occasionally induces a further depression in the reaction. Maddock and Coller (63) brought forth definite proof concerning a mechanism of peripheral vaso-constriction due to tobacco. They blocked the left posterior tibial nerve in two subjects with two per cent procaine which interrupted the nerve supply to the plantar surface of the left plantar surface of the left toes. Upon smoking vaso-constriction occurred in the toes of the right foot in both subjects, but not in the toes of the left foot of either one. In a patient who had undergone a cervico-dorsal

ramisectomy and ganglionectomy and a lumbar ganglionectomy for Raynaud's disease, which abolished all sympathetic control to the extremities, they found smoking caused the usual blood pressure changes, but no peripheral vaso-constriction. Hertheimer and Colas (95) noted that acceleration of heart raté which follows injection of nicotine is present whether the extrinsic nerves are intact or not and an increase in arterial tension even after destruction of medulla and spinal cord. Action, however, is greater on heart and blood vessels when the nerves are intact demonstrating a central as well as peripheral effect.

This peripheral effect brings up another factor in the manner that tobacco acts upon the cardiovascular system. Cannon et al (18) experimenting with cats found injections of nicotine increased the secretion of epinephrine. This was corroborated by Dale and Laidlow (22). Stewart and Rogoff (86) observed a preliminary increase in the output of adrenalin upon injection of nicotine with a corresponding rise in blood pressure. This was followed by a decreased output and subnormal pressure. In their experiments the smaller the dose of nicotineinjected, the longer the stimulatory period

tended to be before depression occurred. LeLair (60) found injections of nicotine intraveinously to dogs caused the blood sugar level to rise, but after double adrenalectomy, the blood sugar level does not rise upon injection. Other workers have found the blood sugar level to rise upon smoking in human subjects also. (Haggard and Greenberg (35) and Short and Johnson (78). Sollmon, ascited by Short and Johnson (78), states that blood pressure may be raised by nicotine injections even without the vasomotor center, but not without the suprarenals.

Tobacco smoking evidently acts primarily upon the nervous system. The nicotine inhaled stimulates the sympathetic ganglia, vaso-constrictor center, and suprarenals to cause tachycardia, vaso-constriction, and an increased blood pressure. It also acts reflexly through the carotid sinus upon the vaso-constrictor and cardio-inhibitory centers to augment the reactions. The reactions are extremely variable for different individuals and in the same individuals at different times, because the vagal centers are also stimulated and tends to counteract the sympathetic effects. However, in most subjects the vagal reaction either tends to be paralyzed after a short time by the increased amount of nicotine

in the system or an increased amount of sympathetic stimulation occurs to overcome it. Nicotine seemingly is not the only factor in tobacco smoking. According to Evans (28), all the above reactions can be obtained upon the inhalation of any type of smoke and nicotine in itself plays a minor role. Theis and Freeland (91) found a decreased O_2 tension in the arterial blood and made the interesting comment that perhaps the tachycardia etc. are physiological adjustments to compensate for the lowered O_2 tension.

ORGANIC EFFECTS FROM THE USE OF TOBACCO

The use of tobacco has been suspected from time to time to cause organic changes in the cardio-vascular system. If such is the truth it can have far reaching consequences.

Baylac (6), in 1906, described atheromatous plaques in the aorta of rabbits that had been injected with nicotine. Lee(59), experimenting with rabbits a short time later, reported extensive fibrosis of the tunica media invading to a slight extent the intima, which in certain areas showed the antecedant stage of fibrosis as an inflammation with plentiful cell proliferation. He also found marked erosion and rupture of the elastic fibers and some of these were encased in calcium salts. Adler and Hensel(1), in 1906 and also working with rabbits, denied any degeneration or inflammatory changes in the intima of the blood vessels but found a calcareous degeneration in the media similar to that produced by adrenalin. Other men using rabbits observed similar results. (61), (76) and (77). Romm and K uschnic (76) injected some rabbits with epinephrine and others with nicotine. Epinephrine injected rabbits showed sclerotic plaques in the great vessels earlier and to a greater degree than did the

nicotine injected rabbits. The evidence compiled during this period would indicate nicotine as a causative agent in sclerosis of blood vessels in the rabbit at least. It was noted that epinephrine caused more degeneration than nicotine. Thienes and Butt(92) in 1938 were doubtful of the results obtained by earlier workers who perhaps did not control their experiments any too carefully. In an attempt to clarify a most doubtful situation concerning nicotine, they ran a series of carefully controlled experiments on both rabbits and rats. Nicotine was injected into the test rats and rabbits and saline was injected into the controls. Their results were approximately the same in both tests and controls; if anything, the more marked results were in the controls. It has been pointed out by Hausemann, as cited by Adler and Hansel (1), that rabbits as all herbiverous animals, tend to show calcareous degeneration much easier than in man.

Byrom(16) however, from clinical studies made prior to 1906, believed heavy smoking caused sclerosis of the vessels in man. Gilfillan(30), in 1912, was of much the same opinion believing that the long continued blood pressure increase caused the changes in

the vessels. Buerger(17) stated that tobacco is probably a predisposing factor and may be regarded at least as causing some alteration in the vessels of man which makes him liable to the attacks of inflammation and thrombosis, but that tobacco is the only and exciting cause is exceedingly doubtful and highly improbable. Maddock and Coller (63) believed it possible that vasoconstriction of the vasovasorum due to tobacco may cause changes in the vessel wall due to poor nutrition.

Although much suspicion has been cast upon tobacco as a causative agent of arteriosclerosis in humans, there has been no definite proof whatsoever. Clinicians are inclined to look upon tobacco as a possible aggravating factor in a process already well on its way to being established. Goodman and Gillman(32).

Experimental work and clinical investigation concerning the effects of nicotine upon the heart have been very enlightening. Experimenters in the latter part of the nineteenth and early part of this century were more concerned with the effect of nicotine on the myocardium than on the coronary vessels which of late has received the most attention.

Attention was called to the heart by the condition known as "smoker's heart", which is characterized by palpitation, irregular rhythm, extra systoles, and precordial pain. Bosworth (11), who reported his studies in 1889 concluded that it was a functional disturbance caused by the action of nicotine upon the vagus nerve as a powerful narcotic and thus impaired the control over the heart action. Even at this early date, Bosworth was largely correct in his explanation of the action of tobacco on heart rhythm. That irregularities of heart action mainly in the form of extrasystoles and palpitation often occurs in smokers is well known and often reported. (2), (7), (8), (11), (15), (30), (66), (79). Brunton (15) noted that very frequently after the above symptoms have once appeared a very small amount of tobacco will keep them going and to cure the symptoms a total abstinence from tobacco for several months is necessary.

Some men were of the opinion that tobacco caused direct changes in the myocardium. Maine (66) in 1902 believed prolonged use of tobacco, if it results in an overaction or irregularity of action of the heart, would result in hypertrophy. Brigham (12) considered tobacco smoke as an etiological factor in myocarditis. There has been no proof that these myocardial changes occur,

nicotine injected rabbits. The evidence compiled during this period would indicate nicotine as a causative agent in sclerosis of blood vessels in the rabbit at least. It was noted that epinephrine caused more degeneration than nicotine. Thienes and Butt(92) in 1938 were doubtful of the results obtained by earlier workers who perhaps did not control their experiments any too carefully. In an attempt to clarify a most doubtful situation concerning nicotine, they ran a series of carefully controlled experiments on both rabbits and rats. Nicotine was injected into the test rats and rabbits and saline was injected into the controls. Their results were approximately the same in both tests and controls; if anything, the more marked results were in the controls. It has been pointed out by Hausemann, as cited by Adler and Hansel (1), that rabbits as all herbiverous animals, tend to show calcareous degeneration much easier than in man.

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but the problem has been investigated by other individuals. Paul White (96) observed transient electrocardiographic changes resembling those of coronary obstruction in a man who exhibited anginal attacks upon smoking, but considered the change purely functional. Graybiel, Starr, and White (33) found fifteen out of forty-five smokers had inversion or lowering of the T wave. They believed the probable explanation for the T wave changes was due to the characteristic paralytic action of nicotine on the cardiac ganglia. Similar effects were produced in the same patients by atropinization. This explanation is accepted by most authorities today and tobacco is not regarded as a cause of myocardial damage in an otherwise healthy heart. (Goodman and Gilman)(32). The condition known as "smoker's heart" is not an organic but a functional condition due to nervous derrangement as explained by Bosworth.

Coronary thrombosis and coronary accidents have been clinically associated with heavy smokers ever since these conditions have been rightly diagnosed as coronary pathology instead of acute indigestion. Coronary accidents often occur in the man who eats a heavy meal and then follows this with a large black cigar.

Pawinski (72) in 1914 reported that 42% of cases of coronary disease were in heavy smokers. Pleuge (74), sixteen years later, observed coronary sclerosis due chiefly to connective tissue replacement of the muscle and elastic fibers of the media, with evidence of fresh necrosis in two supposed victims of tobacco smoke. In 1940 English, Willus, and Berkson (26) published a significant paper dealing with coronary accidents and its relation to tobacco. They noted in a series of a thousand cases of coronaries and another thousand individuals as controls, both being over forty years of age, that of the co onaries, 69.8% we e smokers and ofthe non-coronaries, 66.3% were smokers. Another series of a thousand smokers and a thousand non-smokers all over forty years of age were studied and they found 5.4% of the smokers had had coronary attacks, whereas 3,8% of non-smokers had had attacks. There is not much variation in the above two groups as such, but when the two groups were divided into separate ones according to age, it was found that in those of forty to forty-nine years coronary attacks nearly five times more common in smokers. In the next age group, fifty to fifty-nine years, coronaries were over twice as common, but in those

sixty years or over, there was no difference in the incidence of coronary attacks between smokers and non-smokers. In other words smoking causes coronary lesions to appear earlier in life. Tobacco can be considered to accelerate the process in which coronary occlusion occurs. English et al further reported that in the younger age groups the number of coronaries per thousand individuals was proportional to the amount of tobacco used. Heavy smokers were much more apt to have coronary thrombosis than the light smokers.

Bellet, Kershbaum, Meade, and Schwartz (7) in 1941, by experimental evidence obtained from animals, have probably thrown some light on the manner in which tobacco accelerates the appearance of coronary accidents. They found that normal unanesthetized dogs were able to tolerate a wide range of dosage without much electro-cardiographic changes. However, following myocardial damage produced by coronary ligation, marked electro-cardiographic changes were produced by a dose of one-fourth the amount used before. These changes became less as healing of the infarction occurred. Nevertheless, the electrocardiographic changes after equivalent doses of nicotine were more marked in the healed chronic infarcts than with normal dogs. Correlation can be

made between the evidence above and the process that takes place in the human heart, but further work will be necessary before knowing how this exactly takes place.

Enough is known that the use of tobacco can be condemned in any patient with a history of coronary thrombosis and certainly so in one who is suffering from a recent attack. Here is also a strong point in favor of total abstinence from the use of tobacco by all persons if they wish to live as long and as healthfully as possible.

Angina pectoris cannot be classified as a strictly organic disease or syndrome, but it will be discussed in this section of the paper. Tobacco has been often accused of being an etiological factor. Sir Brunton (15) in 1905 believed one of the results of excessive smoking was precordial pain which may be severe enough to simulate angina pectoris. He based his conclusions upon clinical observations. He noted that once this symptom made itself manifest a very small amount of tobacco would cause a continuation of it. Total abstinence for several months brought about a cure in his cases. Byrom (16) reported a case of anginal pain in a man twenty-five years of age, which was due to tobacco. Gilfillan (30) in 1919, from his clinical experience stated that one of the symptoms of chronic

nicotine poisoning is precordial pain. He believed this pain was due to a constant repitition of toxic irritation of nervous elements causing at least paroxysmal discharges of nerve energy and a spasm of the coronary arteries. Gilfillan did not consider tobacco a very prevalent cause of angina, but he was of the opinion that some cases were due to it. According to him the appearance of cardiovascular symptoms did not depend on the length of time the habit had been present, and periods of tolerance and intolerance alternated without apparent reason. Brooks (13) noted that by no means infrequently, persons long habituated to the use of tobacco suddenly and without apparent cause developed a sensitization to its effects so that very distressing heart symptoms appeared even from very slight doses of tobacco. In his opinion coronary constriction caused the angina. He found in his experience that angina occurs with greater frequency in old habitues accustomed to the drug than in acute cases, although he has known acute angina to develop with the initial dose of tobacco. Maschcowitz (69) reported several cases where severe anginal pains occured until tobacco was stopped for several months. The pain was usually more intense and of longer duration than in true angina pectoris, there being slight, if any, disturbance of heart function.

This would indicate the pain to be on a functional basis and not an organic one. These anginoid pains of tobacco origin did not cease promptly after withdrawal of the tobacco, and they would at times continue for weeks or months. However, there was a gradual lessening of the severity of attacks after abstinence. One patient was so sensitized to tobacco smoke that a smoky room would bring on an attack. Symptoms and attacks reappeared when tobacco was again used. Moschowitz believed tobacco to be an exciting or precipitating factor of pain in certain individuals with pre-existing organic changes. He was of the opinion that a chronic state of increased heart work due to the increased blood pressure, tachycardia, etc, was the cause of the pain. Cornwall (20) cited a few cases of like nature and accepted the view that some cases of angina pectoris are due to tobacco smoking. Ralli and Oppenheimer (75) also also accepted the view that some cases of angina pectoris are due to tobacco smoking. They investigated their patients further and by experimental observation found the blood pressure and vaso-constriction preceded the pain. After giving a nitroglycerine tablet under the tongue, the plethysmograph would give evidence of peripheral dilatation before the cessation of pain.

The trend of clinical opinion can be seen from the conclusions of the above authors. Tobacco is not considered to be a specific cause of angina pectoris, but in certain individuals it may act as a precipitating factor. In these cases tobacco should be discontinued. The incidence of such cases is not very common. Johnson investigated the probably incidence on a statistical basis. He found, that of sixty fatal cases of angina pectoris in males, 70% were smokers and 30% non-smokers. However, in a control group of one thousand adult males, taken at random from telephone directories, 81.8% were smokers and 18.2% were non-smokers.

The manner in which tobacco precipitates angina is still a doubtful question. Graybiel, Starr, and White (37) suggested that the attacks are not the result of coronary vaso-constriction, but is the result of a sudden increase in the work of the heart as indicated by the increase in blood pressure and heart rate. That vaso-constriction of the coronaries is not the cause is probably true, sos far as can be determined by animal experimentation. As stated before in this paper, Laubrey et al (57) found an increased coronary circulation with infusion of tobacco and with nicotine in all but excessive doses in isolated rabbit-

heart preparations. Mansfeld and Hecht (67) introduced tobacco smoke into the lungs of heart-lung preparations of dogs and found coronary dilatation along with an increased cardiac output. The basal metabolism rate was found by Heistand et al (47) to be increased 8.9% in the average smoker after smoking a cigarette. This would add a further burden upon the heart in cases susceptible to anginal attacks. Tobacco smoking is usually accompanied by a reduction in the oxygenation of arterial blood. (Theis and Freeland)(91). As angina is theoretically due to anoxia of the heart muscle, this is probably significant. The increased epinephrine has something to do with producing the pain, probably through its generalized stimulatory action. Levine et al (62) used epinephrine as a diagnostic test for angina pectoris. Cottrell and Wood (21), in a patient with angina pectoris, precipitated a severe attack by injecting epinephrine. In those cases of angina due to tobacco, the above factors and not constriction of the coronary arteries are probably responsible or at least partially so. The question is still open to discussion. Tobacco should be absolutely contraindicated in those patients who experience anginoid pain following smoking. These individuals usually discontinue the use of tobacco

of their own accord.

The relation of tobacco to essential hypertension has recently received considerable attention and promises to be very significant and interesting. Clinicians today regard an exaggerated response to the cold pressor test as a possible indication of a latent or actual hypertension in otherwise healthy individuals. It is an indication of a hyperactive vascular system. Herrel and Cusick (43) found that certain individuals, who had a hyperresponse to the cold pressor test, also had an exaggerated rise in blood pressure following smoking which corresponded very closely to the pressure obtained during the pressor test. Other patients, however, did not give this response. In other words, here as in other conditions, some individuals show abnormal reactions to tobacco while others do not. It is an individual problem. Hines and Roth (49) had similar results from their experiments. They found most patients with essential hypertension, except in those who did not smoke, had an elevation in systolic and diastolic blood pressure following the smoking test, which was greater than in the naormal subjects. The significance of the above observations is not known as the etiology and reasons for progression of essential hypertension

are not known. The relation of essential hypertension to a hyperreactive vascular system from an etiological standpoint is still not understood. The present clinical opinion held by Herrel and Cusick is that a patient with vascular disease and who is a hyperreactor to tobacco and the cold pressor test has everything to gain and nothing to lose by discontinuing tobacco.

There is seemingly a close relationship between tobacco and thromboangiitis obliterans which has been under discussion for many years. Buerger (17) in 1924 was of the opinion that tobacco is probably a predisposing factor and may be regarded at lease as causing some alteration in the vessels that makes them liable to the attacks of inflammation and thrombosis. He found that by far the most cases of thromboangiitis obliterans occurred in heavy smokers. Smoking was denied in only 1% of the cases. He did not believe, however, that tobacco was the only and exciting cause of the disease. Silbert (81) in 1938 remarked that in twelve hundred patients with thromboangiitis obliterans he had not seen a typical Buerger's disease in a non-smoker and believed those reported in non-smokers may have been cases of mistakened diagnosis. He found more than 50%

of patients who continued to smoke required amputations. Horton (50) reported a series of nine hundred forty eight patients with Buerger's disease and of these 93% were smokers. Of these smokers 69% smoked fifteen or more cigarettes a day. It is also significant to note in his series of cases that amputation was necessary more often in smokers, the increase in smokers being ten to fifteen per cent over that necessary in non-smokers. Silbert (82) in 1942 noted that in thirty individuals with early Buerger's disease, cessation of smoking alone was sufficient to cause relief of symptoms and improvement in circulation, whereas patients who continued to smoke were difficult to improve and usually progressive in spite of treatment. He found that when patients who had been in excellent condition for many years again resumed the use of tobacco, recurrance of symptoms was the rule. Silbert stated that two thirds of patients who required amputation had persisted in smoking in spite of warnings to stop. He concluded from his vast clinical experience that smoking will produce thromboangiitis obliterans only in those individuals who have a constitutional susceptibility to tobacco, and this condition is relatively infrequent in the general population.

This close relationship of tobacco smoking and Buerger's disease is known to clinicians, but tobacco is not accepted as a cause. No definite proof has been found to indicate it as such. It is evidently a contributing factor that aggravates the condition and may be the agent which precipitates the disease. (17), (50), (81), (82), (86), (87), (88).

Tobacco is not the only agent that influences Buerger's disease. Ergot, which causes peripheral vasoconstriction, has been implicated as another agent which behaves much like tobacco in aggravating and possibly precipitating an attack. O'Leary (70) believed that rye head, contaminated by ergot, acts as an etiological factor in thromboangiitis obliterans. Goodman (31) made the observation that Buerger's disease is of frequent occurance in the peasants of Russia and south-eastern Europe. Tobacco is a luxury beyond the means of this class of people, but they are in a region where ergotism is common.

The possible manner by which tobacco acts as it does in Buerger's disease remain largely unsolved. Friedländer et al (29) in 1936 injected denicontinized tobacco intra-peritoneally into forty-eight male rats daily. Of these forty-eight, thirty-three developed

gangrene of the toes within five to twelve weeks. None of twelve female rats treated in a like manner developed such lesions. Six rats were subjected daily to inhalations of tobacco smoke over a period of five months and one male animal developed lesions similar to those produced by injections of the extract. One male animal of a group of ten treated with daily intra-peritoneal injections of alkaloid nicotine tartrate also developed a characteristic lesion of one foot. Preliminary microscopic studies showed an inflammatory process involving the vessels. Harkavy (39) in 1937 reported confirmation of the results of Friedländer et al with nicotine free extracts of tobacco and thus placed it on a sensivity or allergic basis to the extract. The conclusions reached by Friedländer and Harkavy must be viewed with caution as Thieves and Butt (91) in 1938 carefully controlled their experiments and produced gangrenous lesions in both male and female rats. Furthermore, in a large cage of twelve stock rats closely related to the experimental rats, but untreated, eight animals developed marked gangrene of the toes.

Considerable attention has been given to the allergic approach as the probable method of influence of tobacco

in Buerger's disease. Harkavy, Hebald, and Siebert (37) in 1932 ran a series of experiments on sixty-eight cases of thromboangiitis obliterans and one hundred seven controls of cigarette smokers. Fifty-eight or 83% of those suffering from Buerger's disease had a positive skin reaction or sensitivity to tobacco extract. Of the one hundred seven controls, ninety-seven were negative and ten were weakly positive. They concluded that a large percentage of patients suffering from thromboangiitis obliterans belong to the category of allergic individuals and that this allergy is essentially characterized by a hypersensitivity to tobacco. They also found that in those with Buerger's disease a large number were sensitive to other well known allergic antigens, but none compared to that of tobacco. In 1933 Sulzberger, sholder, and Feit (87) found eight out of nine cases of Buerger's disease exhibited a hypersensitivity to tobacco, but only two of these were positive to nicotine. They considered their data to be suggestive of a relationship between tobacco hypersensitivity and this disease, but did not believe they had definite proof of such. After further work done by Sulzberger and Feit (86) on twenty-two cases of Buerger's disease, in which they found all but

three of them had positive skin tests to tobacco, they concluded that this is a condition usually associated with a specific and marked hypersensitivity of the vascular apparatus of the skin to tobacco. Sulzberger (88) working independently in 1934 found that although tobacco was the principal allergan causing positive reactions in thromboangiitis obliterans, other allergans and notably inhalants also elicited positive responses. He suggested that cases of Buerger's disease must exist in which other excitants and not tobacco are the major factors. Sulzberger also proved that nicotine is not the part of tobacco responsible for the sensitivity. The portion of tobacco extract which causes the reaction is coctostabile, thermostabile and is not destroyed by ultra violet rays or x-rays. Nicotine does not have the above properties. Harkavy and Romanoff reported, after studying a series of cases in 1934, that tobacco extracts prepared from the cured leaves are comparable in their allergic constancy with those of other well known allergans such as ragweed pollen, timothy pollen, and house dander extracts. They also reported a large percentage, 69%, of patients with Buerger's disease positive to tobacco, whereas only 11% of the controls, all smokers, were positive. This would

seem to indicate tobacco as the dominating allergan in the disease. Later, Harkavy (40) working independently obtained similar results as he and Romanoff had obtained before. He also found a case of Buerger's disease in which injections of tobacco not only increased the vascular symptoms, but also caused a marked generalized dermatitis and both conditions would clear up after withdrawal of the tobacco. Here is one case in which the allergic properties of tobacco extract is rather apparent, but it is the only one such case reported in the literature. Harkavy also observed that the degree of skin reaction does not compare with the degree of clinical symptoms.

The above data gathered as the results of careful observation and experimentation would tend to indicate an allergic reaction to tobacco as the etiological factor concerned in Buerger's disease. However, some evidence has accumulated to the contrary. Chobat (19) noted in a study of fifty-three unselected children who had never smoked that only 11% gave negative, whereas 89% gave positive , reactions of the skin to tobacco extracts. These children could not possibly have had any Buerger's disease. The striking disparity between these figures and those given before makes the

significance of a skin test doubtful as an indicator of value. No definite conclusions can be drawn at the present date. The discrepancy of the deductions obtained by the various workers from their experiments and observations requires further investigation along this line. Probably a large percentage of patients with thromboangiitis obliterans belong to the category of allergic persons and that allergy is manifest more strongly to tobacco than to other allergans. However, there is little relationship between the degree of allergy manifest and the degree of clinical symptoms present. Many individuals who have no Buerger's disease show the same allergic condition to tobacco although the percentage of normal individuals showing this is probably lower than that of patients with Buerger's. There has been only one case reported in the literature where the allergic manifestation to tobacco, as shown by a generalized dermatitis and clinical symptoms of thrombo-angiitis obliterans, were definitely related to each other. The evidence shows an allergic phenomenon between tobacco and the patient with Buerger's disease, but this relationship is so indefinite that it might well be only an accompanying reaction and not an etiological factor. The reason it should be present

more often in patients with thromboangiitis obliterans may perhaps be explained upon the fact that these individuals as a rule expose themselves to large amounts of tobacco.

Other factors must be considered. Johnson and Short (53) in three out of four cases of this disease, observed that the reduction in skin temperature was more marked than in the average individual upon smoking, indicating a more marked vaso-constriction present than usual. They found that this degree of temperature drop was independent of the number of cigarettes habitually smoked daily by these individuals. Moyer and Maddock (69) verified the work of Johnson and Short, but also found extensive arteriosclerosis did not in the least reduce the vaso-constriction in their cases with Buerger's disease. This vaso-constriction caused by tobacco is a factor in the clinical course of thromboangiitis obliterans, but cannot be considered the cause of the disease. Perhaps many early cases of Buerger's would never become clinically evident if the individuals did not smoke, and there may be many sub-clinical cases that will always remain so in the non-smoking category of people. Theis and Freedland (90) in 1941 attempted to explain the relationship between tobacco and thrombo-

angiitis obliterans on a decreased physiological response to tobacco smoke. They noted that the responses of blood pressure increase, tachycardia, etc. are present to a greater degree in women than men, which suggested to them that a decreased response is an etiological factor, it being remembered that Buerger's disease has not been reported in women. They found a reduction in oxygenation of arterial blood after smoking which was more apparent in men than women due supposedly to the less physiological response present in men. They think the lowered oxygen tension in the tissues may predispose to thrombo-angiitis obliterans. The basis of lessened physiological response as a cause is in contraindication to results found by other workers, vaso-constriction seeming to be more apparent in cases of Buerger's disease than in normal individuals.

Though the exact etiology of Buerger's disease is still unknown, the use of tobacco is definitely contraindicated in this condition. It definitely aggravates the disease as already reported earlier in the paper.

Tobacco could be profitably proscribed in any gangrenous condition or lesion which has its origin on a low blood supply basis. The further reduced blood

supply caused by the vaso-constriction from tobacco smoke will aggravate the condition and cause further and more rapid progression of the disease. Blatner (8) in 1936 found the temperature reduction still present in gangrenous extremities due to diabetes and to arteriosclerosis. He assumed that any vascular disorder, causing the tissues to be on the verge of gangrene, would result in gangrene by further vaso-constriction. It is reasonable to contraindicate the use of tobacco in various pathological conditions where peripheral vaso-dilatation is desirable. This should be kept in mind in cases of embolic or thrombotic blockage of arteries where the development of a collateral circulation is necessary. Buerger (17), who reported that cases of migrating phlebitis occurs very often in heavy smokers, advises temporary abstinence from tobacco whenever such a condition is present. Therapeutically it would be good judgment to advise discontinuance of tobacco, at least temporarily, in cases of Raynaud's disease, scleroderma, ergotism, and periarteritis nodosa. It should be kept in mind that Evans (28) has shown that smoking of denicotinized tobacco or other tobacco substitutes causes similar reactions to those found in the use of regular tobacco.

SUMMARY

1. Smoking of tobacco is statistically associated with an impairment of life duration.

2. Symptoms of palpitation, precordial pain or stress, and dyspnea upon exertion are from fifty to one hundred and forty per cent more common in smokers than non-smokers.

3. In the average healthy individual tobacco causes a temporary increase in blood pressure and pulse rate and a peripheral vaso-constriction of a short duration. The coronary arteries are probably dilated in most cases. There is no permanent hypertension resulting from the tobacco habit, but a tendency to a slight tachycardia exists as long as the habit is continued.

4. Nicotine is not the sole agent in tobacco smoke responsible for the above reactions of the human body, but acts in conjunction with the act of inhaling and the irritating effects of smoke itself upon the respiratory tract.

5. Tobacco smoke and especially the nicotine content acts primarily upon the nervous system to cause the various effects.

6. Tobacco does not cause sclerosis of the blood vessels in man.

7. The use of tobacco does not result in any organic

myocardial changes in otherwise healthy individuals. In certain individuals it is responsible for the functional symptoms of palpitation, irregularity of rhythm mainly in the form of extrasystoles, and precordial distress. These symptoms are all part of a condition known as "smokers heart" and is a functional derrangement of the nervous control over the heart. Abstinence from tobacco will cure this condition.

8. Smoking causes coronary lesions to appear earlier in life. Smokers between the ages of forty and forty-nine years have coronary attacks nearly five times as frequent as non-smokers of the same age. This increased incidence in smokers gradually disappears in the older age groups and by sixty years there is no difference. The number of coronary attacks varies directly with the amount of tobacco used. The use of tobacco should be condemned in any patient with a coronary attack or a history of one.

9. Tobacco is an occasional cause of precordial pain resembling angina pectoris. These rare cases can be easily recognized from their history. The attacks of pain are probably the result of increased heart work and not constriction of the coronary arteries. Abstinence from tobacco is necessary for cure.

10. Tobacco is definitely contraindicated in Buerger's disease. The etiological relationship between tobacco and this disease is not known. A large percentage of patients suffering from thrombo-angiitis obliterans belong to this category of allergic individuals and this allergy is essentially characterized by a hypersensitivity to tobacco. This is probably an accompanying phenomenon and not a causative agent. Tobacco aggravates the disease to a marked degree, and makes it very difficult to treat.

11. Tobacco could be profitably proscribed in any gangrenous condition or lesion which has its origin on a low blood supply basis. It is reasonable to contraindicate the use of tobacco in various pathological conditions where peripheral vaso-dilatation is desirable. Therapeutically it would be good judgment to advise discontinuance of tobacco, at least temporarily in cases of Raynaud's disease, scleroderma, ergotism, and periarteritis nodosa.

12. Denicotinized tobacco and tobacco substitutes are contraindicated wherever tobacco is itself.

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