Smoking and Ischaemic Heart Disease

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Few today would doubt the role of cigarette smoking in the causation of lung cancer and chronic bronchitis. The association of cigarette smoking and thromboangiitis obliterans is also accepted by most. Epidemiological studies indicate an association between cigarette smoking and peptic ulcer, greater for gastric than duodenal. It seems certain, too, that habitual smokers who continue during pregnancy produce smaller babies. Tobacco as a cause of amaurosis, especially in pipe and cigar smokers, rests on a less secure basis.

Until recently the importance of smoking in relation to diseases resulting from atherosclerosis, including both ischaemic heart disease and cerebral atheroma, has received less emphasis than the above-mentioned diseases. In the author's opinion, the case has now been fully established that smoking, both cigarettes and to a lesser degree cigars, is an important factor in the aetiology of ischaemic heart disease, and some of the clinical, epidemiological, pathological, and experimental evidence is discussed. Most of the objective research, both human and animal, has been carried out well within the past decade and the literature is already so voluminous that only key references are appended. In the United States Surgeon General's Report of 1967 (*Health Consequences of Smoking*) a review is made of over 2000 papers published since 1964.

Tobacco was introduced to Europe in the 16th century, but cigarettes did not appear until the 17th century. Historically, it is difficult to be certain exactly when physicians first began to suspect that smoking tobacco might produce symptoms of angina, but according to Gélinau (1887), Beau in 1862 was the first to show convincingly that, under certain conditions, smoking tobacco could initiate angina pectoris. In 1887 Gélinau, a one-time ship's surgeon, published in his textbook details of an epidemic of angina on board the *Embuscade* which he considered to be due to smoking and living in a heavily smoke-laden atmosphere below deck. In

1899–1903 Huchard coined the term “tobacco angina” and differentiated *angine spasmo-tabagique*, *angine scléro-tabagique*, and *angine gastro-tabagique*. It is, however, likely that the last of these was probably nothing more than simple dyspepsia resulting from excessive smoking.

PHYSIOLOGICAL EFFECTS OF SMOKING

The effects of smoking are complex, but may be considered in two groups: those due to nicotine, and those due to the non-nicotine components of tobacco. Appreciable amounts of carbon monoxide are present in tobacco smoke, and may be absorbed to produce a total carboxyhaemoglobin concentration in the blood of up to 10 per cent, but it is doubtful whether this amount has any clinical effect. Tobacco also contains oedema-producing irritants, as measured by the effect of smoking on the mucosa of the rabbit eyelid, including pyridine, volatile acids, and tarry and phenolic substances. Insecticidal sprays used on the tobacco plant may cause traces of arsenic and lead to appear in tobacco smoke, but these small amounts are probably harmless. It can be accepted that the changes due to nicotine are by far the most important, and that the immediate effect of smoking tobacco is almost identical with the action of nicotine.

An ordinary cigarette is made up of about 1 g. tobacco, which contains about 20 mg. nicotine. It is probable that rather less than 1 mg. nicotine is absorbed even on deep inhalation. So-called filters remove only a small fraction of the nicotine, less than one and a half times the amount of particulate smoke that would be removed by an alternative packing with tobacco. The merit of a filter tip is not efficiency but economy.

The pharmacological actions of nicotine, particularly in man in the dose usually taken, have been summarized by Oram and Sowton (1963) (Table I). The difficulties of pharmacological investigation of nicotine are numerous, and include the fact that nicotine in high concentration depresses those

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TABLE I
PROBABLE EFFECTS OF LOW CONCENTRATION OF NICOTINE ON THE
HUMAN CARDIOVASCULAR SYSTEM (ORAM AND SOWTON, 1963)

Target organ	Action of nicotine	Effects produced
<i>Indirect effects</i> Sympathetic ganglion cells Adrenal medulla	Release of catecholamines	* { Heart rate increased Blood pressure increased Skin vessels constricted Coronary vasodilatation Cardiac output increased
Carotid body Aortic body	Stimulation of chemo- receptors	Respiratory rate and depth increased, plus above effects*
Skin blood vessels	Direct stimulation of smooth muscle	Vasoconstriction with fall in skin temperature
Supraoptic hypothalamic nuclei	Stimulation	
Posterior pituitary	Liberation of vasopressin and antidiuretic hormone	? Coronary vasoconstriction Antidiuresis
? Psyche	? Sedation	? Tranquillity
<i>Direct effects</i> Cardiac parasympathetic ganglia	Stimulation of post- ganglionic fibres	Heart rate decreased
Cardiac chromaffin tissue	Release of catecholamines	Effects above*
Coronary vessels	Direct dilator effect	Coronary flow increased with fall in coronary vascular resistance

(Reproduced from *Quarterly Journal of Medicine*).

functions which it stimulates in low concentration; the problem of tolerance developing in man to long-continued use of the drug; the great variability in response to similar dosage shown by normal subjects; the route of administration greatly affecting the results obtained; and the results of animal experiments not necessarily being applicable to man. The effects of nicotine on the cardiovascular system must take into account not only the direct effect of that drug on the heart and coronary circulation, but also the indirect effect on the cardiovascular system through the autonomic and central nervous systems. In fact, more is known about the indirect than the direct action on the heart.

The major action of nicotine consists of a primary transient stimulation and a secondary more persistent depression of all sympathetic and parasympathetic ganglia. It is due to direct action on the ganglion cells. A low concentration of nicotine can stimulate all sympathetic ganglion cells, whether in the paravertebral ganglion chain or not, and in high concentration it can paralyse them. Nicotine paralyzes autonomic ganglia only if pre-ganglionic fibres have synapses in them, and if a fibre passes through a ganglion without forming a synapse it is unaffected by nicotine applied to that particular ganglion. The action of nicotine includes the stimulation of the adrenal medulla to liberate catecholamines. A low concentration can thus produce all the known effects of sympathetic stimulation on the heart and blood vessels, as well as on the eye, gut, bronchioles, and bladder. There is also an increase in the metabolic rate and a rise in the blood sugar level and blood of unesterified fatty acids.

In man, tachycardia is an almost constant finding during moderate smoking and both the systolic and diastolic blood pressure rise a few millimetres of mercury.

In low concentration nicotine can also stimulate the parasympathetic ganglion cells, and in high concentration block them. In the human heart, the stimulation of the short post-ganglionic parasympathetic fibres by a low concentration of nicotine does not induce bradycardia, as the effect on the sympathetic ganglia is greater and tachycardia results.

The effect of nicotine inhaled in tobacco smoke on the sensory receptors is also important, and almost all its actions, certainly in the experimental animal, can be brought about by its stimulant effect on certain chemoreceptors, the most important being in the carotid and aortic bodies. Although the physiological role of these receptors is to detect changes in the PO_2 , PCO_2 , and pH of the arterial blood, and to signal the respiratory and vasomotor centres to take appropriate action, they are also stimulated powerfully by minute doses of nicotine. Typical effects are an increase in both rate and depth of respiration, in addition to circulatory effects typical of sympathetic stimulation, such as vasoconstriction, cardiac acceleration, and an increase in blood pressure.

Although nicotine is not an analeptic, a dilute solution applied to the motor cortex produces convulsions, and stronger solutions depress these cells. Nicotine has a subtle effect on the psyche, a pleasurable reaction or feeling of tranquillity which is not entirely due to the physical manipulations

involved in smoking. In some sensitive subjects nicotine can liberate antidiuretic hormone from the posterior pituitary.

The vasoconstrictive effect of nicotine on peripheral arterioles and arteries is due to initial stimulation of sympathetic ganglia, with consequent discharge of impulses along the post-ganglionic fibres, and a well-established index of the peripheral vascular effects of smoking is measurement of the digital skin temperature. However, the constrictor action of nicotine can still be demonstrated on the blood vessels of the ablated ear, indicating that its effects cannot be due solely to passage of impulses along the post-ganglionic fibres.

The effect on the coronary circulation is not yet clear but it has been shown by catheterizing the coronary sinus in man that nicotine tends to increase the coronary flow or at least not to decrease it. The effect is complicated by the fact that both adrenaline and noradrenaline are liberated from the adrenals, and adrenaline increases the oxygen consumption of the heart and may predispose to myocardial ischaemia, whereas noradrenaline dilates the coronary arteries. There is good evidence that the effect of smoking in increasing the heart rate is not due alone to stimulation of the stellate ganglion but to release of noradrenaline in the store in the chromaffin tissue in the heart. The action of nicotine on the coronary vessels is either to dilate them or leave them unaffected. Although the results of animal experiments are conflicting, the earlier experiments appearing to show coronary constriction, there is no doubt that the dosage used was too high compared with the dose taken by man as a result of smoking. Barger and his colleagues (1957) were the first to investigate the effect of smoking on the coronary circulation of man by catheterization of the coronary sinus, and showed that smoking one cigarette increased the coronary flow and heart rate, produced a fall in coronary vascular resistance, and also led to the diminished myocardial extraction of oxygen and glucose. A similar study of patients with arteriosclerotic coronary artery disease (Regan, Hellems, and Bing, 1960) demonstrated a fall or no change in the coronary blood flow during smoking, as measured by the nitrous-oxide method, while the blood pressure and cardiac output rose.

TOBACCO ANGINA

It should be clearly understood that true tobacco angina is a rarity and it receives no mention in the 1967 U.S. Surgeon General's report. It may be defined as the condition in which, with the patient at rest, within a few seconds or a minute or two of puffing a cigarette or cigar, not necessarily inhaling the

smoke, typical anginal pain is produced, and is associated either with the appearance of electrocardiographic changes of coronary insufficiency, or by obvious worsening of such changes if already present. Oram and Sowton (1963) were able to find only 14 such patients previously described and they added a further 3 examples. Although the syndrome is rare, it establishes beyond all doubt the ability of smoking to induce rapidly cardiac pain and pathological electrocardiographic changes, and it enables objective assessment of the effects of various drugs to be carried out in the human subject (Fig.). It was found by these workers that both cigarettes and cigars caused similar clinical and electrocardiographic changes, and identical changes could be induced by intravenous injection of nicotine. It was also shown that it was not the tachycardia resulting from smoking which was responsible. A blocking effect on the pain and S-T segment changes which resulted from smoking was obtained by using various drugs, reserpine being the most effective. As we have seen, nicotine gives rise to coronary vasodilatation and not vasoconstriction as previously supposed, and the most satisfactory explanation of the induced cardiac pain and cardiographic changes appears to be that nicotine gives rise to coronary insufficiency by liberating catecholamines from stores in or near the blood vessels, and in spite of the coronary vasodilatation the blood supply to the myocardium becomes insufficient because of the concomitant increase in cardiac work resulting from an increased cardiac rate, rise in blood pressure, or both. Possibly also the liberation of catecholamines has a deleterious effect on the metabolism of the myocardium.

The commonest patient with tobacco angina is the one who already has typical Heberden's angina pectoris due to coronary atheroma, and precipitated also by the usual causes such as exertion, emotion, cold, and a large meal. A few very rare patients exist, of both sexes, who are young and whose pain is induced *only* by smoking—the so-called “pure tobacco angina” group.

Of much greater statistical and clinical importance is the role of smoking in inducing coronary atheroma. The convergence of so many different types of evidence, clinical, epidemiological, pathological, and experimental, strongly suggests that cigarette smoking can cause death from ischaemic heart disease. These studies not only provide the opportunity of assessing the effects of smoking alone, but also in combination with other recognized “risk factors” known to be important in the production of ischaemic heart disease, such as hypertension and a raised serum cholesterol. It has been shown that cigarette smoking both constitutes a risk factor by

FIG.—Effect of smoking on the phonocardiogram (PCG), arm tremor, electrocardiogram, carotid pulse, skin temperature, and blood-pressure (FAP = femoral arterial pressure). (a) At beginning of experiment, rate 107 per minute. (b) After 1 minute, rate 136. (c) After 4½ minutes, rate 150. Angina appeared within a few seconds. The skin temperature (right index finger) fell by 0.4°C at the end of 6½ minutes. An apical systolic murmur appeared as the heart rate increased. There was no alteration in tremor or carotid wave form. The blood-pressure did not rise. The pattern of acute coronary insufficiency which developed is similar to that induced by exercise. (Oram and Sowton, 1963) (Reproduced from *Quarterly Journal of Medicine*).

itself, and also combines with other risk factors to produce even greater effects.

EPIDEMIOLOGICAL STUDIES

There is overwhelming epidemiological evidence both of a higher incidence of ischaemic heart disease and higher death rate in cigarette smokers. During the past few years many studies have been made in populations differing both geographically and socio-economically. There is remarkable agreement in the conclusions, namely that there exists a significant association between cigarette smoking and an increased incidence of mortality from ischaemic heart disease in men, especially during middle life. Surprisingly little evidence to the contrary has been published. The relative excess mortality associated with cigarette smoking is

generally expressed in terms of a mortality ratio. This statistic is defined as the ratio of the number of observed deaths among smokers, to the expected deaths among smokers if the age-specific mortality rates observed among non-smokers had prevailed. The process of computing the expected number of deaths among smokers takes into account and adjusts for any differences in the age distribution of smokers and non-smokers under observation.

At least five large prospective studies on the ratio of mortality rates due to ischaemic heart disease of male smokers to non-smokers, by age and amount smoked, show that the ratios tend to increase with the number of cigarettes smoked per day and to decrease with advancing age. In one study (Hammond, 1966), in the age-group 40–59, the death rate from coronary disease was three times as high among

heavy cigarette smokers than among non-smokers, and in 36,975 matched subjects there were 654 coronary deaths in smokers as opposed to 304 in non-smokers. The table which appears in the 1967 Surgeon General's report and is taken from Hammond's paper speaks for itself (Table II).

TABLE II

CORONARY HEART DISEASE MORTALITY RATIOS AMONG CURRENT CIGARETTE SMOKERS ONLY, BY AMOUNT SMOKED DAILY (HAMMOND, 1966)

Age and sex			Non-smokers	No. of cigarettes smoked daily			
				< 10	10-19	20-39	40 +
Men:							
45 to 54	..	..	1.0	2.4	3.1	3.1	3.4
55 to 64	..	..	1.0	1.5	1.9	2.0	2.1
65 to 74	..	..	1.0	1.3	1.6	1.6	(*)
75 to 84	..	..	1.0	1.2	1.4	1.1	—
Women:							
45 to 54	..	..	1.0	0.9	2.0	2.7	—
55 to 64	..	..	1.0	1.3	1.6	2.0	—
65 to 74	..	..	1.0	1.1	1.4	1.9	—
75 to 84	..	..	1.0	—	—	—	—

* Expected deaths were less than 10.

(Reproduced from National Cancer Institute, Monograph No. 19.)

The well-known association of high serum levels of cholesterol and other lipids with ischaemic heart disease has resulted in several epidemiological investigations of the relationship of smoking to serum lipid levels. Although in some studies no correlation has been observed, in most references higher concentrations of serum cholesterol and lipoproteins have been found, especially in young male smokers, than in non-smokers.

In several large surveys cigarette smoking was not found to be associated with an increased incidence of hypertension. Although the inhalation of cigarette smoke is frequently accompanied by rapid transient increases in blood pressure, habitual smokers tend to have lower blood pressures than non-smokers. Even so, the mortality ratio was higher for deaths from hypertension in smokers compared to non-smokers. It seems likely that the risk of both developing and succumbing to coronary heart disease, which is already greater in hypertensives than in normotensives, is increased further by smoking.

There is convincing statistical evidence that cessation of cigarette smoking results in a relative decrease in death rates from coronary heart disease.

PATHOLOGICAL STUDIES

The relation between smoking and the degree of coronary atherosclerosis found at necropsy is such that the latter increases with age and the number of

cigarettes smoked. In pipe and cigar smokers the amount of atherosclerosis is about the same as in non-smokers. Auerbach, Hammond, and Garfinkel (1965) studied 1372 male smokers who had died from causes other than ischaemic heart disease. They found that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among non-smokers, and that the percentage increased with the amount of cigarette smoking. Similarly, Strong *et al.* (1966), in a large series, found that the mean percentage of coronary intimal surface occupied by raised atheromatous lesions was approximately twice as great in men who smoked over 25 cigarettes a day as in non-smokers. However, it has been found that differences between heavy smokers and non-smokers include greater obesity, higher dietary fat intake, and higher serum cholesterol levels, so further necropsy data are required before accurate assessment of the independent effects of cigarette smoking on atherogenesis can be ascertained.

It is of considerable interest that in former cigarette smokers less coronary atheroma is found than in current smokers, but more than in non-smokers. This accords with epidemiological observations that if smoking is stopped the death rate from ischaemic heart disease falls.

EXPERIMENTAL STUDIES

In order to determine whether the association, which both epidemiological and pathological studies have shown to exist between smoking and atherosclerosis, represents a causal relationship, investigation must be made into the effect of smoking and nicotine on the production of atherosclerosis and also on the biological processes involved in atherogenesis. In general, results are inconclusive, but experimental studies have been made on the effect of smoking on lipid metabolism, blood coagulation, and haemodynamics.

Relatively few reports have been published concerning the effect of nicotine on experimental atherosclerotic lesions in animals and unfortunately they are contradictory. Nicotine has been added to a hypercholesterolaemic diet, in both rabbits and dogs, and usually does not result in an increase in the amount of aortic atheroma.

It has been shown that an increase in plasma-free fatty acids is followed by a rise in the lipoprotein lipids cholesterol, phospholipids, and triglycerides (Shafir and Steinberg, 1960), and it therefore seems likely that agents that mobilize full fatty acids may be important in the pathogenesis of atheroma. Kershbaum *et al.* (1961, 1962) were the first to show that in the healthy human, after cigarette smoking, there was a rapid and consistent rise in free fatty

acids which might persist for up to 40 minutes. It is probably due to the nicotine stimulating the sympathetic system and adrenals, thus producing an increase in circulating catecholamines. These in turn are thought to stimulate lipolysis in the adipose tissue, with the release of such acids. It was shown that in patients with healed myocardial infarction the rise in free fatty acid produced by smoking was more than double that of normal subjects. In patients who have undergone therapeutic bilateral adrenalectomy there is no significant increase of these acids after smoking. However, it seems generally agreed that in man there is no immediate effect of cigarette smoking on serum concentrations of lipoproteins and lipoprotein lipids. The effect of chronic cigarette smoking on these levels has yet to be shown experimentally.

BLOOD COAGULATION

If the thrombogenic theory of atherosclerosis is accepted, then any factor that affects blood coagulation may be of atherogenic importance. That reports concerning the effect of smoking on blood coagulation have been conflicting may be a reflection on the inadequacy of the tests employed. Even so, there seems proof that smoking both increases platelet adhesiveness and shortens platelet survival, possibly by increasing catecholamines or free fatty acid levels. It has also been shown experimentally that nicotine antagonizes both the lipolytic and anticoagulant properties of heparin, and these effects may help to accelerate coagulation.

HAEMODYNAMIC EFFECTS

The adverse effects of smoking and nicotine on the circulation have already been described, and over a prolonged period they may initiate or accelerate the development of atheroma. In man, in addition to constriction of the skin vessels, nicotine results in an increase in heart rate, cardiac output, stroke volume, systemic blood pressure, increased velocity of myocardial contraction, and cardiac work. The result is an increased demand for oxygen by the myocardial tissue.

ENVOI

Convincing evidence of the role of cigarette smoking in the production of ischaemic heart disease would be that reduction or cessation of smoking reduces

the morbidity and mortality. Over the past ten years in the United Kingdom doctors have reduced their cigarette smoking to that of about one-half of the average male population, and less than one-third smoke cigarettes compared with more than a half previously (Royal College of Physicians Report, 1962). If cigarette smoking is an important factor in atherogenesis it would be expected that the incidence of ischaemic heart disease should fall among British doctors and, in fact, there is already some early evidence of this (Doll and Hill, 1964).

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