

**SECTION 5. ATHEROSCLEROTIC  
PERIPHERAL  
VASCULAR DISEASE  
AND AORTIC  
ANEURYSM**

## **Atherosclerotic Peripheral Vascular Disease**

### **Introduction**

The peripheral arteries include those branches of the aorta supplying the upper and lower extremities and the abdominal viscera. Most peripheral arterial occlusive disease is due to atherosclerosis, although other conditions such as fibromuscular dysplasia, muscular entrapment, cystic adventitial degeneration, and arteritis may cause obstruction of the peripheral arteries. Symptomatic atherosclerotic peripheral vascular disease (ASPVD) occurs most often in the vessels of the lower extremities. The anatomic location of such disease is usually classified according to the major arterial segments involved, including aortoiliac, femoro-popliteal, and tibio-peroneal artery occlusive disease. Occlusive lesions of the origins of visceral arteries commonly involve the renal arteries and the mesenteric arteries, including the celiac and superior and inferior mesenteric arteries.

With many asymptomatic patients, peripheral arterial occlusive disease can be detected on physical examination. Symptomatic patients are usually classified according to the severity of presenting complaints; for example, patients may be classified as suffering intermittent claudication (leg pain brought on by exercise and relieved by rest), ischemic rest pain, or, the most severe complaint, tissue necrosis, including gangrene or ischemic ulceration. Patients with renal artery occlusive disease may present with severe and uncontrollable hypertension, although such patients may respond to medical treatment for hypertension. Patients with arterial occlusive disease of the mesenteric arteries may present with acute ischemia of the intestine, due to thrombosis or embolization, or with more chronic symptoms of pain aggravated by eating and weight loss.

The diagnosis of peripheral arterial occlusive disease can usually be made from the history and physical examination, including the evaluation of peripheral arterial pulsations and detection of arterial bruits. However, more accurate and objective diagnosis of peripheral arterial occlusive disease is possible with noninvasive diagnostic techniques, particularly Doppler ultrasound or plethysmography. Arteriography is reserved for patients with symptoms sufficient to make them candidates for surgery, and is not usually required for the diagnosis of peripheral arterial occlusive disease.

The majority of patients with peripheral arterial disease may be candidates for medical therapy such as exercise regimens and reduction of known risk factors through cessation of smoking, control of diabetes mellitus, dietary measures to control hyperlipidemia and obesity, and medical management of hypertension. Intensive foot hygiene and avoidance of trauma are additional important medical measures for patients with lower extremity ASPVD. The

newly developed treatment of balloon dilatation (percutaneous transluminal angioplasty) may be used to restore pulsatile flow for severely symptomatic patients. Surgical therapy is required in only about 10 percent of the patients with advanced arterial occlusive disease. One surgical approach is arterial reconstruction, usually involving endarterectomy or bypass with vein or prosthetic grafts of diseased segments. Sympathectomy is infrequently used, but it may be helpful in patients with cutaneous ischemia, for whom restoration of pulsatile flow is not possible. Amputation of limbs with advanced arterial occlusive disease that cannot be remedied by surgical reconstruction remains in use, but it is required by only about 5 percent of all patients presenting with peripheral arterial occlusive disease.

### **Risk Factors for Peripheral Arterial Occlusive Disease**

The most powerful risk factor predisposing to atherosclerotic peripheral arterial occlusive disease is cigarette smoking (47); in fact, the rarity of peripheral arterial occlusive disease in patients who have never smoked was noted by Eastcott as early as 1962 (23). The epidemiologic evidence linking cigarette smoking to atherosclerotic peripheral arterial occlusive disease is discussed in detail below.

Several studies have suggested hyperlipoproteinemia as a risk factor contributing to atherosclerotic peripheral arterial occlusive disease. The type of hyperlipoproteinemia and the degree of association with peripheral vascular disease appear to be different, however, from the hyperlipoproteinemia associated with coronary artery disease. Zelis et al. (92) reported that patients with Type III hyperlipoproteinemia are particularly susceptible to the development of peripheral vascular disease, and they noted objective improvement in the peripheral circulation with medical treatment of this disorder. Greenhalgh et al. (30) reported that fasting serum lipid concentrations were abnormally high in 44 percent of a consecutive series of 116 patients with proven peripheral vascular disease. In 39 percent of the patients the serum triglyceride level was raised, and in 15 percent the serum cholesterol level was increased. Ballantyne and Laurie (5) evaluated 353 consecutive patients with peripheral vascular disease and showed a predominance of Type IV hyperlipoproteinemia in males, but a predominance of Type IIa hyperlipoproteinemia in females. Patients with peripheral vascular disease and Type IIa or Type IIb hyperlipoproteinemia were more likely to have associated coronary artery disease. Eighty-four percent of the patients were cigarette smokers, with the majority smoking more than 10 cigarettes daily. There was no relationship between cigarette consumption and the occurrence of hyperlipoproteinemia. However, Farid et al. (25) found that in 122 patients with angiographically proved peripheral arterial occlusive disease, heavy

smoking seemed to be associated with an unexpectedly high proportion of an abnormal lipid pattern: 43 percent of the males exhibited Type IV hyperlipoproteinemia. Lawrie et al. (51) surveyed 4,477 healthy males and females in the west of Scotland and found a high prevalence of hyperlipoproteinemia of Type II and Type IV. Hyperlipoproteinemia occurred more frequently in survivors of myocardial infarction, but also occurred, though to a lesser extent, in patients with peripheral vascular disease.

Olsson and Eklund (57) evaluated 160 men and 123 women with digit plethysmography and found that most atherogenic lipoprotein abnormalities associated with disease of the lower extremities involved the relatively triglyceride-rich part of the low density lipoprotein (LDL) fraction and the relatively cholesterol-rich part of the very low density lipoprotein (VLDL) fraction. These authors found a deleterious influence of smoking even in the preclinical stage of peripheral vascular disease. Davignon et al. (18) evaluated 114 French Canadian patients with angiographically proved peripheral vascular disease. The severity of atherosclerosis correlated positively with plasma triglyceride concentration, but cigarette smoking was the risk factor most frequently found in patients with peripheral vascular disease. In contrast, Erikson et al. (24) did not find a positive correlation between arteriographic changes in 30 patients with intermittent claudication and serum concentrations of lipids and lipoproteins. Trayner et al. (80) compared 32 patients with peripheral vascular disease to control subjects. The vascular disease study group had a significantly higher incidence of hypertriglyceridemia, more marked for the males, and had lower levels of high density lipoproteins (HDL) than did the control subjects. The study group also had a twofold higher prevalence of cigarette smoking than control subjects. Control patients who smoked also had lower levels of HDL than those who did not smoke. Phillips et al. (61) also established a relationship between an increase of VLDL triglyceride and cigarette smoking, while HDL cholesterol decreased with cigarette smoking.

Hypertension is associated not only with coronary and cerebrovascular disease, but also with peripheral arterial occlusive disease (46). Larson et al. (50) established an interaction of hypertension and hypercholesterolemia in an experimental study of mongrel dogs, suggesting that the combination of these two risk factors produces alterations in lipid composition in the canine aorta that appears to be geometric rather than arithmetic in nature. However, Stehbens (74) claimed that epidemiologic studies are less conclusive than experimental studies in establishing the relationship of risk factors in atherosclerosis. He postulated that local hemodynamics associated with hemodynamic stress, rather than the level of lipid intake, is the

principal factor governing the accumulation of lipid in the vessel wall.

It is clear that multiple risk factors have been associated with atherosclerosis not only in the coronary and cerebrovascular arterial beds but also in the peripheral circulation. Rosen et al. (65) evaluated the association of risk factors in 109 patients with peripheral arterial occlusive disease. The arterial disease was established by clinical and arteriographic examination and classified into three anatomic groups—aortoiliac, combined aortoiliac and femoropopliteal, and femoropopliteal disease. Type IV hyperlipoproteinemia and glucose intolerance were significantly more common in patients with isolated femoropopliteal disease. Cigarette smoking was the most prominent risk factor in all groups, occurring in 90 percent of patients with aortoiliac or combined disease and in 75 percent of patients with femoropopliteal artery disease. The onset of clinical symptoms occurred at an average of 8 to 10 years earlier in smokers than in nonsmokers. Heyden et al. (35) established that smoking and coffee drinking interact in affecting LDL and total cholesterol, but coffee drinking alone did not appear to affect blood lipids. Criqui et al. (16) reviewed the relationship between cigarette smoking and HDL cholesterol in 2,663 men and 2,553 women aged 20 to 69 years in 10 North American populations of the Lipid Research Clinics Program Prevalence Study. Cigarette smoking was associated with substantially lower levels of HDL cholesterol; this association was dose related. Hulley et al. (37) found the same association in a longitudinal study of 301 high-risk males 35 to 57 years of age. After 1 year's intervention on diet, hypertension treatment, and smoking counseling, both smoking frequency and serum thiocyanate were significantly and independently associated with the changing plasma HDL-cholesterol concentration. A relationship linking cigarette smoking and abnormal lipoprotein metabolism comes from the report of Topping et al. (78), which found that patients with both Type III hyperlipoproteinemia and cigarette smoking suffer abnormalities of liver metabolism of cholesterol-rich "remnants." Such impaired hepatic metabolism may result in hyperlipoproteinemia and subsequent peripheral vascular disease.

### **Summary of Epidemiologic Studies**

Because peripheral arterial occlusive disease does not pose as severe a mortality threat as coronary artery disease does, there have been fewer major epidemiologic studies of peripheral vascular disease. However, the underlying pathologic lesion, atherosclerosis, remains the same in the two conditions, and there is increasing evidence of an association between peripheral vascular disease and similar lesions in the coronary or cerebrovascular beds. Both clinical and angiographic correlates of peripheral arterial disease with

concomitant coronary artery disease were suggested by the reports of Friedman et al. (28), Kuebler et al. (49), Silvestre et al. (72), and Hertzner et al. (34). These reports not only suggest a clinical relationship between peripheral and coronary artery occlusive disease, but also indicate that the perioperative and long-term risks of treatment for peripheral vascular disease are strongly influenced by the presence of concomitant coronary artery disease.

Several publications have extensively reviewed the evidence associating cigarette smoking with peripheral arterial occlusive disease (81, 82, 83). Early studies by Juergens et al. (44), Begg (7), Schwartz et al. (71), and Widmer et al. (87) documented a much higher prevalence of cigarette smoking (usually exceeding 90 percent) in patients with peripheral arterial occlusive disease, when compared with control patients without vascular disease. Data from the Framingham study (46) suggest that cigarette smoking is one of the major risk factors in the development of intermittent claudication (Table 1). Over a 16-year period of followup, a higher total incidence and a higher annual incidence of intermittent claudication were noted in smokers as compared with nonsmokers. This difference was statistically significant for all age groups of both sexes. Using multivariate analysis to control for other risk factors, this relationship of smoking to intermittent claudication became stronger.

Many other investigators have noted a high prevalence of cigarette smoking in patients with peripheral arterial occlusive disease. Tomatis et al. (77) found that 98 percent of patients with aortoiliac disease and 91 percent of patients with femoropopliteal disease were cigarette smokers. Astrup et al. (3) found a significant correlation between the frequency of severe intermittent claudication and the consumption of more than 15 cigarettes a day in nondiabetic patients with peripheral vascular disease. A significant difference between heavy smokers and other smokers was not found, however, for the development of gangrene. Further, the development of claudication did not vary with the number of years of smoking or the total number of cigarettes consumed in a lifetime. Weinroth and Herzstein (84) noted a 50 percent greater incidence of peripheral arterial occlusive disease in diabetics who smoked than in those who did not. Juergens et al. (44) followed 520 patients with nondiabetic peripheral arterial occlusive disease, approximately 50 percent of whom continued to smoke despite medical advice to quit. Of those who continued to smoke, approximately 10 percent eventually required amputation, but no amputations were necessary in patients who successfully stopped smoking.

Horowitz et al. (36) reported that age was a significant factor in the prevalence of arterial disease, with nearly half of the cases occurring in patients over the age of 70. A higher percentage of patients with

**TABLE 1.—Average annual incidence (over 16 years) of intermittent claudication according to cigarette habit at examination**

Age at examination and cigarettes smoked per day	Men			Women		
	Subjects at risk <sup>1</sup>	Rate per 10,000		Subjects at risk <sup>1</sup>	Rate per 10,000	
		Actual	Smoothed <sup>2</sup>		Actual	Smoothed <sup>2</sup>
45-54 years	6290	16	15.9	7933	4	3.8
None	2342	6	9.8	4514	3	2.4
Under 20	903	17	13.4	1876	0	4.0
20	1486	30	18.3	1090	9	6.5
Over 20	1523	16	24.9	422	12	10.6
55-64 years	4484	51	51.3	5959	19	19.3
None	2170	28	27.6	4276	19	17.5
Under 20	743	61	43.6	1030	19	21.6
20	879	40	68.7	434	0	26.7
Over 20	670	127	107.9	197	76	33.1
65-74 years	1326	57	56.6	1924	31	31.2
None	790	44	55.2	1541	19	23.6
Under 20	254	98	57.3	266	94	45.3
20	167	90	59.5	79	0	86.5
Over 20	111	0	61.7	29	172	164.2

<sup>1</sup> Numbers of subjects at risk according to cigarettes smoked do not add to totals shown because some subjects are in the unknown category.

<sup>2</sup> The "smoothed" rates are based on the mean of the individual probabilities of development of intermittent claudication in the 2 years following examination, where individual probability is calculated according to cigarette use at examination using the values of the parameters estimated in fitting the logistic function to the occurrence of intermittent claudication in the sex-age group.

NOTE: The trend is significantly different from zero at the 0.05 level for women 65 to 74 years of age and at the 0.01 level for men 55 to 64.

SOURCE: Kannel and Shurtleff (48).

arterial disease smoked than did patients without arterial disease. A higher percentage of males than of females had peripheral arterial occlusive disease. De Backer et al. (21) likewise noted an increase in intermittent claudication with increasing age, but also found a significant correlation of serum cholesterol, systolic blood pressure, blood glucose, and cigarette smoking in patients with intermittent claudication.

Future epidemiologic studies of peripheral vascular disease must take into account the merits and limitations of the clinical diagnosis of peripheral arterial occlusive disease. Horowitz et al. (36) suggest that the judgment of trained paramedical personnel compares favorably with that of physicians in screening large numbers of patients for peripheral vascular disease.

De Backer et al. (21) emphasized the importance of using ankle systolic blood pressure measurement with Doppler ultrasound to

objectively screen patients for peripheral arterial occlusive disease. Such useful techniques have been emphasized by Marinelli et al. (54) in a large epidemiologic study of vascular disease in patients with diabetes mellitus.

In addition to clinical studies, several autopsy surveys have reported an association between smoking and peripheral atherosclerosis (59, 60, 66, 67, 75, 89). Such studies have supported a direct association between smoking and the formation of abdominal aortic fatty streaks, as well as their subsequent conversion to raised lesions.

Most reports of peripheral vascular disease emphasize the predominant occurrence of this disorder in males (88). However, diabetes mellitus may predispose females to peripheral arterial occlusive disease in a frequency similar to that of males. Broome et al. (12) reported on 15 women with aortoiliac occlusive disease, all of whom were cigarette smokers (mean, 20 cigarettes a day), and none of whom had diabetes mellitus. The temporal trend toward increased smoking by women may significantly increase their risk of peripheral arterial occlusive disease. The Framingham heart study (47) found that the incidence of peripheral vascular disease was increased among smokers and that cigarette smoking was as strong an independent risk factor in women as in men. Heavy smokers had a threefold increase in the incidence of peripheral arterial occlusive disease. Weiss (86) evaluated 245 women with peripheral arterial occlusive disease. The risk in ex-smokers who had not smoked for 5 years or more was nearly normal, with a risk ratio of 1.06. Patients who had not smoked for 1 to 5 years had a risk ratio of 1.70. Patients who continued to smoke, but smoked less than one pack a day, had a risk ratio of 11.53, and those who smoked more than a pack a day had a risk ratio of 15.56. The risk for arterial occlusive disease was particularly associated with the proximal aortoiliac segment and was less associated with distal or femoral-popliteal artery disease. This study described both a dose-response effect and a benefit following cessation of smoking.

There have been few studies of the association of visceral arterial occlusive disease and cigarette smoking. Mackay et al. (53) reported on the correlation of smoking and renal artery stenosis. They found that smoking was nearly twice as common in patients with nonmalignant hypertension associated with renal artery stenosis as in those patients with hypertension of comparable severity without renal artery disease. Previous studies documented that a higher proportion of smokers was noted in patients with malignant hypertension (10, 39). Cigarette smoking was present in 20 of 22 patients with malignant hypertension and associated renal artery stenosis (53).

Cigarette smoking appears to be the only form of tobacco consumption associated with an increased risk of developing periph-

eral arterial occlusive disease. Smith (73) reported that no cases of intermittent claudication were found in patients who used only smokeless tobacco (snuff, chewing tobacco), provided that patients with a history of diabetes mellitus, heavy ethanol intake, or dietary problems were excluded.

Frishman (29) reviewed the effects of involuntary smoking on the cardiovascular system. Although levels of carbon monoxide commonly found in cigarette-smoke-filled environments have been demonstrated to decrease exercise tolerance in patients with existing angina pectoris and intermittent claudication, studies are not available to document the role that passive smoking might play in the etiology of atherosclerotic cardiovascular disease (69).

### **Clinical Investigations in Humans**

In several studies, the effect of cigarette smoking or the constituents of cigarette smoke on the human peripheral vascular system has been investigated. Cryer et al. (17) studied the effects of cigarette smoking, sham smoking, and smoking with adrenergic blockade in 10 subjects. There was a significant increase in the mean plasma norepinephrine and epinephrine levels associated with smoking. The smoking-related increase in pulse rate, blood pressure, blood glycerol, and blood lactate-pyruvate ratio was prevented by adrenergic blockade. These findings were attributed to local norepinephrine release from adrenergic axon terminals within tissues rather than to increments in circulating catecholamines. In experiments comparing cigarettes of varying nicotine content, the subjective recognition of different cigarette brands may influence the results of clinical experiments. Ossip et al. (58) have suggested that nicotine extraction filters be used to minimize the within-subject differences due to the recognition of cigarette brand. The influence of the type of beta blocker used in therapy of patients who are cigarette smokers was investigated by Trap-Jensen et al. (79). These authors found that the use of a nonselective beta blocker, propranolol, during smoking caused a marked rise in diastolic and mean blood pressure and forearm vascular resistance, due to the blockade of adrenaline-induced vasodilatation, which is mediated by beta-2 receptors in the resistance vessels. Selective beta-1 blockade with atenolol attenuated the systolic blood pressure and the tachycardiac responses induced by cigarette smoking.

Several studies have suggested an association between cigarette smoking and the level of circulating hemoglobin. Castleden et al. (14) evaluated 61 male nondiabetic smokers with peripheral artery disease and compared them with age-matched nondiabetic male smokers and nonsmokers admitted for routine inguinal herniorrhaphy. They found a significant association between smoking and hemoglobin levels and a highly significant correlation between

smoking and peripheral vascular disease. In addition, the carboxy-hemoglobin generated by smoking was associated with increased platelet adhesiveness, decreased fibrinolytic activity, and increased plasma fibrinogen. Yamori et al. (91) suggested that the hematocrit was increased in proportion to the number of cigarettes smoked and that this may be a mechanism for increased mortality rate from cardiovascular diseases in smokers.

Other hematologic effects of cigarette smoke have been observed in blood platelets and with fibrinolysis. Davis and Davis (19) studied 18 volunteers to assess the effect of cigarette smoking on platelet aggregation. The smoking of two unfiltered tobacco cigarettes during a 20-minute period resulted in a significant increase in the platelet aggregate ratio. During this time, the mean plasma nonesterified fatty acid concentration remained unchanged. These same authors (20) subsequently reported that the increase in the platelet aggregate ratio resulting from smoking two unfiltered cigarettes could be prevented with pretreatment with one aspirin tablet. Janzon and Nilsson (43) evaluated the fibrinolytic activity in vein walls among 71 randomly selected heavy smokers and 41 nonsmokers from a population of men born in 1914 residing in Malmö, Sweden. After 12 hours' abstention from tobacco, the smokers were found to have the same fibrinolytic activity as nonsmokers. Smoking six cigarettes during 3 hours increased the fibrinolytic activity in the blood, presumably because of the combined effects of nicotine and carbon monoxide.

Several studies of the effects of smoking on the peripheral circulation have involved noninvasive measurement of limb blood flow using plethysmographic techniques. Janzon (40) used a water-filled plethysmograph to study 71 randomly selected heavy smokers and 41 nonsmokers from the study group of men born in 1914 and residing in Malmö, Sweden. The smokers were found to have lower systolic and diastolic arm blood pressure and lower systolic blood pressure in the big toe with greater pressure gradients from the arm to the big toe compared with nonsmokers. During reactive hyperemia, smokers had decreased blood flow and increased peripheral vascular resistance. This same author (42) studied the acute effect of smoking on heart rate, blood pressure, and calf blood flow in 20 randomly selected 59-year-old male heavy smokers (more than 15 g of tobacco per day). After smoking two cigarettes, there was a significant increase in blood pressure and heart rate. Blood flow and resistance to blood flow in the calf did not change at rest, but during reactive hyperemia, the resistance to blood flow decreased and calf blood flow increased, an effect attributable to the peripheral vascular effects of nicotine. Janzon (41) evaluated 51 randomly selected 59-year-old heavy smokers for changes in peripheral vascular function after smoking cessation of 8 to 9 weeks. He noted an

increase in blood flow during reactive hyperemia in patients who stopped smoking and a decrease in blood flow in patients who continued to smoke. Isacsson (38) performed venous occlusion plethysmography on the calf of 809 randomly selected 55-year-old men residing in Malmö, Sweden. Sixty-two percent of the total population examined were cigarette smokers. A history of intermittent claudication was present in 20 subjects, but arterial insufficiency could be clinically demonstrated in only 6 of the 20. Ilio-femoral occlusive disease was found in another eight patients. These patients had a higher prevalence of systolic hypertension, hypercholesterolemia, hypertriglyceridemia, and lipoprotein abnormalities. The amount of smoking was inversely related to the magnitude of the arterial flow capacity in the legs and directly related to the presence of occlusive arterial disease. More ex-smokers had high blood flow capacity than had a low flow capacity. The arterial flow capacity in the legs was reduced in direct proportion to the tobacco consumption per day. Coffman (15) used plethysmographic and isotope methods to document cutaneous vasoconstriction, increased skeletal muscle blood flow, and decreased venous distensibility in human subjects after tobacco smoking or nicotine injection.

Recent studies have employed Doppler ultrasound to document changes in blood velocity and transit time following cigarette smoking. Sarin et al. (68) noted a reduction in mean digital artery blood flow velocity of 42 plus or minus 6 percent following the smoking of a single cigarette in 10 male volunteers. Lusby et al. (52) evaluated the effects of cigarette smoking on hemodynamics in the large and small vessels of patients with peripheral arterial occlusive disease. Using Doppler probes, large vessel response to smoking was evaluated by measurement of pulse transit time delay. Patients with occlusive arterial disease had significant shortening in transit time delay, suggesting a stiffening in the main vessels in response to smoking. Such changes were not seen in control patients without peripheral arterial occlusive disease. A digit pulse volume recorder was used to measure the amplitude of digit pulsation, a measure of small vessel hemodynamics. The digit pulse amplitudes decreased significantly in response to both low and high nicotine cigarettes, and patients tended to self-titrate their nicotine intake. Due to this maintenance of nicotine level, the study failed to demonstrate a benefit on small vessel hemodynamics accompanying a switch from high to low nicotine cigarettes.

Recent studies suggest that tobacco allergy may play a role in the development of the cardiovascular effects of cigarette smoking. Becker and Dubin (6) reported that approximately one-third of healthy smoking and nonsmoking volunteers exhibited immediate cutaneous hypersensitivity to a glycoprotein antigen purified from cured tobacco leaves and found in cigarette smoke. Denburg et al.

(22) skin-tested 164 peripheral vascular disease patients with purified tobacco glycoprotein. The authors also performed basophil degranulation tests to assess in vitro reactivity to tobacco glycoprotein. Immediate skin-test hypersensitivity to tobacco glycoprotein was found in 11 percent of patients with angiographically demonstrable peripheral vascular disease; a control group of normal patients was not skin tested. The basophil degranulation test was positive in 60 percent of smokers compared with 24 percent of nonsmokers ( $p < 0.01$ ). Forty-three percent of skin-test-negative and 91 percent of skin-test-positive patients with peripheral vascular disease had a positive basophil degranulation test. Only 3 percent of patients with negative basophil degranulation tests had a positive skin test. The percent of patients with positive skin tests increased in proportion to the severity of angiographic peripheral vascular disease. What role tobacco hypersensitivity may play in the development of peripheral atherosclerosis remains to be elucidated.

A final area of clinical epidemiologic study is the relationship of maternal smoking to the fetal cardiovascular system. Asmussen (2) studied the umbilical artery, umbilical vein, and vessels of the placental villi of newborn children in relation to the maternal smoking history. His studies documented that severe damage to vessel walls is associated with maternal tobacco smoking during pregnancy. These fetal vascular changes may lead to vascular lesions later in life.

### **Experimental Studies in Animals**

In several experimental animal studies, the relationship between cigarette smoking and atherosclerotic peripheral vascular disease has been investigated. Birnstingl et al. (9) evaluated the effect of short-term exposure to carbon monoxide on platelet adhesion in rabbits. In rabbits exposed on several occasions to an atmosphere containing 400 parts per million carbon monoxide for 6 to 14 hours, there was a highly significant increase in platelet stickiness immediately after exposure to carbon monoxide, followed the next day by a significant fall to levels below the preexposure value.

Richardson (62) evaluated the effects of nicotine and tobacco smoke on capillary blood flow in the rat. Red blood cell velocity in single capillaries within the mesenteric tissue of anesthetized rats was evaluated immediately before and after either intravenous injection of nicotine or inhalation of tobacco smoke. Blood velocity changes associated with tobacco exposure were considered to be passive consequences of changes in systemic arterial blood pressure. This study did not evaluate differential effects on various vascular beds of cigarette smoke or nicotine.

Fisher et al. (27) evaluated the effect of exposure of cholesterol-fed rabbits to the smoke of one cigarette daily over an 11- to 13-month

period. The study failed to demonstrate quantitative or qualitative differences in atherosclerosis in the aorta or coronary or visceral arteries or significant changes in serum lipids. Booyse et al. (11) administered nicotine in the drinking water of New Zealand white rabbits during a 25-week period. Fasting serum levels of glucose, triglyceride, total cholesterol, and LDL cholesterol were elevated in the nicotine-treated rabbits compared with the controls. However, there was no significant difference between nicotine-treated and control animals in leukocyte, erythrocyte, and platelet counts or in hematocrit or hemoglobin. Endothelial cells from the aortic arch of nicotine-treated animals showed extensive changes, including increased cytoplasmic silver deposition, increased formation of microvilli, and numerous focal areas of "ruffled" endothelium (projections from the cell surfaces).

Marshall et al. (55) evaluated the effects in minipigs of exposure to cigarette smoke or varying concentrations of carbon monoxide for 1- to 16-hour periods. Cigarette smoke and short carbon monoxide exposure resulted in adherence of platelets to the endothelium. After longer exposures, microscopic thrombi were found in the vessel walls. Underlying degeneration in the endothelial cells developed upon exposure to carbon monoxide.

Recent investigations have involved the training of subhuman primates to smoke cigarettes in order to assess the effect on the peripheral circulation and hematologic factors. Schwartz et al. (70) have summarized data on experiments in baboons taught to smoke cigarettes. Rogers et al. (63) reported on 36 young adult male baboons who were fed an atherogenic diet. Twenty-eight baboons were randomly assigned to smoke 43 cigarettes daily, and 18 baboons were taught to puff air under equivalent experimental conditions. The cigarette-smoking baboons demonstrated significantly higher carbon monoxide and thiocyanate concentrations in blood and cotinine concentrations in the urine than did the nonsmoking baboons. There were no significant differences found in serum total cholesterol, VLDL, and LDL cholesterol or triglyceride concentrations in the smokers compared with the controls. Smoking baboons had significantly higher fasting glucose concentrations and lymphocyte counts. Platelet counts, platelet aggregation, food and water intake, and body weight were not significantly different in the two groups. Such experimental models may provide a valuable method to assess the long-term effects of smoking on the peripheral vascular system of primates.

### **Intervention Studies**

There is considerable indirect evidence that cessation of smoking may significantly influence the effect of medical or surgical therapy on peripheral arterial occlusive disease. Unfortunately, the tendency

of some patients with peripheral arterial occlusive disease to continue smoking often defeats the purpose of medical intervention. Thiruvengadam et al. (76) evaluated the effect of diseases at different organ sites upon the smoking habit of chronic smokers. A significant reduction or cessation of smoking was observed in subjects with cardiovascular, pulmonary, neoplastic, or gastrointestinal disease, diabetes mellitus, or cirrhosis of the liver. Medical advice played a role in the reduction for only 19 percent of the subjects. Other reasons for reduction or cessation of smoking were socioeconomic factors, aggravation of disease, or belief in a possible relationship between smoking and the disease. Only subjects with psychiatric illnesses and peripheral vascular diseases showed no significant reduction in the smoking habit in comparison with the controls. Of 89 subjects with peripheral vascular disease, 12 increased their smoking with the advent of disease. Feinleib and Williams (26) emphasized that peripheral vascular disease risk is elevated only in cigarette smokers and not in cigar or pipe smokers. Smokers who quit gradually approach the lower risk of nonsmokers. Birkenstock et al. (8) reported on the role of cessation of smoking on the medical therapy of 390 patients with peripheral vascular disease who were either ineligible or unfit to undergo operative treatment. Conservative management included foot hygiene, walking exercise, cessation of smoking, a low cholesterol diet, and vitamin E therapy. Of 277 patients who smoked, 164 were able to stop smoking. Eighty-five percent of patients who stopped smoking showed improvement in symptoms of peripheral vascular disease on the medical regimen, in comparison with only 20 percent who improved among those who continued to smoke. The degree of improvement was greater in ex-smokers than in nonsmokers. No patient with diabetes mellitus who continued to smoke improved under medical management.

Cessation of smoking appears to play an important role in the long-term success of reconstructive arterial surgery. Wray et al. (90) recorded a significantly higher rate of late arterial occlusion in patients who had undergone aortofemoral bypass and who persisted in smoking when compared with patients who stopped smoking postoperatively. In 30 patients who continued to smoke, 9 late occlusions occurred, but no occlusions developed in 16 patients who ceased smoking postoperatively. Myers et al. (56) reported a retrospective study of 217 patients undergoing aortofemoral (135) or femoropopliteal (107) vascular reconstruction. Patients who stopped smoking or smoked no more than five cigarettes daily after their operation had late patency rates of approximately 90 percent for aortofemoral reconstruction and 80 percent for femoropopliteal vein grafts. Patients who continued to smoke more than five cigarettes daily had a late complication rate approximately three times greater after aortofemoral reconstruction and four times greater after

femoropopliteal vein grafting, compared with ex-smokers. The late patency rate was approximately inversely proportional to the number of cigarettes smoked per day after the operation. The incidence of late complications was not correlated with the number of cigarettes smoked prior to operation. Burgess et al. (13) noted that among patients whose below-knee amputation failed to heal, six of seven (85 percent) were cigarette smokers, whereas among those whose distal amputations healed, only half were smokers.

## **Aortic Aneurysm**

### **Nature of Abdominal Aortic Aneurysm**

Abdominal aortic aneurysm refers to the dilatation or expansion of the aortic wall due to degenerative or inflammatory destruction of the components of the wall. The vast majority of abdominal aortic aneurysms are due to atherosclerosis, although other conditions, including infection, trauma, dissection, or inherited metabolic disease (Ehlers-Danlos syndrome) may be causes. The dilatation may involve only a portion of the arterial wall (saccular aneurysm), but most often involves generalized fusiform enlargement of the artery. Most abdominal aortic aneurysms are located distal to the renal arteries and proximal to the aortic bifurcation. Abdominal aortic aneurysms may coexist with aneurysmal changes in the iliac, femoral, or popliteal arteries. Less commonly, an aneurysm may involve the entire aorta, including the suprarenal and descending thoracic aorta (thoracoabdominal aneurysm).

Most abdominal aortic aneurysms are asymptomatic and are discovered incidentally during a physical examination or on X-ray examination of the spine or abdominal organs. Symptoms, such as back pain or shock, are usually associated with the complication of rupture and constitute the main threat of abdominal aneurysm. Less commonly, distal embolization may lead to acute or chronic peripheral arterial occlusive disease. Although palpation of aortic enlargement is the best clinical indicator of abdominal aneurysm, abdominal B-mode ultrasonography is the most accurate noninvasive method to estimate the exact size of the aneurysm. Arteriography is seldom used before an operation unless there is associated occlusive peripheral vascular disease or a suspicion of renovascular hypertension; this is because the arteriogram may often not depict the true size of the aneurysm owing to the mural thrombus contained within the aneurysm. Surgical repair with a prosthetic graft is recommended for all abdominal aortic aneurysms more than 5 cm in diameter unless associated diseases make the operative risk greater than that of the prognosis of the aneurysm. The risk of rupture increases exponentially with the diameter of the aneurysm.

**TABLE 2.—Mortality ratios and deaths (n in parentheses)<sup>1</sup> from nonsyphilitic aortic aneurysm related to smoking, prospective studies, United States**

Author and year	Number and type of population	Data collection	Followup years	Number of deaths	Cigarettes per day	Pipes	Cigars	Comments
Hammond and Horn 1958 (32, 33)	187,783 white males in 9 States, 50-69 years of age	Questionnaire and followup of death certificate	1.5	68	NS <sup>2</sup> ..... 1.00 (25) (expected) SM <sup>2</sup> ..... 2.72 (68) (p < 0.005)			
Kahn 1966 (45)	U.S. male veterans, 2,265,674 person-years	Questionnaire and followup of death certificate	8.5	491	>39 ..... 7.26 (17) NS ..... 1.00 (58) Current cigarettes. 5.24 (234) 1-9 cigarettes/day. 2.12 (13) 10-20 ..... 5.53 (124) 21-39 ..... 5.95 (76)	NS-1.00 (58) SM-1.13 (8)	NS-1.00 (58) SM-2.06 (24)	
Hammond & Garfinkel 1969 (31)	358,534 males, 445,875 females, 40-79 years of age at entry	Questionnaire and followup of death certificate	6	337	NS ..... 1.00 1-9 ..... 2.62 10-19 ..... 3.85 20-39 ..... 4.54 >40 ..... 8.00			Data apply only to males, 50-69 years of age
Weir and Dunn 1970 (85)	68,153 California male workers, 35-64 years of age at entry	Questionnaire and followup of death certificate	5-8	51	NS ..... 1.00 All ..... 2.64 ±10 ..... 2.44 ±20 ..... 2.88 ≥30 ..... 2.54			SM includes ex-smokers; NS includes pipe and cigar smokers

<sup>1</sup> Unless otherwise specified, disparities between the total number of deaths and the individual categories are due to the exclusion of occasional, miscellaneous, or former smokers.

<sup>2</sup> NS = nonsmokers; SM = smokers.

### **Summary of Epidemiologic Data**

Several large epidemiologic studies have suggested an elevated incidence of death from ruptured abdominal aneurysm in smokers compared with nonsmokers (31, 32, 33, 45, 85) (Table 2). Anderson et al. (1) analyzed 344 autopsies for causes of death and relationship to smoking history. The male to female ratio was 1.9:1.0, with a smoking incidence of more than double that of the general population. The overall longevity of men was less than that of women. There was an inverse relationship between smoking and longevity. Five diseases that accounted for 39 percent of the deaths of smokers were bronchogenic carcinoma, peptic ulcer, aortic aneurysm, acute myocardial infarction, and centrilobular emphysema. The 15 ruptured abdominal aortic aneurysms were in 13 male and 2 female smoking patients.

Auerbach and Garfinkel (4) evaluated atherosclerosis and aneurysm of the aorta relative to smoking habits and age. In 1,412 aortas collected at autopsy from 1965 to 1970 from male patients, there was a direct relationship between the extent of atherosclerotic lesions and both smoking habit and age. The aortic lesions were graded for formation of plaques, ulceration, and calcification. The complexity of the plaques increased with the number of cigarettes smoked and was greater in ex-cigarette smokers and pipe or cigar smokers than in nonsmokers. More extensive alterations were found in the abdominal aorta than in the thoracic aorta. Aneurysms were found eight times more frequently among those smoking one to two packs of cigarettes per day than among nonsmokers. Black subjects showed about one-half the number of aneurysms and fewer extensive atherosclerotic lesions than did white subjects. At ages over 65 years, abdominal aortic aneurysms were found in 11 percent of all men and in 16 percent of the heavy smokers.

Rogot and Murray (64) evaluated the smoking relationship to causes of death among U.S. veterans. Over a 16-year period, there was a significant reduction in mortality rate with the number of years of smoking cessation. Aortic aneurysm, along with bronchitis and emphysema and lung cancer, were among the diseases in which substantial excess risk remained even after 20 years' cessation of cigarette smoking.

### **Conclusions**

1. Cigarette smoking is the most powerful risk factor predisposing to atherosclerotic peripheral arterial disease.
2. Smoking cessation plays an important role in the medical and surgical management of atherosclerotic peripheral vascular disease.

**3. Death from rupture of an atherosclerotic abdominal aneurysm is more common in cigarette smokers than in nonsmokers.**

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