TABLE 5.—*Age-adjusted means for selected coronary heart disease risk factors and personal characteristics, by smoking category: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Variable	Smoking category		Percent difference
	Never smoked	Smoked 26 cigarettes or more per day	
Serum cholesterol	217. 2	231. 8	+6. 7
Beta/alpha ratio	1. 9	2. 1	+10. 5
Lipalbumin	21. 1	19. 4	−8. 1
Systolic blood pressure	126. 3	129. 9	+2. 9
Diastolic blood pressure	82. 0	81. 3	−0. 9
Ponderal index	12. 6	12. 7	+0. 8
Physical activity on job	1. 95	1. 95	0
Amount of exercise	2. 18	2. 05	−6. 0
Income	2. 75	2. 75	0

Source: Rosenman, R. H. (*125*).

TABLE 6.—*Percent distribution by behavior type of smokers and nonsmokers: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Behavior type	Total	Smoking category					
		Never smoked	Former smokers	Current pipe or cigar only	1–15 cigarettes per day	16–25 cigarettes per day	26 cigarettes or more per day
Total	100. 0	100. 0	100. 0	100. 0	100. 0	100. 0	100. 0
Type A	47. 5	41. 3	45. 0	48. 3	44. 8	48. 9	56. 7
Type B	52. 5	58. 7	55. 0	51. 7	55. 2	51. 1	43. 3

Test of difference of distributions: $X^2=24.70$; df=3; p=.001.

SOURCE: Rosenman, R. H. (*125*).

Behavioral pattern type A is characterized by an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency as contrasted to type B. There was a difference in the distribution of personality types A and B among smokers and nonsmokers (table 6).

The foregoing data refer to concurrent observations gathered in 1960–1961 on 3,182 men who were then free of manifestations of coronary heart disease. A follow-up of this population during the

next 4½ years disclosed that cigarette smokers experienced substantially higher rates of coronary heart disease than those who had never smoked. This finding is based on data for men 39–49 years of age, which have been adjusted for the confounding influences of related risk factors, such as age, cholesterol, etc. (table 7).

TABLE 7.—*Incidence of new coronary heart disease by smoking category: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Smoking category	Number of men	Rate per 10,000 population	
		Adjusted for concomitant variables	Not adjusted
Never smoked	540	36	29
Former cigarette smokers	241	67	92
Pipe and cigar only	406	27	16
1–15 cigarettes	212	51	52
16–25 cigarettes	436	89	92
26 cigarettes and over	425	98	104

SOURCE: Rosenman, R. H. (*125*).

The coronary heart disease rate for those men smoking 26 or more cigarettes a day is seen to be about three times greater than for those who never smoked. The rate for former smokers is still rather high, even after adjustment for concomitant variables. The largest impact of the adjustment procedure is noted among this group, and suggests that those who quit may have done so because they were already a relatively high-risk group for reasons other than smoking. The relatively low rate among men smoking only pipes and cigars is noted in this as in other prospective studies.

The nature of the association of smoking and coronary heart disease incidence among type A and type B personality groups is not easy to characterize or interpret. Among the type A group, the pipe and cigar smokers and the light cigarette smokers had the lowest rates of incidence of new coronary heart disease, while the highest rates were found among those smoking 26 or more cigarettes a day. For the type B group, the lowest rates occurred among those who had never smoked, and the highest among the light cigarette smokers. The age-adjusted rates of new incidence of coronary heart disease per 10,000 men 39–49 years of age are shown in table 8.

Additional data to permit concomitant analysis of these variables and those in table 7 are needed.

TABLE 8.—*Incidence of new coronary heart disease by smoking category and behavior type: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Smoking category	Rate per 10,000 population	
	Behavior type A	Behavior type B
Total	91	33
Never smoked	53	13
Former smokers	107	36
Pipe and cigars only	18	36
Cigarettes:		
1–15	18	60
16–25	135	33
26 and over	149	51

SOURCE: Rosenman, R. H. (*125*).

Lane, et al. (*96*) found significant relationships of smoking intensity and duration with personality factors—impulsiveness, emotional instability and belligerence scales.

Thomas (*143*) after reviewing various studies of psychological variables related to coronary heart disease, concludes that smoking may have different effects on different personality types and at different anxiety levels.

Multiple Risk Factors

The acceptance of a multiple factor causation hypothesis for coronary heart disease emphasizes the need for more sophisticated statistical analyses of appropriate data. Our understanding of the relative importance of various risk factors from the limited number of such special analyses has not been altered significantly from that obtained by more conventional statistical analyses (*38*).

Clarification of the apparent independence of several of the major risk factors has resulted.

Truett, et al. (*145*) emphasize that the major risk factors are noted to have a different order of importance by age and sex. Cigarette smoking is particularly important among younger males as noted in table 9.

Genetic and Constitutional Studies

Baer (*5*) found that heavy smokers among college males were taller than light smokers and nonsmokers. Lane, et al. (*96*) also found significant associations between body size measurements, including ponderal index (though not with height or weight individually), and amount of smoking in the study of over 675 aviators.

TABLE 9.—*Linear discriminant function coefficients (in standard units) for various risk factors in coronary heart disease, by sex and age: 12 Year Framingham Study*

Risk factors	Men				Women		
	Combined ages	30–39 years	40–49 years	50–62 years	Combined ages	30–49 years	50–62 years
Age	0. 5934	0. 2394	0. 3334	0. 2370	0. 6259	0. 7325	0. 2600
Cholesterol	0. 4444	0. 9613	0. 3207	0. 3790	0. 2844	0. 7322	0. 1207
Systolic blood pressure	0. 3334	0. 3427	0. 1669	0. 3809	0. 5556	0. 1947	0. 4776
Relative weight	0. 1890	0. 1941	0. 3619	0. 1036	0. 0975	0. 0751	0. 1481
Hemoglobin	−0. 1050	0. 0313	−0. 0134	−0. 2206	0. 0392	−0. 0304	0. 0734
Cigarettes smoked	0. 4192	0. 6823	0. 5084	0. 3004	0. 0625	−0. 0731	0. 1262
ECG abnormality	0. 2626	0. 2685	0. 2556	0. 2197	0. 3048	0. 2234	0. 2526

SOURCE: Truett, J. (*145.*)

Cederlof (*18*) has emphasized the value of studies of twins for investigating aspects of coronary heart disease and presents certain suggested modifications in methodology. The 1967 Report (*146*) discussed the studies by Cederlof on Swedish twin pairs (*19, 20*). His data on American twin pairs was recently presented and showed results similar to those of the Swedish twins (*18*).

The problems with interpretation of these studies are several. The small numbers of cases and the combining of data for both sexes in various subcategories make rates and ratios subject to significant chance variations. In addition, use of a questionnaire for angina, with only modest levels of reliability and validity requires a larger study population before definitive conclusions can be made. The lack of information on the distribution of risk factors other than smoking in subsamples of discordant twin pairs and the total group of twin pairs makes the comparison of ratios for prevalence of symptoms difficult to evaluate. The inclusion in the "smoking" group of those who had stopped smoking up to 3 years previous to the study, would also tend to diminish the differences between smokers and nonsmokers. Definitions of discordant smoking habits must conform to those differences identified as significant in the large-scale population studies.

The fact that discordance for smoking does occur among monozygotic twins certainly indicates that the smoking habit cannot be determined by genetic factors alone. Twin studies with further sophistication of design, larger number of cases, better definitions of disease, and more significant identification of discordant exposures have the potential of contributing substantially to our understanding of the interactive factors in coronary heart disease.

In an article reviewing some of the epidemiological evidence in the 3½ years subsequent to the 1964 report, Seltzer (*129*) concluded that there was no substantial evidence to indicate a further association of cigarette smoking with coronary heart disease beyond that stated in the 1964 report.

Seltzer alluded to what he called "inconsistencies" in the recent literature relating to duration, amount, age, inhalation and mode of tobacco smoking with coronary heart disease.

The addition of many more person years of experience, from the new and continuing studies, provides data since the 1964 Report that can be analyzed age-specifically. When this is done most of these "inconsistencies" disappear.

Seltzer's conclusion is contrary to that of most epidemiologists who are familiar with the current research. Furthermore, he has not considered the important relevance of the experimental, pathological, and clinical data that have been reported since 1964 concerning cigarette smoking and cardiovascular diseases.

Influence of Smoking and Nicotine on Blood Lipids

Epidemiological Studies

The results of epidemiological studies on the relationship of smoking to serum lipid levels have not been consistent. Several studies reported no significant difference in serum cholesterol (*36*, *40*, *61*, *150*) and triglyceride levels (*40*, *61*) between smokers and nonsmokers. In their study of twins, Blomstrand, et al. (*11*) state that prolonged smoking had an insignificant effect on all serum lipid levels in their monozygotic twins and only elevated phospholipids in their dizygotic group. However, they quote a personal communication from Carlson, et al. who found elevated trigylceride levels in smokers in a prospective study of 6,000 persons.

In a very comprehensive study of 657 former naval aviation cadets over a period of 23 years, Harlan, et al. (*56*) investigated the relationship of various constitutional and environmental factors to serum lipid and lipoprotein levels. They found that serum Sf 0–12 (beta) lipoproteins and cholesterol levels were related to cigarette smoking and that the duration of smoking also had a significant correlation. The authors felt that the relationship of smoking to these lipids was presumably direct, because cigarette smoking did not correlate with other factors related to lipids.

Experimental Studies—Animal

Studies in dogs of the immediate effects of tobacco smoke inhalation and nicotine administration showed an increase in serum triglycerides but not cholesterol, in addition to a rise in free fatty acids (*76*). There

were no differences in cigarette, cigar or pipe smoke effects when the depth of inhalation was kept constant. Chronic administration of nicotine in dogs resulted in a 50 percent rise in serum cholesterol levels but did not affect triglycerides (*82*). Kershbaum, et al. (*83*) have also shown that pronethalol (a beta-receptor blocker) inhibits the serum-free fatty acid and triglyceride rise induced by nicotine in dogs.

In studies of the lipid and atherogenic effects of chronic nicotine administration in cholesterol-fed rabbits, one report found no effect in serum lipid levels but a significantly higher incidence of aortic fibrosis (*51*). Other investigators found that nicotine increased the amount of cholesterol in the blood and the intensity of lesions in the aorta (*28*). In cholesterol-fed rabbits administered vitamin D, Hass, et al. (*59*) found that nicotine induced severe calcific athero-arteriosclerosis and occlusive thromboarteritis, especially conspicuous in cardiac, smooth and skeletal muscle.

Astrup (*2*) has shown that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure had a marked atherogenic effect.

Gudbjarnason (*52*) has shown that chronic nicotine administration in dogs leads to a diminution in the rate of cholesterol turnover.

Studies in Humans

It has previously been reported (*78*) that cigarette smoking mobilizes free fatty acids, resulting in increased plasma concentrations. It was also found that this effect of smoking was the result of increased sympathetic and adrenal activity initiated by the absorbed nicotine (*84*), the latter having no direct lipolytic action in adipose tissue (*85*). This response to smoking has now been confirmed by other investigators (*41,90,110*).

Studies in man, on the immediate effect of cigarette smoking, have shown no effect on serum concentrations of lipoproteins and lipoprotein lipids (cholesterol, phospholipids, triglycerides) (*78*, *92*, *115*). In a recent study, however, an increase in serum beta-lipoproteins was observed 10 minutes after smoking (*72*).

In a study of the comparative effects of cigarette, cigar and pipe smoking on free fatty acid mobilization and catecholamine excretion, cigarette smoking was found to have a much greater effect (*81*). Less nicotine absorption in cigar and pipe smoking, due to the absence of inhaling, was considered to be the explanation for the milder biochemical effects with these two forms of smoking (*80*). Kershbaum, et al. also compared the effects of various types of cigarettes on these parameters (*79*). They found no difference in free fatty acid and catecholamine response or nicotine absorption with several brands of filter and non-filter cigarettes. Cigarettes containing shredded lettuce leaf had no effect.

In other lipid studies it was observed that smoking might increase the tendency of human blood serum to crystallize cholesterol (*87*). Kershbaum has also shown that cigarette smoking increases the blood steroid levels in humans (*86*).

Studies on Thrombus Formation

The 1967 Report reviewed the effects of smoking on *in vitro* thrombus formation, varying platelet characteristics and other serum factors associated with blood coagulation. It is not in the scope of this report to go into a detailed analysis of blood coagulation and/or thrombosis. However, the role of smoking and blood lipids on thrombogenesis will be briefly discussed, as they relate to thrombosis and cardiovascular disease.

Catecholamines

The role of catecholamines (especially epinephrine) in thrombogenesis must be stressed (*111*). The nicotine-induced catecholamine release, which plays a major role in cardiovascular dynamics might also be the mediating factor in the relation between cigarette smoking and thrombosis. Ardlie (*1*) has shown that catecholamines enhance ATP or ADP induced platelet aggregation. ADP and noradrenaline in low concentration (up to 0.05 μg./ml.) were found to increase platelet mobility (*55*). The reverse was true in higher concentration. Rowsell (*128*) has shown increases in both thrombus formation in an extracorporeal system and clotting time in silicon-coated tubes with moderate doses of epinephrine. Large doses gave values closer to the control state. Besterman (*8*) has shown a diurnal variation in "platelet" stickiness which might be associated with diurnal variations in catecholamine release. Glynn (*48*) found no difference in platelet aggregation between smokers and nonsmokers.

Shimamoto (*133*) proposes that epinephrine has a primary effect on the arterial wall causing the release of a thromboplastin-like substance which then leads to increased platelet aggregation. An autopsy study in humans by Auerbach (*3*) showed increased fibrous thickening in the walls of arterioles and small arteries of 5 organs, in smokers as compared to nonsmokers. This effect might be secondary to platelet changes which then caused damage to the arterial wall. As discussed earlier in the study by Hass (*59*), in which rabbits on a high cholesterol and vitamin D diet were given nicotine, at the site of the occurrence of thrombus there was usually an inflammation of the arterial wall.

Blood Lipids

Conner, et al. (*26*) and Warner, et al. (*153*) have described various experiments in dogs and rabbits, in which infusion of long-chain saturated free fatty acids caused extensive thrombosis and death. *In*

vitro coagulation and platelet aggregation were also increased. Long-chain unsaturated free fatty acids, however, did not have these effects although microscopic platelet aggregation was observed (*66*). *In vitro* studies have shown that linoleic and linolenic acids might have a protective effect against platelet aggregation induced by long-chain saturated fatty acids (*73*, *101*).

The rise in plasma-free fatty acids which follows cigarette smoking was associated with increased platelet adhesiveness (*110*). The long-chain fatty acid-induced platelet aggregation was suggested to be due to ADP release from platelets (*58*). Harrison (*57*) suggests that *in vitro* platelet adhesiveness tests are influenced by ADP release from damaged red cells and that the platelet change might really be a reflection of red cell abnormalities.

Bray (*14*) found that coronary heart disease patients have an exaggerated platelet adhesiveness in response to ADP or ATP.

Several studies have shown disturbances in lipid and carbohydrate metabolism in coronary heart disease patients (*24*, *95*, *136*).

Kurien (*95*) postulates that the increases in free fatty acid levels immediately after either an acute myocardial infarction or cerebrovascular accident result from tissue anoxia with a secondary catecholamine release, which then leads to the increases in free fatty acids. Malhrotra (*103*) studied two population groups in India. There was no difference in the cholesterol, triglyceride, and free or esterified fatty acid levels between the two groups. However, the incidence of coronary heart disease was much higher in the population whose diet and fat absorption predispose to an abundance of long-chain fatty acids.

A majority of coronary heart disease patients have an abnormal glucose tolerance test. In most of these patients there is a greater decrease in free fatty acids in response to glucose and a slower return to normal values (*24*, *136*).

Soloff and Schwartz (*136*) have determined two subgroups of these patients: one "A", in which the free fatty acid response to glucose resembled a normal curve except for an exaggerated rise after 5 hours; another "B", in which the free fatty acid response to glucose resembled that of diabetics, there being a slower decrease and a subnormal return of free fatty acid levels after 5 hours. The significant effect, however, is that type "B" patients had a relative hyporesponse of stearic acid (long-chain saturated) decline with a relatively decreased rise in linoleic acid (long-chain unsaturated) after 5 hours.

These findings may be related to the effect of saturated and unsaturated fatty acids on blood coagulation and suggest further research to delineate the specific fatty acids elicited after smoking and in coronary heart disease patients.

This section should be read in conjunction with the findings reviewed in the 1967 report.

Experimental Studies

Nadeau, et al. (*112*) cannulated the sinus node artery in anesthetized dogs and noted chronotropic changes in response to doses of nicotine ranging from 1.0 to 100 μg./ml. Intranodal atropine abolished bradycardia and intranodal propranolol or hexamethonium abolished tachycardia. Nicotine inhibited the effects of cervical vagus nerve stimulation without modifying the response to intranodally injected acetylcholine. Nicotine did not inhibit the effect of stellate ganglion stimulation. These results illustrate the varying effects of nicotine under experimental conditions on the complicated neural and humoral mechanisms affecting heart rate and rhythm.

Sleight (*135*) and Bergel, et al. (*7*) have demonstrated cardiovascular depressor reflexes in dogs elicited by nicotine stimulation of the surface of the left ventricle. Studies have been undertaken in dogs to determine the effect of beta sympathetic receptor blockade by propranolol on the cardiac actions of nicotine. Westfall (*158*), Edmundowicz (*32*), Papacostas, et al. (*116*), Shanks (*131*) and Puri (*120*) have noted that propranolol can prevent the usual positive inotropic effects of nicotine or norepinephrine stimulation on the myocardium as well as the indirect beta dilator effects on peripheral vessels. This results proportionately in a greater increase in left ventricular afterload accompanied by a reciprocal decline of the velocity of myocardial fiber shortening (*120*). It was also noted that resulting unopposed alpha receptor activiation by nicotine could lead to increased total peripheral resistance with impaired storke volume and cardiac output. This is further evidence that catecholamines, the release of which is induced by smoking, intermediate the cardiovascular response to nicotine.

The effect of nicotine in single and repeated administrations was studied on the terminal vascular bed of the heart by Corsini, et al. (*27*). Results indicated that in dogs with intact coronary circulations, the single intravenous infusion of nicotine (150 μg./kg. body weight/minute) increased both the left ventricular capillary blood flow as well as the terminal vascular capacity; the chronic intramuscular administration (0.5 mg./kg. body weight given 5 times/day for 2 months), however, had no such effect. In contrast, in dogs with constriction of the coronary arteries, nicotine administration in either (single or repetitive doses) form resulted in a fall of capillary blood flow but an increase in the terminal vascular capacity. Capillary blood flow as measured in these studies represents a nutrient inflow to the myocardium. Nicotine administration resulted in an increase in both

the velocity of myocardial shortening as well as the force of contraction, and these effects of nicotine are identical to those of norepinephrine. In addition, there was also an increase in the rate of left ventricular pressure rise (dp/dt) and a decline in left ventricular end-diastolic pressure (*121*).

Coleman, et al. (*25*) studied isolated cat papillary muscles to determine the mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption. They found that norepinephrine does not increase the myocardial tissue oxygen demand unless contractility is increased, other factors being held constant. Norepinephrine is known to increase myocardial contractility.

Further studies (*49, 142*) on anesthetized open-chest dogs to determine the relative influences of changes in either the contractile state or in tension development on myocardial tissue oxygen consumption, indicate that both are significant factors. Basal oxygen requirements, activation energy, and the cost of contractile element shortening against a load appear to influence myocardial tissue oxygen consumption to a lesser degree.

Chidsey, et al. (*21, 22*) studied the relationship of norepinephrine to heart failure and the functional state of the human myocardium. They reemphasize the role of norepinephrine in altering myocardial fiber length and contractile status as demonstrated in human left ventricular papillary muscles removed from patients at the time of mitral valve replacement.

Ayres (*4*) has noted products of anaerobic cardiac metabolism in dogs made ischemic by exposure to carbon monoxide. These will be presented in a subsequent section of this chapter. Weissler, et al. (*156*), in experiments with isolated perfused rat hearts, have reported on the importance of glucose as a substrate for anaerobic metabolism of the heart subjected to anoxia for 30 minutes. When glucose was added to the anaerobic perfusate, the electrical and mechanical performance of the heart improved markedly, as did the recovery of the heart during the subsequent period of reoxygenation. Lactate production was fivefold greater in the glucose-supported anoxic heart than in the anoxic heart without glucose. In similar fashion, morphologic changes of the mitochondria and longitudinal tubules of the anoxic heart noted by electron microscopy, were averted by the inclusion of glucose in the perfusion fluid. This experiment suggests that glucose might help temporarily to prevent myocardial infarction, caused by relative myocardial anoxia, by providing a substrate for anaerobic cardiac metabolism.

The isolated perfused rat heart was also studied by Brachfeld, et al. (*12*) to determine the effects of nicotine on lysosomal, mitochondrial, and supernatant enzyme systems of the myocardium. They suggested that nicotine toxicity may be expressed in terms of damage to the

lysosomal membrane and the cell wall. Shibata, et al. (*132*) studied the action of nicotine on the transmembrane potential and contractility of isolated rat atria. They suggest that while nicotine may influence membrane electrodynamics, there may also be a direct action on the contractile mechanism of the cardiac muscle cell by changing the duration of the action potential, which implies alterations in potassium fluxes.

Nicotine-induced changes, in dogs, in action potentials and conduction depression, with enhancement of Purkinje fibre "automaticity," may lead to the development of ventricular fibrillation (*50*). Post myocardial infarction dogs were much more sensitive to the administration of nicotine, as measured by electrocardiographic changes, than were normal dogs, especially in the acute stage of myocardial infarction (*6*). Webb, et al. (*154*) state that changes in fibrillation thresholds after cigarette smoking noted in dogs, by analogy, "may have relevance to the higher incidence of coronary deaths without increased incidence of angina in cigarette smokers."

Studies in Humans

The 1967 report noted that sudden death from previously undetected coronary heart disease appeared to occur frequently among cigarette smokers. Kuller (*94*) showed in a study of sudden death in Baltimore that arteriosclerotic heart disease was a major cause (61.4 percent) of death. No smoking histories were recorded. Luke, et al. (*99*) reviewed 275 consecutive autopsied cases of sudden unexpected death from natural causes, in individuals age 20 to 45 years, and noted that asymptomatic coronary artery disease comprised 28 percent of the causes of sudden death. Again, no smoking data were taken. Data pooled from 10 studies available to Burch, et al. (*17*), indicated that cardiovascular disease accounted for 51 percent of 8,151 adult sudden deaths.

Present clinical evidence indicates that ventricular asystole or fibrillation may be the mechanism of sudden cardiovascular death in most cases. It is known that hypoxia, hypercapnia, ischemia, electrolyte disturbances, and increased catecholamine activity all can predispose to ventricular fibrillation. From available physiological evidence noted elsewhere in this and the bronchopulmonary chapter, and also in the 1967 Report, it would appear that smoking can directly or indirectly contribute to the development of these predisposing conditions. It is well accepted clinically that ventricular, nodal, or atrial premature contractions can be increased or induced by cigarette smoking, as well as by other factors, and can be reduced by the cessation of cigarette smoking in both normal and ischemic hearts. These premature contractions are frequently precursors of their respective tachycardias. Also, a person with an acute or impending myocardial infarction subjected to the sympathoadrenal effect of smoking could

more readily develop a fatal arrhythmia (*75*). The relationship of smoking to cardiac arrhythmias must be studied further to determine more exactly both the physiology and the mechanisms involved in sudden deaths from cardiovascular disease.

Kerrigan, et al. (*74*) studied cardiac output in both smokers and nonsmokers who had no evidence of coronary heart disease and found rises in cardiac output in response to exercise and to cigarette smoking separately and then in combination. They note that the total increase in cardiac output appears to be the sum of the exercise and the smoking effects. Smoking may create an additional myocardial tissue oxygen demand above and beyond the demand attributable to exercise.

Moses, et al. (*105*) reported that pretreatment of healthy normals with glucose blocks the increased cardiac output response to cigarette smoking by inhibiting the increases in stroke volume but not heart rate.

Frankl, et al. (*42*) noted that after 5 normal male chronic smokers were given propranolol, cigarette smoking caused a significant increase in systemic blood pressure and a significant decrease in cardiac output. Thus cigarette smoking after propranolol administration may be especially hazardous. Yamamoto noted similar results (*160*).

Sen Gupta, et al. (*130*) studied 11 ischemic cardiac patients and 14 healthy controls for abnormal ECG changes after smoking one cigarette and noted specific or nonspecific changes in almost all of the cardiac patients as compared to few changes in the healthy smokers and no abnormalities in the healthy nonsmokers. Pentecost, et al. (*117*) studied the acute effects of cigarette smoking in patients with angina or post-myocardial infarction as compared with normal controls. Normal men and those with angina in the absence of infarction behaved similarly with an increase in pulse rate, mean pressure, stroke volume, and cardiac output. The majority of the patients among the post-myocardial infarction group showed a marked fall in stroke volume and cardiac output while smoking. In another study (*43*) to evaluate the interrelationship of smoking and exercise effects on cardiac output, a fall in cardiac output that occurred in some post-infarction coronary patients as a result of smoking alone was noted. Also noted were decreases in cardiac output after smoking and exercising as compared to post-exercise cardiac output in the same patients before they smoked.

Starr (*139*) suggests that the ballistocardiographic (BCG) findings in cardiac disease and after cigarette smoking may provide valuable information about the rate of acceleration of myocardial contractile velocity that cannot be determined by studying cardiac output or stroke volume alone. A diseased heart has a slower accelerative rate of contraction. BCG abnormalities have frequently been

related to cigarette smoking in subjects with or without heart disease, including angina pectoris. The BCG findings of Jackson, et al. (*68*) indicate that cigarette smoking itself may have acute and chronic harmful effects on myocardial function, since duration of smoking was also correlated with certain abnormalities.

Gazes, et al. (*47*), Braunwald, et al. (*13*), and Klensch, et al. (*91*) have found higher plasma norepinephrine levels in coronary patients at rest and after smoking as compared to normals. Kershbaum, et al. (*77*) have reported that the rise in free fatty acids after cigarette smoking is also greater in patients with coronary heart disease, probably due to an enhanced norepinephrine response.

Burch, et al. (*16*) also stress the importance of the action of norepinephrine on the venous vascular system. "Greater than 70% of the blood volume is contained within the systemic venous system and a 10% reduction in venous capacity would result in the sudden shifting of 350 ml. of blood (assuming a blood volume of 5 L.) centrally into the pulmonary veins and atria. In the presence of a diseased left ventricle, such a sudden increase in central blood volume may result in acute left ventricular failure" (*17*). (Additional cardiopulmonary considerations are noted in the bronchopulmonary disease chapter of this Report).

Human Myocardial Tissue Function in Relation to Anoxia and to Carbon Monoxide

Likoff, et al. (*98*) suggest that an oxygen-diffusion impairment or inappropriate oxygen utilization at the myocardial microcirculatory or cellular level could be responsible for the anginal symptoms and ECG signs of apparent myocardial ischemia in the presence of adequate arterial saturation and patent coronary arteries by coronary arteriography. Ayres (*4*) and Eliot (*33*) suggest that these mechanisms may be related to the carbon monoxide effect and abnormal hemoglobin function.

In addition to a review of the coronary circulation as related to myocardial ischemia and angina pectoris, Elliott, et al. (*35*) studied zonal myocardial ischemia (*60*) by ECG, coronary angiography and regional lactate metabolism in 50 patients with proven coronary heart disease. They found that the ECG findings could be normal even when severe coronary disease was present with myocardial production of lactate. The regional lactate pattern was very helpful in determining the location of myocardial ischemia and significant coronary artery lesions.

In studies of coronary patients exposed to relatively low levels of carbon monoxide, Ayres (*4*) has reported that myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting the presence of anaerobic metabolism. These data support his

previous findings noted in the 1967 report that carboxyhemoglobin can interfere with oxygen delivery to the myocardium to the degree that relative myocardial anoxia can occur. The shift to anaerobic cardiac metabolism, which is relatively ineffective as a source of energy, indicates the presence of myocardial anoxia, and should be regarded as a warning sign. In these same experiments Ayres has noted that the myocardial oxygen extraction is decreased in response to carbon monoxide inhalation, and thus has further demonstrated the relationships of carbon monoxide with relative myocardial anoxia and anaerobic myocardial metabolism. The shift to the left of the hemoglobin-oxygen dissociation curve, describing the decreased ability of hemoglobin to release oxygen at the tissue level, is directly related to increased carboxyhemoglobin levels.

The animal experiments of Weissler (*156*), noted in the previous section, suggest that glucose might possibly help to temporarily prevent myocardial infarction from relative myocardial anoxia, by providing a substrate for anaerobic metabolism. Since myocardial ischemia may be caused not only by complete coronary arterial obstruction, but also by increased myocardial tissue oxygen demand above and beyond available oxygen supply, it would be important to know whether cigarette smokers have more products of anaerobic myocardial metabolism than do nonsmokers.

Eliot (*34*) has noted apparent hemoglobin abnormalities in patients with signs of myocardial ischemia or acute necrosis, and in smokers as compared to controls. However, he suggests that there are other hemoglobin abnormalities also present besides the well documented carboxyhemoglobin abnormalities associated with the carbon monoxide effect of cigarettes. Some reverted to normal hemoglobin status after stopping smoking.

Anomalous hemoglobin-oxygen dissociation was noted in "heavy" cigarette smokers (more than one pack per day) without known coronary heart disease. In experiments where the amount of cigarette smoking was controlled, there appeared to be a threshold effect: more than 12 cigarettes per day caused this anomalous dissociation to occur (*53*). Birnstingl (*9*) reports finding an increased hemoglobin affinity for oxygen in smokers, which does not appear to be explained solely by the increased carboxyhemoglobin levels in smokers.

Research to further study the interrelationships of carbon monoxide to the myoglobin of heart muscle should be performed because it is possible that carbon monoxide may replace oxymyoglobin with carboxymyoglobin and disturb the oxygen-dissociation phenomena of myoglobin (*88, 126, 159*). The limitations of blood supply and the high energy output of heart muscle as compared to skeletal muscle may make the myoglobin impairments by carbon monoxide of possible etiologic importance in cigarette smoking and heart disease.

Hydrogen cyanide appears to be rapidly converted to thiocyanates by the body, but the absorption by the lung of cyanide from cigarette smoke might possibly result in higher serum cyanide levels in the coronary arteries than in the systemic circulation. As noted in the 1964 Report, the cyanide ion is capable of stopping cellular respiration abruptly through inactivation of cytochrome oxidase. In sublethal exposures, the cyanide ion is gradually released from its combination with the ferric ion of cytochrome oxidase, converted to thiocyanate ion and excreted in the urine. Thiocyanate blood levels in smokers are three times higher than in nonsmokers and relative differences in urinary excretion are even more pronounced. Cytochrome oxidase is very important in cellular respiration of all body cells. In view of the extremely high myocardial cellular needs for aerobic metabolism, it is possible that the cyanide ion inactivation of cytochrome oxidase also can occur in myocardial cells and be of critical importance, especially in light of other risk factors such as impaired coronary blood flow, the carbon monoxide effect, and the known increases in myocardial tissue oxygen demand caused by the smoking/nicotine-induced catecholamine release. Further research is needed to determine whether or not cyanide ions in concentrations equivalent to those found in cigarette smokers, have a harmful effect on the myocardium, in terms of both acute and chronic exposures.

Glucose Metabolism and Possible Cardiovascular Effects

Epstein (*37*) has reviewed the relationships of hyperglycemia to coronary heart disease. Although he states that there appeared to be no relationship of cigarette smoking to the hyperglycemia that was associated with the prevalence of coronary heart disease in the Tecumseh population, Higgins (*63*) reports that the Tecumseh cigarette smokers, both male and female, had approximately a 10 mg. percent elevation in blood glucose as compared to nonsmokers, although the percentage elevations above the median levels were not statistically significant. Since Epstein (*39*) reported that cigarette smokers in the Tecumseh study population had a higher incidence of coronary heart disease, it would be interesting to see what the interrelationship of the incidence of coronary heart disease is to the cigarette smokers who have elevated blood glucose levels.

Cohen, et al. (*24*) have reported abnormal glucose tolerance in some postinfarction patients, suggesting the possibility that this group has difficulty utilizing glucose. It is known that smoking induces release of catecholamines which can create an increased demand for glucose by the body. Wahlberg (*152*) had noted that in patients with atherosclerotic disease but without clinical diabetes mellitus, the glucose tolerance was pathologic in 46 percent as compared with 10 percent of controls, and normal in 33 percent as compared with 71 percent

controls. From this he infers that subclinical diabetes mellitus may predispose to vascular disease in the same way as clinical diabetes mellitus.

Kingsbury, et al. (*89*) studied a small group of male patients with peripheral arteriosclerotic disease to determine the serum glucose, nonesterified fatty acids, and immunoreactive insulin responses to subcutaneous adrenaline and to smoking. Under basal conditions, the fatty acid response was normal. While adrenaline consistently caused a rise in serum glucose, cigarette smoking either had no effect or lowered the fasting concentration. In 5 patients smoking caused an elevation in the immunoreactive insulin which could not be explained by blood sugar changes. The implication is that these patients were hypersecretors of insulin. Unfortunately, detailed smoking histories are not available for these individuals. Szanto (*141*), in a very small study of habitual smokers, noted a "hyperinsulinism" response during oral glucose tolerance testing after smoking two cigarettes. This response was markedly reduced when the test was repeated after a 14-day abstinence from smoking. The view that hyperinsulinemia is associated with atherogenesis has been suggested (*114*, *118*, *149*, *157*) and discussed by Mahler (*102*). If smoking directly or indirectly causes a hyperinsulin response in some individuals, then this may possibly be one mechanism by which cigarette smoking may enhance atherogenesis.

Kershbaum, et al. (*86*) have noted higher plasma 11-hydroxy corticosteriod levels in smokers. Whether the "hyperinsulinism" reported to be present in smokers is related to increased adrenal corticosteriods remains to be determined. Hyperinsulinism could be a response to the frequent catecholamine-induced hyperglycemia caused by cigarette smoking in individuals without significant clinical or subclinical coronary heart disease; but conceivably the hyperinsulinism response might be more pathological in coronary patients. Also, the potassium and other ion changes caused by glucose shifts in response to shifts in insulin levels may predispose to cardiac arrhythmias and sudden death.

Additional Considerations Regarding Coronary Blood Flow

Coronary blood flow, besides being influenced by the size of the inner lumen of the coronary vessel wall and its ability to dilate for the purpose of increasing flow of oxygenated blood when needed by heart muscle, is also dependent upon the viscosity of the blood (*16*). The concepts of fluid mechanics, such as laminar or turbulent flow, are well known. For any given aperture and pumping pressure, fluid flow will depend somewhat upon the physical characteristics of the fluid itself. It has been demonstrated in both cigarette smokers (*100*) and in patients with myocardial infarction that hemoconcentration occurs (*15*, *137*), sometimes to a relatively small degree in terms of absolute changes in hematocrit, but the changes in viscosity are much greater

than might have been predicted from consideration of hematocrit changes alone. At this point, other factors related to fluid mechanics also enter in, such as the quality and amount of lipids in the blood. Burch, et al. (*15*) have demonstrated that increased fatty acids increase the force necessary to "shear" the blood, thus contributing to a reduction in the capacity of the blood to flow in laminar fashion through a given aperture. When coronary arteries are impaired by partial obstruction of the inner lumen or by decreased distensibility, there may be a critical interaction with blood viscosity causing marked turbulence of flow and thus reducing further the potential for increasing coronary blood flow.

SUMMARY, CONCEPT AND CONCLUSION

Additional evidence has been presented which tends to confirm and extend the positive findings previously reported in the 1964 and 1967 reports.

1. Epidemiological studies show that "heavy" cigarette smoking is strongly associated with an increased risk of dying from coronary heart disease.

2. New data confirm and help to clarify the relationship between cigarette smoking and other "risk factors" in the development of coronary heart disease suggesting that both independent and interacting effects are involved.

3. Evidence indicates that cigarette smoking may accelerate the pathophysiological changes of pre-existent coronary heart disease and contribute to sudden cardiovascular death. This relationship helps to explain why stronger epidemiological correlations between cigarette smoking and coronary heart disease tend to be found in incidence studies rather than in prevalence studies where the population is under-represented for those people who have had fatal outcomes from coronary heart disease.

4. Present evidence continues to support the position that giving up cigarette smoking is beneficial to cardiovascular health.

5. Some progress is being made in the study of the interrelationships of selected psychological factors, smoking behavior, and the development of coronary heart disease.

Recent data provide a basis for the formulation of a theoretical concept by means of which it is possible to correlate the interaction of several known coronary heart disease risk factors with the physiological mechanisms by which cigarette smoking may affect the myocardium.

The epidemiological studies continue to indicate that "heavy" cigarette smoking is strongly associated with a fatal outcome from coronary heart disease. This fact may be accounted for by a mechanism

whereby, in the presence of impaired coronary circulation due to coronary heart disease, cigarette smoking may "trigger" myocardial oxygen deficits of critical degree. One or more of the following mechanisms may be involved in this process:

1. The increase of myocardial wall tension and velocity of contraction, largely mediated through norepinephrine released in response to cigarette smoking, thereby increasing the myocardial demand for oxygen and other nutrients.
2. The relative reduction of nutrient capillary blood flow in the region of the myocardium distal to and dependent upon blood flow through a partially occluded coronary artery.
3. The impairment of oxygen dissociation from hemoglobin due to the formation of carboxyhemoglobin from carbon monoxide, thereby diminishing the availability of oxygen to the myocardium.
4. The reduction of the supply of oxygen available to the myocardium as a consequence of hypoxemia due to severely impaired pulmonary function from chronic obstructive bronchitis.
5. The impairment of coronary blood flow as a result of the increased blood viscosity associated with hyperlipemia or hemoconcentration.
6. The increase in platelet adhesiveness which might contribute to thrombus formation or coronary occlusion.
7. The predisposition to acute cardiac arrhythmias as a consequence of harmful neurogenic reflexes or catecholamine release.
8. The possible, although presently speculative, contributions to impairment of myocardial cellular respiration by cyanide ion.

Thus, the interaction of the factors which decrease oxygen supply to the myocardium and those which increase the myocardial demand for oxygen may play a major role in precipitating the fatal outcome in some individuals with coronary heart disease. On the other hand, it is possible that the same factors, in less severe clinical circumstances, could precipitate temporary coronary insufficiency or contribute to nonfatal myocardial infarctions or cardiac arrhythmias.

The pathophysiological factors associated with cigarette smoking may further interact with other known epidemiological risk factors associated with coronary heart disease such as high serum cholesterol and high blood pressure. Although not a "risk factor", unusually high physical stress may also create physiological demands for additional oxygen supply to the myocardium.

The finding that those who discontinue cigarette smoking have a lower risk of dying from coronary heart disease than those who continue to smoke might be accounted for by the potential reversibility of many of the pathophysiological effects of smoking on the cardiovascular system. It is reasonable to expect partial reversibility of factors that interfere with oxygen supply, such as the carbon monoxide

effect, and the increased platelet adhesiveness, hyperlipemia, and hemoconcentration noted in cigarette smokers. Moreover, the increased myocardial oxygen requirements associated with the cigarette smoking-induced catecholamine response and neurogenic reflexes could be expected to be eliminated upon cessation of cigarette smoking. In some patients, the cardiopulmonary benefits of stopping smoking may reduce pulmonary hypertension.

An increased ability to predict future cardiovascular events in individual persons will depend upon more precise definition and measurement of the pathophysiologic factors associated with cigarette smoking and their correlation with information about the epidemiological risk factors.

Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease.

SMOKING AND CEREBROVASCULAR DISEASES

Many of the pathophysiological considerations noted in the above section may also pertain to the relationship of smoking and cerebrovascular disease.

A mortality study in Japan by Hirayama (*65*) reports findings different from those cited in the 1967 Report (*146*), in which smokers under age 75 had a mortality ratio of 1.40, or more, for stroke.

Hirayama found that deaths due to vascular lesions of the central nervous system, after age 40, were one-third less frequent among smokers than among nonsmokers. Several factors may account for these different findings. One is that the etiologic spectrum for stroke in Japan includes more hemorrhagic strokes than in the United States. Another is that the Japanese study included all stroke deaths over age 40, whereas the studies in the United States found the positive association between smoking and stroke mortality occurred under age 75 (*54*).

In a study reported by Kuhn (*93*), 20 habitual smokers refrained from smoking for one-half day and baseline retrograde brachiocerebral angiograms were taken: then they smoked one cigarette, inhaled deeply, and had repeat angiograms. Only those over 60 years of age failed to have significant acceleration of flow in cerebral precapillary vessels and markedly increased vessel counts as in carbon dioxide inhalation experiments.

As in coronary heart disease, it may be that smoking has different effects depending upon the degree of underlying arteriosclerotic disease present. Among patients with stroke, many have arteriosclerotic heart disease and a significant number die of myocardial infarcts (*104*).

The rate of oxygen uptake in the brain is very high, being approximately 5 cc. oxygen/100 g. brain/min. (*104*). As discussed in the cardiovascular section, if carbon monoxide causes a shift to the left in the oxygen hemoglobin dissociation curve, it would make less oxygen available to the brain tissue. Those people with an arteriosclerotic cerebrovasculature who cannot increase their cerebral blood flow in response to smoking may therefore more easily develop a state of relative cerebral hypoxia; a situation which could be a factor in the etiology of stroke.

CITED REFERENCES

(*1*) ARDLIE, N. G., GLEW, G., SCHWARTZ, C. J. Influence of catecholamines on nucleotide-induced platelet aggregation. Nature (London) 212 (5060) : 415–417, October 22, 1966.

(*2*) ASTRUP, P., KJELDSEN, K., WANSTRUP, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 7 : 343–354, 1967.

(*3*) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Thickening of walls of arterioles and small arteries in relation to age and smoking habits. New England Journal of Medicine 278(18) : 980–984, May 2, 1968.

(*4*) AYRES, S. M. Personal communication. March 1968.

(*5*) BAER, D. J. Height, weight, and ponderal index of college male smokers and nonsmokers. Journal of Psychology 64 : 101–105, September 1966.

(*6*) BELLET, S., KERSHBAUM, A., MEADE, R. H., JR., SCHWARTZ, L. The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. American Journal of the Medical Sciences 201(1) : 40–51, January 1941.

(*7*) BERGEL, D. H., MAKIN, G. S. Central and peripheral cardiovascular changes following chemical stimulation of the surface of the dog's heart. Cardiovascular Research 1(1) : 80–90, 1967.

(*8*) BESTERMAN, E., MYAT, G., TRAVADI, V. Diurnal variations of platelet stickiness compared with effects produced by adrenaline. British Medical Journal 1 : 597–600, March 11, 1967.

(*9*) BIRNSTINGL, M., COLE, P., HAWKINS, L. Variations in oxyhaemoglobin dissociation with age, smoking and Buerger's Disease. British Journal of Surgery 54(7) : 615–619, July 1967.

(*10*) BLACKBURN, H., KEYS, A., KARVONEN, M., VAN BUCHEM, F. S. P., TAYLOR, H. L. Relation of "positive" postexercise electrocardiographic responses to other characteristics of risk. Circulation 36(4) (Supplement II) : 70, October 1967.

(*11*) BLOMSTRAND, R., LUNDMAN, T. Serum lipids, smoking and heredity. Acta Medica Scandinavica (Supplement 455) : 51–60, 1966.

(*12*) BRACHFELD, N., KUEHN, P., KAWADE, M., ORAN, E. Nicotine medicated release of myocardial cell and lysosomal enzymes. Annals of Internal Medicine 66(5) : 1034, May 1967.

(*13*) BRAUNWALD, E., CHIDSEY, C. A., HARRISON, D. C., GAFFNEY, T. E., KAHLER, R. L. Studies on the function of the adrenergic nerve endings in the heart. Circulation 28(5) : 958–969, November 1963.

(*14*) BRAY, C., MCDONALD, L. A new platelet defect in patients with ischaemic heart disease. British Heart Journal 28(3) : 429, May 1966.

(*15*) BURCH, G. E., DEPASQUALE, N. P. The hematocrit in patients with myocardial infarction. Journal of the American Medical Association 180(1) : 63–70, April 7, 1962.

(16) BURCH, G. E., DEPASQUALE, N. P. Hematocrit, viscosity and coronary blood flow. Diseases of the Chest 48(3): 225–232, September 1965.

(17) BURCH, G. E., DEPASQUALE, N. P. Sudden, unexpected, natural death. American Journal of the Medical Sciences 249: 86–97, January 1965.

(18) CEDERLOF, R. The value of twin studies in epidemiology. World Medical Journal 14(6): 168–171, November–December 1967.

(19) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Morbidity among monozygotic twins. Archives of Environmental Health 19(2): 346–450, February 1965.

(20) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. Archives of Environmental Health 13(6): 726–737, December 1966.

(21) CHIDSEY, C. A., BRAUNWALD, E., MORROW, A. G. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. American Journal of Medicine 39(3): 442–451, September 1965.

(22) CHIDSEY, C. A., SONNENBLICK, E. H., MORROW, A. G., BRAUNWALD, E. Norepinephrine stores and contractile force of papillary muscle from the failing human heart. Circulation 33(1): 43–51, January 1966.

(23) CLARK, V. A., CHAPMAN, J. M., COULSON, A. H. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. Journal of Chronic Diseases 20: 571–581, 1967.

(24) COHEN, A. M., SHAFRIR, E. Carbohydrate metabolism in myocardial infarction. Behavior of blood glucose and free fatty acids after glucose loading. Diabetes 14(2): 84–86, February 1965.

(25) COLEMAN, H. N., SONNENBLICK, E. H., BRAUNWALD, E. Mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption as studied in the isolated cat papillary muscle. Circulation (Supplement II) 36(4): 89, October 1967.

(26) CONNOR, W. E., HOAK, J. C., WARNER, E. D. Fatty acids and thrombus formation. In: Sasahara, A. A., editor. Pulmonary Embolic Disease. London, 1965. Pp. 50–58.

(27) CORSINI, G. C., PURI, P. S., BING, R. J. Effect of nicotine on capillary flow and vascular bed of the heart in presence and absence of experimental coronary artery insufficiency. Federation Proceedings 27(2): 632, March–April 1968.

(28) CZOCHRA-LYSANOWICZ, Z., GORSKI, M., KEDRA, M. Wplyw nikotyny i kofeiny na rozwoj miazdzycy u krolikow. Annales Universitatis Mariae Curie-Sklodowska: Section D: Medicina 14(20): 181–206, 1959.

(29) DÖRKEN, H. The etiology of myocardial infarction—with special reference to cigarette smoking among young coronary patients and those with second heart attacks. In: Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(30) DÖRKEN, H. Die Rauchgewohnheiten bei Jungeren Frauen mit Herzinfarkt. Münchener Medizinische Wochenschrift 109(41): 2129–2134, January 1967.

(31) DÖRKEN, H. Die Rauchgewohnheiten bei Jungeren Herzinfarkt-Patienten. Münchener Medizinische Wochenschrift 109(4): 187–192, January 27, 1967.

(32) EDMUNDOWICZ, A. C., CIPOLLONI, P. B., PENROD, K. E. Cardiovascular responses to cigarette smoke and nicotine in dogs following beta-adrenergic blockade with propranolol. (Abstract) Federation Proceedings 24: 713, March–April 1965.

(33) ELIOT, R. S., BRATT, G. S. Personal communication, April 1968.

(34) ELIOT, R. S., MIZUKAMI, H. Oxygen affinity of hemoglobin in persons with acute myocardial infarction and in smokers. Circulation 34: 331–336, August 1966.

(35) ELLIOTT, W. C., GORLIN, R. The coronary circulation, myocardial ischemia, and angina pectoris. Modern Concepts of Cardiovascular Disease 35(10): 111–116, October 1966.

(36) Epidemiological studies related to coronary heart disease: Characteristics of men aged 40–59 in seven countries. F. Smoking habits. Acta Medica Scandinavica (Supplement 460): 304–315, 1967.

(37) EPSTEIN, F. H. Hyperglycemia. A risk factor in coronary heart disease. Circulation 36: 609–619, October 1967.

(38) EPSTEIN, F. H. Predicting coronary heart disease. Journal of the American Medical Association 201(11): 795–800, September 11, 1967.

(39) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine 60(1): 4–8, January 1967.

(40) FIDANZA, F., IMBIMBO, B., DI BENEDETTA, C. Indagine epidemiologica delle cardiopatie ischemiche nei reclusi del penitenziario di S. Stefano di Ventotene. Giornale dell'-Arteriosclerosi 4: 255–267, 1966.

(41) FRANKL, W. S., FRIEDMAN, R., SOLOFF, L. A. Cardiac output, blood pressure and free fatty acid responses to smoking in the nonbasal state. American Journal of the Medical Sciences 252(1): 39–44, July 1966.

(42) FRANKL, W. S., SOLOFF, L. A. The hemodynamic effects of propranolol hydrochloride after smoking. American Journal of the Medical Sciences 254(5): 623–628, November 1967.

(43) FRANKL, W. S., WINTERS, W. L., SOLOFF, L. A. The effects of smoking on the cardiac output at rest and during exercise in patients with healed myocardial infarction. Circulation 31(1): 42–44, January 1965.

(44) FRIEDEMANN, M., STEIM, H., EMMRICH, J., REINDELL, H. Der Herzinfarkt in Atiologiscer und katamnestischer Sicht. Deutsches Archiv fur Klinische Medizin 211: 261–296, 1965.

(45) FRIEDMAN, E. H., HELLERSTEIN, H. K. Occupational stress, law school hirearchy, and coronary artery disease in Cleveland attorneys. Psychosomatic Medicine 30(1): 72–86, January–February 1968.

(46) FRIEDMAN, G. D. Cigarette smoking and geographic variation in coronary heart disease mortality in the United States. Journal of Chronic Diseases 20: 769–779, 1967.

(47) GAZES, P. C., RICHARDSON, J. A., WOODS, E. F. Plasma catecholamine concentrations in myocardial infarction and angina pectoris. Circulation 19(5): 657–661, May 1959.

(48) GLYNN, M. F., MUSTARD, J. F., BUCHANAN, M. R., MURPHY, E. A. Cigarette smoking and platelet aggregation. Canadian Medical Association Journal 95: 549–553, September 10, 1966.

(49) GRAHAM, T. P., JR., COVELL, J. W., SONNENBLICK, E. H., ROSS, J., JR., BRAUNWALD, E. Control of myocardial oxygen consumption: Relative influence of contractile state and tension development. Journal of Clinical Investigation 47: 375–385, 1968.

(50) GREENSPAN, K., KNOEBEL, S. B., FISCH, C. Effects of nicotine upon human and canine cardiac action potential and contractile state. (Abstract) The Project for Research on Tobacco and Health 1964–1968. American Medical Association Education and Research Foundation. June 1968. Pp. 24–25.

(51) GROSGOGEAT, Y., ANGUERA, G., LELLOUCH, J., JACOTOT, B., BEAUMONT, J. L., PATOIS, E., MANIER, E. L'intoxication chronique par la nicotine chez

le lapin nourri au cholesterol. Effets sur la paroi aortique et sur la lipidemie. Journal of Atherosclerosis Research 5(3) : 291–301, 1965.

(52) GUDBJARNASON, S. Effect of nicotine administration on cholesterol metabolism of liver, serum, heart and brain. Journal of Pharmacology and Experimental Therapeutics 161(1) : 47–54, May 1968.

(53) GUTENKAUF, J. J., BRATT, G. T., ELIOT, R. S. Effect of cigarette smoking on the hemoglobin-oxygen dissociation curve. Circulation (Supplement II) 36(4) : 129, October 1967.

(54) HAMMOND, E. C. Smoking in relation to the death rates of 1 million men and women. In: Haenszel, W., editor. Epidemiological Approaches to the Study of Cancer and Other Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 127–204.

(55) HAMPTON, J. R., MITCHELL, J. R. A. Effect of aggregating agents on the electrophoretic mobility of human platelets. British Medical Journal 1: 1074–1077, 1966.

(56) HARLIN, W. R., OBERMAN, A., MITCHELL, R. E., GRAYBIEL, A. Constitutional and environmental factors related to serum lipid and lipoprotein levels. Annals of Internal Medicine 66(3) : 540–555, March 1967.

(57) HARRISON, M. J. G., MITCHELL, J. R. A. The influence of red blood cells on platelet adhesiveness. Lancet 2: 1163–1164, November 26, 1966.

(58) HASLAM, R. J. Role of adenosine diphosphate in the aggregation of human blood-platelets by thrombin and by fatty acids. Nature (London) 202: 765, 1964.

(59) HASS, G. M., LANDERHOLM, W., HEMMENS, A. Production of calcific athero-arteriosclerosis and thromboarteritis with nicotine, vitamin D, and dietary cholesterol. American Journal of Pathology 49(4) : 739–771, October 1966.

(60) HERMAN, M. V., ELLIOTT, W. C., GORLIN, R. An electrocardiographic, anatomic, and metabolic study of zonal myocardial ischemia in coronary heart disease. Circulation (5) : 834–846, May 1967.

(61) HEYDEN-STUCKY, S. SCHIBLER-REICH, S. Cardiologische Risikofaktoren bei Schweizer Mannern. Schweizerische Medizinische Wochenscrift 97 (1) : 20–25, January 7, 1967.

(62) HEYDEN-STUCKY, S. Epidemiologie des Herzinfarktes 1965. Schweizerische Medizinische Wochenschrift 95(45) : 1535–1540, November 6, 1965.

(63) HIGGINS, M. W., KJELSBERG, M. Characteristics of smokers and nonsmokers in Tecumseh, Michigan. II. The distribution of selected physical measurement and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers. American Journal of Epidemiology 86(1) : 60–77, January 1967.

(64) HINKLE, L. E., Jr., WHITNEY, L. H., LEHMAN, E. W., DUNN, J., BENJAMIN, B., KING, R., PLAKUN, A., FLEHINGER, B. Personal Communication, 1968.

(65) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center Research Institute, September 1967. 14 pp.

(66) HOAK, J. C., WARNER, E. D., CONNOR, W. E. Platelets, fatty acids and thrombosis. Circulation Research 20(1) : 11–17, January 1967.

(67) HYAMS, L., SEGI, M., ARCHER, M. Myocardial infarction in the Japanese. A retrospective study. American Journal of Cardiology 20(4) : 549–554, October 1967.

(68) JACKSON, D. H., OBERMAN, A., MITCHELL, R. E., GRAYBIEL, A. Factors contributing to the ballistocardiographic waveform in healthy middle-

aged men. American Journal of Cardiology 20(4): 531–540, October 1967.

(69) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. Cigararette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis: The Framingham Study. In: Wynder, E. L., Hoffmann, D., editors. Toward A Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(70) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. The coronary profile: 12-year follow-up in the Framingham study. Journal of Occupational Medicine 9(12): 611–619, December 1967.

(71) KANNEL, W. B., DAWBER, T. R., MCNAMARA, P. M. Detection of the coronary-prone adult: The Framingham Study. Journal of the Iowa Medical Society 56(1): 26–34, January 1966.

(72) KEDRA, M., POLESZAK, J., PITERA, A. Wplyw tytoniu na poziom tluszczowcow krwi. Polski Tygodnik Lekarski 20(3): 1452–1554, September 27, 1965.

(73) KERR, J. W., MAC AULAY, I., PIRRIE, R., BRONTE-STEWART, B. Platelet-aggregation by phospholipids and free fatty acids. Lancet 1: 1296–1299, June, 19, 1965.

(74) KERRIGAN, R., JAIN, A. C., DOYLE, J. T. The circulatory response to cigarette smoking at rest and after exercise. American Journal of the Medical Sciences 255: 113–119, February 1968.

(75) KERSHBAUM, A. Personal communication. March 1968.

(76) KERSHBAUM, A., BELLET, S. Cigarette, cigar, and pipe smoking: Some differences in biochemical effects. Geriatrics 23: 126–134, March 1968.

(77) KERSHBAUM, A., BELLETT, S., CAPLAN, R. F., FEINBERG, L. J. Effect of cigarette smoking on free fatty acids in patients with healed myocardial infarctions. American Journal of Cardiology 10(2): 204–208, August 1962.

(78) KERSHBAUM, A., BELLET, S., DICKSTEIN, E. R., FEINBERG, L. J. Effect of cigarette smoking and nicotine on serum free fatty acids. Based on a study in the human subject and the experimental animal. Circulation Research 9(5): 631–638, May 1961.

(79) KERSHBAUM, A., BELLET, S., HIRABAYASHI, M., FEINBERG, L. J. Regular filter-tip, and modified cigarettes. Nicotine excretion, free fatty acid mobilization, and catecholamine excretion. Journal of the American Medical Association 201(7): 545–546, August 14, 1967.

(80) KERSHBAUM, A., BELLET, S., HIRABAYASHI, M., FEINBERG, L. J., EILBERG, R. Effect of cigarette, cigar and pipe smoking on nicotine excretion. The influence of inhaling. Archives of Internal Medicine 120(3): 311–314, September 1967.

(81) KERSHBAUM, A., BELLETT, S., JIMENEZ, J., FEINBERG, L. J. Differences in effects of cigar and cigarette smoking on free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association 195(13): 1095–1098, March 28, 1966.

(82) KERSHBAUM, A., BELLET, S., KHORSANDIAN, R. Elevation of serum cholesterol after administration of nicotine. American Heart Journal 69(2): 206–210, February 1965.

(83) KERSHBAUM, A., JIMENEZ, J., BELLET, S., ZANUTTINI, D. Modification of nicotine-induced hyperlipidemia by antiadrenergic agents. Journal of Atherosclerosis Research 6: 524–530, 1966.

(84) KERSHBAUM, A., KHORSANDIAN, R., CAPLAN, R. F., BELLET, S., FEINBERG, L. J. The role of catecholamines in the free fatty acid response to cigarette smoking. Circulation 28(1): 52–57, July 1963.

(85) KERSHBAUM, A., OSADA, H., SCRIABINE, A., BELLET, S., PAPPAJOHN, D. J. Influence of nicotine on the mobilization of free fatty acids from rat adipose tissue *in vitro* and in the isolated perfused dog limb. Circulation 36 (Supplement II) : 20, October 1967.

(86) KERSHBAUM, A., PAPPAJOHN, D. J., BELLET, S., HIRABAYASHI, M., SHAFIIHA, H. Effect of smoking and nicotine on adrenocortical secretion. Journal of the American Medical Association 203(4) : 275–278, January 1968.

(87) KERSHBAUM, A., PAPPAJOHN, J., OSADA, H. BELLET, S. The influence of tobacco smoking on the crystallization of cholesterol. (Abstract) Clinical Research 15(2) : 322, April 1967.

(88) KEYES, M. MIZUKAMI, H. LUMRY, R. Equilibrium measurement in the reactions of heme-proteins with gaseous ligands. Analytical Biochemistry 18: 126–142, 1967.

(89) KINGSBURY, K. J., JARRETT, R. J. Effects of adrenaline and of smoking in patients with peripheral atherosclerotic vascular disease. Lancet 2(7505) : 22–23, July 1, 1967.

(90) KLENSCH, H. Blut-Kathecholamine und -Fettsauren beim Stress durch Rauchen und durch korperliche Arbeit. Zeitschrift fur Kreislaufforschung 55(10) : 1035–1044, October 1966.

(91) KLENSCH, H., SPECKMANN, K., MAETZEL, F. W., MEYER, J. D. Der Plasma-Noradrenalinspiegel bei Koronarkranken in Ruhe und im Nikotin-Stress. Zeitschrift fur Kreislaufforschung 56(12) : 1164–1169, December 1967.

(92) KONTTINEN, A., RAJASALMI, M. Effect of heavy cigarette smoking on postprandial triglycerides, free fatty acids, and cholesterol. British Medical Journal 1(5334) : 850–852, March 30, 1963.

(93) KUHN, R. A. Mode of action of tobacco smoke inhalation upon the cerebral circulation. Annals of the New York Academy of Sciences 142 (Article 1) : 67–71, March 15, 1967.

(94) KULLER, L., LILIENFELD, A. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. Circulation 34: 1056–1068, December 1966.

(95) KURIEN, V. A., OLIVER, M. F. Serum-free-acids after acute myocardial infarction and cerebral vascular occlusion. Lancet 2: 122–127, July 16, 1966.

(96) LANE, N. E., OBERMAN, A. The thousand aviator study: Smoking history correlates of selected physiological, biochemical, and anthropometric measures. U.S. Naval Aerospace Medical Institute, NAMI–961. Under the Joint sponsorship of the U.S. Public Health Service, and the National Aeronautics and Space Administration, NASA Order R–136, April 27, 1966. 12 pp.

(97) LEREN, P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. Acta Medica Scandinavica (Supplement 466) : 1–92, 1966.

(98) LIKOFF, W., SEGAL, B. L., KASPARIAN, H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. New England Journal of Medicine 276(19) : 1063–1066, May 11, 1967.

(99) LUKE, J. L., HELPERN, M. Sudden unexpected death from natural causes in young adults. A review of 275 consecutive autopsied cases. Archives of Pathology 85(1) : 10–17, January 1968.

(100) MCDONOUGH, J. R., HAMES, G. G., GARRISON, G. E., STULB, S. G., LICHTMAN, M. A., HEFELFINGER, D. C. The relationship of hematocrit to cardiovas-