The distress or pain of angina pectoris and of acute myocardial infarction is consequent to ischemia. In angina pectoris the ischemia is transitory because of temporary disproportion between the blood supply and the myocardial requirements; in acute myocardial infarction the ischemia is prolonged and leads to the irreversible changes of necrosis. The actual stimulus at the nerve end-organs that give rise to the pain has not been identified with certainty. Sir Thomas Lewis termed it the "P factor." It has certain characteristics in common with lactic acid: it is acid, is destroyed by alkali and by oxidation, and develops most rapidly under oxygen deprivation and carbon dioxide accumulation.

The predisposing cause of these two conditions is coronary obstruction. Atherosclerosis is the most prevalent lesion. Syphilitic arteritis distorting the coronary ostia and rheumatic arteritis are next in frequency. Rarely, periarteritis nodosa, scleroderma, amyloid, hemorrhagic diseases, vegetations of bacterial endocarditis or tumors impinging on the ostia, emboli, and the arteritis associated with systemic infections may be responsible. Congenital malformations and trauma are sometimes encountered. The chief effect of these lesions is to interfere with coronary blood flow and to prevent an adequate blood supply to the myocardium.

Various factors greatly influence the degree of ischemia. Among these are the anatomic distribution of the coronary arteries, the localization of the atheromatous lesions and the rates of development of the lesions, and the compensatory collateral channels.

Anatomic Pattern of the Coronary Arteries: the Incidence and Localization of Arterial Occlusions

The 3 main coronary arterial branches, the left anterior descending, the left circumflex, and the right coronary vary from heart to heart in the relative size of the area they supply. Schlesinger classified hearts in 3 groups according to the anatomic distribution of these 3 arteries. In group I, comprising half the hearts in his series, the right coronary artery predominated in the blood supply of the heart, nourishing the right ventricle and a large part of the posterior wall of the left ventricle. In group II, comprising approximately one third of human hearts, the coronary artery blood supply was balanced between the right and left coronary arteries. The right coronary artery supplied the right ventricle plus the posterior wall of the interventricular septum, and the left coronary artery supplied the left ventricle and the anterior part of the interventricular septum. In group III, comprising one sixth of human hearts, the left coronary artery predominated and supplied more than the entire left ventricle and interventricular septum. In some instances the left coronary artery extended to the free surface of the right ventricle. There are various degrees of this preponderance of the left coronary artery. In the least marked form both the right coronary artery and the left circumflex coronary artery extend to the crux of the heart, and both terminate in parallel posterior descending branches. In other hearts the terminal branch of the left circumflex coronary artery constitutes the sole posterior descending coronary artery.

There is no great sex difference in the distribution of the groups although women evi-
ently have a somewhat disproportionately large number of the balanced group II hearts.

The degree to which these anatomic groups are hereditary and may be responsible for familial tendencies to myocardial infarction and angina pectoris is unknown.

Another variation in local anatomy of the coronary arteries that may significantly influence the effects of coronary occlusion is the presence or absence of a coronary artery to the area of the conus arteriosus (conus artery). The coronary vessel supplying this area may arise as a branch of the right coronary artery or as a separate, third, supernumerary coronary artery with its own ostium from the aorta. Because of its separate origin the conus artery is independent of obstruction so often found at or near the mouth of the right coronary artery. The conus artery also appears particularly suited as a collateral source of blood supply to the heart. Its direct communication with the aorta and its location between the main left descending and right coronary arteries make it a ready source of anastomotic connection between the aorta and the coronary arterial system distal to the zones in which the incidence of occlusion is highest. Furthermore, the low incidence of occlusions in the conus artery, lower than in the other coronary arteries, enhances its value as an effective pathway of collateral blood supply.

The presence of a large, third division of the left coronary artery was described in the Bantu and suggested by Brink as an explanation for the low incidence of angina pectoris and myocardial infarction in that race. Although the presence of this racial anatomic variation has been confirmed, it is not associated with significant anastomotic circulation between the left and right coronary arteries and does not appear to be of primary importance in the lowered incidence of clinical manifestations of coronary disease in this race.

**Pathologic Characteristics of Coronary Arteriosclerosis**

Coronary artery occlusions are limited to the 3 main coronary arteries and their primary branches, and are almost entirely epicardial. The highest incidence of occlusions is not directly at the mouth of the vessel but a short distance distal to the mouth. One half are within 3 cm. and 70 per cent are within 4 cm. of the coronary ostia. The lesions are mostly localized and segmental. In a study of almost 200 occlusions of the main coronary arteries and their branches in a series of 400 hearts, 64 per cent were less than 5 mm. in length and 40 per cent were less than 3 mm. in length. More than half of all the occlusions were in the main stems; the remainder were in the primary branches. Fibrosis and calcification may involve not only the intima but also the entire media. Occlusions in affected hearts tend to be multiple. In 100 consecutive hearts with occlusions, there were 248 occlusions or an average of 2.5 occlusions per heart. Only 33 of these hearts had but 1 occlusion.

Atherosclerotic narrowing or occlusion of a coronary artery may be caused by an atheroma with progressive fibrosis, by a superimposed thrombus, by intramural hemorrhage in an atheroma, or by rupture of an atheromatous abscess. Thus, in 6,800 consecutive autopsies, thrombosis on an arteriosclerotic basis (43 per cent), occlusions due to arteriosclerosis per se (41 per cent), and intramural hemorrhage (8 per cent) presumably on an arteriosclerotic basis made up 92 per cent of the causes of occlusion, with the remaining 8 per cent distributed among embolism, inflammation, and syphilis.

The arteries are metabolically active structures that may be altered even in the absence of atherosclerosis. They participate, as do other tissues, in the aging process. The media, initially made up of circular, smooth muscle and elastic fibers, and the adventitia, a meshwork of connective tissue containing elastic fibers, both lose elastic fibers with age. These changes are most rapid in the left anterior descending artery and slowest in the right coronary artery. Fibroelastic changes occur in the intima and media, atrophy of the smooth muscle is seen in the media, and irregular patches of connective tissue develop.
Comparison of Blood Supply to Skeletal and Cardiac Muscle

The circulation of the heart presents many interesting differences from the rest of the body. Skeletal muscle on vigorous contraction can increase its oxygen consumption 30 or more times. This vastly increased requirement is met in part by an increase in arterial and capillary blood flow and in part by greater extraction of oxygen from each unit of blood passing through the capillaries. Thus, the oxygen content of venous blood, which is approximately 12 volumes per 100 ml. with skeletal muscle at rest, may be reduced to 5 volumes per cent or less on exercise. This ability to borrow on the "reserve" oxygen is not enjoyed by the heart. Under normal conditions the venous blood of the coronary sinus contains only 2 to 5 volumes per cent of oxygen. There is little to borrow and so the heart must "pay as it goes" by increasing the coronary arterial blood flow proportionately when the myocardium needs more oxygen to do more work. Skeletal muscle is also different in that it can continue to contract during exercise, even if the oxygen supply is momentarily inadequate, by incurring an oxygen debt which is repaid later during rest. The myocardium, however, cannot do this; it depends for its contractility on the oxygen immediately available in the coronary blood. It ceases to contract when it has incurred only one fifth of the oxygen debt skeletal muscle can endure.

Skeletal and cardiac muscle also present an interesting difference in their vascular supply. The smaller arteries and arterioles of striated muscle communicate freely with each other by large anastomotic vessels. Except for sudden occlusion of large trunks such as the brachial, iliac, or femoral arteries, infarction of skeletal muscle is rare. The coronary arteries, on the other hand, are end arteries in a physiologic or functional sense. It has gradually become the consensus that the connections that exist normally among the coronary arteries are only fine communications of an arteriolar or capillary nature, which are less than 40 μ in diameter. These intercommunications, while of some limited functional value, are not sufficient to prevent infarction of the myocardium when coronary arteries are ligated experimentally in animals or are suddenly occluded by thrombi or emboli in man.7,8

Obviously, therefore, anatomic patency of the coronary arteries is of cardinal importance in the maintenance of normal cardiac nutrition and performance. The very large extraction of available oxygen by the normal heart, the inability of the myocardium to incur a sizable oxygen debt, and the fact that coronary arteries are functional end arteries in the normal heart make it necessary that any significant increase in oxygen need by the heart be met by an increase in coronary blood flow.

Failure to meet the demands of the myocardium as a whole may lead to congestive heart failure; ischemia of certain areas may lead to the clinical symptom of cardiac pain or disturbances of impulse formation and conduction in the form of arrhythmias; if the ischemia is sustained, actual injury or necrosis of heart muscle, i.e., myocardial infarction, may develop.

Effect of Acute Coronary Occlusion

When a coronary artery is suddenly and completely occluded in a previously normal heart, a myocardial infarct is usually produced. This sequence is observed experimentally and clinically. The coronary arteries consequently must be considered to be end arteries in the physiologic sense.8 The size of the infarct, however, is always less than the total territory supplied by the artery.9 This difference is related to the fact that minute intercoronary capillary and arteriolar connections less than 40 μ in diameter are normally present. These may be readily demonstrated in the normal heart upon injection of a colored watery solution into a coronary artery by its immediate appearance in other areas of the heart that are supplied by the other coronary arteries. The peripheral border of the infarcted muscle may be supplied by blood oozing through these fine channels.
or, as Wiggers maintained, by diffusion from the surrounding myocardium.

Within a minute following acute occlusion myocardial contraction diminishes progressively as ischemia continues. As the contractions become feeble, they are balanced by the intraventricular pressure, and the ischemic area expands paradoxically with each systole. The small collateral channels that normally exist in the coronary arterial system do not supply enough blood to support useful contractions for many minutes.

In an extensive study of 1,200 human hearts, the clinical manifestations were interpreted on the basis of the findings disclosed by the Schlesinger technic. By this technic, the coronary arterial system is injected with a lead-agar suspension which penetrates regularly as far as 40 μ in diameter. Only the larger intercoronary communications that have been demonstrated to be functionally important are delineated by this method.

In 9 per cent of normal human hearts, larger intercoronary communications, 40 μ or larger, may be observed. They are not sufficiently numerous to prevent infarction; however, clinical, electrocardiographic, and pathologic data indicate that the heart may recover without structural damage if the duration and degree of ischemia are not too great. Experimentally, myocardial ischemia produced by temporary occlusion of the main stem of a coronary artery for 40 minutes generally produces areas of irreversible damage and necrosis. At any time during or after occlusion, ventricular fibrillation or other arrhythmias may appear. Their development may well be related to differences in the gradient of oxygen potential.

**Effect of Gradual Coronary Occlusion: Importance of Intercorony Arterial Anastomoses**

In human hearts with old occlusions, intercoronary collateral channels of a size greater than 40 μ were observed in practically 100 per cent of cases. These collateral vessels served as a bypass or detour and supplied the myocardium distal to the area of marked narrowing or occlusion from neighboring unoccluded arteries. This anastomotic circulation evidently develops as a compensatory phenomenon in relation to marked arterial narrowing or occlusion.

These phenomena have been reproduced by the authors under controlled experimental conditions in the domestic pig, the coronary arterial tree of which is strikingly similar to that of man. Intercorony collateral channels of more than 40 μ may be seen within 24 hours after marked coronary narrowing but their rich development usually requires 7 to 21 days. After 5 to 12 days of preliminary narrowing, sudden acute occlusion of the narrowed artery no longer regularly results in death. Examination of the myocardium grossly and microscopically showed that these collateral channels not only permitted survival of the animal but at times protected the myocardium from serious damage. Somewhat similar results in dogs have been reported by others. Under favorable conditions the major portion of the coronary artery system can be gradually occluded with minimal or no infarction in the animals that survive.

The clinical counterpart of these experiences, i.e., the occurrence of complete coronary artery occlusions without myocardial infarction has been noted repeatedly. In a small series, Snow and his associates also observed gross infarction to be smaller than anticipated but they encountered no instance of complete occlusion without infarction. There is general agreement, however, regarding the prevalence of functionally important anastomotic channels in response to coronary arterial obstruction and their great protective value against myocardial damage.

In contrast to this general agreement regarding the development of extensive collateral channels in hearts with marked coronary narrowing and complete occlusion, divergent results have been reported regarding the incidence of sizable, functionally significant intercorony anastomoses in the normal heart. In an extensive series of over 1,500 consecutive normal hearts studied by the Schlesinger technic, the incidence of...
anastomoses was 9 per cent after exclusion of anemia, cardiac hypertrophy, valvular heart disease, and other categories in which hypoxia evidently leads to an increased incidence of anastomoses.\textsuperscript{10} Although this experience has been confirmed by many others\textsuperscript{9,17} certain observers using other technics have reported an incidence greater than 10 per cent. Laurie and Woods,\textsuperscript{18} indeed, alone among investigators, observed sizable intercoronary arterial anastomoses in 75 per cent of patients over 4 years of age and in only 23 per cent of patients with severe atherosclerosis.\textsuperscript{18} There is reason to believe that the role of anemia and technical differences in pursuing the study account for their aberrant results.\textsuperscript{4,10,19}

The development of intercoronary collateral vessels also can be demonstrated experimentally by measurement of retrograde flow and pressure from a severed main coronary branch. Immediately following abrupt occlusion of a main coronary branch, the retrograde coronary flow approximates 5 to 5.8 ml. per minute compared to control values of 2 to 3 ml. per minute and is relatively constant in any one dog for a few hours.\textsuperscript{7} Measurements of retrograde flow during temporary clamping of the other coronary arteries indicate that the latter are the major source of flow.

After long-continued obstruction of a coronary artery or a branch in an otherwise normal animal heart, the flow of blood from the cannulated end of the artery becomes quite large. It begins to increase within a few hours, may double within 2 days, and may become 3 to 4 times the control level within a week. Within a few weeks, the flows approximate the values for the normal rate of inflow before occlusion in that coronary artery or branch. The observation that the retrograde blood had the same content of oxygen and carbon dioxide as that in a systemic artery leaves no doubt that the collateral circulation is on the arterial side of the coronary capillary bed. The gradual augmentation of retrograde flow is attended by similar elevations of systolic and diastolic pressures in the peripheral end of the occluded coronary artery.

Observations of the heart post mortem in man are in accordance with these experimental studies and explain the apparent inconsistency between the presence of long-standing obstructive lesions, on the one hand, and the absence or relatively slight pathologic or clinical evidence of myocardial damage, on the other hand. Indeed the hearts of patients with angina pectoris may show one or more occlusions in 2 or even 3 main stems, a rich collateral development, and only scattered myocardial fibrosis.\textsuperscript{20,21} While there is a general relationship between the incidence of coronary occlusion and the occurrence of angina pectoris, other modifying factors such as the exact site of the occlusion, the importance of the vessel involved, the adequacy of the collateral circulation, the rate at which such occlusions or narrowings develop, the temporary influence of emotion, exertion, and vasomotor reflexes are also of great importance. Although damage to the heart is minimized by the development of the collateral circulation, the margin of safety or, as it may be termed, "the coronary reserve" is reduced.

**Augmentation of Coronary Blood Flow by Medical Measures**

Augmentation of the coronary collateral circulation beyond that occurring naturally following marked coronary narrowing or complete obstruction inevitably is limited because the extent of the natural development appears to be well nigh maximal and marked in the area where it is most effective. Vaso-dilator drugs have not been demonstrated to accelerate the rate of development or augment the extent of the intercoronary anastomoses.\textsuperscript{22} In grossly normal hearts from anemic patients the incidence of anastomoses was 39 per cent compared to 9 per cent in grossly normal hearts from nonanemic patients.\textsuperscript{10,19} Anemia may conceivably have some therapeutic application in the treatment of coronary artery disease but its application seems hazardous and to date its practical use has not been feasible.
Augmentation of the coronary collateral circulation after a program of exercise has been observed experimentally by Eckstein after coronary occlusion in the dog. ²³ Although the clinical implications are important, they do not afford a therapeutic approach of major proportions. Furthermore, exercise in dogs with coronary artery occlusions was attended by increased risk of myocardial damage and death. ²³ It is a plausible assumption that relative anoxia is the factor that stimulates the formation of the collateral circulation after coronary obstruction, in anemia, exercise, cardiac hypertrophy, and cor pulmonale. ¹⁰, ²²

The Question of Vasomotor Control of the Coronary Circulation

"Spasm" of the coronary arteries with diminished blood flow has also been invoked frequently to explain the precipitation of episodes of angina pectoris. Attacks of angina brought on by exposure to cold or "by a disturbance of mind" ²⁴ and prevented or terminated by nitroglycerin are difficult to explain solely on the basis of long-standing anatomic changes in the coronary arteries or myocardium. Spasm could result from a direct effect of epinephrine or other circulating substances on the smooth muscle of the arteries, or it could be induced by vasomotor reflex impulses. The vast accumulation of experimental observations of coronary vasoconstriction in animals cannot be transposed to man with assurance, but recent observations in patients with angina pectoris now afford strong evidence of the existence and significance of vasomotor influences. Vasomotor reflex changes account in part at least for the effects on anginal attacks of atropine, local chilling, and anesthesia of the hands, carotid sinus stimulation, tobacco smoking, pulmonary emboli, and gastrointestinal disorders. Indeed, reflex coronary vasomotor spasm may be important in increasing the extent of myocardial necrosis and the mortality following acute coronary artery occlusion. ²⁵

The existence of vasomotor effects that reduce coronary flow is in no way incompatible with the demonstration and importance of widespread pathologic changes in the hearts of patients with angina pectoris. The primary etiologic factors of coronary obstruction, valvular disease, and arterial hypertension are not to be considered the exclusive cause of cardiac pain; rather they constitute the stage upon which various transitory precipitating factors may operate. Thus, coronary vasoconstriction, anemia, tachycardia, fever, hypermetabolism, or hypotension may act as precipitating agents in the production of pain in a patient whose coronary circulation is already compromised by arterial obstruction.

In the absence of an adequate pathologic substrate, these factors rarely, if ever, are sufficient in themselves to produce angina pectoris. In a series of 1,200 patients studied clinically and at postmortem examination by injection of the coronary arteries not a single instance was found of angina pectoris in the absence of structural heart disease. ²¹

Summary

Some of the unique physiologic characteristics of the coronary circulation have been pointed out. In the normal heart, the coronary arteries are functionally end arteries. Watery injections, however, reveal anatomic fine anastomotic communications between the coronary arteries measuring less than 40 µ. But they are of limited functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion. Complete occlusion or considerable narrowing of one or more coronary arteries may exist without giving rise to any clinical signs or symptoms and without having produced myocardial damage. The apparent inconsistency between the presence of long-standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage is dispelled by the demonstration of a collateral circulation which serves as a bypass in relation to the obstruction in each of these hearts. The pathologic and physiologic substrates of angina pectoris, coronary failure, and acute myocardial infarction have been discussed.
**Symposium on Coronary Heart Disease**

Es signalate certes del distinctive características del circulation coronarí. In le corde normal, le artérias coronarí es—ab le puncto de vista de lor function—arterías terminal. Tamen, injectiones aqüose revela le presentia anatomic de finissime communicantes anastomotic inter le artérias coronarí. Le diametro de iste communicantes es minus que 40 μ. Illos es de signification functional, a grados restrin- gite, in tanto que illos servi a obviar le adverse effectos de un subite constreccion o occlusion coronarí. Le complete occlusion o un restriction considerable de un o pluris de artérias coronarí pote existir sin occasionar ulle signo o symptom e sin provocar ulle injuria myocardial. Le apparente paradoxo del presentia possibile, durante prolongate periodos de tem- pore, de obstructive lesions arterial sin ulle resultante evidentia pathologic o clinic de injuria myocardial es resolvite per le demonstration de un circulation collateral que servi como detorno con respecto al sito del obstruction in tal corde. Le substratos pathologic e physiologic de angina de pectoris, disfallimento coro- nari, e acute infarcimento myocardial es discutite.

**References**

1. **Schlesinger, M. J.:** Relation of anatomic pattern to pathologic conditions of the coronary arteries. Arch. Path. 30: 403, 1940.
22. —, **and Norman, L. R.:** The effects of vasoactive drugs and of anemia upon interarterial anastomoses. Circulation 6: 832, 1952.

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