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Prognosis in coronary artery disease

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INTRODUCTION

Today heart disease ranks among the foremost causes of mortality and morbidity. Among the reasons for this is that the advent and use of chemotherapeutic agents and antibiotics have lessened the incidence of diseases caused by bacteria and other organisms. Another reason may be the increasing life expectancy of humans which accounts for a larger percentage of persons in the age when heart disease, especially coronary artery disease, is more prevalent.

Coronary artery disease is among the more common of heart ailments. There is a more or less generally accepted idea that the prognosis in this disease is most unpredictable. This is true in the respect that there are still found cases of sudden death with or without a previous history of the disease. However, the literature has many examples of statistics which show that a large percentage of persons with diagnosed coronary artery disease have survived for varying lengths of time. This favorable prognosis has been partly due to the advance in the understanding of the disease, its etiology, diagnosis and treatment.

In this thesis coronary artery disease refers to coronary arteriosclerotic disease which comprises about 90 per cent of all coronary artery disease. (1) The subject is treated under two broad divisions. The first part attempts to include the points that combine to give us the fullest understanding of the disease to the present time and includes its history, pathogenesis and pathology, classification and clinical picture, etiological factors and diagnosis and treatment. The second part discusses specific factors which affect its prognosis with the aid of the most recent statistics in the literature.

HISTORY

The history of our knowledge of the coronary circulation and the recognition and treatment of coronary artery disease shows a lack of understanding and interest in the subject before the last few decades. By the end of the sixteenth century the arteries had been seen and portrayed as the illustrations of Vesalius in the De Fabrica (1543) bear witness (2). However, it was only in the first half of the seventeenth century that Harvey's work gave some clear notion of their function as the nourishing vessels of the heart. Their importance in relation to heart disease was not appreciated because there was still felt the influence of the notion handed down from the time of Hippocrates that the heart was relatively immune to disease.

In the latter part of the seventeenth and early part of the eighteenth centuries more was learned about the anatomy of the arteries. Lower (1631-1619) studied the coronaries showing their anastomoses by experimentally injecting one artery from the other. Several writers referred to ossification of these arteries and some noticed ossification associated with aneurysmal dilatation of the heart. In general, however, these

writers did not bring out clearly the functions of the coronary arteries and did not realize that the changes in the size, contour and working efficiency of the heart were largely due to the inability of the diseased arteries to properly convey nourishing blood to the heart muscle.

In 1763, Heberden gave his classical description of angina pectoris. Nothing has been added to this syndrome. He and his contemporaries, Jenner and Parry, attributed this disorder to disease of the coronary circulation. This group must get credit for the earliest productive work on the coronary arteries and their relation to angina pectoris. Theirs was the myocardial ischemia theory of angina pectoris.

The first half of the 19th century showed a striking lapse of interest in this subject. The second half of that century saw three papers that deserve mention. These are Weigert (1880), Cohnheim and Schultless-Rechberg (1881) and Huber (1882). These papers included descriptions of thrombotic and embolic obstructions resulting in atrophy of cardiac muscle and showed the relation of heart failure and sudden death to coronary artery disease and proposed the theory that anginal pain was due to anoxemia. Adam Hammer of Vienna placed the first

antemortem diagnosis of coronary occlusion on record in 1878. George Dock in 1896 recorded the first American case. During this time the concept of the coronary circulation was that of Hyrtl who in 1879 announced that anastomoses existed only through the capillaries. This opinion was vigorously confirmed by Conheim in 1883.

Interest in the disease continued to be low in the first two decades of the twentieth century. However, two important contributions were made which were to spark interest in the disease from the third decade to the present time. The first was in the field of anatomy. Spalteholz (3) in 1907 demonstrated that there are not endarteries in the coronary circulation but that there are abundant anastomoses. The second was the record of a case of coronary thrombosis by Herrick (4) in 1912.

Herrick (2) gives some reasons why before 1920 interest in the coronary arteries and its relation to diseases of the heart was low. (1) There was acceptance of the views of Rokitansky and Virchow that softened areas or fibrous patches in the myocardium were primarily inflammatory in nature. (2) Experimental work on dogs showed that sudden death resulted from coronary obstruction and so there was lack of interest by the clinician. (3)

(3) There was the belief that absence of physical signs denoted a healthy heart. (4) The unity of coronary disease was hidden by a variety of misleading terminology such as angina pectoris, cardiac neurosis, infarct of the myocardium, rupture of the heart, acute and chronic myocarditis, acute and chronic heart failure, fatty degeneration, partial aneurysm of the heart and pericarditis. (5) The attention of the world at the end of the nineteenth century was diverted by the discoveries and interest in bacteriology.

From 1920 to the present time great interest has been shown in coronary artery disease. We shall merely make mention of the important aspects that have held and are now holding attention to this subject because these will be considered in later parts of this thesis as important contributions to our knowledge of the disease. These include in the field of diagnosis: electrocardiography and more recently ballistocardiography; in treatment: management of the patient and use of anticoagulants and advances in treatment of the complications; and also studies of series of cases with statistics on the survival and mortality.

PATHOGENESIS AND PATHOLOGY

Coronary artery disease results from impaired circulation in the sclerotic arteries with resulting impaired blood supply to the heart wall. Before we consider this, let us review the normal anatomy and physiology of the coronary arteries. The right and left coronary arteries arise from the sinuses of two of the cusps of the aortic valve. Each artery in its course divides into large and small branches. In a balanced circulation the right coronary artery supplies all the right ventricle except its left anterior third, the right half of the posterior portion of the left ventricle and the posterior portion of the interventricular septum. In addition it supplies the posterior papillary muscle of the right ventricle and posterior papillary muscle of the left ventricle and sends branches to both auricles and to most of the neuromuscular conduction system. The left coronary artery supplies the left anterior third of the right ventricle, the anterior portion of the interventricular septum and all of the left ventricle except the right half of its posterior portion. It also supplies the anterior papillary muscle and portions of the posterior papillary muscle of the left ventricle,

the anterior papillary muscle of the right ventricle, the left bundle branch of the conduction system and sends some branches to the surface.

There are certain changes and adaptations in the coronary arteries during life. At birth both sides of the heart are equally vascularised and anastomoses are negligible. With increase in years, the total vascularisation in increased in the left heart and decreased in the right. During this time, anastomoses are increased in both sides. After thirty years, extensive anastomoses become evident. Anastomoses continue to increase with age and also with valvular and other heart disease. Important studies bearing out the anastomotic possibilities of the coronary arteries have been done by Prinzmetal and Simkin (5), Blumgart et al (6) and others. As the anastomotic by-passes and possibilities do not seem so well established in the younger individuals, they may suffer more serious consequences than older people in whom anastomoses are more important.

The fundamental basis of coronary artery disease is arteriosclerosis. We include here the basis of 90% of all coronary artery disease, the group with which this thesis deals. The ultimate cause of arteriosclerosis

is not known. Studies tend to show that cholesterol is an important factor but this knowledge has not yet been utilized to prevent the disease ~~of~~ or affect its course. Moon and Rinehart (7) studied the coronary arteries of 250 individuals dying suddenly from traumatic or natural causes. They found that many different histopathologic processes participated in the development of coronary arteriosclerosis. The earliest changes which occurred, even in infants, were increased fibroblastic activity, deposits of mucopolyssacharide and degeneration of elastic tissue. These changes were not related to lipid deposition. Moderately advanced lesions were characterised by regeneration of elastic tissue, formation of collagen and lipid deposition. The far advanced lesions showed hyalinization, abundant lipid deposition, calcification, intramural hemorrhage and thrombosis. This study brings out the evolution of atherosclerosis, the form of arteriosclerosis which is found in coronary arteries. It also illustrates that many persons live with coronary atherosclerosis but do not have clinical manifestations of coronary artery disease.

Paterson suggests that other factors besides atherosclerosis or complicationg it play a major part in the production of coronary artery disease. He had done

considerable work on this for some years and his concepts are widely accepted. According to his work, capillaries are produced in the intima of the coronary arteries because of the extra nutritional requirements of an abnormally thickened intima in the atherosclerotic process. Under certain conditions hemorrhage may take place in these intimal capillaries and may result in any of the following: (1) coronary artery spasm (questionable) (2) acceleration of the atherosclerotic process (3) coronary occlusion from massive intimal hemorrhage (4) initiation of coronary thrombi. Other less frequent causes of coronary artery disease are: (1) simple thrombosis on an atherosclerotic plaque (2) rupture of an atheromatous abscess (3) embolus from elsewhere.

Coronary artery disease is established with a decrease in blood supply to any part of the heart wall. This decrease is caused by narrowing due to atherosclerosis with spasm or occlusion. This results in anoxemia which may be temporary and cause no necrosis or fibrosis or it may be more severe with occlusions of small branches causing small scattered areas of necrosis and fibrosis, or there may be occlusions of a large artery causing a large infarct with necrosis from endocardium to pericardium.

Blumgart (1) explains the healing process after acute myocardial infarction. In the first week following occlusion there is necrosis of muscle and infiltration by polymorphonuclear leukocytes, followed in the next five weeks by removal of necrotic muscle and replacement by connective tissue. There is massive formation of connective tissue in three months. During this time rupture of the heart may be the cause of death.

CLASSIFICATION AND CLINICAL FEATURES

It was pointed out in the history that interest in coronary artery disease may have been lacking before the third decade of this century because of the confusion of terminology. However even at the present time the terminology identifying various phases of the disease is confusing. Boas (9) discusses the subject under (1) angina pectoris, (2) coronary insufficiency without and with myocardial infarction and (3) coronary artery occlusion without and with myocardial infarction. Niehaus (10) suggests that coronary artery arteriosclerotic disease should be recognised as a progressive disease and that the symptoms and pathology are dependent on the stage and exact situation which produces symptoms. Therefore he suggests the following classification:

I Angina pectoris

II Coronary insufficiency

III Acute coronary occlusion

A brief discussion of the pathology and clinical features of the above classification follows.

I Angina pectoris. This is now usually accepted as a clinical entity indicating a decreased and inadequate coronary capacity from narrowing of the lumen of the coronary arteries without occlusion, thrombosis or infarction. It is to be differentiated from the term angina pectoris or anginal syndrome used to designate the pain from all phases or stages of coronary artery disease and also from conditions independent of arteriosclerosis of the arteries which cause similar pain e.g. disproportion between the coronary vascular bed and myocardial hypertrophy from vascular disease, anemia and occlusion of the ostia of the coronary arteries from syphilitic aortitis. The clinical features include typical anginal pain of short duration occuring with physical effort or emotion. The pain has been variously described as oppressive, uncomfortable, vise-like, sometimes crushing, boring or burning but not sticking. The location is usually substernal but may be over the left pectoral muscles near the apex of the heart. The pain commonly radiates to the left shoulder and along the inner aspect of the arm. Less commonly the pain radiates to both shoulders and arms, to the jaw, teeth, interscapular area or the the epigastrium. In angina

pectoris there is usually absence of other physical or laboratory findings. Electrocardiographic changes may be found during attacks.

II Coronary insufficiency. This term was proposed by Masters (12). The coronary circulation is inadequate. There may be and usually are occlusions of small branches of the coronary vascular tree. These may be gradual and cause diffuse disseminated focal areas of necrosis and fibrosis in the subendocardium and papillary muscles. There is the characteristic pain as in angina pectoris. The onset of pain is usually with effort and emotion, rarely at rest. Pain is of moderate severity and lasts from hours to days. There usually are found other associated clinical and laboratory signs such as shock, dyspnea, increase of pulse rate, fall in blood pressure, fever, leukocytosis and electrocardiographic changes.

III Acute Coronary occlusion. This stage of coronary artery disease is the sudden complete closure of a large branch of a coronary artery resulting in massive confluent infarction frequently extending from endocardium to pericardium. There is serious interference with cardiac function. Clinically this presents a severe type of heart attack which may terminate fatally.

There is usually the characteristic anginal pain with onset at rest, severe and lasting for days to weeks. There may be a feeling of impending death. Other clinical symptoms are frequent-- shock, tachycardia, fall in blood pressure, gallop rhythm, changes in heart sounds, vomiting, fever, leukocytosis, increased sedimentation rate and characteristic electrocardiographic changes.

It is necessary to review the complications of coronary artery disease because the prognosis can be influenced by their prevention or their recognition with efficient treatment and management. The complication in a small percentage of cases may be the initial manifestation of a coronary occlusive episode (13). Of the causes of death in coronary artery disease the larger percentage is due to cardiac causes which are chiefly a result of the complications. Sigler (14) found 83.5% and White et al (15) 76% of mortality in patients who had coronary artery disease was due to cardiac causes.

Arrhythmias and conduction disturbances. Arrhythmias and conduction disturbances are frequent complications of the coronary occlusions. Occasionally an

arrhythmia is the initial or perhaps the only sign of the presence of an acute coronary occlusion. Certain factors which may be present in coronary occlusive disease are of etiological significance in arrhymias. These include anoxemia, decreased nutrition of cardiac muscle, disturbed autonomic nervous reflexes, increased irritability of the myocardium, anatomical lesions and heart failure. Masters (16) in an analysis of 300 cases of acute coronary occlusion found 25% incidence of premature beats, 7.3 % of auricular fibrillation, 1% auricular flutter and 3% of paroxysmal supraventricular and ventricular tachycardia. Simple prolongation of PR interval, second degree partial block, complete heart block and intraventricular conduction disturbances are among the conduction disturbances seen. Smith (17) in a study of 920 cases of acute myocardial infarction found some form of arrhythmia in 16.3%. Of these there were 7.7% with premature beats, 4.8% with auricular fibrillation and the rest included auricular flutter, complete heart block and nodal and ventricular tachycardia.

Heart Failure. Congestive heart failure ia a common late sequel in patients with coronary artery disease and a frequent cause of invalidism and death. Often left

ventricular failure precedes congestive heart failure and is recognised by the characteristic symptom of dyspnea. Heart failure may occur immediately after a myocardial infarction and may be temporary or permanent depending on whether compensation is complete after healing of the infarct. More commonly, heart failure appears many years after onset of anginal symptoms and after the patient has experienced several episodes of myocardial infarction. A small percentage of patients with acute myocardial infarction have congestive failure preceding the acute episode. Smith (17) in his series of 920 cases of acute myocardial infarction found an incidence of 16.9% of cases in which congestive heart failure was a complication.

Thrombo-embolic phenomena. Following an acute episode of myocardial infarction, thrombo-emboli may arise secondary to endomural thrombi, shock or phlebothrombosis of the lower extremities or pelvis. The exact incidence of thrombo-embolic phenomena in coronary artery disease is unknown and varies widely in the reported series from 9% to 60% (13). Thrombo-embolic complications arise after an acute episode with the peak incidence in the first two weeks followed by rapid decrease after that, although they may be found as late as the 6th week.

Among the complications are pulmonary infarction, cerebral embolus, phlebitis, mesenteric embolus, splenic and renal infarcts and emboli to extremities.

Cardiac aneurysm. Myocardial infarction is followed by fibrous transformation of the myocardium and in turn this may be followed by aneursym. The usual site is in the ventricles and occasionally in the interventricular septum. The aneursym begins as an acute lesion and if rupture does not follow it becomes chronic. The aneursym may be reinforced by pleural-pericardial adhesions about the lesion or the formation of a fixed thrombus in the aneursym. It may be followed by heart failure. The first heart sound may be weak. X-ray may show an enlarged heart.

Cardiac rupture. There is an incidence of about 9% of cardiac ruptures in cases of acute myocardial infarction (18). It occurs most frequently in the age range from 65 to 75 years. The site of rupture is usually limited to the left ventricle and interventricular septum. Wessler and his associates (15) found that rupture takes place where the infarction is transmural and in an area poorly supplied by collateral circulation and in which fibrosis is entirely absent in some part.

There was found to be a decrease in cases with episodes of myocardial infarction in which fibrotic scars of the myocardium are expected to exist. These workers found that patients with persisting hypertension or excessive effort usually had ruptures. Consequently there was a higher incidence in women because they have a greater incidence of hypertension.

ETIOLOGY

A number of predisposing and precipitating factors have been found to be concerned in the production of coronary artery disease. It is important for the clinician to be aware of these for they may be of great help in diagnosis, treatment and prevention as far as this is possible.

Age. Although coronary artery disease has been found in isolated cases in children and in a small percentage in advanced age, the greatest incidence in in the 5th, 6th, and 7th decades. Sigler (14) and Parker and his associates (19) in their large series of cases found the peak incidence in th 6th decade. Recent studies of the disease in patients below 40 years have been made by Gertler et al (20) Newman (21) and Smith (22). The majority of these patients had a family history of coronary artery disease or hypertension, were of stocky build and had high blood cholesterol levels. Gertler et al (20) conclude that criteria can be drawn up for persons likely to have myocardial infarction before the age of 40.

Sex. It is common clinical observation that coronary artery disease is more common in men than in

women. In their large series Parker et al (19) found the ratio of men to women to be 4.3:1 while Sigler (14) found it to be 3.2:1. In women the disease is found to be more often in a slightly older age group than for males. Parker it al (19) found the average age at onset for women to be 58.0 years as compared with 56.9 years for men. Coronary artery disease is rare in women below 50. In studies of patients below forty, Gertler et al (20) and Newman (1) found the incidence of women to be 3% and 1% respectively. A greater percentage of women have diabetes mellitus or hypertension associated with coronary artery disease.

Habitus. Coronary artery disease appears to be more common in the florid, robust, obese and overweight. Several investigators have noticed that most younger patients are overweight. Smith (22) in his study of patients below 40 years with coronary occlusion found about one third were 20% overweight, one third about 10 percent overweight, and the remainder of normal weight or underweight. Garn et al (23) found that in this same age group when patients with myocardial infarction were compared with controls that both patients and controls were overweight according to tables of normals. Heyer (24) in his study of patients of all age groups concluded that

tables of normal weight do not readily fit patients. However, he still felt that there seemed to be a definite relationship between obesity and coronary artery disease. He thought that the time elapsing between the onset of obesity and the onset of coronary artery disease was important and that during this period there were high lipid blood levels which may have some relationship to the development of the disease.

Heredity. Clinical observation discloses a strong familial tendency to the development of coronary artery disease (9). The development of atherosclerosis is especially apt to occur in persons both of whose parents are affected. The manner of hereditary transmission remains obscure. Recent studies indicate that a disturbed cholesterol metabolism may be inherited even in patients who do not evince the gross evedence of xanthomatosis and that in such families coronary atherosclerosis is common. (25). Dock (26) and Schlesinger (27) suggest that inheritance of a certain type of vascular architecture, namely the anatomic pattern of the coronary arteries, may determine the familial occurrence of the disease. Gertler et al (20) found that 27% of patients with coronary artery disease as compared with 14% of a control group

had parents with coronary artery disease and that 8.6% of siblings of patients as compared with 1% of siblings of the control group had the disease.

Hypertension. Coronary artery disease and hypertension are commonly associated but a causal relationship has not been established. A greater percentage of women with coronary artery disease have hypertension but yet the sex incidence of coronary artery disease is greater in men. The incidence of severe coronary artery disease is about the same for hypertensives of all ages, whereas among non-hypertensives there is a progressive increase in frequency of severe coronary artery disease with advancing years. Patients with severe hypertension and marked cardiac hypertrophy do not have more coronary disease than patients with mild hypertension. Patients with primary renal hypertension show less coronary disease than do non-hypertensives. There seems to be a relationship between heredity and existing hypertension in their association with coronary disease. Master (28) thinks that hypertension in women should be viewed as of some importance in future development of coronary disease or as influencing the outcome of existing coronary artery disease.

Diabetes. Approximately 10% of all patients with coronary artery disease have diabetes. Like hypertension, diabetes mellitus in encountered in a strikingly higher percentage of females with coronary occlusion than among males. Robinson (20) found 64.8% of diabetics with coronary occlusion were women while only 21.2% of non-diabetics with coronary occlusion were women. The development of atherosclerosis depends primarily on the duration of diabetes rather than on its severity. It becomes manifest in 8 to 10 years after the onset of diabetes. Thaler et al (30) found that patients with good diabetic control had onset of coronary artery disease after an average of 17.7 years duration of diabetes while patients with poor control after 12 years duration. However, they found that it was difficult to appraise the effect of diabetic control on the onset of coronary artery disease because other etiological factors must be taken into consideration. Robinson (29) suggests that diabetes should be suspected in all patients showing evidence of coronary artery disease because he found that 11 out of 54 patients did not know of the existence of their diabetes before the onset of coronary thrombosis. He also emphasized the increasing importance of coronary thrombosis as the cause of death in diabetic patients.

It has been found that other conditions which manifest hypercholesteremia are prone to be found associated with coronary artery disease. Among these are xanthomatosis and myxedema. Sudden death may result from coronary artery disease in xanthomatosis. In patients with myxedema with arteriosclerotic arteries, the administration of thyroid may induce symptoms of angina pectoris and may even cause death from cardiac infarction. The diseased and narrow arteries cannot respond to the need for increased blood flow that accompany the return of BMR to normal.

The race incidence of coronary artery disease shows a predominance among whites over negroes and among Jewish whites over non-Jewish whites. Occupation, tobacco, coffee, tea, alcohol, hard work and anxiety have not been shown to be important etiological factors in coronary artery disease (9).

DIAGNOSIS

The correct diagnosis of coronary artery disease is now being made more frequently. This makes for more adequate treatment and consequently a better prognosis.

Clinical features: The greater number of cases are correctly diagnosed by clinical history, symptoms, physical signs and laboratory finding. This is true for any stage of the disease. These features have been discussed in an earlier part of this thesis.

When an unusual type or location of pain is present, or other confusing manifestations, the differential diagnosis is important. These include (1) other cardiac conditions: acute pericarditis, neurocirculatory asthenia, dissecting aneurysm of the aorta, massive pulmonary embolism (2) non cardiac conditions: lesions of the cervical or thoracic vertebrae, inflammatory affections of the shoulders, herpes zoster of the intercostal nerves, acute abdominal conditions including ruptured peptic ulcer, acute cholecystitis, gall bladder colic and acute pancreatitis and other abdominal conditions including hiatus hernia, esophageal diverticula and cardiospasm.

X-ray: (31) The roentegenographic examination of the heart is a common procedure with patients presenting cardiorespiratory complaints. However, it is not often necessary to make a diagnosis of coronary artery disease

with it. Often there are no abnormalities. In those cases of acute myocardial infarction with X-ray evidence, there may be some degree of cardiac dilatation and a hazy outline to the cardiac silhouette. With fluoroscopy, pulsation of the left ventricular segment may be poor, and paradoxical pulsation may be present. Roentgen-kymographic and electrokymographic studies will usually show a systolic contractile pulsation.

Electrocardiography: The position of electrocardiography has become firmly established as an aid in diagnosis of coronary artery disease, and in following the outcome of episodes of acute myocardial infarction. In angina pectoris E.K.G. changes are seen if study is made during an attack of pain but this is not often possible because of the short duration of the attack. In coronary insufficiency E.K. G. studies can be made, but changes are not easily evident. Several tests have been devised to produce anoxemia of the heart muscle in the lowered coronary reserve found in angina pectoris and coronary insufficiency. The resulting anoxemia produces E. K. G. changes evident in the RS-T segment and T wave changes. The tests used to induce anoxemia include the anoxemia test, the exercise test, and less commonly the administration of epinephrine or pituitrin and exposure to cold. Mathers and Levy (32) state that these

tests should be employed only when the diagnosis is in doubt and that a positive result affords objective evidence of coronary insufficiency and that a negative result does not rule out the possibility of the coronary heart disease. In acute myocardial infarction there are typical E. K. G. changes according to the stage of the pathologic p process from the onset of infarction to replacement by fibrotic tissue. The changes are noted in Q wave, RS-T segment and T wave. The restitution of E. K. G. changes to the form before infarction may take place within varying periods of time after infarction.

Ballistocardiography: This is a comparatively new method of investigation of cardiac action and function. It employs a machine which records mechanical heart action. This action may be estimated by analysis of the amplitude, regularity, and definitiveness of the various wave patterns of the ballistocardiogram. Brown et al (33) made a study of patients with typical and atypical symptoms of angina pectoris who were also with or without evidences of cardiac abnormality. They concluded that studies of typical cases of angina pectoris established a definite relationship between this symptom complex and abnormal mechanical heart action as determined by the ballistocardiogram and that this relationship enables one to use the instrument as a diagnostic aid in the

atypical cases of angina pectoris.

Friedgerg (34) summarises the diagnosis of arteriosclerotic heart disease as follows:

(1) Clinical or E. K. G. evidence of a recent or past attack of myocardial infarction warrants a diagnosis of arteriosclerotic heart disease.

(2) E. K. G. abnormalities, including T wave inversions and S-T deviations, the presence of Q waves and auriculoventricular and intraventricular conduction disturbances often permit a presumptive diagnosis of arteriosclerotic heart disease if due regard is given to the age and clinical history of the patient and if other causes of such E. K. G. changes can be reasonable excluded.

(3) Angina pectoris usually denotes arteriosclerotic heart disease but less common causes of this syndrome must be excluded.

(4) Cardiac enlargement and congestive heart failure in middle aged or elderly subjects may suggest the presence of arteriosclerotic heart disease but these abnormalities should provoke a careful review of the history and findings on physical and E. K. G. examination in an effort to confirm the diagnosis or discover other etiologic factors.

TREATMENT

The treatment of coronary artery disease is concerned with the immediate relief of symptoms, prevention of extension of the pathologic process, prevention and treatment of complications and restoration of normal or nearly normal function of the heart. Theoretically it would be desirable to direct treatment against the basic cause, namely, arteriosclerosis, but as yet no definite progress has been made in this respect. (34)

Angina pectoris: Relief of pain usually is prompt with nitroglycerin which causes coronary vasodilatation, thus improving coronary blood flow. This drug is also used to prevent or anticipate attacks. During their daily routine patients often learn that a particular act or set of circumstances frequently precipitates an attack. Other medications for relief of pain in case of failure of nitroglycerin include inhalation of amyl nitrite and oral use of alcohol. In rare cases the use of drugs may be unsuccessful, while mechanical or surgical treatment may be effective. Levine (35) found that frequently anginal pain can be made to disappear in several seconds by massaging one or the other carotid sinus. Sympathectomy and sympathetic nerve block with alcohol have been found effective in some cases. Surgical procedures have been devised to improve

the circulation to the heart muscle but these are still in the experimental stage.

The general management of the patient with angina pectoris consists in the avoidance of factors which precipitate anginal attacks. These factors include certain physical activities, eating habits, exposure to cold and other activities. Patients rapidly learn what factors may precipitate an attack and learn to avoid them. The use of nitroglycerin in preventing or anticipating an attack has already been mentioned. It is now being greatly stressed that the patient's activities should not be restricted to the point of making him an invalid. The psychologic approach to the patient with angina pectoris is important. He should not be scared by the loose use of the term 'heart disease', which may result in instilling the fear of sudden death and voluntary invalidism.

In patients with frequent recurrences the use of sedation and other vasodilators such as the xanthine drugs are widely used.

Coronary insufficiency: The treatment of this phase of coronary artery disease is perhaps the most difficult as it may begin with the stage of angina pectoris and end with the stage of myocardial infarction (10).

Medication is like that outlined above for angina pectoris, and include xanthine drugs and sedatives. Following the onset of pain, the presence and extent of cardiac abnormalities should be a guide to restriction of activity and bed rest. Usually the patient should be at bed rest for about two weeks for observation to note if myocardial infarction develops. If this develops then treatment must be directed towards this. The subsequent management and therapy is dependent on the extent of cardiac injury. Restriction of physical activity can generally be expected to be greater than following angina pectoris.

Acute myocardial infarction: In this stage of coronary artery disease the patient is critically ill, and the prognosis may be significantly affected by the treatment. There are certain methods that meet with general acceptance and others that are not yet fully evaluated.

Relief of pain is of first importance and is best obtained by liberal use of morphine. Demerol is sometimes effective. These opiates serve also to abolish apprehension and shock (36). Vasodilators such as papaverine and aminophylline are often used to increase coronary blood flow. The administration of oxygen may

be of use. Borden et al (37) found that patients with uncomplicated myocardial infarction, that is without pulmonary edema or shock, had 94.1 percent oxygen saturation of hemoglobin, while those with these complications had 80.8 percent saturation. They concluded that oxygen administration is mandatory in patients with these complications and of questionable value in patients without them. Anticoagulants are now being widely used during the acute attack. However, their value is not universally accepted. Contraindications to their use include the presence of any of the following disease states in the patient: severe renal or hepatic insufficiency, jaundice, purpura or severe blood dyscrasias, postoperatively in brain or spinal cord cases, immediately after any major operation, open wounds and severe nutritional deficiency. Russek et al (38) classified patients with acute myocardial infarction as 'good risk' and 'poor risk' patients. They found a significantly greater mortality and greater incidence of thromboembolism in 'poor risk' patients and therefore suggest that anticoagulant therapy should be used with these patients. The criteria for 'poor risk' patients include one or more of the following: previous myocardial infarction, intractable

pain, extreme degree or persistence of shock, significant heart enlargement, gallop rhythm, congestive heart failure, auricular fibrillation or flutter, ventricular tachycardia or intraventricular block and diabetic acidosis or other complicating serious diseases.

The general management of the patient in the acute stage aims at providing complete mental and physical rest. Most workers have patients at complete bed rest for two weeks. Depending on cardiac signs, bed rest may be continued six weeks followed by convalescence of a few months. These are followed by an inventory of the physical assets and liabilities of the patient to determine how fully they can return to a normal life.

The prognosis of coronary artery disease has been significantly influenced by the recognition and treatment of the complications. The subject is receiving great attention at the present time and there is much yet to be learned. A discussion of the treatment of the complications is outside the scope of this thesis.

SPECIFIC FACTORS IN PROGNOSIS

Since the growth of interest in coronary artery disease during the last three decades, workers have been making statistical studies of series of cases with the aim of throwing light on the prognosis of this disease. In trying to evaluate these studies one encounters several problems. Some series are not large enough, some consider the survival rates of only patients who died during the period of study, some treat the different phases of the disease as separate entities, some have not had a long enough follow-up of patients. During recent years there have appeared some studies which have attempted to overcome some of these difficulties (14) (15) (16). The prognosis of coronary artery disease may be considered in two parts, the immediate and the ultimate prognosis

A. THE IMMEDIATE PROGNOSIS

The immediate prognosis refers to the outcome of an acute attack of the disease, usually a coronary occlusion, within about six weeks. This includes sudden death, especially when the syndrome of angina pectoris is present. Sudden death occurs in about 10 per cent to 15 per cent of cases (31). In a much larger percentage of cases death is not sudden but unexpected and

rapid, occurring within six weeks after a brief manifest attack of myocardial infarction. In the literature the immediate mortality varies from 25 to 45 per cent, depending on the status of the heart before the acute episode (39).

Age and Sex: The immediate mortality has been found by most observers to increase with the age of the patients. Billings et al (39), Smith (17), and Russek et al (40) found the immediate mortality of patients regardless of whether they had previous attacks of acute myocardial infarction or not, to be greater in the group over 50 years of age. Jacobs (41) in his series of cases without previous myocardial infarction, found that the mortality was significantly greater in the age group over 60 years. Russek et al (40) concluded that the higher mortality rate in older age groups was due to the greater frequency of serious attacks, probably as a result of senile deterioration of the myocardium. They found that when individuals were grouped according to 'poor' and 'good' risks there was no difference in mortality in the different age groups.

Most observers find that the immediate mortality is greater among women (31) (14). At the same time it is found that they belong to an older age group

compared with the men. Therefore the conclusion is reached that the greater mortality in women is due to the fact that they belong to an older age group.

Previous myocardial infarction: Sigler (14) found in his large series of 1700 cases that in about 50 per cent manifestations of coronary artery disease developed over months to years, while in the other 50 percent the onset was abrupt in the form of a coronary occlusion. However, even in the latter group some patients gave a history of antecedent vague digestive disturbances and other unexplainable symptoms for a variable period before the acute episode. There is disagreement among observers as to the effect previous angina pectoris has on the immediate prognosis of an attack. Most observers find that a history of previous attacks of acute myocardial infarction carries a higher rate of immediate mortality than an initial attack. Billings et al (39) found 36.4 percent immediate mortality after the first attack of acute myocardial infarction as compared with 53.6 percent in patients with previous attacks. Smith (17), Master et al (42), and Woods and Barnes (43) found that previous myocardial infarction carried a poorer immediate prognosis.

Congestive heart failure: Patients with congestive heart failure prior to or during attacks have been

found to have a poor immediate prognosis. Some degree of heart failure is found in a certain percentage of patients with acute myocardial infarction and is evident by some or all of the following: dyspnea, pulmonary congestion and edema, hepatomegaly, and peripheral edema. Billings et al (39) found an incidence of 47 per cent of patients with acute myocardial infarction who had congestive failure. The mortality rate of this group was 55 percent as compared to 30 percent in the group without congestive failure. Levine and Rosenbaum (44) found that the mortality increased with increasing severity of congestive failure.

Shock and Blood Pressure: The degree of shock and fall in blood pressure affects the immediate prognosis (39) (41) (44). An extreme degree of shock, or shock persisting after several days makes the immediate outlook poor. A fall in blood pressure to 80 mm Hg. or less is considered unfavorable. When hypertension exists prior to the attack, the fall in blood pressure appears to alter the prognosis but little, if at all.

Pain: The prognostic significance of pain is in doubt. Billings et al (39), Jacobs (41), and Chambers (45) found no effect on immediate prognosis with location, radiation or degree of pain. Chambers (45) and Russek et

al (40) found that intractable precordial pain and epigastric pain carried a greater mortality. Observers have recorded a small percentage of cases of acute myocardial infarction without pain, 3 to 10 percent (39) (44)(46). Billings et al (39) and Levine and Rosenbaum (44) noticed that the mortality was higher in cases without pain. Papp (46) found that cases without pain but associated with heart failure had a poor prognosis.

Other clinical and laboratory findings: Most observers find that the immediate prognosis is influenced by the pulse rate, temperature, white blood count, and the quality of the heart sounds. (39) (41) (43). Changes from the normal are usually found in these in patients with acute myocardial infarction. The degree of the change is of prognostic significance. A pulse rate of 110 or higher per minute, leukocytosis of 15,000 or over, and fever above 101 degrees are found to carry a poor prognosis. Pericardial friction rub, gallop rhythm, 'weak' or 'poor' quality of heart sounds are the auscultatory abnormalities, excluding arrhythmias, that are found associated with myocardial infarction and seem to carry a poor prognosis. Neither Chambers (45) nor Levine and Rosenbaum (44) found that the height of the erythrocyte sedimentation rate had any influence on the prognosis.

Arrhythmias and E. K. G. changes: Electrocardiography may be of help in prognosis. In some patients no electrocardiographic abnormalities are found, and in these there is a more hopeful immediate outlook (44). The arrhythmias carry a poor prognosis. Smith (17) in his series of 920 cases of acute myocardial infarction found 58.3 per cent mortality in patients with ventricular tachycardia and 50.3 per cent in patients with complete heart block, with lower rates for patients with auricular fibrillation and nodal tachycardia. Wood and Barnes (43) found that very frequent ventricular extrasystoles carried a poor prognosis, because they may lead to ventricular tachycardia. Observers are not agreed as to the prognostic importance of the location of the myocardial infarction as shown by electrocardiography.

Thromboembolic complications and anticoagulant therapy: The presence of thromboembolic phenomena makes the immediate prognosis worse. Smith (17) in his series of 731 patients with acute myocardial infarction treated without anticoagulants found an incidence of 19.4 per cent of patients with thromboembolic complications and a mortality of 42.2 per cent of this group with these complications as compared with a mortality of 19.8 per cent for those without these complications. Mintz and

Katz (47) in their series of 572 cases of recent myocardial infarction found an incidence of 9.9 percent of patients with thromboembolic phenomena, with a mortality rate of 55.8 per cent in this group.

Many recent studies show that the use of the anticoagulants, dicumarol and heparin, has reduced the immediate mortality (17) (49) (50). However, other workers, like Rytand (48) in a critical review of the studies done, doubt the favorable effect of the use of the anticoagulants on the prognosis. The American Heart Association's Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction (49) (50) in their study of 1000 patients up to 1949 concluded that the use of anticoagulants reduced the immediate mortality. Smith (17) in his group of 731 patients with myocardial infarction treated without anticoagulants had an incidence of 19.4 per cent with thromboembolic phenomena with 42.2 per cent mortality in this group, and an overall mortality of 19.8 per cent for the total 731 patients. In his group of 189 cases of myocardial infarction treated with anticoagulants there was an incidence of 7.9 per cent with thromboembolic complications, and a mortality of 14.2 per cent in the whole group of 189 cases.

B. THE ULTIMATE PROGNOSIS

The ultimate prognosis refers to the survival period after the onset of the disease, the survival after recovery from an acute attack and the degree of restoration of activity. Sigler (14) in his series of 1700 patients studied over a period of 25 years found that the shortest survival was three hours in a case of acute coronary occlusion with no previous history of coronary artery disease and the longest survival was 35 years of age and who finally succumbed at 70 years of age with acute coronary occlusion. The average length of survival for the patients who died during the study was 4.7 years for males and 4.5 years for females; for patients still living the average length of survival was 5.3 years for males and 5.6 years for females. White et al (15) in their series of 500 patients followed over 23 years found the average survival period for patients who died during the study was 7.9 years and for living patients was 18.4 years giving an average for both living and dead of 9.5 years. Parker et al (19) made a follow-up study to 1946 of 3440 patients with a diagnosis of angina pectoris in the period 1927 to 1936. Block et al (51) in 1952 made a forther follow-up study of the cases of Parker et al and added 3442 patients with a diagnosis of angina pectoris in the period from 1936 to 1947, making a total of 6882 cases with a minimal follow-up of 5 years.

The findings of Block et al as to factors affecting ultimate prognosis are in close agreement with those of Parker et al. Block et al found the 5 year survival rate of the total series was 58.4 per cent as compared with 86.9 per cent for the normal population and the 10 year survival was 37.1 per cent of the series as compared with 70.4 percent for the normal population. These were determined by the actuarial method and the 5 year and 10 year survival periods were calculated from the time of diagnosis at the clinic. The average duration of angina pectoris prior to diagnosis at the clinic was 2.5 years with the range being 0 to 10 or more years. One third of the patients were seen at the clinic within one year of the onset of symptoms and more than one half within two years.

Age and Sex: Block et al (51) in their total series of patients who died and who were alive during the period of study found the 5 year survival for females was 66.8 per cent as compared with 55.9 per cent for males and 10 year survival for females 49.0 per cent as compared with 34.2 per cent for males. White et al (15) found the 3 year survival of 84 per cent for females and 78.5 per cent for males and 14 or more years survival of 13.3 for females and 9.6 per cent for males. Sigler (14) found the 5 and 10 year survival rates to be essentially the same for both sexes whether he considered the patients

who died or were still living at the time of the study. Block et al (51) found the 5 and 10 year survival rates were highest in the younger age group and dropped consistently with an increase in age and also found this to be consistent with normal survival rates. When the survival rates were adjusted for normal death rates, they were about the same in each decade. They concluded that the prognosis for length of survival was not affected by age. White et al (15) in their curve of life expectancy found that the normal expectancy curve was steeper than the expectancy curve for patients with angina pectoris indicating that the prognosis for length of survival was poorer for younger patients. These studies throw doubt on the influence of age and sex on ultimate prognosis. The largest series, that of Block et al (51), indicates that the prognosis is better for females, and is not affected by age.

Previous and subsequent myocardial infarction: Block et al (51) found that patients with previous myocardial infarction or with subsequent myocardial infarction following survival of an acute attack had a poorer ultimate prognosis. Patients with previous myocardial infarction had 46 per cent 5 year and 26 per cent 10 year

or more survival as compared with 58.4 per cent 5 year and 37.1 per cent 10 or more years survival for all patients with coronary artery disease. Patients with subsequent myocardial infarction had 41 per cent 5 year and 22 per cent 10 or more years survival.

Congestive heart failure: Congestive heart failure during or following an acute attack of coronary aftery disease carries a poor prognosis for longevity. White et al (15) found that of 100 patients dead within 3 years 22 per cent had congestive heart failure while none of 52 patients who lived 14 years or more had congestive failure. Block et al (51) found 20.2 per cent 5 year and 8.0 per cent 10 or more years survival for patients with congestive heart failure. Billings et al (39) in a smaller series found a large percentage of patients unable to return to their previous occupation had congestive failure.

Cardiac hypertrophy: Cardiac hypertrophy carries a poor prognosis for longevity. White et al (15) found 83 per cent of 100 patients who died within 3 years had cardiac enlargement and only 40.3 per cent of the 52 patients alive 14 or more years had cardiac enlargement. Block et al (51) found that patients with cardiac hypertrophy had 41.4 per cent 5 year and 19.7 percent 10 or more years survival while patients without cardiac hypertrophy had 64.2 per cent 5 year and 39.3 per cent 10 or more years survival.

Hypertension: The presence and the degree of hypertension have an unfavorable effect on longevity. White et al (15) found that there was 42 per cent of patients with hypertension among those who survived up to 3 years while only 13.4 per cent of patients surviving 14 or more years had hypertension. Block et al (51) graded the degree of hypertension according to fundus examination and found patients with normal fundi had 63.3 per cent 5 year and 40 per cent 10 or more years survival. Patients with grade I hypertension had corresponding 61.2 and 32 per cent survivals, grade II 46.1 and 17 per cent, grade III 21.6 and 1.3 per cent and grade IV no 5 year or 10 or more years survival.

E. K. G. changes and arrhythmias: The presence of arrhythmias and the E. K. G. changes following survival of an acute attack of coronary artery disease seem to have prognostic significance on longevity. Block et al (51) using only the standard limb and one precordial lead, which were the only leads used when their study started, found that patients with normal E. K. G. had 73.1 per cent 5 year and 50.0 per cent 10 or more years survival. In comparison 5 and 10 or more years survival for patients with inverted T1 and T2 were 29.1 and 10.6 per cent; with complete heart block 20.0 and 0 per cent; with auricular fibrillation 27.0 and 13.5 per cent; and

with left bundle-branch block 36.6 and 13.9 per cent. White et al (15) found E.K. G. changes and arrhythmias in 32 per cent of patients surviving up to 3 years and in 17.3 per cent of patients surviving up to 14 or more years. Mills et al (52) in a study of the E. K. G. of 100 patients who survived up to 6 years after acute myocardial infarction found 77 per cent had little E. K. G. restitution, 14 per cent with partial restitution (without S-T segment deviation) and 7 per cent with complete restitution. All the patients had resumed their previous occupations. Heart failure was the only clinical condition found in the group with little restitution. They concluded that the E. K. G. pattern after infarction did not prognostocate the length of survival of patients. However, since heart failure carries a poor prognosis and was found in a greater percentage of patients with little E. K. G. restitution, they felt that in this respect electrocardiography was of help in prognosis.

Other factors: Block et al (51) found that of the diseases usually associated with coronary artery disease diabetes mellitus and neoplasms carried an unfavorable prognosis for longevity. They did not find that obesity carried an unfavorable prognosis. However they thought that this point should be investigated further.

SUMMARY

1. A review of the literature is made to study coronary artery arteriosclerotic disease with special reference to its prognosis. The first part of this thesis deals with the history, pathogenesis and pathology, classification and clinical features, etiological factors, diagnosis and treatment of the disease. The second part deals with specific factors in prognosis.

2. Although the coronary circulation and pathology of the arteries had been studied and observed before the beginning of the 20th century, it is only in the last three decades of this century that great interest has arisen in this disease and great strides made in understanding its pathology, diagnosis and treatment.

3. The anatomy of the coronary arteries and coronary circulation are described. The life history of the arteries shows increasing vascularity of the left ventricle and increasing anastomoses in advancing age. The fundamental basis of coronary artery disease is arteriosclerosis, the ultimate cause of which is not known, although cholesterol metabolism is considered to be an important factor. Angina pectoris results from narrowed arteriosclerotic vessels in association with certain etiological factors causing anoxemia. Coronary insufficiency has the

added factor of several small infarctions due to occlusion of small branches. Acute myocardial infarction results from occlusion of large arteries. Occlusion may be caused by intimal hemorrhage, simple thrombosis or atherosclerotic plaques, rupture of an atheromatous abscess or embolus from elsewhere. Myocardial infarction is followed by fibrosis unless death results before healing is complete.

4. The classification of the disease is based on the recognition of the disease as progressive in stages. The classes are angina pectoris, coronary insufficiency, and acute coronary occlusion. The clinical features of each class is described.

5. Certain factors are found to be predisposing or precipitating causes of coronary artery disease. The disease is found more often in the older age group, in males, in the white race and in the stockily built. The common association of the disease with hypertension and diabetes, especially in women is noticed but a causal relationship to these diseases is not established. Diseases manifesting hypercholesteremia are prone to be associated with this disease. Occupation, tobacco, coffee and tea, alcohol, hard work and anxiety have not been shown to be important causes of this disease.

6. The majority of cases of this disease are diagnosed

by the clinical features. It is important to make a differential diagnosis when the clinical manifestations, such as pain, are unusual. Electrocardiography is of help in diagnosis. Characteristic changes are seen in acute myocardial infarction. Less characteristic changes are seen in coronary insufficiency. In angina pectoris no changes may be seen unless studies are done during anoxemia, exercise or other tests. X-ray and fluoroscopy may show some changes which may aid in diagnosis. Mention is made of the comparatively recent use of ballistocardiography.

7. The treatment of this disease is discussed as to the specific treatment of symptoms and the general management during and after the acute manifestations of the disease. A short period of eight to ten days of rest and observation is necessary after the onset of acute coronary insufficiency to note if myocardial infarction occurs. In acute coronary occlusion, during the acute stage, treatment is directed towards relief of pain and shock, if present, and the reduction of heart load by complete mental and physical rest. Mention is made of the use of vasodilators, oxygen and anticoagulants during this stage. After the acute stage general management consists of treatment of complications and continued rest for a period of time.

8. The immediate prognosis refers to the outcome within six weeks after an acute attack and includes sudden death. Sudden death occurs in 10 to 15 per cent of cases. Mortality within six weeks varies from 25 to 45 per cent. The factors that seem to affect the immediate prognosis are age, sex, history of previous myocardial infarction, congestive heart failure, shock, blood pressure, pulse rate, temperature, leukocytosis, quality of heart sounds, thromboembolic complications and arrhythmias. The significance of pain and the use of anticoagulants is discussed.

9. The ultimate prognosis refers to the outcome after the acute stage is passed in terms of length of survival and restoration of activity. Studies of large series of cases followed over a long period of time are reviewed. Factors affecting the ultimate prognosis are age, sex, history of previous or subsequent myocardial infarction, congestive heart failure, cardiac hypertrophy, hypertension, electrocardiographic changes, arrhythmias, and the associated diseases of diabetes and neoplasms.

CONCLUSIONS

The outlook for patients who may develop or who have coronary artery disease, on the basis of arteriosclerosis, is not gloomy. This is due to increase in the general understanding of the disease, its pathogenesis, pathology, clinical features, etiology, diagnosis and treatment. As greater progress is made in the study of the disease the outlook should improve. Meanwhile the search for the basic cause of arteriosclerosis should be steadily pursued.

The immediate outcome of the disease in an individual still carries an element of unpredictability, since there are still found patients who die suddenly at the onset of the disease or during an acute episode. When this element of unpredictability is excluded, certain factors are shown by the majority of observers to affect both the immediate and ultimate prognosis. In so far as these factors can be controlled the outlook for patients should be brighter.

BIBLIOGRAPHY

1. Blumgart, H. L.: Coronary disease: clinical-pathologic correlations and physiology. Bull. N.Y. Acad. M. 27: 12 693-710, 1951.

2. Herrick, J. B. A Short History of Cardiology. Springfield, Illinois. Thomas 1952, Chap. IX.

3. Spalteholz, W. : Die Arterien der Herzwand, Leipzig, 1923.

4. Herrick, J. B.: Clinical features of sudden occlusion of the coronary artery. J.A.M.A. 59: 2015-2020, 1912.

5. Prinzmetal, Myron and Simkin, Benjamin: The collateral circulation of the human heart. Mod. Con. C. V. Dis. 15: 10 (Oct) 1946.

6. Blumgart, H. L., Schlesinger, M.J., Zoll, P.M.: Angina pectoris, coronary failure, and myocardial infarction: the clinical importance of inter-coronary collateral circulation. Mod. Con. C.V. Dis. 10: 6, 1941.

7. Moon, H.D., Rinehart, J. F.: Histogenesis of coronary arteriosclerosis. Circulation 6: 481 (Oct.) 1952.

8. Paterson, J. C.: Factors in the production of coronary artery disease. Circulation 6:732-739 (Nov) 1952.

9. Boas, E. P., Boas, N. F.: Coronary Artery Disease. Chicago. Yearbook Publishers. L949. Chaps. 8-12.

10. Niehaus, F. W.: Management of coronary heart disease. Nebr. State Med. J. 36: 47 (Feb.) 1951.

11. Goldberger, Emanuel: Heart Disease: its diagnosis and treatment. Philadelphia. Lea and Febriger. 1951.

12. Masters, A. M.: Acute coronary disease. Am. J. Med. 2: 501-506 (May) 1947.

13. Chambers, M. S., Johnson, R. E., Knzonis, M. C.: Complication of coronary occlusive disease. J. Mich. M. Soc. 50: 1402-1409 (Dec.) 1951.

14. Sigler, L. H.: Prognosis of angina pectoris and coronary occlusion: follow-up of 1700 cases. J.A.M.A. 146:988, 1951.

15. White, P. D., Bland, E. F., Miskall, E. W.: The prognosis of angina pectoris. J.A.M.A. 123: 801, 1943.

16. Masters, A. M., Dock, S., Jaffe, H.: Disturbances of rate and rhythm in acute coronary thrombosis. Ann. Int. Med. 11: 735, 1937.

17. Smith, F. J.: Myocardial infarction: a study of the acute phase. J. Mich. M. Soc. 50: 1388, 1951.

18. Wessler, Stanford, Zoll, P.M., Schlesinger, M. J.: The pathogenesis of spontaneous cardiac rupture. Circulation. 6:334, 1952.

19. Parker, R. L., Dry, T. J., Willins, F. A., Gage, R. P.: Life expectancy in angina pectoris. J.A.M.A. 131: 95, 1946.

20. Gertler, M.M., Garn, S,M., White, P. D.: Young candidates for coronary heart disease. J.A.M.A. 147: 621, 1951.

21. Newman, Maurice: Coronary occlusion in young adults. Lancet p. 1045-1047 (May) 1951.

22. Smith, J. G.: Coronary occlusion before the age of forty. N. C. Med. J. 13: 1, 1952.

23. Garn, S. M., Gertler, M. M., Levine, S. A., White, P. D.: Body weight versus weight standards in coronary artery disease and a healthy group. Ann. Int. Med. 34: 1416, 1951.

24. Heyer, H. E.: The lifetime weight curve and coronary artery disease. South M. J. 45: 428, 1952.

25. Boas, E. P., Parets, S. D., Adlersberg, David.: Hereditary disturbance of cholesterol metabolism: a factor in the genesis of atherosclerosis. Am. Heart J. 35: 611, 1948.

26. Dock, William: The predilection of arteriosclerosis for the coronary arteries. J.A.M.A. 131: 875, 1946.

27. Schlesinger, M. J.: Significant variations in the anatomic pattern of the coronary vessels, in Moulton, F. R. (ed.): Blood, Heart and Circulation. Am. A. Adv. Sc. Pub. 13: 61 (Washington, D.C.: Science Press, 1940)

28. Masters, A. M.: Relationship of hypertension to the onset of coronary occlusion. Bull. N.Y. Acad. M 28: 608, 1952.

29. Robinson, J. W.: Coronary thrombosis in diabetes mellitus. N. Eng. J. M. 246:332, 1952.

30. Thaler, R. W., Wornas, C. G.: Coronary arteriosclerosis in diabetics, Am. J. Digest. Dis. 19: 33, 1952.

31. Friedberg, C. K.: Diseases of the Heart. Philadelphia. Saunders. 1950. page 441.

32. Mathers, J. A. L., Levy, R. L.: The prognostic significance of the anoxemia test in coronary heart disease. Am. Heart J. 43:546, 1952.

33. Brown, H. R. Jr., Hoffman, M. J., DeLalla, V. Jr.: Ballistocardiographic findings in patients with symptoms of angina pectoris. Circulation 1: 132, 1950.

34. Friedbeeg, C. K.: Diseases of the Heart. Philadelphia. Saunders. 1950. p. 439-350.

35. Levine, S. A.: Clinical Heart Disease. Philadelphia. Saunders. 1951 Chap. 6.

36. Gilbert, N. C.: Treatment of coronary thrombosis. Mod. Con. C. V. Dis. 15: 6, 1946.

37. Borden, C. W., Ebert, R. V., Wilson, R. H.: Anoxia in myocardial infarction and indications for oxygen therapy. J.A.M.A. 148:1307, 1952.

38. Russek, H. I., Zohman, B. L., White, LaV. G., Doerner, A. A.: Indications for dicumarol in acute myocardial infarction. J.A.M.A. 145: 390, 1951.

39. Billings, F. T., Kalstone, B. M., Spencer, J. L., Ball, C. O. T., Meneely, G. R.: Prognosis of acute myocardial infarction. Am. J. Med. 7: 356, 1949.

40. Russek, H. I., Zohman, B. L., Doerner, A.A., Russek, A. S.: Age and survival in cases of acute myocardial infarction. J. A. M. A. 147: 1731, 1951.

41. Jacobs, T. P.: The initial attack of acute myocardial infarction. Ann. Int. M. 34: 114, 1951.

42. Masters, A. M., Jaffe, H. L., Dock, S.: The treatment and the immediate prognosis of coronary artery thrombosis. Am. Heart J. 12: 549, 1936.

43. Woods, R. M., Barnes, A. R.: Factors influencing immediate mortality after coronary occlusion. Am. Heart J. 24:4, 1942.

44. Levine, S. A., Rosenbaum, F. F.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. I. Immediate prognosis. Arch. Int. Med. 68: 913, 1941.

45. Chambers, W. N.: Acute myocardial infarction. N. England J. Med. 235: 347, 1946.

46. Papp, Cornelio: Acute cardiac infarction without pain. Br. Heart J. 14: 250, 1952.

47. Mintz, S. S., Katz, L. N.: Recent myocardial infarction: an analysis of 572 cases. Arch. Int. Med. 80: 205, 1947.

48. Rytand, D. A.: Anticoagulants in coronary thrombosis with myocardial infarction. Arch. Int. Med. 88: 207, 1951.

49. Wright, I. Sl, Marple, C. D., Beck, D. F.: Anticoagulant therapy of coronary thrombosis with myocardial infarction. J.A.M.A. 138: 1074, 1948.

50. Wright, I.S., Marple, C. Dl, Beck, D. F.: The use of anticoagulants in the treatment of myocardial infarction. Mod. Con. C. V. Dis. 18: 55, 1949.

51. Block, W. J., Crumpacker, E. L., Dry. T. J., Gage, R. P.: Prognosis of angina pectoris: Observations in 6882 cases. J.A.M.A. 150: 259, 1952.

52. Mills, G. Y., Simon, A. J., Cisneros, F., Katz, L. N.: Myocardial infarction: Observations on 100 patients who survived up to 6 years. Arch. Int. Med. 84: 632, 1949.