Subintimal atheromatous disease localized at the orifices and bifurcations in the coronary arteries is responsible for the most serious and ominous and the most common clinical pictures of cardiovascular disease. It is the most frequent single basic pathological process found in men with heart pain who have died prematurely and suddenly.

The clinical pictures produced are basically similar but vary according to the pathological anatomy but also according to the type of individual afflicted. Unfortunately the conditions may be entirely asymptomatic for varying periods of time and usually until late in the disease process after irreparable damage has been done.

Symptoms may be vague with merely inexplicable wariness, restlessness and anxiety or epigastric qualmishness, nausea, fullness and burning indigestion, particularly after a heavy meal. Choking smothering, tightness and shortness of breath, or unpleasant discomfort in the chest, deep chest organ, may develop. Vise-like constriction, or a sensation of a heavy weight or pressure in the substernal region or precordium, interscapular or shoulder region, radiating into the left arm are characteristic.

Physical signs are likewise absent until late in the disease. A slight increase in the aortic dullness in the retromanubrial area, accentuation of the aortic second sound and reverberation, with or without an aortic systolic murmur, in the presence of low blood pressure, all are suggestive of aortitis. From these signs we may infer that the process probably involves the coronary arteries. Radiographic and electrocardiographic studies reveal very little more.

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TYPES OF CORONARY FAILURE

When coronary insufficiency develops, the clinical picture of three types of anginal failure and one of congestive failure must be differentiated as associated with coronary artery disease: 1) Acute or Angina Pectoris; 2) Subacute, protracted coronary insufficiency or failure; 3) Persistent, acute, or subacute coronary occlusion; 4) Chronic diffuse coronary insufficiency.

1 - Classic angina pectoris occurs in certain types of individuals, as an excrutiatingly, sharp, precordial or substernal pain, brought on by one of the four E’s: exertion, eating, emotion, or exposure. The paroxysm lasts from a few to 15 minutes at the most, and the pain may radiate into the arm, and is dramatically relieved by nitroglycerin or disappears on rest. The patient assumes a statuesque attitude momentarily with his hand to the precordium. The blood pressure usually rises, and the aortic second sound is accentuated, and an aortic systolic murmur is present. Sometimes electrocardiograms made during an attack may show typical or atypical changes. Usually the electrocardiograms are normal. The patients develop no fever, leukocytosis, or increased sedimentation rate.

2 - Protracted anginal pain may result in intramural, subendocardial myocardial changes, or in a myocardial infarction, depending upon whether the coronary insufficiency is general or local. It may be the result of compression of the terminal coronary branches by increased intraventricular pressure of acute hypertension, or decreased systemic pressure and gradient of shock or hemorrhage, or a local obstruction of the lumen of a coronary artery due to occlusion of a plaque or a local thrombus or an embolus.

Coronary insufficiency due to anyone of these causes produces prolongation or persistence of pain. The mechanism may be determined by therapeutic tests which should be applied promptly and according to the blood pressure level. If elevated, nitroglycerin is given; and if depressed or low, whiskey should be used. Other vasodilators have been tried, including papaverine, aminophyllin intravenously, and tetraethylammonium chloride.

In coronary insufficiency with intramural ischemia, the pain may be temporarily relieved by nitroglycerin, and the electrocardiogram often shows depressed ST segments. The condition of subendocardial infarction develops gradually. Usually no fever and only slight, if any, leukocytosis or increase in the sedimentation rate develops.

3 - In coronary thrombosis the pain is usually not relieved by nitroglycerin or vasodilator tests, and morphine is usually necessary
to bring relief. This is indicated if the pain persists after 15 minutes or more. Characteristic progressive electrocardiographic signs are elevation of the ST segments and negativity of the T wave beginning in the terminal part, recorded in leads 2 and 3, or in 1 and 4, and in precordial leads.

4 - In chronic diffuse coronary insufficiency, generally called arteriosclerotic coronary heart disease, the symptoms and signs of myocardial insufficiency develop.

TREATMENT OF CORONARY FAILURE

Treatment must be both immediate or palliative and subsequent or corrective. Cardiac pain demands relief but the steps taken depend upon the clinical judgement and diagnosis. Acute paroxysmal cardiac pain may be angina pectoris, coronary insufficiency or thrombosis if prolonged. In angina pectoris the patient soon learns that stopping in his steps, and assuming a statuesque attitude and remaining absolutely motionless will bring relief.

The physician should immediately give nitroglycerin 0.3 mg. or 1/200 grain under the tongue, which usually brings relief promptly or aborts an attack. This dose may sometimes cause collapse. In patients with low blood pressure, alcoholic beverages may accomplish the same results more slowly, but more safely. After the pain has subsided, the patient should remain quiet at least ten minutes for every minute of pain.

Recognize and modify the precipitating factors, as effort to the point of fatigue, eating, emotional stress, strain, worry or anger, and exposure to sudden cold wind or rain. Steps must be taken to treat and correct progressive chronic illness, anemia, hemorrhage, or shock from trauma of a sudden severe type, surgical operation, or anesthesia, gaseous distention or overloading of the stomach, excessive drinking of alcohol or smoking tobacco. Any of these may bring on an attack, of cardiac pain.

Prevention of further attacks by the avoidance of all precipitating factors is a matter of primary concern. The removal of causative pathologic processes may be considered, but as a rule these cannot be successfully attacked. The treatment of these factors and those concerned in atheromatous disease has been touched upon in this paper.

Potential etiological factors must come in for some consideration even though at the present time little may be accomplished in their cure. The current trend in the management of coronary artery disease is to try to do something about it but particularly to remove the predisposing condition. Some of these, as obesity, may be favorably in-
fluenced by sharp restriction of fat intake and reduction of body weight. The control of diabetes mellitus, especially hyperlipemia and the maintaining of a normal acid-base balance, does much to postpone trouble. The hereditary factors, of course, cannot be changed in any individual.

Hypertension may be controlled by a very sharp restriction of the salt intake and as nearly an absolutely sodium free diet as possible. Vasodilators and vascular alteratives as aminophylline 0.3 grams (3 gr.) three times daily or 0.5 grams (71/2 gr.), by rectum, or potassium iodide saturated solution 10 drops three times daily, increasing a drop a dose a day, are the time honored remedies. The oral administration of niacin 50 mg. and niacinamide 50 mg. or doubling both of these helps some patients. Etamon (tetraethylammonium chloride), and priscol are still in the experimental state. The use of tobacco or nicotine in any form, is, of course, absolutely interdicted.

Syphilitic or athermatous aortitis or valvular disease, as aortic stenosis with or without insufficiency, in some cases seem to be ameliorated by potassium iodide. Aortic and mitral disease of rheumatic origin, in spite of very little history of rheumatic activity, are recognizable and usually irreversible. Valvular diseases, except in the acute stages, warrant the use of vasodilators, especially for pain or edema.

Prophylactic treatment may be carried out by the use of nitroglycerin at the very suggestion at the beginning of an attack or under circumstances which might precipitate an attack. Every attack should be aborted or cut short as soon as possible.

ACUTE CORONARY INSUFFICIENCY

The more recently recognized state of acute coronary insufficiency in which pain has persisted in prolonged attacks is accompanied by myocardial ischemia, which should be relieved promptly or prevented. The terminal branches of the coronary bed that come off at right angles from the main arteries, penetrate the myocardium and end just before reaching the endocardium may be compressed by high intraventricular pressure of hypertension. On the other hand, when the pressure in the systemic circulation falls suddenly in hemorrhage or shock, the pressure gradient drops off sharply in the coronary arteries; the circulation in the terminal branches may also be interrupted. The compression of the subendocardial arterioles should be promptly relieved or a precipitous drop in the general pressure should be overcome as quickly as possible. Such inadequate irrigation may produce irreversible myocardial changes, the so-called intramural diffuse infarction from prolonged anoxia.
If the seizure of cardiac pain is protracted, emergency steps should be taken to prevent coronary insufficiency and myocardial damage. The circulation usually responds better in such cases to whiskey than to nitroglycerin, because of the stimulating effect of alcohol tending to maintain blood pressure. Caffeine sodium benzoate, 0.25 to grams (33/4 gr. to 71/2 gr to 15) or nikethamide 1-5 cc. may be desirable as estimulants.

*Shock* should be combated with oxygen under 2 to 4 cm. water pressure, and injections of serum albumin or plasma; if hemorrhage has taken place, whole blood should be substituted to restore the blood volume. Oxygen, sedation and complete rest must be maintained. Adequate water balance should be established with 5 per cent glucose rather than normal saline. The general metabolism may be improved by saturation with vitamins and plasma proteins.

**Persistent pain** calls for narcotics, as morphine 15 mg. (1/4 gr.) intravenously, or demerol 25-50 mg. (1/3 to 2/3 gr.) intravenously. Papaverine 0.2 gram (3 gr.) may be used and may be repeated every 2 or 3 hours, and/or aminophyllin 0.5 gram (71/2 gr.) may be given intravenously. Atropine 1 mg. (1/65 gr.) is used to relieve the vagus reflex tone from gastric distention. Etamon (tetraethylammonium chloride) 1 to 5 cc. intravenously may be tried if the blood pressure remains high, and the paroxysms of pain recur.

_STATUS_ *anginosus* or a series of frequently recurring attacks may be interrupted by a course of intravenous niacin (nicotinic acid) injections of 100 mg. in 500 cc. of 0.19 per cent saline or 5 per cent glucose at a rate just sufficient to produce flushing, usually 1.5 to 2 cc. per minute. One infusion is given and 24 hours later a second; 12 hours later a third, and 8 hours later a fourth, and thereafter every 8 hours for 5 days. The course may be repeated if relief has not been obtained.

**Chronic coronary insufficiency** may also be improved by niacin intravenously. Alcohol 5 per cent in 5 per cent glucose, aminophyllin 0.5 gram (71/2 gr.) slowly intravenously and in suppository by rectum at 12-hour intervals have been found effective.

In acute *coronary thrombosis* emergency management is necessary. The acute excruciating pain must be relieved with morphine sulfate: 10 mg. to 30 mg. intravenously. If the patient is sensitive to morphine, use demerol 50 mg., and papaverine 65 mg. intravenously. Atropine sulfate, 1 mg., may be added as an antispasmodic. Repeat if necessary to relieve pain.

*Oxygen* administration by mask in as near 100 per cent concentration as possible is advantageous and often relieves pain and should be continuous in the presence of dyspnea, cyanosis, and pulmonary
edema. A mixture of diuretics as aminophyllin, 0.5 gram (71/2 gr.) in 25 to 50 cc. of 50 per cent glucose or alcohol 5 per cent in 5 per cent glucose may be given instead as a vasodilator with or without a mercurial diuretic, 2 cc., and ascorbic acid 0.3 gram may be given intravenously if there is cardiac asthma or pulmonary edema.

Serious coronary occlusion cases with massive myocardial infarction, critically low blood pressure or embolism are the indications for anticoagulant therapy.

If embolism occurs, given heparin intravenously intermittently in doses of 50 mg. of heparin in 5 cc. normal saline (1 cc. containing 10 mg.) intravenously every 4 hours or 100 mg. in 10 cc. of normal saline or in 5 per cent glucose by intravenous drip continuously, starting at 15 to 20 drops per minute. The rate is controlled by determining the coagulation time by the Minot-Lee method every 3 to 6 hours for 24 hours and then every 12 hours. The coagulation time should be maintained between 15 and 25 minutes. Heparin, 200 mg. in 2 cc. Pitkin’s menstruum may be given intramuscularly, but it causes much pain and often some bleeding. At the same time dicumarol should be started by mouth in a 300 mg. dose and the prothrombin level should be established. Give dicumarol 100 to 300 mg. daily after the morning prothrombin level has been determined and until 50 per cent of normal activity has been reached. Proceed more carefully after the prothrombin activity has been depressed to 50 per cent, giving 50 to 100 mg. each morning until a level of 30 per cent of normal prothrombin activity is reached. After reaching a 30 per cent level it is best to stop dicumarol for several days since the level of activity is likely to drop lower without further dosage. When the level again rises to 50 per cent. give 50 to 100 mg. daily, attempting to hold level between 30 and 50 per cent of normal. Maintain the prothrombin activity for four to six weeks, or certainly as long as the patient is in the hospital, and then discontinue the use of dicumarol unless evidence of thrombophilia.

If prothrombin activity gets below 30 per cent, watch for hemorrhagic phenomena, such as red cells in the urine, petechial spots or purpuric areas. Give 60 to 75 mg. of synthetic vitamin K intramuscularly or intravenously. Give a second dose in four hours, and repeat if bleeding persists. In the event of an alarming hemorrhage, give freshly citrated blood as often as it is needed. It is to be remembered that stored blood loses its prothrombin in from 24 to 36 hours.

If myocardial insufficiency intervenes, phlebotomy oxygen, under pressure, morphine, sedation, and digitalization must be carried out with care. A mercurial diuretic especially the new combination of thiomerin, has in our experience been most safe and most effective.
EXPERIMENTAL THERAPEUTICS

The age-old quest for the fountain of youth and its miraculous rejuvenating elixir is now being led by biochemical researchers in the search for more effective lipotropic, lipid mobilizers, or decholesterolizing substance. Dietary regimens, along with the sharp restriction of animal fat intake, are prophylactic measures, but the effects are usually not enough to control situations in which the abnormal chemical processes have gone on for years. The desired substance is one which would promptly decrease the lipid levels in the blood and thus delay the development of subintimal atheromatous plaques.

If the high blood cholesterol level can be reduced, it may contribute not only to halting the increase in size, but might possibly lead to the removal of part of the fatty substances from the subintimal pathologic deposition of cholesterol and cholesterol esters and some other lipids. This is really more than should be hoped for, since in long established plaques, degenerative changes, fibrosis and calcification have usually taken place and probably made the process practically irreversible. Some patients proven to have atheromatous disease have been shown to have had normal blood cholesterol levels. Hypercholesterolemia may be refractory to decholesterolizing agents.

In patients with hypercholesterolemia and coronary artery disease, the restriction of animal fats in the diet and the administration of potassium iodide and of thyroid extract have been shown to lower blood cholesterol levels after several months or years. The administration of choline, methionine and inositol has produced, in a majority of patients, some slight reduction of blood cholesterol levels and slight rises in lipid phosphorus after 2 to 6 months of treatment. Higher dosages of these parts of vitamin B complex from 10 to 20 grams may be the basic diet and are of considerable importance, and in some refractory cases the exhibition of high doses and other substances will probably be necessary to accomplish decholesterolization. The enzyme systems responsible for the mobilization and degradation of cholesterol to lecithins must be established.

SUMMARY

The present concepts of the factors concerned in the development of coronary atheromatosis and the clinical pictures that result have been delineated. The subintimal plaques in the coronary arteries are incriminated as basically responsible for the pathologic physiology. Possible new approaches to the prevention, postponement, arrest, or possibly decrease have been described.
Dietary restrictions of the sterol intake and the judicious use of potassium iodide and thyroid extract in selected cases seem to be justified. The success of administration of other lipotropic agents seems to have opened another promising method of therapeutic attack of the serious process of premature aging.

REFERENCES