REFRESHER COURSE FOR GENERAL PRACTITIONERS**CORONARY ARTERY DISEASE—II. TREATMENT**

BY

A. RAE GILCHRIST, M.D., F.R.C.P.*Physician, the Royal Infirmary, Edinburgh; Reader in Clinical Cardiology, University of Edinburgh*

As the causes of coronary sclerosis remain undetermined, a direct therapeutic approach is at present denied to us. There is as yet no conclusive evidence that such remedies as iodides, thyroid, sex hormones, choline, or vitamin E, which have been used in the experimentally induced arteriosclerosis of animals, retard or reverse the arteriosclerotic process in the human coronary tree. Nevertheless, when treatment is directed to the leading clinical manifestation much good can be done.

Although the three syndromes—angina pectoris, coronary insufficiency, and coronary thrombosis with infarction—overlap and may on occasion be difficult to distinguish, yet the methods employed in their treatment can be sharply defined. In each instance the objects should be to avoid the precipitating cause of the attack, to promote healing if myocardial damage has been sustained, and to prevent incapacitating and commonly fatal complications.

Angina Pectoris

Many factors contribute to attacks of effort pain. Attention should first be directed to body weight. The practitioner can obtain useful help from height and weight tables if he will weigh his patient and take note of the deviation from the theoretical standard for sex, age, and height. If obesity be reduced at a rate of 1 to 2 lb. (0.45 to 0.9 kg.) each week by the use of a low-calorie diet, a corresponding freedom in bodily activity is commonly observed and greatly appreciated by the patient. The aim should be to maintain weight within 10% of normality.

Even a minor degree of anaemia can contribute to the ease with which attacks of pain are induced. Haemoglobin determinations take only a minute or two. Treatment with iron or liver, according to the type of anaemia present, can be of immense benefit to the anginal patient.

There are other contributory factors. Foci of infection about the teeth or elsewhere should be corrected, tobacco should be interdicted for a month or two as a therapeutic trial, and efforts should be made by medical means to relieve dyspepsia whether it be peptic, biliary, or nervous in origin.

Exercise should be encouraged up to the limit of tolerance and needless restrictions should be avoided. In effect this usually means some reorganization of the way of life, but most patients soon discover their limitations and act accordingly. It is a good rule to recommend a short rest (thirty minutes or more) after each meal, an extra hour in bed each night, and half a day or more in bed each week. It is necessary to advise two to three weeks in bed only when anginal attacks are severe, exhausting, or increasing in frequency, or when an actual coronary thrombosis appears imminent.

It is important to instil a measure of confidence. Rest and reassurance are of value from this point of view, and in patients of nervous temperament and emotionally sensitive the gentle sedation derived from small doses of barbiturates has a definite place in treatment. Phenobarbitone can be given by mouth in doses of $\frac{1}{2}$ gr. (32 mg.) or more in tablet form twice or thrice daily. It is necessary to correct insomnia and relieve anxiety.

Glyceryl trinitrate in tablet form (1/400 to 1/50 gr.—0.16 to 1.3 mg.) is the drug of choice. Until its effects have been determined a small dose should be used. It must be allowed to dissolve in the mouth. When used in this way the action of the drug is at its height in two to three minutes and passes off within half an hour or so. It can therefore be used both for the relief of pain and for its prevention. Tablets of nitroglycerin, taken in anticipation of discomfort, do much to make life more tolerable for many sufferers from angina. When attacks are more frequent and difficult to anticipate a tablet can be sucked at regular intervals of an hour or two during the day; additional tablets can be taken should the necessity arise. The patient should be encouraged to use them freely with the object of preventing attacks.

Other drugs are seldom necessary and seldom as effective. Papaverine, in virtue of its prolonged antispasmodic action, is sometimes useful in the prevention of nocturnal attacks when taken by mouth at bedtime in tablets or powders containing $1\frac{1}{2}$ to 3 gr. (0.1 to 0.2 g.). Although commonly prescribed, there is little convincing evidence to justify the continued oral use of xanthine drugs such as theophylline in its various combinations in the day-to-day treatment of coronary sclerosis. Recently khellin, an extract of the seeds of an Eastern Mediterranean plant, has been shown experimentally to have coronary dilator properties. It has been given intramuscularly in doses of 50 to 100 mg. daily, and by mouth in tablets of 40 mg. or more thrice daily, but in anginal patients the reports on its use are conflicting.

Coronary Insufficiency

Coronary insufficiency depends for its effective treatment upon the correction of the precipitating cause. Undue physical or mental strain, intense enough to produce severe anginal symptoms, with the possibility of irreversible change in the deeper sub-endocardial layers, implies at least a week to ten days' rest in bed. Nitrites and sedatives may be used freely in these attacks, and opiates if necessary. Under other conditions different remedies will prove desirable. A paroxysm of tachycardia productive of anginal symptoms will require, in addition to rest and sedatives, digitalis or quinidine sulphate according to its nature. Normal rhythm may thus be restored and precordial

distress relieved. A hypertensive crisis may call for a free venesection, whereas a blood transfusion will prove necessary for the prompt relief of the myocardial ischaemia of post-operative shock or a massive haemorrhage.

For recurrent and severe anginal attacks at rest, when no precise exciting cause can be determined and when the response to full and repeated nitrite dosage is only partial and transient, resort may be made to division of the pain-conducting pathways either by the technique of paravertebral alcohol injection or by cervical sympathectomy on one or both sides. Neither procedure has yielded encouraging results in my experience.

Bold attempts to revascularize the impoverished heart muscle have also been practised. Grafts of intercostal muscle, lung, or omentum, supposedly carrying a fresh blood supply to the inadequate coronary circulation, have been used without much benefit. These procedures are largely experimental and the beneficial clinical results so far claimed lack conviction.

Conservative Treatment of Coronary Thrombosis

An attack of coronary thrombosis usually responds well to treatment aimed at the relief of pain, correction of shock, promotion of healing, and prevention of further thrombotic or embolic episodes and their complications.

For the excruciating pain, the restlessness, the paroxysmal dyspnoea, or the attack of acute pulmonary oedema there is no better drug than morphine ($\frac{1}{4}$ gr.—16 mg.) which may be repeated in half an hour if symptoms are not abating. In the most urgent cases $\frac{1}{6}$ gr. (11 mg.) of morphine diluted in 5 to 10 ml. of sterile water may be *slowly* injected intravenously. In doing so the injection should be stopped before completion if obvious relief is obtained or if the respirations are unnaturally slowed.

Shock may be countered by reassurance, warmth, and relief from pain and restlessness. Transfusion of 150 to 250 ml. of blood, plasma, or normal saline is sometimes justifiable if given very slowly to the worst cases, but there is always the danger of overloading the heart and inducing pulmonary oedema, itself a contraindication to an increase in blood volume. Nikethamide and leptazol (each 1 ml.) are commonly used intramuscularly. Their main influence appears to be the counteraction of respiratory depression.

There is sound justification for the use of oxygen, but to be effective in the relief of cyanosis, pain, and restlessness it must be delivered in high concentration (50 to 75%) at 6 to 10 litres a minute by B.L.B. mask or tent. Nasal catheters smeared with a local analgesic ointment are useful substitutes if comfortably tolerated. Oxygen therapy should be continued as long as the ashen-grey hue in the skin and nail-beds persists.

Rest in bed must usually be maintained for six weeks or thereabouts, and the more complete the inactivity during the first three or four days the better. During this time the patient should do nothing for himself. He is to be fed and washed; visitors must be excluded, and sleep ensured. Constipation can be encouraged for the first few days and the diet restricted to fluids and soft foods. When the acute symptoms have subsided increasing liberties may be granted. Patients can then begin to move about in bed, practise leg exercises, feed themselves, and be permitted the use of a bedside

commode in preference to all the inconvenience and discomfort of the bed-pan. In the presence of cardiac asthma or acute pulmonary oedema permission to leave bed and sit upright in a chair is a concession which has a physiological basis. The change of posture eases the respiratory and circulatory burdens, lessens fatigue, and makes for greater comfort. By the end of four weeks, massage and active movements should be in daily use preparatory to the patient getting up and moving about quietly in his room.

During the entire illness great care should be taken of the bowels. While constipation is usual and of advantage during the acute phase of the illness, thereafter the daily evacuation of a soft easy motion may be aided by an emulsion of liquid paraffin and agar (2 to 4 dr.—7 to 14 ml.) or small repeated doses of milk of magnesia (1 to 4 dr.). The addition of suitable quantities of fresh and dried fruit to the diet should be encouraged. Brisk purgatives and bulky enemata are exhausting and therefore better avoided.

It is not considered good practice to prescribe digitalis in the early weeks after an acute infarction. It is said to enhance the clotting tendency and to favour the development of abnormal rhythms, ventricular tachycardia in particular. On the other hand, its use is justified in the presence of congestive failure of sufficient degree to produce respiratory distress, particularly when the patient's state is obviously deteriorating. It is better given in moderate amount—1 to 2 gr. (65 to 130 mg.) of powdered digitalis thrice daily—rather than in massive doses. In these circumstances my preference is to select digoxin (0.25 mg. by mouth thrice daily), supplemented by mersalyl intramuscularly in doses of 1 ml. on alternate days—a combination very effective in clearing the lungs of oedema and congestion. Quinidine should be used only with electrocardiographic control for the arrhythmias.

Among hospital patients, treated as we believe under the best available conditions, conservative measures yield a mortality rate of 33% in this country.

Anticoagulants in Coronary Thrombosis

Heparin and "tromexan," begun early in the illness, are believed to owe their effectiveness to their ability to restrict the spread of the thrombus and thus limit the size of the infarct and prevent its extension. They reduce the tendency to deposition of thrombi within the ventricles and peripheral veins. Pulmonary and other infarcts are thus seldom encountered when anticoagulants are used efficiently. It may well be that these drugs have other actions of benefit to the patient stricken with an acute infarct. Increasing experience confirms their undoubted value and marks the use of these drugs as an outstanding advance in therapy.

Both are started simultaneously, heparin by injection and tromexan by mouth. The former, if given intravenously at six- to eight-hour intervals in doses of 10,000 units, will prolong the clotting time to 20 minutes, three or four times the normal value, an hour after the injection. It is usually necessary to continue heparin for only 24 to 36 hours, by which time the tromexan has generally produced a sufficient reduction of the prothrombin content of the blood.

Two doses of tromexan are given daily, usually at 12 noon and 8 p.m., a total of four 300-mg. tablets being taken by mouth on the first day of treatment.

Thereafter daily laboratory control is essential, the quantity of tromexan prescribed being adjusted from day to day with the object of maintaining the patient's prothrombin clotting time at a level two to two and a half times the control prothrombin time. There is unfortunately no clinical guide to tromexan dosage. The normal prothrombin time lies between 17 and 19 seconds, varying considerably with the technique employed. The effective therapeutic level therefore ranges between 34 and 48 seconds.

When tromexan yields a prothrombin time of 35 seconds or more, the injections of heparin are stopped. The tromexan is continued for four weeks from the onset, or for three weeks from any thrombo-embolic complication, whichever is the longer. The daily dose is regulated according to the laboratory report on the 9 a.m. prothrombin time for that day.

The response to the drug varies greatly from patient to patient and from day to day in the same individual, but, if the dose is regulated according to the standards advocated, difficulties are seldom encountered and serious bleeding is rarely observed.

Tromexan is a much safer drug than dicoumarol. Its dose is larger and more easily regulated, and on its discontinuation the prothrombin time returns to normal in 24 hours—an advantage should haemorrhage occur.

The haphazard use of these drugs without competent laboratory control cannot be too strongly condemned. The practitioner can always begin treatment with heparin in the patient's own home, but at present tromexan, which has replaced dicoumarol, cannot be used without daily estimations of prothrombin time, which is a laboratory procedure demanding the co-operation of competent technicians. Furthermore, continuous supervision, such as only the hospital can provide, safeguards the patient against the risk of serious haemorrhage by constant observation and ready availability of the blood bank.

Bleeding may be sudden and profuse. A transfusion may be required at short notice. Blood which has been stored for more than 24 hours is said to be less effective than fresh blood in the correction of the hypoprothrombinaemia. As the beneficial effect of a blood transfusion on the bleeding tendency may last only for two to six hours, repeated transfusion over a period of several days may be necessary. A prothrombin clotting time in excess of 75 seconds is usually regarded as a danger signal and an indication for vitamin K (intravenously), a dose of which may be repeated four-hourly until the prothrombin time is reduced to well within the therapeutic range.

It should be emphasized that anticoagulants are contraindicated, or at best used with great caution, in the presence of hepatic or renal disease, during pregnancy, or shortly after major operations. Severe anaemias also countermand their use. Peptic ulcer occasionally coexists with serious coronary disease. As fatal bleeding may occur from a duodenal or gastric ulcer, when the prothrombin time is reduced by tromexan the patient should be questioned about recent dyspeptic symptoms before anticoagulants are employed.

Treated in this way patients stricken with acute myocardial infarction make remarkable progress. They look better and feel better in a shorter space of time than those denied this form of treatment. Com-

plications are reduced, embolic phenomena are infrequent, convalescence advances more quickly (though advantage should not be taken of this to shorten the time in bed), and the mortality rate is reduced by more than half. It is therefore a method of treatment which should be made available for every sufferer from acute coronary thrombosis.

Other Syndromes

The arrhythmias of coronary origin are generally permanent, though auricular fibrillation in a paroxysmal form can recur frequently, prove difficult to prevent, and cause distress in virtue of the tachycardia. The continuous use of digitalis in regular courses of seven to ten consecutive days with three or four days' intermission between each often proves helpful, not so much in preventing attacks as in easing their distress by restraining the ventricular rate and thereby avoiding the embarrassment of the tachycardia. Complete heart-block is an irremediable condition, but recurrent Stokes-Adams seizures can be prevented by ephedrine, $\frac{1}{2}$ gr. (32 mg.), by mouth thrice daily.

A major problem in therapeutics is the rational treatment of acute left ventricular failure as manifested by attacks of paroxysmal dyspnoea (cardiac asthma) or pulmonary oedema. When precipitated by coronary thrombosis, shock (or peripheral forward failure) is combined with congestive or backward failure. In these circumstances the energetic treatment of the one may aggravate the other form of failure. For instance, a venesection may well be justified in many cases of acute pulmonary oedema, but if aggravation of the shock-like state occurs, with a further fall in blood pressure and a lowering of haemoglobin, the heart may be weakened further and the patient's condition be worsened. It is necessary to steer a middle course, using cautiously approved methods of known value. Morphine, $\frac{1}{4}$ gr. (16 mg.), is of great benefit. Wheezing denotes bronchospasm and may be taken as an indication for aminophylline, 0.5 g., administered intravenously over a five-minute period or by rectum in the form of a suppository when the distress is milder. Oxygen is indicated. If these measures are not helpful within half an hour, then, despite the presence of a possible infarct, 1 mg. of digoxin may be given intravenously, diluted in 5 to 10 ml. of normal saline, as a life-saving measure. To help unload the pulmonary oedema intravenous digoxin injections can usefully be combined with 1 ml. of mersalyl. A venesection is justified only when shock is absent or mild.

The methods employed in the treatment of the more chronic forms of congestive failure occurring in the course of arteriosclerotic heart disease do not differ significantly from those in common use. Adequate rest, the correction of insomnia, a low-sodium diet, digitalis according to tolerance, and mercurials intramuscularly are the main items which require to be adapted to the individual's particular requirements.

Recent tests on over 11,000 unselected persons of varying ages from all walks of life, using the Ishihara pseudo-isochromatic plates, have shown a colour-blindness incidence of 4.97% for Chinese males and 0.71% for Chinese females (*British Journal of Ophthalmology*, 1950, 34, 744). These figures are considerably lower than those previously produced from smaller scale investigations.