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CORONARY THROMBOSIS AND ITS RESPONSE TO TREATMENT*

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In its power to strike down those in the prime of life, coronary thrombosis, by its increasing frequency, may be regarded as the outstanding malady of our time. Thirty years ago it was a rarity even in pathological experience. To-day we count our cases in hundreds and pass on to the next.

Over these years diagnosis has been in the forefront, to the neglect of therapy. So it is that with instrumental aid the recognition and localization of the myocardial infarct have become progressively more and more refined. Only within the last few years has any material advance been made in the management of the patient stricken with so grave a malady. It is satisfactory to record at the outset that the days of "masterly inactivity" are being gradually replaced by a positive therapeutic programme which has halved the mortality rate and which opens the way to further endeavours on behalf of these patients.

Diagnosis

Before considering present trends in the treatment of the acute phase of the illness it is necessary to have in mind the clinical features of this particular form of coronary disease so that it may be distinguished from its immediate associates. Amongst many clinical entities there are at least three which have coronary sclerosis as a common denominator and require clarification.

Midway between the transient myocardial ischaemia of angina pectoris and the major attack of coronary thrombosis stands a group of cases notable for the ease with which spontaneous cardiac pain occurs at rest—pain longer and severer than the usual attack of effort angina and yet not as severe as the clear-cut episode of coronary thrombosis. To this group, so ably and clearly differentiated by Master (1947) and Master *et al.* (1949), the term "acute coronary insufficiency" is applied. The usual attack of angina pectoris is a manifestation of a temporary and local oxygen lack, too transient to imperil the muscle cells; acute coronary insufficiency is a severer grade of the same process which, when prolonged, leads to a diffuse myocardial asphyxia resulting in a speckled patchy necrosis, subendocardial in distribution. By contrast, acute coronary thrombosis leads to abrupt interruption of blood flow with the formation of a circumscribed myocardial infarct.

Few practitioners can be unfamiliar either with the dramatic onset and treacherous course of the fully

developed syndrome of coronary thrombosis or with its equally common but often deceptive variants. Prolonged substernal pain, a greater or less degree of shock, and signs of tissue destruction are the main components of a clinical picture all too common. When pain is not excruciating or prolonged, shock in greater or less degree is an indication of the seriousness of the situation. The diagnosis is supported by the discovery of tachycardia, a feeble apical impulse, poor-quality heart sounds, a falling arterial pressure, and a triple rhythm. Shock and exhaustion may overshadow the pain, respiratory distress increase, and signs of left ventricular failure develop readily. Tissue necrosis accounts for the prompt leucocytosis, the febrile reaction, the increase in urinary urobilinogen (Focht and Hanson, 1948), the disturbance of the sedimentation rate, and the sequence of changes in pattern observed in serial electrocardiograms. The main features aiding diagnosis, as encountered in the severer grades, are presented in Fig. 1.

Minor attacks of coronary thrombosis are even more commonly encountered. They are readily mistaken

FIG. 1.—Showing from above downwards the day-to-day response of the temperature, white-cell count, blood pressure, erythrocyte sedimentation rate, urinary urobilinogen excretion, after an acute coronary thrombosis sustained by a man aged 57 on the day of his admission to hospital. A polymorph leucocytosis precedes and accompanies the rise in temperature. The blood pressure falls to shock levels. A gradual increase in the sedimentation rate reaches a maximum 11 to 13 days after the infarction, when the white-cell count has returned to normal. A sharp increase in urobilinogen excretion occurs on the fifth day of the disease—a sign sometimes helpful in distinguishing the myocardial infarct from other forms of angina (Focht and Hanson, 1948). Shock persisted for three days and was followed by congestive heart failure six days later. The patient made a good recovery on anticoagulant therapy.

*Based on an address given to the Cardiff Medical Society on April 9, 1952.

for acute coronary insufficiency. The patient already handicapped by angina pectoris is always suspect. Any unusual, unexpected, or unprovoked attack of his pain may well prove to be an actual occlusion, if not premonitory of a major disaster in the immediate future. To establish the diagnosis of infarction a search should be made for signs of tissue destruction, and among these the practitioner, when other laboratory methods are denied to him, will find helpful the long-sustained disturbance of the sedimentation rate. The readings commonly reach a maximum by the end of the second week and do not return to normal for four to eight weeks. By this procedure a clue to the diagnosis can often be reached in retrospect (Fig. 1).

It is well known that a myocardial infarct may occur painlessly (Rinzler, 1951; Papp, 1952). Shock and fever are not invariably present. The clinical pattern of acute infarction therefore varies greatly, but an undisturbed sedimentation rate after such an episode must be very exceptional: it is a valuable diagnostic procedure, easily applied and readily repeated. Every attack of cardiac asthma or sudden and acute pulmonary oedema should suggest the possibility of an acute infarction. Sudden syncopal attacks or giddiness, particularly if followed by prostration, residual exhaustion, and general bodily weakness, can often be explained on a similar basis. Nocturnal dyspnoea with insomnia and restlessness in the elderly should never be lightly dismissed. It is in these instances that the application of the clinical procedures outlined in Fig. 1 may help to clarify the diagnosis, even when a twelve-lead electrocardiogram—the usual court of appeal—is equivocal.

Response to Anticoagulants

After five years' personal experience of the use of anticoagulants in the treatment of coronary thrombosis, the time is appropriate for a stock-taking of results. In an illness of the gravity of coronary thrombosis an adequate test of the efficacy of a remedy can be found in comparative studies of mortality rates amongst a series of treated patients presented side by side with adequate controls. Of 1,800 patients observed at various centres the death rate among those receiving anticoagulants during the first few weeks of the illness was 16.2%, as compared with 30.6% in the controls. Similarly, the incidence of thrombo-embolic phenomena amongst the same large series of patients fell from 21.8% to 9% in the treated groups (Tulloch and Gilchrist, 1951). There is little doubt that the employment of anticoagulants in the first few weeks after an acute coronary thrombosis marks a distinct advance in treatment.

Apart from statistical proof, an effective remedy influences the pattern of the disease, the recovery process, and the frequency and severity of the major complications. In this respect anticoagulants in coronary thrombosis are no exception. A study of their influence on the course of the more acute phase of the illness reveals beneficial effects more widely dispersed than hitherto suspected. Moreover, the successful application of these remedies opens the way for further therapeutic endeavours.

Material for Study

Our experience is based on a consecutive series of 318 patients confined to hospital practice. In general the hospital receives a selected group composed of the moderately severe or complicated cases. All grades of severity may be encountered, but many patients die immediately or within an hour or two of the onset and hence fail to be included in a hospital series. Some of the milder attacks occur in patients who never seek hospital care. Thus hospital experi-

ence, while a reasonably large sample, is not necessarily representative of the general community as a whole. Further, the character of the hospital clientele varies in different localities. In Edinburgh nearly 60% of patients suffering from acute coronary thrombosis reach the wards within 48 hours of the onset of the attack. As a result, our experience tends to be weighted with severe and commonly fatal cases. Similarly, in those surviving the first 24 to 48 hours serious complications are common.

One group, composed of a consecutive series of 161 patients, received treatment along the usual conservative lines, consisting of rest in bed for four to six weeks, analgesics and mild sedatives when necessary, a low-calorie diet, and simple symptomatic measures for such complications as arose. These patients received no particular remedy. The last 84 of the 161 consecutive patients in this series formed a small simultaneous control for a series of 70 patients treated in the same way but with the additional use of the anticoagulant dicoumarol. On this basis it was possible to substantiate the claims made for the beneficial effects of heparin and dicoumarol (Tulloch and Gilchrist, 1950). Since then our experience has been enlarged by a further study of the use of "tromexan" in the treatment of 87 consecutive patients (Tulloch and Gilchrist, 1951). A total of 157 consecutive patients have therefore been treated with anticoagulants, but only the dicoumarol group is supported by a simultaneous and strictly comparable control series. Thus the present studies are based on 161 conservatively treated patients and 157 receiving either dicoumarol or tromexan.

Use of Anticoagulants

Anticoagulant therapy was begun on admission to hospital, unless some serious contraindication to its use was discovered. Of these, peptic ulceration and cirrhosis of the liver are the two most likely to be encountered among coronary patients. Heparin is begun as soon as the diagnosis is established. It is given at six-hour intervals in a dose of 10,000 units (77 mg.) by interrupted intravenous injection during the day and by intramuscular injections during the night, usually for the first 36 to 48 hours, depending upon the degree of reduction in the prothrombin time produced by the simultaneous action of the oral anticoagulant.

Tromexan proves to be an efficient substitute for dicoumarol and has the advantage that its daily dosage is more easily regulated. It is quicker and shorter in action, safer in use, and equally efficient (Tulloch and Gilchrist, 1951). The total quantity administered on the first day of treatment is 1,200 mg., and on the second day usually 900 mg. The prothrombin content of the blood, which is the guide to further dosage, is estimated each day about 9 a.m., after a light breakfast. The heparin injections are discontinued when the morning prothrombin time reaches 35 seconds or more. Tromexan is employed daily for 28 days after the onset of the infarction or for 21 days after the last thrombo-embolic complication, whichever is the longer. The aim is to maintain the patient's prothrombin time at a level two to two and a half times the control reading for that day in the laboratory. The quantity of tromexan administered for each day's treatment is gauged from the reading of the patient's prothrombin time, determined on that particular morning. Individual requirements vary greatly, and on occasion the prothrombin time may fluctuate through a wide range from day to day in the same patient. As a general rule a maintenance dose of 1½ to 2½ tablets (450 to 750 mg.) is about the average daily quantity required to hold the morning prothrombin time within the therapeutic range, but the requirements of different patients vary enormously.

Satisfactory maintenance of the prothrombin time within the therapeutic range is shown in Fig. 2. In this particular patient the daily dose of tromexan was reasonably steady. On only one occasion, the twelfth day, did the morning prothrombin time fall below the desired level. By way of

Fig. 2.—Showing the response of the prothrombin time to the daily adjustment of the tromexan dosage. The intention is to maintain the patient's morning prothrombin time at a value slightly greater than twice the control figure for that day. In this patient the daily tromexan dose was reasonably steady, only minor fluctuations being observed in the prothrombin times. (Reproduced from *American Heart Journal* (Tulloch and Gilchrist, 1951), by permission of the editor and publishers.)

contrast, Fig. 3 illustrates wide fluctuations in the prothrombin time, which can prove more harmful to the patient than a moderately sustained hypoprothrombinaemia. Many factors are known to influence the response to the coumarol compounds, particularly the state of the alimentary tract. A reduced food intake, even for a few days, acute and chronic alcoholism, and the simultaneous use of a gut-sterilizing antibiotic (Wright, 1952), such as "aureomycin" or chloramphenicol, are among the factors which seem to increase the patient's sensitivity to the coumarol compounds.

With adequate laboratory control, haemorrhagic complications are usually trivial, taking the form of a mild epistaxis, melaena, or haematuria. A haematemesis and a pontine haemorrhage contributed to death in two instances. Treatment of bleeding consists in the temporary interruption of the anticoagulant and the administration of vitamin K, 50 mg. intravenously. Blood transfusion was required on only one occasion.

Results of Treatment

The favourable influence of anticoagulants on the outcome of the disease in this series of patients is emphasized by the reduction of the mortality rate over the first six weeks of hospital care from 42.2% in our conservatively treated group to 20.4% among those receiving anticoagu-

Fig. 3.—Showing wide fluctuations in the morning prothrombin time. This patient required a high average dose, which was difficult to adjust. The abrupt climbs in the prothrombin times suggest a delayed response to tromexan with accumulation thereafter. Abrupt fluctuations in prothrombin time are harmful and are commonly associated with complications. Haematuria occurred on the eighteenth and nineteenth days. (Reproduced from *American Heart Journal* (Tulloch and Gilchrist, 1951), by permission of the editor and publishers.)

lants. Similarly, only 38% of the control patients ran a course free of one or more of the four major complications—shock, congestive heart failure, thrombo-embolic episodes, or sudden death—whereas in 51% of those receiving anticoagulants the illness was uncomplicated by any major episode.

It has often seemed that both the dicoumarol-treated and the tromexan-treated patients, particularly the latter, look better and feel better from an earlier stage in the illness than do the controls denied this form of therapy. Even the severely shocked patient will commonly show within a few days of the start of treatment a return of colour to the cheeks, a fresher expression, a general look of well-being, and an increased confidence, not often encountered at the same stage of the illness amongst the conservatively treated. On these grounds alone it would be reasonable to suspect that tromexan conferred benefits other than those directly concerned with prolongation of the clotting mechanism.

Course of Illness.—A study of the course of the illness indicates that major complications are apt to occur in a definite sequence and on occasion can be anticipated. For instance, as shown in Fig. 1, an onset accompanied by shock in a severe or protracted form is, if survived, commonly followed even within a few days by the development of congestive heart failure. The recovery process is punctuated by a succession of major and minor hurdles, each a test of cardiac reserve and therapeutic management. The first hurdle is shock, at which a stumble may be said to predispose to a fall at the next jump, heart failure. Throughout the course thrombo-embolic episodes are an ever-present danger, and not until four weeks have elapsed are the immediate risks surmounted.

Complications

The accompanying Table illustrates the frequency of the main complications and their influence on the mortality rate of the first six weeks of hospital care. Approximately 43% die in the control series and 21% in the treated. The notable features are the reduction in deaths from shock and from thrombo-embolic episodes in those treated with anticoagulants.

Incidence and Mortality Rates of the Four Major Complications of Acute Coronary Thrombosis as Observed During the First Six Weeks among a Group of Conservatively Treated Patients as Compared with a Corresponding Group Receiving Anticoagulants

Complication	Control Group			Anticoagulant Group		
	Incidence	Deaths from All Causes	Deaths from the Complication	Incidence	Deaths from All Causes	Deaths from the Complication
Shock	29%	24%	15%	20%	10%	4%
Heart failure	29%	20%	13%	33%	20%	13%
Thrombo-embolic incidents	28%	15%	10%	10%	7%	1%
Sudden deaths	5%	5%	5%	3%	3%	3%
Deaths			43%			21%

Thrombo-embolic Incidents

It is natural to consider first the influence of anticoagulants on the incidence of thrombo-embolic episodes, which prove to be a more frequent and serious complication of acute myocardial infarction than is commonly realized. A recurrence of thrombosis in an additional coronary branch, or an extension of the original thrombus to involve an adjoining arterial twig, is a frequent and serious happening. The occlusion of a systemic artery as a result of detachment of intraventricular clot, or the development of peripheral phlebothrombosis in the calf veins or elsewhere with resulting pulmonary infarctions, as single or multiple episodes, are examples of the risks to which these patients are exposed during the first few weeks. Death from this cause usually occurs before the fourth week. As shown in the Table, the

frequency of this complication is reduced from 28% to 10%, and deaths directly attributable to this cause fall from 10% in the control group to 1% in the treated. Wright and his colleagues (1948) concluded that anticoagulants reduced the death rate at each week of the illness. Unless anticoagulants are begun within the first 24 to 48 hours, occasional thrombo-embolic episodes cannot be avoided, as there is always the risk of detachment of clot from the thrombus already formed on the intraventricular endocardium overlying the infarct. An occasional embolic death is therefore bound to occur, but with early and efficient treatment over the first four weeks deaths from this cause can be reduced to negligible proportions.

Shock

This complication is so common as to constitute in many instances an important diagnostic feature differentiating infarction from other causes of cardiac pain. It varies greatly in degree, being occasionally absent in some patients and serious enough to cause death in others. In an admittedly arbitrary fashion the grade of shock has been classified on a purely clinical basis as severe, moderate, and mild or absent.

The importance of this outstanding complication of the illness can be judged from the fact that the severe grades carry a mortality rate exceeding 80% within six weeks of the onset of the attack, whereas only 25% of patients die when shock is moderate, mild, or absent. Similar findings have been reported by Mintz and Katz (1947) and by Epstein and Relman (1949).

The Table shows that the incidence of the severer grades of shock was 29% in the control and 20% in the treated series. Admittedly, the numbers available for analysis in this subgroup are small and must not be overemphasized, yet the discovery that only one-fifth of the severely shocked patients (4 in 20) died from this cause in the treated group as compared with approximately half those in the control (15 in 29) suggests that the early and efficient use of heparin and tromexan may have a favourable influence on the outcome of the shock syndrome. In support of this probability clinical experience indicates that an increase in the severity of the shock state after treatment with anticoagulants has been started is exceptional. Furthermore, the Table indicates that the overall reduction in the mortality rate among those receiving anticoagulants cannot be due solely to a decrease in frank thrombo-embolic deaths. It seems probable that the prompt and energetic use of anticoagulants contributes to the reduction in mortality rate by decreasing the deaths from shock.

By way of explanation for this finding it may be suggested that the early employment of heparin supplemented by tromexan may limit the spread of multiple thrombotic extensions in and through the zone of demarcation separating the necrotic from the adjoining healthy muscle. The hypotension of profound shock favours further thromboses in the coronary distribution, in the periphery, and subsequently in the pulmonary circuit. A succession of minor thrombotic episodes of this nature, perhaps insufficient in themselves to yield localizing signs, will tend to perpetuate the state of shock and favour an extension of the original infarct. By controlling the thrombotic tendency anticoagulants may thus limit the extent of the original infarct, save uninfarcted muscle, and thereby prevent an advance in the vicious circle of thrombosis, infarction, and hypotension.

Heart Failure

Some degree of left ventricular failure, as demonstrated by signs of moisture in the lungs, is very common after a myocardial infarct. When unaccompanied by any symptoms of respiratory distress such minor examples of cardiac failure have not been included in this analysis. Early signs of right-sided failure often consort with left ventricular failure. Both have been included under the heading of heart failure when symptoms attributable to this cause were in evidence. Approximately 29% of the patients developed frank signs and symptoms of one or other form of heart

failure within six weeks of the onset. In about half the cases failure was of the left ventricular type. In the remainder a greater or less degree of right-sided failure was also present. The incidence was a little greater in the treated groups.

Had the incidence of severe shock been as heavy in the treated group as in the controls, then with larger numbers surviving the early days of the illness it would be natural to suppose that the proportion showing signs of congestive failure in subsequent weeks might well have exceeded the incidence of 33% recorded among those receiving anticoagulants. In the groups, as they exist in this series of patients, there is no evidence to support the view that anticoagulants reduce the incidence of congestive failure or the deaths attributable to it. Indeed, the reverse may prove to be true.

Sudden Death

On the assumption that a proportion of the sudden deaths observed in the weeks after a coronary thrombosis are attributable to thrombo-embolic episodes of one kind or another, it is reasonable to expect a small reduction in the death rate from this cause among those receiving anticoagulants. The actual figures show a fall of from 5% amongst the controls to 3% amongst the treated.

Further Therapeutic Requirements

It is therefore apparent that the efficient use of anticoagulants makes a substantial contribution to the patient's welfare and his ultimate recovery. The conquest of one of the major complications—the thrombo-embolic episode—naturally leads to a consideration of the others in the hope that measures as effective for their prevention and treatment may be forthcoming.

It is clear that if further advances in treatment are to be made more attention must be devoted to the practical problems involved in the prevention and treatment of the severer grades of shock and congestive heart failure. With the risks of thrombo-embolic episodes controlled, these are now the outstanding causes of death. In this disease shock and congestive failure are essentially manifestations of myocardial damage. They may overlap in some degree, but shock is the primary event in the first 24 to 48 hours. Congestive failure may be present from the beginning or become manifest a few days later, but if the original shock is mild or of short duration congestive failure may never appear. The patient should then make a good recovery. It appears that protracted shock, if survived, predisposes to a greater or less degree of congestive failure at an early date. The latter can therefore be anticipated on occasions and appropriate therapeutic measures taken in advance. There are good grounds for believing that the prompt and efficient treatment of cardiogenic shock may well be the means of preventing the subsequent development of congestive heart failure.

Mechanics and Treatment of Shock

Although the clinical picture is similar to that seen after mutilating trauma or profuse haemorrhage, the mechanism of the production of shock in coronary thrombosis centres round the abrupt destruction of a portion of left ventricular muscle. Survival depends on the integrity of the remaining myocardium. In cardiogenic shock the acute hypotension is attributed to sudden left ventricular weakness associated, probably through reflex nervous channels, with a decreased peripheral resistance in the deeper organs and tissues. Coronary flow, depending largely on diastolic pressure, is correspondingly reduced, and possibly diminished further by vasoconstriction throughout the entire coronary tree.

The healthy myocardium suffers as a result of shock. Hypotension, whatever its origin, can produce significant ischaemia of large areas of myocardium and lead to degenerative fatty change and an irregular patchy cellular necrosis (Mallory, 1949–50; Melcher and Walcott, 1951). Hypotension in the coronary circuit favours myocardial

depression and defective flow in the intercoronary anastomotic channels, with ballooning of the infarcted area and of the surrounding myocardium under experimental conditions (Corday *et al.*, 1949), and shock, no matter how produced, may lead in elderly patients, and particularly those the subjects of coronary sclerosis, to the development not only of single but often of multiple fresh coronary arterial occlusions (Blumgart *et al.*, 1941). A reduced cardiac output is an essential feature, but, in contradistinction to the other forms of shock in which venous return is reduced, it is not uncommon to find in the severe shock of coronary thrombosis evidence of pulmonary congestion—a sign indicative of a venous return in excess of that which the left ventricle can accommodate. Cardiogenic shock is an entity of considerable complexity (Boyer, 1944).

Aggravating factors are well known. Treatment must be directed to the relief of the overpowering pain. Anxiety, fatigue, exposure to cold, excessive sedation, and the fluid loss of profuse sweating, vomiting, or haemorrhage may all have a detrimental influence. Morphine, oxygen, warmth, and reassurance are the first considerations in the correction of shock.

With a mortality rate in excess of 80%, the criticism that the acute hypotension of the severer grades of shock is salutary and relieves the work of the heart can be dismissed. Shock demands energetic treatment. The object is to maintain from the outset an adequate head of pressure in the aorta and thereby ensure a blood supply to the uninfarcted muscle generous enough to maintain its maximum efficiency. The risk of the extension of irreversible myocardial damage should thus be minimized or avoided.

It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date. Other vital organs will receive corresponding benefit with improvement in their blood supply. While the level of the blood pressure is not in itself a measure of the severity of the state of shock, yet it would seem advisable to maintain the systolic pressure at a figure greater than 100 mm. in those previously hypertensive and certainly over 90 mm. in the remainder.

In the worst situations the myocardium is shattered by the extent of the initial damage, and therapy will prove unavailing. The degree of shock is not, however, a reliable guide to the extent of the infarct, and it is therefore fair to assume that the employment at the outset of energetic measures may save enough myocardium to permit recovery in a proportion of the most gravely ill patients who might otherwise be expected to die within the first two or three days of the illness. These considerations allow of a therapeutic approach from various angles.

Pressor Drugs

There is a place for the pressor drug, which increases peripheral resistance and augments coronary flow, without stimulating metabolism, decreasing cardiac output, or initiating serious arrhythmias. Adrenaline, which increases myocardial excitability, is unsuitable, but various other pressor amines are under trial at the present time and encouraging results are being reported. Brams (1948) recommends desoxyephedrine in 5-mg. doses intravenously at short intervals with a sustaining intramuscular injection of 10 mg. later. Ephedrine, 35–70 mg. diluted in 100 ml. of 5% glucose in water administered intravenously over a period of two hours, has been employed (Hellerstein and Brofman, 1951), after which the pressor effect may be maintained by intramuscular injections of ephedrine, 25–30 mg. at intervals of two or three hours. Noradrenaline (Barnett *et al.*, 1950; Goldenberg *et al.*, 1949), by intravenous infusion, elevates systolic and diastolic pressure without a quickening of the heart rate. It can be very effective in the emergency of an acute infarct, and has the advantage that the pressure level, which is very sensitive to alterations in the infusion rate, can be readily adjusted. Brofman *et al.*

(1950) and Brofman (1952, personal communication) have had encouraging results in 18 severely shocked patients treated with mephentermine (methyl desoxyephedrine) given intravenously in an initial dose of 5–15 mg., the blood pressure being thereafter maintained by a slow drip at a rate of 10–70 mg. an hour, depending on the response. Of these patients, 14 emerged from the state of shock and 7 recovered sufficiently to be discharged from hospital in good health. Until further experience has been gained from the use of these drugs more definite recommendations cannot be made. They are certainly worthy of extended trial.

Transfusions

In haemorrhagic and traumatic shock transfusion has long been the mainstay of treatment. The obvious dangers of overloading the pulmonary circuit, and thereby adding to the embarrassment of a heart already overburdened, has resulted in a natural hesitation to employ this method in the presence of cardiogenic shock. Nevertheless, in selected cases transfusions of blood or plasma are occasionally beneficial (Epstein and Relman, 1949; Sampson and Singer, 1949). Experimentally, Corday *et al.* (1949) found that after coronary ligation the transfusion of heparinized blood restored the contractility of the ischaemic region around the infarct, raised the blood pressure, and decreased local cyanosis as a result of enhanced flow through the collateral circulation. There are therefore good physiological reasons for attempting to correct shock and low blood pressure by this means. Under clinical conditions the benefits of intravenous transfusions are less striking, the response being limited by the slow rise in arterial pressure and by the development of pulmonary oedema, a complication difficult to avoid in the presence of an increasing blood volume and a failing heart.

For the reason that hypotension can be more rapidly corrected by intra-arterial infusion, using little more than half the quantity of blood required when the intravenous route is employed, this method of treatment suggested by Page (1949) has been employed recently by Berman and Akman (1952), but without great benefit. While maintained, the infusion, delivered at a pressure in excess of the patient's diastolic reading, acts as an auxiliary heart (Page, 1949) and under experimental conditions leads to a retrograde flow through the aorta to the renal, coronary, and medullary arteries. If by this method aortic pressure can be maintained for some hours above the shock level without overloading the heart, an increased coronary flow should limit the area infarcted and support the surviving myocardium. Until the indications have been more precisely defined and the technique has been perfected to maintain the pressure at optimum levels, which at present are unknown, intra-arterial infusion is likely to be restricted to a limited number of desperately ill patients. Pressor drugs both on theoretical and on practical grounds appear to be a more rational form of therapy.

Digitalization

In the treatment of traumatic or haemorrhagic shock digitalis is valueless, but there are strong arguments in favour of its employment in cardiogenic shock when signs of left ventricular failure begin to develop. On theoretical grounds there has been a disinclination to use digitalis in the presence of a recent infarct lest it should favour rupture of the ventricle, induce serious arrhythmias, or enhance the clotting tendency and with a more powerful systole dislodge cardiac thrombi within the arterial system. It is probable that such accidents are as common when digitalis is not in use, but, should the danger seem real, quinidine or procaine amide may lessen the risks of the arrhythmias and anticoagulants may safeguard the patient from thromboembolic episodes. Rupture of the ventricle is uncommon before the end of the first week, by which time the stage of shock is past.

In severe cardiogenic shock the use of "digoxin," 1 mg. intravenously, is therefore justifiable, after which its oral

use may be recommenced in 12 to 24 hours. It is well recognized that digitalis poisoning readily occurs in elderly people with badly damaged hearts, and therefore careful supervision is all the more necessary.

Treatment of Congestive Heart Failure

The development of congestive heart failure within the first few weeks of a coronary thrombosis is regarded as a sign of ill omen. Its occurrence can often be anticipated and measures taken accordingly, for the more severe and the more protracted the initial shock the more probable is the early development of congestive failure.

Treatment should be directed to forestall the development of this serious complication. If digitalis has been used in the correction of the shock phase it should be continued in gentle doses for at least a week or two thereafter in the hope that the efficiency of the uninfarcted muscle may be maintained and enhanced. Bedford (1939) has noted the value of mercurial diuretics in acute left ventricular failure when oedema is confined to the pulmonary circuit.

After a coronary thrombosis, if moisture in the lungs persists for more than a few days or threatens to increase, digitalis and mercurials can be used cautiously, and even energetically should there be any hint of dyspnoea at rest. By so doing the formidable difficulties of advanced congestive failure, which is apt to develop rapidly in the week or two following recovery from the shock phase, can be eased or prevented and the patient guided through a treacherous stage of the recovery process in greater comfort. The importance of adequate rest and sound sleep during the early days of the illness cannot be over-emphasized, and there is no doubt of the value of a low-calorie diet, small meals, and simple salt restrictions.

It therefore seems that if a further advance is to be made in the treatment of the acute myocardial infarct the prompt correction of shock and the early adoption of measures to prevent the development of congestive heart failure are aspects worthy of more attention. The more adequate treatment is in the early days of the illness the greater the prospects of recovery.

Summary

Active measures in the treatment of acute coronary thrombosis are now yielding better results than ever before, even in the most gravely ill patients.

The employment of anticoagulants is an outstanding contribution to the treatment of this disease. By their efficient use the death rate over the first six weeks can be halved.

The dangers of thrombo-embolic complications can be reduced to negligible proportions.

Moreover, it appears that the prompt use of anticoagulants exerts a favourable influence on the outcome of the shock syndrome. Deaths from shock are less frequent when anticoagulants are in use.

The conquest of the thrombo-embolic aspects of the disease leads to a consideration of the other major causes of death—shock and congestive heart failure—in the hope that therapeutic measures as effective for their prevention and treatment may be forthcoming.

There is reason to believe that the occurrence of the severer grades of shock exerts a profound influence on the subsequent course of the illness. Severe and persistent shock, if survived, predisposes to death from congestive heart failure.

Prompt reversal of the shock mechanism should protect the healthy myocardium, reduce the death rate from this cause, and lessen the likelihood of congestive heart failure. The place of pressor drugs, intravenous and intra-arterial transfusions, and rapid digitalization in the treatment of shock is discussed. The early adoption of

routine measures to prevent the development of congestive heart failure is also considered.

Anticoagulants have revealed our therapeutic shortcomings so far as these complications are concerned, but further advances in treatment can be anticipated as our understanding of the mechanism of cardiogenic shock improves.

In the conduct of these investigations I am most grateful for the co-operation of my colleagues, Dr. W. A. Alexander, Professor Stanley Davidson, Professor D. M. Dunlop, and Dr. W. D. D. Small. Dr. John A. Tulloch has been my constant collaborator.

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TUBERCULOUS MENINGITIS

SOME ASPECTS OF ITS TREATMENT*

BY

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Large numbers of cases of tuberculous meningitis have now been treated in many countries and the results reported in full in the literature. This paper deals only with some aspects which have seemed important during treatment at this centre. During the period October, 1948, to May, 1951, 26 cases of tuberculous meningitis, admitted without selection, were started on treatment at Southfield Sanatorium. The youngest patient was aged 1 year and the oldest 27 years. Miliary tuberculosis was present in addition in 10 of the cases. In January, 1952, 14 (54%) of the patients were alive, with a minimum observation period of nine months and a maximum of 35 months since the beginning of treatment. Twelve of the 14 survivors have completed treatment and made a good recovery. The period of observation since finishing treatment is over twelve months in 10 of these 12 cases. The two cases remaining under treatment have been observed for twenty-eight and nine months respectively. In both a successful outcome is now confidently expected.

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