AN EVALUATION OF LONG-TERM ANTICOAGULANT THERAPY

By M. M. SUZMAN, M.D.(Durham), M.R.C.P.(Lond.).
Senior Physician, Johannesburg General Hospital, Johannesburg, South Africa

Thrombotic disease is extremely widespread and is responsible for a high and increasing morbidity and mortality in the adult populations of Western civilization and, until the fundamental reasons for this have been elucidated and appropriate corrective measures adopted, any therapeutic regime which is likely to afford significant protection to patients suffering from this disorder merits consideration.

Despite the recent recognition in blood of a system of new factors involved in the normal clotting mechanism, little light has been thrown on the causation of thrombosis to provide a basis for its prevention in different clinical states, and the only prophylactic measure available at the present time is the long-term continuous administration of anticoagulant agents.

Since the beneficial effect of anticoagulants in acute thrombotic states was considered to be largely prophylactic, in the sense that the propagation of an existing thrombus or the formation of fresh thrombi is prevented or impeded, it was a natural sequence to institute this form of therapy on a long-term continuous basis with a view to preventing the recurrence or extension of thrombus formation in patients experiencing recurrent attacks of thrombosis or thromboembolism and in those deemed likely to do so after recovery from an acute episode. Early experiences gained soon showed that the continuous long-term use of anticoagulants afforded some degree of protection against recurrence of thrombotic episodes and was a practical and relatively safe procedure, with the result that in the past decade this therapeutic regime has been widely adopted by an increasing number of workers for the prevention of various forms of thrombotic and thromboembolic disease.

Anticoagulant Agents

Coumarin and indandione derivatives are the agents usually used for prolonged therapy. All of these drugs share the common pharmacologic action of depressing 'prothrombin activity,' but vary widely in potency, rate of action and duration of effect. Recent studies indicate that agents with a rapid rate of action and a prolonged duration of effect are well suited for long-term continuous use, since they produce a response which is both predictable and stable, thus rendering long-term therapy safer and less complicated.

A drug with a slow rate of action, such as Dicoumarol, or a short duration of effect, such as Tromexan, gives a less predictable response and wide variations in prothrombin activity tend to occur so that maintenance is made more difficult. The characteristics of several anticoagulant agents in current use are given in Table 1.

The usual method for the determination of prothrombin activity is the Quick one-stage test, which measures the clotting time of recalcified plasma or of whole blood in the presence of excess (standardized) thromboplastin, and is expressed as the clotting time compared with the normal, which may be given as a percentage, the 'prothrombin index'; alternatively, the clotting time may be converted into 'prothrombin concentration' by interpolation on a curve obtained from the clotting times of saline dilutions of normal plasma, and given as percentage concentration.

Micro-methods, using capillary blood, such as those described by Stein and Wallace (1952) and Manchester and Rabkin (1954), are simple bedside procedures and are particularly useful and time-saving when a large number of determinations are to be carried out on ambulatory patients attending a clinic.

Dosage is controlled by tests performed at intervals of from one to four weeks, depending on the stability of the response obtained. When resistance to a particular drug or an erratic response is encountered, the substitution of a different preparation will frequently provide a satisfactory result.

In order to maintain an effective anticoagulant action with the minimum risk of haemorrhage, the dosage should be so adjusted as to maintain the prothrombin time at approximately twice the normal, a prothrombin index of 50 per cent.
### Table 1

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Name of Drug</th>
<th>Rate of Action</th>
<th>Duration of Effect</th>
<th>Average Daily Dose (Mg.)</th>
<th>References</th>
<th>Rate of Action</th>
<th>Duration of Effect</th>
<th>Average Daily Dose (Mg.)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COUMARIN DERIVATIVES:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bishydroxycoumarin</td>
<td>Dicoumarol</td>
<td>Slow</td>
<td>Long</td>
<td>1st day: 250-300</td>
<td>50-150</td>
<td>Succrine et al. (1952)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylbiscoumaceate</td>
<td>Tromexan</td>
<td>Very rapid</td>
<td>Very short</td>
<td>2nd day: 125-200</td>
<td>300-900</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acetonylbenzylhydroxycoumarin</strong></td>
<td>Cumopyran</td>
<td>Slow</td>
<td>Very long</td>
<td>100-150</td>
<td>12-5</td>
<td>Blaustrin et al. (1950)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phenylpropylhydroxycoumarin</strong></td>
<td>Marcumar</td>
<td>Slow</td>
<td>Very long</td>
<td>75 mg. (Lmg./Kg.) Oral, intravenous or intramuscular</td>
<td>Bourgain et al. (1954)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INDANDIONE DERIVATIVES:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylindandione</td>
<td>Dindevan</td>
<td>Rapid</td>
<td>Short</td>
<td>200</td>
<td>50-150</td>
<td>Blaustrin et al. (1950)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indema</td>
<td>Hedulin</td>
<td>Danilone</td>
<td>Dipaxin</td>
<td></td>
<td></td>
<td>Preston et al. (1952)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diphenylacetylinandione</strong></td>
<td></td>
<td>Rapid</td>
<td>Very long</td>
<td>25-30</td>
<td>3-5</td>
<td>Toohey (1953)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pascale and Olwin (1954)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Katz et al. (1954)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Field et al. (1954)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(40 to 60 per cent.), which corresponds to a promthrombin concentration of 10 to 30 per cent. These levels are referred to as the 'therapeutic range.'

Recent studies have shown that the prolongation of the one-stage cloting time by coumarin and indandione drugs is dependent mainly on a depression of a prothrombin conversion accelerator (Factor VII, proconvertin, stable factor) (Hunter and Walker, 1954) and that when bleeding occurs while the one-stage clotting time is within the therapeutic range, it is usually due to a marked reduction of prothrombin, which could be avoided with a smaller dosage of anticoagulant (Doidal et al., 1954). With coumarin therapy it is found that thromboplastin generation is impaired (Douglas, 1955), even with doses sufficient only to produce a slight prolongation of the one-stage clotting time (Hunter and Walker, 1954), an effect which presumably might impede thrombosis. Sise (1954, 1955) has demonstrated that prolongation of the whole blood clotting time occurs after these drugs have been administered continuously for periods longer than three weeks. This is thought to be due to a reduction of plasma thromboplastin component (PTC, Christmas factor) and the delay is explained on the basis of the long turn-over time of this component, as shown by Beaumont et al. (1954). This anticoagulant effect may occur even when the one-stage clotting time for prothrombin activity is only moderately prolonged, suggesting that, during long-term administration, effective therapeutic protection may be provided at dosage levels of these drugs smaller, and therefore safer, than hitherto considered necessary.

**Toxic Effects.** Haemorrhage due to overdosage is the most important complication and occurs usually with inadequate control of prothrombin activity. When mild, it is usually sufficient to lower the dosage or to discontinue the drug temporarily until the bleeding ceases. Persistent bleeding of moderate degree is readily counteracted within several hours by the oral administration of a synthetic preparation of Vitamin K₁ (Konokion, Roche) in a dosage (10 to 20 mg.) sufficient only to restore the one-stage clotting time to within the therapeutic range. With large or repeated doses of Vitamin K₁, excessive prothrombin activity of the blood is likely to ensue, necessitating re-introduction of anticoagulant therapy with the possibility that the patient will be rendered refractory to the oral anticoagulants for a considerable time. Vitamin K₁ in high dosage should be reserved for the control of serious bleeding, combined in some cases with transfusions of fresh whole blood.

Haemorrhagic manifestations are not necessarily due to overdosage of the anticoagulant agent, but may occur because of the presence of an associated disorder likely to give rise to bleeding, examples of which include renal calculus, haemorrhoids, alimentary ulceration and neoplasms and also purpura due to sedormid or quinidine sensitization.
Heparin has not been used widely for long-term anticoagulant therapy but under certain circumstances this is considered desirable. The intermitting administration of concentrated aqueous heparin (200 to 250 mg./ml.) by deep subcutaneous injection in the dosage of 125 to 150 mg. at intervals of 12 hours or of 250 to 300 mg. once daily is the method of choice and will provide adequate prolongation of clotting time in the majority of cases and allows of self-administration (Artz and Amspacher, 1952; Engelberg, 1954; Suzman, 1955).

Prolongation of the clotting time to approximately two or three times the normal control is generally regarded as therapeutically effective, but with the above dosage only occasional determinations are needed. Bleeding from overdosage, although rare with this method of administration, may be combated with the intravenous injection of protamine sulphate (50 to 100 mg.) or with transfusions of fresh whole blood.

Contraindications to Anticoagulant Therapy

The use of anticoagulant agents is precluded in advanced liver disease, jaundice, blood dyscrasias, haemorrhagic diathesis, advanced renal insufficiency, uraemia and ulcerating lesions of the alimentary and urinary tracts. Caution is needed in patients with peptic ulceration and severe hypertension, in those who are malmnourished or debilitated or are receiving intensive X-ray irradiation. In many instances, the problem of the need for anticoagulant therapy resolves itself into the fact that a calculated risk must be taken.

Evaluation of Results

A critical evaluation of long-term anticoagulant therapy presents many difficulties, not only on account of the wide variations which may be observed in the natural history of thrombotic and thromboembolic disease, but also because the published results vary considerably in wealth of detail concerning the time of onset, incidence and mortality of subsequent complications during the course of long-term therapy. Furthermore, control series of comparable groups of patients were rarely observed parallel in time with those treated.

Recurrent Thrombophlebitis, Persistent Deep Vein Thrombosis with or without Pulmonary Emboli

Significant protection against recurrence for prolonged periods during continuous anticoagulant therapy is reported in a small series of patients by Foley and Wright (1949), Hines and Barker (1949), Hellem (1953) and Lund (1953). Anticoagulant drugs were administered by Tulloch and Wright (1954) for periods ranging from one month to eight years (average 26 weeks) to 117 patients with recurring thrombophlebitis, who had experienced 288 episodes of thrombophlebitis and 55 pulmonary embolism prior to treatment, whereas only seven incidents of thrombophlebitis occurred during therapy and there were no deaths attributable to thrombosis.

Foley et al. (1955) used long-term anticoagulant therapy for from one to eight years (average months) for recurrent thrombophlebitis in patients, who had previously experienced thromboembolic episodes, including 63 of thrombophlebitis and 20 of pulmonary emboli, whereas only seven of these patients experienced a total of seven incidents of thrombophlebitis while receiving anticoagulant therapy.

Rheumatic Heart Disease and Auricular Fibrillation with Systemic or Pulmonary Emboli

A favourable prophylactic effect during prolonged continuous anticoagulant therapy was reported by Wright and Foley (1947), Sprague and Jacobson (1948), Foley and Wright (1949), Cosgriff (1950), Wood and Conn (1954) and Tulloch and Wright (1954). Askey and Chern (1950) maintain that anticoagulant prophylaxis is indicated even when clinically recognizable embolic episodes have not appeared, and, support of this contention, quote Weiss and Davis (1933) who provided post-mortem evidence that 45 per cent. of patients with rheumatic heart disease and auricular fibrillation harboured intracardiac clots and that in 20 per cent. thromboembolism was the cause of death.

Cosgriff (1953) obtained considerable success in preventing thromboembolism in 28 patients, but noted a high incidence of recurrent embolism within a short period after stopping the anticoagulants. In 14 patients with mitral stenosis treated for an average period of 23 months, Beaumont et al. (1954) reported only five embolic incidents, whereas 50 had occurred during the year prior to the commencement of treatment. During the administration of anticoagulants for periods of one to eight years (average 46 months) in 29 patients, Foley et al. (1955) reported only 18 thromboembolic episodes in seven of these patients, whereas a total of 117 had occurred prior to the commencement of treatment.

The prognosis of rheumatic heart disease in patients with auricular fibrillation and systemic embolism is so unfavourable (Daley et al., 1951; de Graaf and Lingg, 1935) that the continuous long-term use of anticoagulants would seem imperative. Since a fatal outcome is frequent with the first embolic episode (Daley et al., 1951) and because of the great likelihood that patients with auricular fibrillation due to heart disease are harbouring intracardiac clots, it would appear
rational to maintain anticoagulant therapy also in those who have not as yet experienced an embolic incident. Although insurance against dislodgement of a pre-existing thrombus cannot be provided, there is ample evidence that the formation of fresh thrombi is impeded or prevented during continuous anticoagulant therapy.

Whether long-term anticoagulant therapy may ever be discontinued with impunity in this clinical syndrome cannot be answered on the basis of available clinical data. Recurrent embolism following cessation of therapy is common, but on the other hand, since auricular fibrillation and congestive cardiac failure are the chief factors responsible for the formation of intracardiac thrombi, it may be reasonable to dispense with anticoagulants when these complications have been controlled continuously for several months by drugs or valvulotomy.

**Coronary Artery Disease, including Myocardial Infarction and Angina Pectoris**

The evaluation of the effect of long-term anticoagulant therapy on coronary artery disease presents problems of great magnitude, because the subsequent course of patients who have survived an attack of acute myocardial infarction and of those with angina pectoris is both variable and unpredictable. It is influenced not only by the severity of the presenting attack of infarction and the incidence of subsequent episodes of coronary thrombosis, but also by the extent and rate of progression of the underlying atherosclerosis, as well as by the extent of pre-existing coronary artery disease, and by other factors, known and unknown.

Consequently, a critical evaluation of long-term anticoagulant therapy can be made only by comparing those treated with a control group of untreated patients observed for similar periods, preferably parallel in time, and for long enough to bear comparison with the observed survival times in the natural history of the disease. In assessing the significance of observed differences between treated and untreated groups, due regard must be given to the degree of severity of the disease, and moreover, the conditions of management of the patients of both groups, other than that of the anticoagulant medication, should be similar in as many respects as possible, particularly as regards dietary restrictions. Although not yet fulfilled, these strict criteria have been approached in a few reported studies, but in the majority a control series of untreated patients has not been observed.

The first recorded attempt to forestall acute coronary thrombosis with the use of long-term anticoagulant therapy is that of Nichol and Fassett (1947) who treated five patients with dicoumarol for periods ranging from 6 to 32 months. Favourable results in several uncontrolled series of patients treated for longer periods are reported by Foley and Wright (1949), Nichol and Borg (1950), Rice et al. (1950), Scott (1952), Owren (1953), Lund (1953), Tulloch and Wright (1954), Bay et al. (1954), Beaumont et al. (1954a), Nichol (1954) and Foley et al. (1955).

In a controlled study, Keyes et al. (1953) compared the prognosis of a group of 63 survivors of acute myocardial infarction treated continuously with dicoumarol, all for one year and 41 for two years, with that of an untreated group of 147 patients observed parallel in time for two years. The annual mortality rates were 4.8 per cent. for the first year and 2.4 per cent. for the second year in the treated group, and 15.6 per cent. and 13.6 per cent. respectively in the control group. These differences were considered all the more significant since a greater number of patients with severe coronary artery disease were included in the treated group. Seven patients discontinued their anticoagulant therapy and developed a new infarct 2 to 12 weeks later. These authors noted that approximately four times as many patients died without long-term anticoagulant therapy as did with it. In both groups the mortality rate was higher in those with recurrent than with single infarcts. That over 30 per cent. of patients die in the acute phase of recurrent myocardial infarction is cited as a fact strengthening the case for protecting the patient with a single infarct.

In a preliminary report of a controlled study, Goldberg and Suzman (1953) noted fewer recurrent infarcts and a lower mortality in a group of 29 survivors of acute myocardial infarction treated continuously for periods of two to 60 months, as compared with a control group of 22 patients, who received anticoagulants only during the acute phase of the disease and were observed for similar periods.

Owren (1954) reports the mortality, incidence of recurrent infarction and the effect on angina of continuous dicoumarol treatment given for periods up to five years in 234 patients with coronary artery disease. Of 106 survivors of infarction there were seven recurrences and six deaths, and of 128 patients with angina pectoris alone, ten experienced subsequent infarction and eight died. It is claimed that the mortality rate in each of the first two years compares favourably with results previously reported for patients not treated with anticoagulants. Marked relief of angina was noted in a considerable proportion of the patients.

Nichol, Phillips and Jenkins (1954), in a study of 265 patients with coronary atherosclerosis treated with anticoagulants for periods of three months to seven years, report that of those who discontinued therapy, 33.6 per cent. died within
ten days to three years, the majority within six months, whereas in the patients receiving anticoagulants, the mortality was 13.8 per cent.

In a co-operative study from 12 different centres of the U.S.A., reported by Nichol (1954), oral anticoagulants were used for periods of six months to eight years for coronary artery disease in 1,100 patients, 30 per cent. of whom eventually discontinued treatment. While on the regime, 16 per cent. died, but autopsy seldom revealed fresh transmural infarction. Judging by comparison with a control group of 500 patients it was concluded that the use of long-term anticoagulant therapy probably prevented recurrent infarction and prolonged life in many patients.

Suzman et al. (1955) evaluated the effect of continuous long-term anticoagulant therapy given for periods of 3 to 76 months on the prognosis of myocardial infarction in 82 patients and compared the results with those observed in a control group of 88 patients followed for similar periods whose treatment with anticoagulants was limited to the acute phase of an infarction. The mortality and incidence of recurrent infarction were significantly lower in the patients on long-term anticoagulant therapy, and, whereas cardiac failure occurred with similar frequency in both groups, the mortality associated with this complication was considerably lower in the treated group. Separate comparisons are made of mild and severe cases and of single and recurrent infarctions in respect of the subsequent prognosis in the two groups. When the infarction is not only the first attack, but is also mild, and anticoagulants are given during the acute phase, the subsequent prognosis appears to be favourable irrespective of whether or not the anticoagulant therapy is continued indefinitely. By contrast, when the presenting attack of infarction is severe and is also a recurrent one, the ultimate prognosis is likely to be significantly improved by continuous long-term anticoagulant therapy, without which the outlook is extremely poor.

Heparin Therapy. In recent years the use of heparin has been advocated for the prevention of recurrent infarction and for the relief of angina pectoris. The favourable effect on angina when administered intermittently twice weekly, as observed by Graham et al. (1951) and Engelberg (1952), could not be confirmed by several workers (Russek et al., 1952; Miller et al., 1952; Binder et al., 1953; Gruner et al., 1953; Rinzler et al., 1953; Chandler and Mann, 1953). However, Engelberg et al. (1955) administered 200 mg. of heparin by the subcutaneous route twice weekly to 105 survivors of myocardial infarction for a total period of 2,067 patient-months with only four deaths, whereas of 118 control patients receiving placebo treatment, 21 died during a similar period of observation. The protection afforded could not be due to an anticoagulant effect and is attributed to an improvement in the coronary circulation, brought about by the clearing action of heparin on the blood fats, through the elaboration of a heparin-induced lipolytic enzyme (Hahn, 1943; Anderson and Fawcett, 1950), the effect of which is said to persist for two or three days following the single administration of an adequate dose of heparin (Graham et al., 1951).

Patients with severe post-infarction angina, refractory to treatment with conventional drugs and to the long-term use of oral anticoagulants, have responded favourably to daily subcutaneous injections of 125 to 250 mg. of concentrated aqueous heparin administered for prolonged periods (Suzman, 1955).

The use of heparin for long-term anticoagulant therapy would seem to be indicated in patients, who, in addition to ath erosclerotic and thrombotic disease, present with abnormally high levels of blood fats, the existence of which is thought to promote atherogenesis (Gofman, 1950). Moreover, hyperlipaemia has been shown to increase the coagulability of the blood (Duncan and Waldron, 1949; Fullerton et al., 1953; Waldron and Duncan, 1954; Fullerton, 1955) as well as its viscosity and the adhesiveness and aggregation of red blood cells (Swank, 1951; Swank, 1954; Cullen and Swank, 1954), but these effects are reversed by heparin (Moolten, et al., 1949; Hurwitz et al., 1952). That postprandial hyperlipaemia not only may increase blood coagulability, but is likely also to provoke acute coronary ischaemia in the presence of coronary artery disease (Kuo and Joyner, 1955), may provide further evidence for the possible value of the long-term use of heparin in patients with coronary atherosclerosis and myocardial infarction.

Comment

Despite the fact that the general consensus of opinion concerning the prophylactic value of long-term anticoagulant therapy in myocardial infarction and angina pectoris is favourable, a critical evaluation of this regime is not yet possible for lack of sufficient numbers of adequately controlled and well documented clinical studies. However, composite data (derived from various sources) of the course of survivors of acute myocardial infarction, followed till death or to the end of the first and of each subsequent year, show that the mortality rate is substantially lower in the patients receiving continuous long-term anticoagulant therapy (Keyes et al., 1953; Owren, 1954; Suzman et al., 1955) than in those whose treatment with anticoagulants was limited to the acute phase.
of the infarction (Tudhope et al., 1954; Suzman et al., 1955) or in those who received no anticoagulants (Bland et al., 1951; Fisher et al., 1946; Katz et al., 1949; Keyes et al., 1953).

The differences in mortality between the three groups are shown in Table 2. Sufficient data suitable for comparison are not available for patients observed longer than three years. However, since most of the fatalities subsequent to recovery from acute myocardial infarction take place in the first three years, an analysis of the observations confined to this period provides an adequate basis for comparison. The mortality rate during each year is below 5 per cent. in the long-term group and, by contrast, over 10 per cent. in both the short-term and untreated groups. The higher death rate during the first year in the untreated patients as compared with those who received short-term therapy is of interest, as it suggests that the use of anticoagulants for an acute attack of infarction may influence the subsequent prognosis favourably during the ensuing year, as pointed out by Tudhope and Donald (1954).

That the observed differences can be attributed entirely to the effect of anticoagulants cannot be stated with certainty, because of a lack of similarity in the conditions of management of the treated and untreated patients. Long-term anticoagulant therapy entails close medical supervision, and this not only ensures the timeous recognition and treatment of complications, but also, by providing added reassurance and a sense of security, is likely to allay undue fear and apprehension, thereby favourably influencing the prognosis, since stressful emotional factors are known to hasten the blood clotting time and may play a part in the pathogenesis of intra-vascular thrombosis (Cannon and Mendenhall, 1914; Cannon, 1929; Schneider and Zangari, 1951; Schneider, 1951; Macht, 1952). Moreover, dietary restriction of fat, a regime advocated widely to impede the progression of atherosclerosis, is likely to have been adhered to more strictly in the patients under close medical supervision.

Perhaps a better evaluation of long-term anticoagulant therapy could be obtained by the application of the 'double-blind placebo' method of clinical trial (Cornell Conference on Therapy, 1954) to groups of patients graded according to the degree of severity of the presenting attack of infarction and maintained on similar dietary regimes.

The question as to when, if ever, a patient may discontinue anticoagulant therapy cannot be answered with certainty on the available clinical data. Studies of the natural history of myocardial infarction (Billings et al., 1949) indicate that in patients who show little or no disability following recovery from the acute episode, the mortality rate is increased to a moderate degree during the first three years, but thereafter falls considerably and life expectancy in these survivors approaches that of the rest of the population of corresponding age and sex. On the other hand, in those who are severely disabled following recovery from the acute attack, the mortality rate continues to remain significantly high at all times. It would seem reasonable, therefore, to discontinue anticoagulant therapy in patients who have remained essentially asymptomatic for a period of three years. However, a high proportion of the long survivors are likely to be those in whom the acute attack of infarction was mild or uncomplicated, since it appears, though not established (Suzman et al., 1953), that the outlook of these patients is favourable irrespective of whether or not they continue to receive anticoagulant therapy.

The prophylactic value of prolonged anticoagulant therapy in survivors of myocardial infarction has been questioned, the doubts expressed being based mainly on the fact that in the natural history of the disease, a significant proportion of fatal cases exhibit coronary atherosclerosis but fail to show the presence of recent thrombosis (Evans, 1954). On the other hand, Duguid (1946, 1948, 1949, 1952, 1954, 1955) has shown that mural thrombi become incorporated in the arterial wall leading eventually to the formation of lesions indistinguishable from

| Table 2 |

**Comparison of Long-term, Short-term and no Anticoagulant Therapy on the Mortality Rate in Composite Groups of Survivors of Acute Myocardial Infarction followed for Varying Periods**

<table>
<thead>
<tr>
<th>Period Followed in years</th>
<th>Long-term Anticoagulant Therapy</th>
<th>Short-term Anticoagulant Therapy</th>
<th>No Anticoagulant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Mortality Rate %</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>1</td>
<td>177</td>
<td>4.5</td>
<td>175</td>
</tr>
<tr>
<td>2</td>
<td>127</td>
<td>3.2</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>4.2</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>5.0</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>--</td>
<td>10</td>
</tr>
</tbody>
</table>

Perhaps a better evaluation of long-term anticoagulant therapy could be obtained by the application of the 'double-blind placebo' method of clinical trial (Cornell Conference on Therapy, 1954) to groups of patients graded according to the degree of severity of the presenting attack of infarction and maintained on similar dietary regimes.
atheroma. These observations, later confirmed by Harrison (1948), Heard (1952), McLetchie (1952) and Crawford and Levene (1952, 1953), provide evidence that thrombus formation may be a causative factor in the origin of atheroma as well as one of its complications, so that it can be appreciated how a long-term therapeutic regime, which decreases the coagulability of the blood, may not only prevent recurrent episodes of thrombosis, but is likely also to impede further progression of the underlying atherosclerotic disease.

**Chronic Peripheral Obliterative Arterial Disease**

Prolonged anticoagulant therapy to prevent acute and progressive arterial thrombosis in patients with peripheral arteriosclerosis or thromboangetis obliterans is reported by Allen et al. (1947), Hines and Barker (1947), Tulloch and Wright (1954) and Burt (1955). Heparin has been employed for prolonged periods, both as anticoagulant and anti-atherogenic agent, with apparent benefit for peripheral atherosclerosis by Engelberg and Massel (1953) and for aorto-iliac thrombotic stenosis by Martorell (1955) and Suzman (1955).

Wide variations are observed in the natural course of peripheral vascular disease, so that the value of anticoagulant therapy is difficult to assess. However, a beneficial effect is frequently observed, in that recurrence or extension of thrombosis appears to be prevented or retarded, and, in a number of instances, striking improvement in the peripheral circulation is obtained.

**Miscellaneous Thrombotic Diseases**

Prolonged anticoagulant therapy has been employed to prevent recurrent thrombotic episodes in patients suffering from cerebral thrombosis (Olwin, 1949; Scott, 1952; Tulloch and Wright, 1954), mesenteric thrombosis (Scott and Lissmore, 1954; Scott, 1952) and central retinal vein thrombosis (Olwin, 1949; Tulloch and Wright, 1954). The results are difficult to evaluate owing to the small numbers of patients treated and because in these conditions the subsequent course is extremely unpredictable and little is known of their nature.

In the clinical syndrome termed cerebral thrombosis, widely divergent views are held concerning the nature of the morbid process responsible for the vascular occlusion, particularly as regards the part played by actual thrombus formation. Duguid (1955) postulates a thrombogenic theory of atherosclerosis and it is accepted generally that the final occlusion is due to the formation of a thrombus, whereas Bruetch (1955) could find no histological evidence of thrombosis in occlusive arteriosclerotic disease of the brain. The rationale for the prophylactic use of anticoagulants in this condition thus remains in doubt.

**Conclusions**

Long-term continuous anticoagulant therapy is a safe and practical procedure provided adequate laboratory facilities are available for the proper control of dosage and the prevention of haemorrhage.

Its prophylactic value is established for recurrent thrombophlebitis and pulmonary embolism and for thrombo-embolism associated with auricular fibrillation.

Available clinical data strongly suggest that the subsequent prognosis is influenced favourably in patients who have recovered from a severe attack, of acute myocardial infarction, but further well-controlled studies are needed to establish this firmly and to ascertain the prophylactic value of long-term therapy for patients in whom the presenting attack is mild.

If criticism of long-term anticoagulant therapy is merited, it should be directed not to the general principles surrounding its use, but towards the current imperfections inherent in its applications and the gaps in knowledge of the causative mechanisms of thrombosis and its relation to vascular disease.

Since thrombosis occurs under many different circumstances and in association with a wide variety of diseases, it is reasonable to presuppose that thrombus formation may be initiated by several different specific defects in the mechanism whereby circulating blood maintains its fluidity. At the present time, the choice of anticoagulant is not determined by any consideration pertaining to the possible cause of the thrombotic disease and yet in experimental thrombosis it has been demonstrated that the anticoagulant best suited for prevention depends on the means by which the thrombosis is induced (Jewell et al., 1954; Wessler, 1953; Wessler and Morris, 1955).

Until specific measures are available to prevent clotting on an aetiological basis, or methods of clot dispersion by thrombolytic agents are developed sufficiently for clinical application, long-term anticoagulant therapy will continue to find a place in the prophylactic management of thrombotic disease, but further perfections as regards efficacy and safety can be anticipated.

**BIBLIOGRAPHY**


