EVALUATION OF ANTICOAGULANT THERAPY IN
CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION.

A THESIS
SUBMITTED FOR THE DEGREE
OF
DOCTOR OF MEDICINE
OF
THE UNIVERSITY OF EDINBURGH

BY
WILLIAM AGNEW LAWS MACFADYEN, M.B., Ch.B., M.R.C.P. Ed.

April 1949.
ACKNOWLEDGMENT.

It is with pleasure that I record my gratitude to Dr. A. Fergus Hewat, Physician, Royal Infirmary of Edinburgh for his kindness in permitting me to investigate the cases under his care and for his constant interest and encouragement in the pursuit of this study.
CONTENTS.

I. INTRODUCTION.

II. THROMBO-EMBOLIC COMPLICATIONS OF MYOCARDIAL INFARCTION. .......... 5.
   (a) Incidence, severity and significance. 5.
   (b) Causes. .................. 13.
   (c) Conclusions. ............... 22.

III. ANTICOAGULANTS. .................. 24.
   (a) Heparin. (i) Historical review . 24.
   (b) Dicumarol. (i) Historical review . 29.
   (c) Combined heparin-dicumarol therapy. 36.

IV. ANTICOAGULANTS IN MYOCARDIAL INFARCTION - REVIEW OF THE LITERATURE. ..... 38.

V. CLINICAL STUDY.
   (a) Plan, material studied and results. 62.
   (b) Dicumarol dosage and administration. 72.
   (c) Estimation of blood prothrombin level. ....................... 75.
   (d) Heparin. Administration and control. ............. 86.
       Heparin tolerance test. 91.
       Heparin (in vitro) clotting test. ...... 93.

VI. VITAMIN K THERAPY OF MYOCARDIAL INFARCTION. 95.

VII. DISCUSSION. ...................... 99.

VIII. SUMMARY. ......................... 105.

REFERENCES. ......................... 107.
I. **Introduction.**

It is one of the mysteries of medical history that acute myocardial infarction, with its dramatic symptoms and its gross and obvious pathological lesions, was not established as a clinical entity until as late as 1910. Accurate pathological accounts had been given many years before (Weigert 1880, Cohnheim 1881, Huber 1882), the clinical features had been clearly described (Huchard 1890) but pathology and symptoms had not been wedded in a systematic account of the condition as an entity quite distinct from angina pectoris, until the publication of a paper by Obrastzow and Straschesko (1910). They described three cases, two of which they had diagnosed in life, and emphasised many of the clinical features which are now common knowledge. Their report did not arouse much interest but in 1912 there appeared a noteworthy paper by Herrick which stressed the complexity and variability of the clinical features of cardiac infarction and, in particular, pointed out that all cases were not fatal. This article earned more conviction and further papers by Herrick (1918) were followed quickly by the appearance of an extensive American literature. Out of many authors, Levine & Tranter (1918), Libman (1919), Pardee (1920), Robinson and Hermann (1921), Longcope (1922), Wearn (1923), Gordinier (1924) and Faulkner, Marble & White (1924) may be mentioned as having each added some detail/
detail to the final and definitive clinical picture which eventually emerged and which was convincingly presented in an excellent review by Hamman (1926).

British physicians appear to have been slow to accept the reality of cardiac infarction as an entity distinct from angina pectoris. Mackenzie in 1923 failed to make the distinction in his monograph on angina pectoris. However, McNeely (1925) described the clinical picture in a study of 3 cases of coronary thrombosis and the report by Parkinson and Bedford (1928) of a clinical series of 100 and a post-mortem series of 83 is an indication that they had been aware of the condition for some years. The delay in acceptance of coronary thrombosis as an entity is indicated by the fact that it was not included until 1930 in the International List of Causes of Death and in the Registrar-General's Report.

Greater familiarity with the clinical picture on the part of physicians and progressive improvements in diagnostic methods, notably in electrocardiography, have naturally led to progressive increase in the reported incidence of coronary thrombosis in hospital admissions, and also to progressive increase in the number of deaths due to disease of the coronary arteries noted in the Registrar-General's Report. Pathological studies, Meakins & Bakin (1932) have not shown any increase in the incidence of coronary thrombosis in routine autopsies carried out over comparable/
comparable five-year periods. However, Master (1947) in a convincing paper has inferred from an analysis of United States Census reports and from the sampling of death certificates that there is an undoubted increase in the prevalence of coronary artery disease and more particularly of acute coronary occlusion. He calculates that every year at least 1 man in 50, 40 years of age and over, and 1 woman in 150 in the same age group, sustain closure of a coronary artery. He attributes the increasing incidence to (1) lengthened span of life, (2) ageing of the population, (3) improved diagnosis and treatment, and (4) accuracy in terminology.

Improved diagnosis by leading to earlier recognition and treatment has brought about some improvement in mortality rate. But the disease has lacked any specific therapy. It is known that if the first month is survived then the prognosis progressively improves (Bland & White 1941). Causes of death in the first month are:— (1) Acute circulatory failure from the massivity of the original infarct. (2) Congestive heart failure from severe myocardial damage—often due to repeated episodes in different branches of the coronary tree. (3) Cardiac rupture. (4) Heart-block and other arrhythmias. (5) Thrombo-embolic complications.

It has frequently been noted that what appears to/
to be a satisfactory recovery from myocardial infarction may be suddenly marred by a second episode or by some other thrombo-embolic process which may result in death or permanent invalidism. The realisation of the importance of such complications in this condition and the remarkable success achieved with the use of the anticoagulants heparin and dicumarol in the treatment of post-operative and puerperal thrombo-phlebitis and pulmonary embolism, has led to the trial of these substances in cases of myocardial infarction.

This disease frequently strikes down men in the most productive years of life who have great professional and family responsibilities - men whom the world can ill spare. Any line of treatment which offers a hope of a lessened mortality is worth the most serious scrutiny and evaluation.

In this paper an attempt will be made to elucidate and define the pathological justification for lessening the coagulability of the blood (Part II), the methods available will be discussed (III), the reported results of other workers will be reviewed (IV) and the author's experience in a short clinical series will be presented (V). After a brief critical consideration of a form of therapy directly contrary in rationale to the subject of this paper (VI.), the author's conclusions will be embodied in a final discussion (VII.) and summary (VIII.)
II. Thrombo-embolic complications of myocardial infarction.

(a) Incidence, severity and significance.

That coronary thrombosis is frequently complicated by thrombo-embolic phenomena has long been recognised. Various observers in both clinical and pathological studies have recorded, in varying incidence, the occurrence of the following conditions subsequent to or accompanying an episode of acute myocardial infarction:

(1) The presence of mural thrombi in the heart chambers.

(2) The onset of sudden occlusion of systemic arteries in the extremities, brain, kidney, spleen, mesentery or aorta.

(3) Peripheral phlebothrombosis - notably in the calf veins.

(4) The appearance of pulmonary infarction as a consequence of (1) or (3).

(5) Development of a secondary coronary thrombosis in a previously uninvolved branch of the coronary tree.

The existence of mural thrombi can be only a matter of surmise during life. A sudden arterial occlusion is not necessarily due to an embolus detached from a mural thrombus, since pathological studies/
studies have shown that such occlusions may occur in cases which show no evidence of thrombi within the heart chambers at post mortem. Hellerstein & Martin (1947) in an autopsy series of 160 cases of recent and remote myocardial infarction found mural thrombi in 65. Though 36 of these showed arterial occlusions, yet 37 of the 95 cases free of mural thrombi showed similar lesions. It is clear then that the incidence of mural thrombi cannot be estimated in a clinical series but only in post-mortem material. It is of interest that such experienced observers as Wolff and White (1926) state that a mural thrombus always occurs in myocardial infarction though they found such thrombi in only 30% of their post-mortem cases.

Table I. records the incidence of mural thrombi found at autopsy by a number of different observers.

Table I. Incidence of mural thrombi found at autopsy in cases of myocardial infarction.

<table>
<thead>
<tr>
<th>Author.</th>
<th>No. of autopsies</th>
<th>Cases with mural thrombi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolff &amp; White (1926)</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Parkinson &amp; Bedford (1928)</td>
<td>83</td>
<td>14</td>
</tr>
<tr>
<td>Levine &amp; Brown (1929)</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Lisa &amp; Ring (1932)</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>Meakins &amp; Eakin (1932)</td>
<td>62</td>
<td>29</td>
</tr>
<tr>
<td>Appelbaum &amp; Nicholson (1935)</td>
<td>150</td>
<td>81</td>
</tr>
<tr>
<td>Bean (1938)</td>
<td>300</td>
<td>142</td>
</tr>
<tr>
<td>Garvin (1941)</td>
<td>133</td>
<td>89</td>
</tr>
<tr>
<td>Nay &amp; Barnes (1945)</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Hellerstein &amp; Martin (1947)</td>
<td>160</td>
<td>65</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>1068</strong></td>
<td><strong>506 = 47%</strong></td>
</tr>
</tbody>
</table>

Though/
Though these figures conclusively show that almost half of subjects dying from myocardial infarction have mural thrombi in the heart chambers, it must be remembered that post-mortem series represent the most severe cases and are not necessarily typical of the usual pathology in non-fatal cases. Furthermore, it has been shown that the incidence of mural thrombi is high in cases dying from other forms of heart disease. Garvin (1941) in a study of 771 deaths from heart disease found mural thrombi in 35.1%, of cases of coronary disease without infarction, in 31.9%, of cases of rheumatic heart disease and in 31.3% of cases of hypertensive heart disease. However, Garvin points out that congestive heart failure which predisposes to mural thrombi was almost always present in the last 3 groups but complicated the fatal cases of myocardial infarction in a much smaller percentage. This fact increases the significance of the greater incidence of mural thrombi in fatal cases of myocardial infarction and suggests there is a much greater thrombosing tendency in this condition.

That systemic arterial occlusion embolic or thrombotic frequently complicates convalescence from myocardial infarction has been shown by many observers. Table II. lists the recorded post-mortem incidence of such conditions from a number of different sources.

Table II./
Table II. Incidence of systemic arterial occlusions found at autopsy in cases of myocardial infarction.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of autopsies</th>
<th>No. of arterial occlusions</th>
<th>Site of occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolff &amp; White (1926)</td>
<td>19</td>
<td>11</td>
<td>2, 6, 2, 0, 0, 1</td>
</tr>
<tr>
<td>Parkinson &amp; Bedford (1928)</td>
<td>83</td>
<td>24</td>
<td>1, 9, 8, 2, 1, 3</td>
</tr>
<tr>
<td>Meakins &amp; Eakin (1932)</td>
<td>62</td>
<td>40</td>
<td>4, 14, 9, 11, 2, 0</td>
</tr>
<tr>
<td>Bean (1938)</td>
<td>300</td>
<td>73</td>
<td>15, 29, 17, 8, 1, 3</td>
</tr>
<tr>
<td>Woods &amp; Barnes (1941)</td>
<td>60</td>
<td>10</td>
<td>9, 0, 0, 1, 0, 0</td>
</tr>
<tr>
<td>Garven (1942)</td>
<td>133</td>
<td>83</td>
<td>18, 32, 19, 11, 0, 3</td>
</tr>
<tr>
<td>Nay &amp; Barnes (1945)</td>
<td>11</td>
<td>9</td>
<td>4, 2, 0, 3, 0, 0</td>
</tr>
<tr>
<td>Hellerstein &amp; Martin (1947)</td>
<td>160</td>
<td>78</td>
<td>14, 28, 17, 13, 0, 6</td>
</tr>
</tbody>
</table>

Totals. 828 328 = 39.6%.
There is considerable discrepancy between the figures recorded in the various series above and it is clear from the original papers that some observers have not made a special search for infarcts in particular sites such as brain and viscera. The true incidence is probably higher than 39.6%, and is better reflected in the carefully analysed series of Meakins and Eakin (1932) and Garvin (1942) noted in Table II, which give an incidence of 63%.

Pulmonary infarction is a well recognised complication of coronary thrombosis. Whether the source of the embolus is more commonly the right side of the heart or the peripheral veins, cannot be stated with certainty. In the experience of Bean (1938) 75% of patients with right ventricular thrombi had pulmonary emboli, but he found that massive emboli occluding the lumen of the pulmonary artery were always derived from the systemic veins. Woods and Barnes (1941) found that the iliac veins were the source of the emboli in all their fatal cases of pulmonary infarction. The incidence recorded in the literature is listed in Table III.

Table III. Incidence of pulmonary infarction found at autopsy in cases of myocardial infarction.

Authors/
9.

Authors. | No. of autopsies | No. of pulmonary infarctions.
--- | --- | ---
Parkinson & Bedford (1928) | 83 | 7
Meakins & Eakin (1932) | 62 | 47
Kugel & Lichtman (1933) | 95 | 33
Saphir et al. (1935) | 34 | 10
Bean (1938) | 300 | 43
Eppinger & Kennedy (1938) | 200 | 46
Woods & Barnes (1941) | 60 | 6
Garvin (1942) | 133 | 45
May & Barnes (1945) | 11 | 6
Hellerstein & Martin (1947) | **160** | **33**

1138 | 276 = 24%

Tables I., II. & III. amply illustrate the frequency of thrombo-embolic phenomena in deaths from myocardial infarction. It may be objected that such phenomena are also found, though in a small/percentage (Garvin 1941 & 1942), in patients dead from other froms of heart disease. While this is true it is emphasised that thrombo-emboli frequently mar what appears to be satisfactory recovery from myocardial infarction, whereas in other types of heart disease such manifestations (except in subacute bacterial endocarditis and auricular fibrillation) are more commonly terminal complications of congestive heart failure.

The significance of thrombosis and embolism in myocardial infarction can perhaps be better appreciated by studies of clinical material (Table IV.) and by a consideration of their importance as the chief cause of death.

Table IV. Incidence of thrombo-embolic complications in clinical series of myocardial infarction.

Parkinson/
A striking feature of the figures noted in Table IV. is the very marked increase in thrombo-embolic complications which has been recorded since 1945, an increase from 11.4% to 27.8%. It is very unlikely that this represents a real increase in incidence. It is the result, rather, of a heightened awareness of the possibility of thrombo-embolic complications and of more careful clinical scrutiny. The authors of the reports published since 1945 have directed their attention specifically to such complications in their clinical studies as a contribution to the evaluation of the use of anticoagulants. The most recent figures therefore probably present a truer picture of the frequency of thrombo-embolic manifestations following cardiac infarction. It is easy to see how some of these conditions may have been missed in the earlier series since it is only comparatively recently that attention has been drawn to the clinical picture of deep quiet venous thrombosis in the legs (Homs, 1944).
Minor non-fatal pulmonary infarctions from such a source may easily be diagnosed as pleurisy or other pulmonary infection or may fail of recognition altogether. Hines & Hunt (1941) reported a striking infrequency of clinical diagnosis of pulmonary infarction. Out of 81 cases proved by post-mortem examination only 2 had been recognised in life. Clinicians today are more keenly aware of the risk of pulmonary embolism following coronary thrombosis and are more suspicious of such features as slight chest pain and a rise in pulse, temperature and respiratory rate.

The development of a second myocardial infarction during convalescence from an initial episode is well recognised clinically but has received little attention in the literature. Two observations have been recorded which are in close agreement. Nay & Barnes (1945) in their careful study of the incidence of embolic and thrombotic processes following acute myocardial infarction noted a secondary coronary thrombosis in 14 of 100 cases. Wright et al. (1948) in a preliminary report on a combined investigation into the value of anticoagulants carried out in 16 American hospitals, record in the control untreated series of 368 cases, extension of the original thrombosis in 9% and infarction of new areas of the myocardium in 6.5%.

It is clear from the foregoing considerations that/
that intravascular embolism and thrombosis are common events during convalescence from an episode of myocardial infarction. Tables II, III & IV illustrate their frequency but not the severity and significance of such complications. Few of the reports listed state with what frequency they were the main cause of death or how serious their effects were in those who survived. Nay and Barnes (1945) considered these points and found that in their clinical series of 100, thrombotic or embolic processes were directly responsible for 4 of their 13 deaths and were important contributory factors in 8 others. Out of 25 who survived thrombo-embolic complications, there were grave consequences in 17. Of these, 14 with a second episode of coronary thrombosis had a further impairment of cardiac reserve and 3 became permanent invalids from cerebral damage. Hellerstein and Martin (1948) record that in 43 of their 160 post-mortem cases it is certain that thrombo-embolic lesions were important as a cause of death. Eppinger and Kennedy (1938) found such lesions to be a main or contributory cause of death in 49 of 200 cases.

The time of onset of thrombo-embolic complications has been studied by Nay & Barnes (1945) and Wright et al. (1948). The former found that the great majority of secondary coronary thromboses and of cerebral vascular lesions occurred between the 4th and 20th day of illness, of pulmonary emboli between the 17th and 36th/
36th day and of peripheral phlebothromboses between the 10th and 16th day. Wright reports that the incidence of thrombo-embolic complications is highest in the second week but is marked throughout the first four weeks.

A description has been given of the types of thrombotic and embolic process which are prone to complicate acute myocardial infarction. Evidence has been proposed in a summary of the literature for the frequency, severity, significance and usual time of development of such complications.

(b) Cause.

The existence of a tendency towards intravascular clotting during the four weeks following an acute myocardial infarction is established but the ultimate causes of this tendency are not clearly understood. Wright (1946) suggests there is a profound change in the thrombosing balance of the blood which is either initiated by the local coronary thrombosis or else is the primary condition responsible both for the initial thrombosis and for thrombosis in numerous other focal points at the same time.

There is some evidence in the literature for Wright's suggestion. De Takats (1943) has shown that patients with coronary thrombosis have an increased resistance to heparin i.e. there is a disturbance in the coagulation system with a tendency towards clotting/
clotting. Brambel (1945) found a shortening of the prothrombin time of diluted (12.5%) plasma in coronary thrombosis but he does not state in what proportion of cases. Peters et al. (1946) record a shortened prothrombin time of whole and/or diluted plasma in three-quarters of their cases of coronary thrombosis. They think that the clotting tendency is attendant upon vascular occlusion rather than the cause of it, since in some cases it did not make its appearance until the 2nd or 3rd day of illness.

In striking contrast to these observations are the findings of Doles (1943). He carried out routine prothrombin time estimations in 457 consecutive admissions to his care. 13 of these were suffering from or developed coronary thrombosis. He found in all a marked lowering of prothrombin level (i.e. an increase in prothrombin time) to 45-60% of normal. This was most marked 12-48 hours after infarction. Doles was so impressed by these findings that he treated his cases with vitamin K with return of prothrombin time towards normal and, he thought, clinical improvement. It is unfortunate that Doles has used a most confusing term in his report which he does not precisely define. He speaks of his cases showing a lowered prothrombin time per cent of normal. It is clear from the fact that he adopted treatment with vitamin K and from consideration of a previous publication (Doles, 1941) that by this term he means an actual/
actual increase in prothrombin time since in the latter report he indicated that 25 seconds is 100% prothrombin time and 30 seconds 80% prothrombin time. This unfortunate choice of expression has been perhaps understandably misinterpreted in a widely read textbook. White (1947) quite erroneously quotes Doles as having reported a tendency to thrombosis with shortened prothrombin time in acute coronary occlusion.

In a personal series of 19 cases of acute myocardial infarction which are considered in detail in part V. of this paper, 8 showed a definite lowering of whole or diluted (25%) plasma prothrombin time, whereas 11 showed normal or raised figures. Evidence of a clotting tendency in the shape of an increased resistance to heparin was found in 7 out of 8 cases in which a heparin tolerance test was performed. In 3 of these 7 cases the prothrombin time was normal. On the other hand, all cases showing a lowered prothrombin time in whom heparin tolerance was estimated showed an increased resistance. These figures are too small to be of much significance, but they suggest that a clotting tendency can be demonstrated in some cases of myocardial infarction but not in all and that this tendency is better revealed by a heparin tolerance test than by reliance on estimations of prothrombin time. The methods of performance and significance of these tests is dealt with in detail in a later section.
Apart from the probability of fundamental changes in the coagulation system of the blood there are certain factors which are known to be of importance in the genesis of intravascular thrombosis following myocardial infarction. There is increased viscosity of the blood in the presence of the haemoconcentration of "shock" or congestive heart failure (Best & Taylor) The lowered blood pressure is associated with a diminished cardiac output and a slowing of the circulation. The consequent tendency to peripheral venous stagnation is enhanced by prolonged bed-rest with its attendant immobility of the legs and diminished respiratory excursion. Certain drugs commonly used in the treatment of cases of myocardial infarction have been held to increase the clotting tendency, though there is some conflict of evidence on this point. Drugs which have been incriminated are digitalis, the methylated xanthines and the mercurial diuretics.

de Takats et al. (1944) have recorded that in both man and experimental animal digitalisation increases resistance to heparin. Macht (1943) found that the various digitaloids added to shed blood in vitro hasten coagulation. Massie and his co-workers (1944) found that the coagulability of the blood was increased in each of 24 patients during administration of full doses of digitalis. Massie's paper is open to criticism on the grounds that he compares a single figure/
figure, the lowest clotting time reached during digitalisation, with the average of clotting times recorded during a short period before digitalis. In the 2 control untreated cases which he charts there is a spontaneous fall in clotting time comparable to that in the treated cases. Furthermore, some of his treated cases show a return of clotting times to previous levels while still under digitalis.

Sokoloff & Ferrer (1945) and Moses (1945) in 2 short series of cases, 10 and 8 respectively, which are more convincingly presented than that of Massie, failed to find any support for the hypothesis that oral digitalisation increases the coagulability of the blood.

On the other hand, Askey & Neurath (1945) stress the danger of digitalis in coronary thrombosis. In 32 cases of coronary thrombosis with auricular fibrillation and congestive heart failure 31 died, 13 of them with arterial emboli, whereas in 16 similar cases treated with quinidine, with a combination of quinidine and digitalis or receiving no medication there were no arterial emboli, though 11 died. Their best results were on combined quinidine and digitalis therapy. (It is of interest that quinine is reported to lower the prothrombin level in the blood (Pirk & Engelberg, 1945). It appears likely that quinidine has a similar action and hence may act as an antidote to digitalis in respect of its presumed/
presumed action on the coagulability of the blood.) They conclude that treatment by digitalis alone is contra-indicated in myocardial infarction with auricular fibrillation. Peters et al. (1946) record that of 17 cases of myocardial infarction with congestive heart failure treated with digitalis, 9 died, most of them from embolism, but in 8 similar cases treated with digitalis and anticoagulants, there were no emboli and 1 death only - and that from renal complications.

With regard to the methylated xanthines there appears to be general agreement that they induce a clotting tendency. Morawitz (1926) lists euphyllin as a substance which hastens coagulation. Field & Larsen, quoted by Link (1943), have shown that large single doses of caffeine, theophylline and theobromine given orally to dog, rabbit or rat induce hyperprothrombinaemia. Investigations by Scherf and Schlachman (1946) have revealed that there is a definite shortening of the prothrombin time and of the plasma coagulation time in man following an intravenous injection of aminophylline.

The mercurial diuretics have been shown by Macht (1946) to produce a prompt and marked fall in clotting time when injected intravenously into experimental animals. Link (1943-4) states that they are potent hyperprothrombinaemia-producing agents.

The
The various factors which may be considered to play a part in the genesis of the thrombo-embolic complications of acute myocardial infarction have been considered in detail. The evidence for a fundamental upset of the coagulation system of the blood, responsible both for the initial coronary thrombosis and for any subsequent thrombo-embolic process is strong but it is not complete. However, we must remember, with Goethe 'Blut ist ein ganz besonderer Saft' and the methods at our disposal of detecting changes in the thrombosing balance are at the best crude and incomplete. Estimation of the prothrombin time is not necessarily an accurate reflection of the prothrombin level (Macfarlane 1948) and even if it were completely reliable, it measures only one of many factors concerned in coagulation. The clotting time of whole blood in vitro is a crude device, subject to great variation and what happens in a test-tube or capillary tube may bear little relation to events within a living blood vessel. It appears likely that some form of heparin tolerance test is at present the best means at our disposal of assessing the existence of a clotting tendency, though even this test gives negative results in a small proportion of cases with known intravascular thrombosis. (Hagedorn & Barker 1948).

Disease of the arterial wall has always been considered the chief factor in the production of a coronary/
coronary thrombosis. The local thrombus has usually been regarded as the mechanical result of necrosis or erosion of the atheromatous intima or of rupture of an atheromatous "abscess". The existence of a clotting tendency has received little attention but it appears likely that it plays the primary role in those cases of coronary thrombosis in which little atheroma is demonstrable at post-mortem, and also in those cases in which coronary thrombosis is but one of many widespread thrombotic processes occurring simultaneously. Gibson (1949) has advanced the remarkable theory that a clotting tendency may be the cause not only of the local thrombosis but also of the disease of the arterial intima. He instances the findings of Duguid (1948) and Harrison (1948). The former claims that the lesions commonly described as atherosclerosis may arise by organisation of a mural thrombus and substantiates his statement with convincing photomicrographs. Harrison went one step further and produced lesions indistinguishable from arteriosclerosis in the pulmonary arteries of rabbits by injecting finely fragmented fibrin clot into their ear veins. Gibson concludes that increased coagulability of the blood is the beginning and end of the process that ends in coronary thrombosis, and that it is for the biochemists to discover the origin of this disorder. The pathologists' findings require further confirmation and Gibson's conclusions are premature though/
though thought-provoking. The warning sounded by Clifford Allbutt in this very connection must be borne in mind. In discussing the causes of arteriosclerosis he remarks "Our path is cumbered with guesses, presumptions and conjectures, the untimely and sterile fruitage of minds which cannot bear to wait for the facts, and are ready to forget that the use of hypotheses lies not in the display of ingenuity but in the labour of verification." At risk of standing retrospectively under Allbutt's obloquy it is suggested that cholesterol metabolism may have some bearing on Gibson's theory. There is a wealth of experimental evidence that disturbance of lipoid metabolism plays a part in the pathogenesis of arteriosclerosis (Leary 1941, Dauber and Katz 1943). Though the level of blood cholesterol is variable in cases of myocardial infarction, conditions in which blood cholesterol is high, diabetes mellitus and myxoedema, are liable to be complicated by coronary disease. Morrison and his associates (1948) found hypercholesterolaemia in 68% of 75 patients under the age of 60 with proven acute coronary occlusion, though normal levels were found in 52% of 125 patients over 60 with similar lesions. Hobson and Witts (1941) state that lipaemia lowers the prothrombin time. They found that the addition of lecithin to the reagents markedly lowers the prothrombin time of normal plasma, that is it increases the prothrombin activity. It is/
is suggested that the estimation of prothrombin time and heparin tolerance in patients with hypercholesterol-aemia might yield information of value. Prothrombin time estimations carried out in 5 such cases (3 coronary thrombosis, 1 diabetes mellitus and 1, surprisingly, extrahepatic obstructive jaundice of six weeks standing) were markedly lowered in all. It seems possible that there is an association between disorder of lipoid metabolism and changes in the thrombosing balance of the blood.

(c). Conclusions.

It has been shown that thrombo-embolic processes are frequently associated with episodes of acute myocardial infarction and that they increase the risk of death or subsequent invalidism. The causes of such complications have been considered and evidence presented for the existence of a clotting tendency in the blood. The theory that such a disturbance of the coagulation system is the fons et origo of coronary thrombosis has been discussed and a tentative link forged with a fundamental disorder of lipoid metabolism.

Whether the existence of an alteration in the thrombosing balance of the blood is agreed to or not, the reality and significance of thrombo-embolic complications of coronary thrombosis cannot be gainsaid. If intravascular clotting can be prevented following such
such lesions, then it is likely that mortality and morbidity will be reduced.

The trial of anticoagulants in acute myocardial infarction is based on sound pathological grounds.
III. Anticoagulants.

In animal experiments many substances have been shown to have the property of inhibiting coagulation. Most of these, such as hirudin, Germanin, neodymium, salvarsan, Liquoid Roche and various azo-dyes have proved inapplicable to human medicine on account of toxicity or some other insuperable disadvantage. Two anticoagulants, however, heparin and dicumarol have been applied with success to the prophylaxis and treatment of thrombo-embolic conditions in man.

(a) Heparin.

(i) Historical Review.

Heparin was discovered by Howell and McLean in 1916. They isolated it from tissue extracts of liver, muscle, heart, lymph nodes and later from lung. In a Harvey Lecture in 1917 Howell spoke of its lack of toxicity and of its possible future application in 'the therapeutic treatment of disorders of coagulation'. His prophecy was slow of realisation. But after Charles & Scott (1933) had developed an improved method of extraction and Jorpes (1935) had elucidated its chemistry as a complex of esters of mucoid polysulphuric acid, production was begun on a large scale. Murray and his associates (1936 & 1937) reported success in the prevention of experimental thrombosis in animals and Solandt and Best (1938) showed that prior heparinisation prevented the experimental/
experimental cardiac infarction in dogs which is normally produced by intra-arterial injection of sodium ricinoleate. By this time it had already been established that heparin could be administered by repeated intravenous injection successfully and with safety to man (Howell & MacDonald, 1930) (Hedenius & Wilander, 1936). Therapeutic trial was instituted by Crafoord in Stockholm and by Murray and his associates in Toronto and a series of papers from both centres during the next few years clearly indicated that thrombosis, post-operative or puerperal could be prevented by regular treatment with heparin in sufficient doses over an adequate period (Crafoord (1937, 1941, 1942) Murray et al. (1936, 1937)).

The prophylactic effectiveness of heparin was expected but it was not generally foreseen that it would prove even more useful as a therapeutic agent in thrombosis. Crafoord (1939) and Murray and Best (1938) were the first to testify to this and since then a host of authors, too numerous to quote, have confirmed their findings. Crafoord and Murray first proved the curative value of heparin in peripheral phlebothrombosis and pulmonary embolism but subsequent reports have shown that it is also effective in other thrombotic conditions such as thrombosis of the central retinal vein (Holmin 1938) thrombosis of the posterior inferior cerebellar artery (Magnusson 1938), mesenteric thrombosis (Murray and Mackenzie 1939, Luke 1943) and cavernous sinus thrombosis (Lyons 1941, Wiesenfeld/
Wiesenfeld & Phillips 1944). The thrombolytic action of heparin has been demonstrated by Rabinowitch and Pines (1943). They showed that a course of heparin started on the first or second day after the induction of a jugular venous thrombosis in rabbits, caused the thrombus to disappear.

The history of the discovery of heparin and of its sudden rise to therapeutic prominence many years later is a dramatic one comparable to that of penicillin. The expense and difficulty of its production had for too long been barriers to the experimental and clinical assessment of its value and expense still to some extent limits its more widespread exploitation in the prophylaxis of thrombo-embolisation.

(ii) Pharmacology.

Howell aptly described heparin as a physiological anticoagulant. Researches by subsequent workers (Mellanby 1934, Quick 1935, Ferguson 1937-8, Brinkhous et al. 1939) have confirmed the physiological role of heparin in the coagulation system. It has a multiple effect, neutralising thrombokinase, acting as an antiprothrombin (an action which is inhibited by excess of thrombokinase) and also, in the presence of plasma and neutral salts acting as an antithrombin. Its mode of interference appears to be a physico-chemical reaction dependent upon the very strong electrical charge which its molecule carries, the strongest charge apparently of all organic compounds of the animal body (Jorpes/
Fig. I. represents diagrammatically the Schmidt-Fuld Morawitz theory of coagulation and the action of heparin in the coagulation system.

Scheme of coagulation of the blood.

Fibrinogen → Calcium → Prothrombin → Thrombokinase → Thrombin → Heparin (+ Plasma Albumen) → Fibrin

Fig. I.

Careful investigations by Jorpes (1936) Holmgren & Wilander (1937) have shown that the site of formation of heparin is in the mast cells which are found widespread in the body tissues, mainly in the connective tissue in the vicinity of capillaries and in the walls of blood vessels. As would be expected from the fact that heparin is a normal constituent of the body, its toxicity is low. True anaphylactic reactions have occasionally been recorded in a very small proportion of cases (Jorpes 1946) Cortes and his associates (1947) were unable to produce, in Schultz-Dale studies, any evidence of anaphylactic sensitivity in the guinea-pig following attempts at sensitisation with heparin. The danger of haemorrhage appears to be surprisingly small. Haematomata may appear post-operatively but this risk is/
is obviated if heparinisation is not started until 24 hours after operation. Transient insignificant haematuria has been recorded (Ershler & Blaisdell 1941, Priestley, Essex & Barker, 1941). Haemorrhage into the pleura following heparin treatment for pulmonary embolism has been infrequently reported. In respect of the 2 cases mentioned by Falconer (1943) Jorpes states that in one, which died of pulmonary embolism, the dose of heparin was totally inadequate and in the second it was excessive. In the rare event of severe haemorrhage due to heparin the intravenous injection of 5 to 10 cc. of 1% protamine sulphate will restore the clotting time of the blood instantaneously to normal. Heparin is usually administered intravenously either by intermittent injections or by a continuous drip. The latter method is theoretically sounder since the blood clotting time returns to normal within 3 hours of a single injection but the former is the more common and the more generally useful method, and has proved quite as effective in practice. The dosage varies from 5,000 - 12,500 units every 4-6 hrs., the exact dose being controlled by daily estimations of the clotting time. Some simple methods of overcoming the difficulties of arranging for repeated intravenous injections are considered in part V. of this paper. Intra-muscular injections of heparin have been recommended by Walker (1945) but in the authors experience, the effect on the clotting time is capricious/
capricious and unpredictable and haematomata may form at the site of injection.

Attempts have been made to obviate the tedium of repeated intravenous injections and to economise in heparin by means of preparations designed to delay the absorption of heparin from a subcutaneous depot (Loewe & Rosenblatt, 1944) or an intramuscular one (Vorzimer et al. 1948, Stats & Neuhof 1947). The value of such preparations has not been widely confirmed and their use has not been considered in the present study since they are not suitable for combined heparin-dicumarol therapy.

The historical development of heparin as a therapeutic agent and its present place in prevention and treatment of thrombotic conditions have been reviewed. Its physiological aspects, mode of action, method of administration and disadvantages have been briefly considered. It is concluded that there are sound pharmacological grounds for the trial of heparin in acute myocardial infarction but that its expense and the necessity for parenteral administration make it impractical to use heparin throughout the period of risk of thrombo-embolic complications.

(b) Dicumarol

(i) Historical review.

The story of the emergence of dicumarol as a potent anticoagulant is an absorbing one. As is common in biology, the discovery of its therapeutic value/
value was incidental to an apparently unrelated piece of research. "Sweet-clover disease" of cattle, which is characterised by massive, usually fatal, haemorrhages had interested and baffled veterinarians for many years. Careful and determined research at the Wisconsin Agricultural Research Station finally led to the isolation from 'spoiled sweet-clover' of the causative agent in crystalline form (Campbell & Link 1941). It was identified chemically in the same year by Stahmann, Houbner & Link as 3,3'-methylenebis (4 hydroxycoumarin) and finally synthesised by the same team, who showed that it caused haemorrhage by lowering the prothrombin activity of the blood. These studies, which are admirably presented by Link in the Harvey Lectures (1943-4), were carried out at a time when the increasing use of heparin in the treatment of thrombo-embolisation had made anticoagulant therapy the subject of frequent discussion and the possibilities of the new substance were immediately realised. It was named "dicumarol" by the Council of Pharmacy of the American Medical Association and animal experiment and clinical trial were immediately instituted.

Administration of dicumarol was shown to prevent the arterial and venous thrombosis which can be produced in dogs by a variety of experimental techniques (Bollman & Preston 1942, Dale & Jaques 1942, Richards & Cortell 1942). Extensive clinical trial/
trial has affirmed the value of dicumarol as a prophylactic and therapeutic agent in thrombosis. A steady stream of favourable reports has appeared since 1942. In prophylactic studies the largest and most convincing series have been the 1448 cases of Bruzelius (1945) the 1000 surgical cases of Barker and his associates (1945) and Allen's (1947) series of 1686 cases. All these observers found a marked reduction in thrombo-embolic complications in cases receiving dicumarol prophylactically. The same workers also found, in smaller series, that dicumarol is effective in the treatment of established thrombosis. Zilliacus (1946), in a study of surgical, obstetric and medical cases, found that in 214 patients with deep venous thrombosis who received no specific treatment, the average length of confinement to bed was 35 days, pyrexia persisted for 21 days on the average and 59 patients developed pulmonary embolism. On the other hand in 131 similar cases treated with dicumarol, the average confinement to bed was 9.5 days, the average duration of pyrexia was 8.2 days and pulmonary embolism occurred in only 2.

The reports do not indicate that dicumarol is 100% effective in preventing venous thrombosis or the extension of an already existing thrombus but that the incidence of such complications is very markedly lessened.

(ii) Pharmacology.

Link/
Link and his co-workers showed that dicumarol acts by depressing the prothrombin activity of the blood. The effect is delayed for a variable period after the initial dose of dicumarol—usually from 24-72 hours. The exact mechanism of production of hypoprothrombinaemia is not clearly known but it is generally believed that the drug acts by preventing synthesis of prothrombin in the liver. There is also evidence that it diminishes the production of fibrinogen in the liver (Jaques & Irish 1944). The effect of a given dose in different individuals is unfortunately highly variable. Dosage from day to day can be controlled only by the daily estimation of prothrombin time. This is a tedious procedure and is only an indirect and not altogether satisfactory means of assessing the level of prothrombin in the blood. However it is the only method at present available.

It is obvious that treatment by dicumarol uncontrolled by prothrombin time estimations is very likely to produce in man an attack of the haemorrhagic sweet-clover disease of cattle. It has also unfortunately become clear that careful control of dosage by daily prothrombin estimations will not entirely obviate the risk of haemorrhage in a small number of cases. In Bruzelius’ whole series of 1656 cases treated with dicumarol, haemorrhage occurred in 13 with 3 deaths. Evans (1944) reported 8 cases of haemorrhage in a series of 55 with death in 2. In
the more recent report of Allen (1947) minor haemorrhage is recorded in 3.1% of 1686 cases, major bleeding in 1.9% and there were 2 deaths from haemorrhage. Allen states that dicumarol was not the cause of bleeding in one of these cases and its responsibility was doubtful in the other case. Reich and Eisenmenger (1948) have recorded the occurrence of frank haemorrhages in cases with a "safe-level" of prothrombin and have noticed that very high, apparently dangerous, prothrombin times are not necessarily attended by bleeding.

Prothrombin deficiency induced by dicumarol can usually be corrected by large doses intravenously of a Vitamin K analogue. Cromer & Barker (1944) showed that intravenous injection of 64 mg. of menadione bisulphite was effective in 35 out of 37 cases of dicumarol hypoprothrombinaemia and that haemorrhage was promptly controlled. The return of prothrombin levels to normal started 2 hours after the injection and was complete in 18 hrs. Reich & Eisenmenger (1948) found that 60-120 mg. of water soluble vitamin K intravenously successfully restored normal prothrombin levels in all hyper-reactors to dicumarol. De Bakey (1943) on the other hand, states that vitamin K has no effect on haemorrhage due to dicumarol but produces no evidence in support of his statement. Miller and Drucquer (1948) found that vitamin K was ineffective in their case of dicumarol poisoning but they administered the vitamin intramuscularly/
It is unanimously agreed that transfusion of 500 cc. of fresh blood will temporarily raise the prothrombin level sufficiently to control haemorrhage, but in severe cases the level may fall again and further transfusion may be required. Allen (1947) suggests that careful prothrombin time estimations and the use, where necessary, of intravenous vitamin K and blood transfusion will prevent any fatalities from dicumarol.

Intravenous administration of large doses of the sodium salt of dicumarol to dogs has an immediate toxic effect with hyperglycaemia, pyrexia (without hypoprothrombinaemia) and circulatory collapse with capillary dilatation, Wakim & Gatch (1943). Such an effect has not been described in man on therapeutic oral doses but evidence of damage to capillaries has been described in the shape of petechiae and positive capillary fragility test, usually in cases with dangerously low prothrombin levels but also in some cases with prothrombin times at a safe level within the therapeutic range (Reich & Eisenmenger 1948).

Hepatic necrosis occurs in 50% of animals receiving massive doses of dicumarol but no liver damage has been recorded in man even in cases which have suffered profuse haemorrhage from accidental overdosage.

Dicumarol therapy is contra-indicated in haemorrhagic blood dyscrasias, in conditions in which there/
there is likely to be a low prothrombin level in the blood, such as obstructive jaundice, the sprue syndrome and advanced hepatic disease and also in renal failure which tends to prevent elimination of the drug. The administration of dicumarol is also held to be unwise in the presence of ulceration of the alimentary tract, owing to the risk of haemorrhage. The danger of haemorrhage under dicumarol treatment must be viewed in a proper perspective and must be balanced against the benefits of such therapy. Allen (1947) in his study of 1686 surgical cases receiving dicumarol prophylactically or therapeutically calculated the expected incidence of thrombo-embolic complications and the expected death rate from such complications on the basis of the careful statistical study of Barker and others (1940). He found that approximately 73 lives were saved by the use of dicumarol and 211 patients were spared venous thrombosis and pulmonary embolism. There was only 1 death from haemorrhage that might possibly have been attributed to dicumarol.

The evolution of dicumarol as an anticoagulant and its value in the prophylaxis and treatment of venous thrombosis and pulmonary embolism have been briefly reviewed. A short account has been given of its mode of action and disadvantages. It is felt that there is sound justification for the controlled and cautious trial of dicumarol in the management of cases of acute myocardial infarction.
(c) Combined heparin - dicumarol therapy.

Neither heparin nor dicumarol is the ideal anticoagulant. Heparin has the disadvantage of expense and the need for parenteral administration which counterbalance its safety, ease of control and rapidity of action. Dicumarol, though cheap and easy to administer, requires the employment of a tedious and time-consuming laboratory procedure to control dosage and, even so, its use is by no means free of risk. It carries the further drawback that its effect is delayed for some time after administration and continues for a variable period after the drug is stopped.

Some of these disadvantages can be overcome by combined heparin and dicumarol therapy. If administration of both anticoagulants is started simultaneously an immediate effect is obtained from the heparin and, when the dicumarol takes effect, usually in 2-3 days, then the heparin can be discontinued. Further injections of heparin can be given, if at any time the prothrombin level rises above the intended therapeutic range.

Such a technique, which is considered in detail in part V. of this paper, would appear to be the best method at present available for the application of anticoagulants to the treatment of myocardial infarction. Most workers in this field have used dicumarol alone on the grounds that thrombo-embolic complications are/
are not commonly observed in the first 2 or 3 days following the episode of infarction. It is very likely, however, that spreading retrograde thrombosis and possibly mural thrombosis do occur in some cases during this period. Furthermore there is sufficient experimental and clinical evidence for the contention that anticoagulants actually dissolve a preformed clot. Loewe and his associates (1947-1948) showed conclusively that both heparin and dicumarol can cause resumption of patency in veins of experimental animals which have been thrombosed for periods as long as 2 weeks. The recognised therapeutic efficacy of anticoagulants in established deep venous thrombosis can hardly be explained on any other grounds than recanalisation by dissolution of thrombus. Such an action is strong support for the use of heparin at the earliest possible moment in cases of coronary thrombosis in the hope that patency might possibly be restored to the blocked vessel.
IV. Anticoagulants in Myocardial Infarction.

Review of literature.

Solandt & Best demonstrated the effectiveness of heparin in preventing experimental myocardial infarction in dogs in 1938 and later showed (Solandt, Nassim & Best, 1939) that heparin was equally effective in preventing the experimental production of mural thrombi in dogs. Though they concluded from this experiment that clinical trial of heparin was indicated, clinicians were slow to follow up their suggestion. It was apparently felt that heparin would increase the risk of intimal haemorrhage which was at that time considered to be an important factor in the production of coronary thrombosis (Graybiel & White 1939). It has more recently been shown (English & Willius 1943) that intimal haemorrhage, though a common phenomenon in coronary atherosclerosis, plays a major role in the production of coronary thrombosis in very few instances.

The first clinical trial of anticoagulants in coronary thrombosis appears to have been made by Holten & Lundsteen (1942) but their report unfortunately has not been accessible to the author. The first available clinical study is that of Wright (1945) who treated his first case with dicumarol in 1942. He selected patients to receive dicumarol who had suffered repeated episodes of thrombosis in different branches of the coronary tree or whose original thrombus had propagated or who had suffered repeated embolic/
embolic incidents, pulmonary or systemic. These indications were based on analogy with the rationale of anticoagulant therapy in other forms of thromboembolic disease. The use of dicumarol was not long restricted to patients with such complications and a number of reports have appeared in the American literature on the use of anticoagulants in all cases of myocardial infarction without selection. An extensive combined investigation on these lines is at present being pursued in 16 American hospitals under the auspices of the American Heart Association.

Before these reports are reviewed, some interesting observations that have recently been recorded in relevant experimental and clinical studies will be considered. Blumgart and others (1948) studied the effect of dicumarol on the heart in experimental acute coronary occlusion in dogs. They found no difference between treated and control animals in respect of the incidence and magnitude of haemorrhagic extravasations in the endo- and pericardium, the extent of microscopic miliary haemorrhages, the size and healing of infarcts, the presence of thrombi in smaller arteries in the infarcted area and the development of an anastomotic circulation. They found that severe hypoprothrombinemia in 3 dogs caused no increase in haemorrhage. They conclude that dicumarol produces no adverse effects on the myocardium of dogs which retard the healing process or development of collateral circulation in experimentally produced myocardial infarction.

Leroy/
Leroy & Nalefski (1948) in a similar study, reached the same conclusion. They found no evidence that intimal haemorrhage was of significance in any of their cases. Serial electrocardiograms did not show any consistent significant difference between treated and control animals.

These reports suggest that the action of dicumarol, recorded by Loewe et al (1948), of dissolving a preformed clot and opening up collateral channels, does not operate in coronary thrombosis. However it must be remembered that in the experiments of Blumgart and Leroy a coronary artery was ligated and therefore patency could not be restored whereas in clinical coronary thrombosis the dissolution of the clot and opening up of the lumen of the vessel is theoretically possible. That such an event is unlikely is shown by the studies of Balkin & Gootnick (1948) on the effect of dicumarol on the electrocardiogram. They found that the administration of dicumarol for several weeks had no effect on the electrocardiograms of patients with cardiac infarction, nor incidentally of normal subjects nor of patients with varying types of cardiovascular disease. Serial electrocardiograms of those with infarction showed the expected progressive changes of healing infarction. The rate of progress did not differ materially from that observed in patients not receiving dicumarol.

These studies appear to establish that dicumarol has neither a harmful nor a beneficial effect on an area/
area of infarcted cardiac muscle. If dicumarol therapy lessens mortality from myocardial infarction it must be by prevention of thrombo-embolic complications. These conclusions probably apply to heparin therapy also but not with certainty, for Loewe (1948) has shown that heparin is more effective than dicumarol in dissolving a preformed in vivo clot.

These side-lights on anticoagulant therapy are of interest but assessment of the value of anticoagulants in the treatment of myocardial infarction must of course ultimately depend on their observed effect in actual clinical practice. The experiences of the various workers in this field in respect of reduction of mortality rates, reduction in incidence of thrombo-embolic complications, methods of control and incidence and severity of toxic effects will be discussed and summarised.

Wright (1946), in his second publication in this connection, recorded a mortality rate of 25% in his initial series of 43 complicated cases as contrasted with an anticipated mortality of 60-70%. In uncomplicated cases, in which he anticipated a mortality of 20-30%, the death rate was 12%. In 38 of the 43 complicated cases there was no further evidence of extension of the thrombosis or of additional thrombi or emboli after the start of dicumarol therapy. Toxic effects were confined to minor purpuric eruptions in three patients. In 8 autopsies no/
no evidence was found of damage attributable to dicumarol. Wright did not study a control series and the figures that he quotes of anticipated mortality, were based, on his own admission, on clinical impressions and not on any adequate statistical data. It may be objected that he placed the anticipated risk too high. He quotes case histories of patients in whom a series of thrombo-embolic episodes ceased promptly under the effect of dicumarol. He concluded that dicumarol was likely to prove of value in cases of coronary thrombosis complicated by further thrombo-embolic processes but that his material did not justify the conclusion that dicumarol would effect the results in uncomplicated coronary thrombosis.

In series subsequently reported no such selection of cases has been exercised and anticoagulant therapy has been applied to cases of myocardial infarction whether complicated or not. Peters, Guyther & Brambel (1946) selected their cases for dicumarol therapy on different grounds. They noted that 3 out of 4 cases of coronary thrombosis showed a clotting tendency as judged by a definite lowering of the prothrombin time of 12.5% diluted plasma and regarded this as their indication for anticoagulant administration. In 50 treated cases there were 2 deaths, 1 from heart failure, 1 from renal failure as compared with 13 deaths, 6 of which were from emboli, in 60 controls. They do not state if the 60 controls included these cases/
cases which did not show a clotting tendency, nor if any of the latter developed thrombo-embolic complications. Their 50 treated cases showed only 1 embolic incident. Dicumarol therapy had been delayed in this case until the 8th day. On the 9th day there was twitching and weakness of the left hand and on the 10th when the prothrombin time showed that he was well under the influence of dicumarol, the patient had a generalised convulsion and developed a transient left hemiparesis. Recovery thereafter was uneventful and the authors thought that the delay in dicumarol therapy might well have favoured the building up of a sizeable mural thrombus. In the 60 untreated cases there were 10 with clinical embolism, pulmonary, cerebral or peripheral. The authors also studied the effect of digitalis. 17 of the 60 control cases received digitalis for congestive failure and 9 of these died, most of them from embolism, whereas of 8 treated cases receiving digitalis, only 1 died (from renal complications). Few toxic reactions from dicumarol were noted in this series. Microscopic haematuria occurred in 3, there were no gross haemorrhages and no delayed toxic effects. It is noteworthy that the prothrombin level was maintained at 35-50% of normal, a level which later authors regard as too high (Wright et al. 1948) and dicumarol was administered for 6 weeks, which is considerably longer than in any other series. The authors concluded that further clinical evaluation of dicumarol in myocardial infarction/
infarction was warranted.

Nichol (1947) treated with dicumarol all cases of myocardial infarction seen by him from June 1943 to June 1946. In 68 attacks occurring in 62 patients there were 11 deaths - a mortality rate of 16%. 3 of the deaths occurred before dicumarol could take effect. There were 2 possible embolic incidents under dicumarol, a doubtful pulmonary embolism, and a mesenteric arterial occlusion. In 8 post mortem cases there was no evidence of mural thrombi or emboli nor of haemorrhage or liver damage.

Parker & Barker (1947) report the use of anticoagulants in 50 cases, 10 on combined heparin-dicumarol therapy, 40 on dicumarol alone. There were 5 deaths, 2 from acute heart failure, 2 from congestive failure and 1 from a second coronary thrombosis. Vascular complications occurred in 4, 2 patients developing a second coronary thrombosis and 2 cerebral emboli. There were also 2 cases of pulmonary embolism and 2 of peripheral arterial occlusion before anticoagulants were started. Haemorrhage occurred in 3 cases, haemarthrosis of the knee in 1, epistaxis in 1 and haematuria in 1. They are the first authors to point out the difficulty of controlling the prothrombin level. They endeavoured to keep it within the range of 10–30% of normal, but found that it fell too low in 12 cases, 6 of whom required vitamin K to restore it to the optimum range. In 18 cases (36%) there was difficulty in maintaining the/
the desired deficiency of prothrombin and in one of these a second myocardial infarction occurred. They concluded from their findings that the continued use of heparin and dicumarol in coronary thrombosis was warranted.

The series reviewed above, with the possible exception of that of Peters and his associates, carry less weight than they might because of the lack of comparable control series of untreated cases. Glueck and her co-workers (1948) obtained a control group by administering anticoagulants to every alternate case of myocardial infarction admitted to their hospital. Their groups were reasonably comparable in respect of age, sex, previous heart disease and cardiac enlargement. Treatment was by simultaneous dicumarol by mouth and heparin by continuous intravenous drip (300 mg. heparin in 1 litre of 5% glucose - 20 to 35 drops per minute) until prothrombin level was 20-30%, when heparin was stopped. In 25 treated cases there were 3 deaths and 1 doubtful embolic complication (a transient facial palsy and aphasia) whereas in the control untreated group of 25 there were 8 deaths and 6 cases with emboli. The authors state that in many cases the intensity of the pain and its duration seemed markedly reduced by the intravenous administration of heparin in glucose but think that further observations are necessary before conclusions can be drawn. All the treated cases who died were found to have massive infarction at autopsy - none showed mural thrombi/
thrombi or emboli. 2 patients showed evidence of haemorrhage probably attributable to dicumarol, one with a prothrombin concentration of 13% had gross haematuria, the other had one tarry stool when the prothrombin fell to 17%. The former responded well to intravenous vitamin K, the latter required no such treatment and had no recurrence of melaena. In a brief addendum to their report, the authors record their study of a further 19 cases in each series, treated and controls, and give final consolidated figures of 20% mortality and 7% emboli in those receiving anticoagulants and 43% mortality and 27% emboli in the control series. The authors do not claim any dramatic success for anticoagulant therapy but are content to observe that it does not seem to do any harm to cases of myocardial infarction.

Greisman and Marcus (1948) administered dicumarol to 75 cases and studied 100 comparable cases not receiving anticoagulants. There were 7 deaths, 2 of which were due to cerebral thrombosis, in the treated cases and 35 deaths in the control series. Thromboembolic lesions occurred in 3 of the treated series and in 21 of the controls. They omitted from both series, treated and controls, cases which died within 48 hrs. of admission to hospital. This omission has the effect of increasing the relative superiority of the mortality rate in treated cases over that in the controls and makes their figures not strictly comparable with/
with the mortality rate generally reported in other series which are not selected in this way. 17 control cases required digitalis for congestive heart failure and of these, 9 died, 5 of them from emboli, whereas in 15 cases with congestive failure requiring digitalis among the treated group there were only 3 deaths, none of them from embolic processes. The authors state that prothrombin estimation every second day is adequate for control of dicumarol dosage. They regard a prothrombin level of 10-30% of normal as the optimum therapeutic range and found that where bleeding occurred in the presence of a prothrombin level lower than 10%, intravenous vitamin K controlled the bleeding and raised the prothrombin above 10% within 24 hours. No major haemorrhagic episodes were seen under the effect of dicumarol but 2 patients had minor rectal bleeding from haemorrhoids and one had macroscopic haematuria. The authors feel that dicumarol should be administered to patients with acute myocardial infarction, particularly those who are in congestive heart failure and are receiving digitalis.

Among 300 varied cases treated with anticoagulants, prophylactically or therapeutically, Reich and Eisenmenger (1948) studied dicumarol therapy in 24 cases of myocardial infarction. There were 4 deaths in this small series, 2 from progressive cardiac failure, 1 with clinical and electrocardiographical evidence/
evidence of progressive cardiac damage and 1 from a fresh episode of coronary thrombosis whilst receiving dicumarol. A similar but non-fatal episode occurred in one other case under adequate dicumarol dosage. They record no other thrombo-embolic complications and advance the opinion that anticoagulants are unable to influence the development of further coronary thromboses where degenerative disease is sufficiently advanced but that their main usefulness lies in preventing embolisation from peripheral veins or mural thrombi. The prothrombin level which they recommend is the upper level of the therapeutic range recommended by other workers. They state that the object is to prolong the prothrombin time by Quick's method to twice normal. This is equivalent to a prothrombin level of 30% and may not be quite low enough. However they quote cases to show that haemorrhage may occur at reputedly safe prothrombin levels and also that extremely low prothrombin levels may occur without bleeding. They stress the great individual variation in response to dicumarol. They found that some coronary patients, particularly those with congestive heart failure and presumable reduction in renal blood flow, were unduly sensitive to dicumarol. McCall (1948) treated with dicumarol 71 cases of myocardial infarction, consecutively admitted to his care. He omitted from his series 3 patients who died within 48 hrs. of admission. There were 9 deaths, 1 from a pulmonary/
49.
pulmonary embolism on the 6th day, 1 from progressive extension of a second infarction on the 20th day, 6 from heart failure and 1 from a ruptured ventricle. Thrombo-embolic complications numbered 2 only. In post-mortem cases no mural thrombi were found. Gross haematuria occurred in 3 cases, but was readily controlled by intravenous injection of 60 mg. of menadione bisulphite. 2 cases had mild epistaxis. The authors record an unexplained difficulty in maintaining the desired prothrombin level in 21 cases. In 10 of these a lapse of 4 days occurred initially before a therapeutic range was attained. On 4 occasions the prothrombin fell to dangerously low levels without haemorrhage. There were 6 patients in whom effective therapeutic control lapsed for a day or more without mishap. The authors conclude that though certain features of dicumarol therapy are undesirable, the therapeutic approach is sound.

The most significant and authoritative analysis of anticoagulant therapy of myocardial infarction that has yet appeared is embodied in the preliminary report, from the pen of Wright and his associates (1948), on the combined investigation at present being pursued in 16 American Hospitals. The plan in this project has been to administer anticoagulants, either dicumarol alone or combined heparin and dicumarol at the discretion of the physician in charge of the case, to all patients with myocardial infarction admitted on odd days/
days of the month and to withhold such treatment from those admitted on even days, the latter group to serve as control cases. The anticoagulant, odd-day group has numbered 432 cases and the control, even-day, 368. The groups were comparable in age, sex, history of previous infarction and severity. 12% of the control group did receive some anticoagulant therapy, usually for short periods only, due to pressure of the family or private physician. In the treated group, 81% received dicumarol only, 14% dicumarol and some heparin, 3% no anticoagulants because of specific contra-indications and 2% no anticoagulants because of miscellaneous errors.

In presenting their figures the authors have made small conservative corrections for some of these anomalies. In the control group, rates have been corrected for exceptions to the 'no anticoagulant' rule; the figures differ only slightly from those actually reported but are believed to present a truer picture. In the treated group rates have been justifiably corrected for erroneous omission of anti-coagulants but not for those cases in which anti-coagulants have been withheld because of specific contra-indications. Such omissions are held to be disadvantages inherent in this type of therapy.

The death rates were 15% in the treated group, 24% in the controls. The greatest improvement was in those who had suffered one or more thrombo-embolic complications/
complications, for whom the figures were controls 10% deaths, treated 3%. Mortality was greatest in the first 2 weeks but was significantly high in 3rd and 4th week also. Study of death rates by age groups showed great reduction of mortality in treated patients over 60. In those under 60 there was no significant difference between the treated and control groups.

The incidence of thrombo-embolic complications recognized clinically was 36% in the controls and 14% in those treated - but of these, 5% occurred in patients not receiving anticoagulants and 2.5% occurred during the first 3 days of dicumarol treatment giving a corrected incidence of 6.5% thrombo-emboli in those actually under the influence of anticoagulants. Study by age groups showed that anticoagulants were apparently equally effective at all ages in preventing thrombo-embolic complications. Study of the incidence of different types of thrombo-embolic process showed that each type occurred much less frequently in treated cases. This applied equally to spreading coronary thrombosis, second episode of coronary thrombosis, pulmonary, cerebral and peripheral embolism and peripheral venous thrombosis.

The authors found that haemorrhagic manifestations occurred in 6% of the control group and in 12% of those treated, but of the latter 2% were not receiving anticoagulants and in 3% haemorrhage was definitely not due to the therapeutic agent. Out of a total/
total of 30 haemorrhagic incidents due to dicumarol, only 1 was severe. There were no deaths due to anti-coagulants.

In this series dicumarol has been administered for 30 days as a minimum, preferably for 30 days after the last thrombo-embolic episode. The elected therapeutic prothrombin level has been a prothrombin time by Link-Shapiro technique of 30-35 secs., equivalent to a prothrombin of 20-30%. The authors think that where thrombotic processes have occurred in patients receiving dicumarol it has been because the prothrombin had not fallen to the therapeutic level. Out of 38 complications under dicumarol 4 only occurred in patients whose prothrombin time had been adequately prolonged for 3 days preceding the complication.

Wright and his associates state that the results in every category studied indicate that the use of anticoagulants improves strikingly the outlook of the patient suffering from myocardial infarction. They point out that, though in their series the mortality under 60 was not improved, this is because the younger patient is more likely to survive a thrombo-embolic complication, but that he does so at the risk of a permanent disability, a risk which is greatly diminished by anticoagulant treatment. They conclude that anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contra-indication exists and/
and that the hazards from haemorrhage due to anti-coagulants are not sufficient to contra-indicate their use provided adequate laboratory control is available.

While all the authors reported above record, with greater or less vehemence, their favourable impressions of the anticoagulant therapy of myocardial infarction, a more clear-cut picture may be drawn by an analysis and summary of their results and by a brief consideration of some points on which there is a difference of opinion.

The recorded mortality rates under anticoagulant therapy are summarised in Table V. and compared with the rates of control series where such were studied.

Table V. Deaths in cases of myocardial infarction treated by anticoagulants and in control cases not so treated.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Anticoag.Cases</th>
<th>Control Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. treated</td>
<td>Deaths</td>
</tr>
<tr>
<td>Wright (1946)</td>
<td>76</td>
<td>15</td>
</tr>
<tr>
<td>Nichol (1947)</td>
<td>68</td>
<td>11</td>
</tr>
<tr>
<td>Peters et al. (1946)</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Parker &amp; Barker (1947)</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Greisman &amp; Marcus (1948)</td>
<td>75</td>
<td>7</td>
</tr>
<tr>
<td>Glueck (1948)</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td>Reich &amp; Eisenmenger (1948)</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>McCall (1948)</td>
<td>71</td>
<td>9</td>
</tr>
<tr>
<td>Wright et al. (1948)</td>
<td>432</td>
<td>65</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>890</strong></td>
<td><strong>127</strong></td>
</tr>
</tbody>
</table>

Death rate = 14.3% - 27.3%

( % Cases dying within 48 hrs. of admission not included)
It is seen that the mortality rate is almost halved in cases receiving anticoagulants. The figures shown are statistically significant. The death rate in the control series correlates with the figures of 25-30% given by Bedford (1936) as the expected death rate in the 6 weeks following an episode of coronary thrombosis. In 3 of the series noted in table V. cases dying within 48 hrs. of admission to hospital were not included. This omission invalidates comparison with death rates recorded elsewhere in cases of myocardial infarction on conventional therapy. If these 3 series are left out of table V. the amended figures read - 109 deaths in 694 cases treated with anticoagulants, giving a mortality rate of 15.9%. The difference from the death rate in controls is still statistically significant.

Such a reduction in mortality in treated cases in so significantly large a series is a very powerful argument for the effectiveness of anticoagulant therapy. However, a comparable reduction was achieved by simpler measures by Master and his associates (1936) over a decade ago. They treated 267 episodes of coronary thrombosis occurring in 243 patients by an 800 calorie diet, prolonged bed rest and the avoidance of digitalis, adrenalin and nitrites. They recorded an all-over mortality rate of 16.5% and a mortality in first attacks of 8% only. The effectiveness of this form of management does not appear to have been confirmed.
confirmed or disproved by other workers. A combination of Master's regime and anticoagulant therapy might well prove to be the most effective treatment of myocardial infarction.

The incidences of thrombo-embolic complications recorded in the various anticoagulant treated series and in control groups are noted in table VI.

Table VI. Incidence of thrombo-embolic complications occurring in cases of myocardial infarction receiving anticoagulant treatment and in control cases not so treated.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Anticoagulant cases</th>
<th>Control cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>No. with thrombo-emboli</td>
<td>No. with thrombi-emboli</td>
</tr>
<tr>
<td>Nichol (1947)</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>Peters et al. (1946)</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Parker &amp; Barker (1947)</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Greisman &amp; Marcus (1948)</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Glueck (1948)</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>McCall (1948)</td>
<td>71</td>
<td>2</td>
</tr>
<tr>
<td>Wright et al. (1948)</td>
<td>432</td>
<td>48*</td>
</tr>
<tr>
<td>Totals</td>
<td>790</td>
<td>63</td>
</tr>
</tbody>
</table>

Incidence = 8% = 23.6%

(22 of these complications occurred in patients not under the influence of anticoagulants.)

It is seen that thrombo-embolic processes complicate myocardial infarction very much less frequently when anticoagulants are administered. The difference in the figures recorded is statistically significant. If the cases in Wright's series which were not under the influence of anticoagulants when complications occurred, are omitted, the incidence in the/
the anticoagulant group is 5.2%. However, as Wright suggests, complications occurring in such circumstances, must be regarded as disadvantages inherent in anticoagulant therapy. Such complications are of course more common when dicumarol alone is used without heparin. There are less specific contra-indications to heparin and furthermore the thrombo-embolic processes which develop in the first three days of dicumarol therapy (in Wright's series they occurred in 1.5% of all cases in the treated group) would presumably be obviated by the simultaneous administration of heparin. If all observers had adopted the same strict criteria as Wright the incidence of thrombo-embolic complications recorded in their treated series would no doubt have been higher, but there is no reason to suppose that it would greatly have exceeded Wright's figure of 11%, a figure which is a marked and statistically significant improvement on the recorded incidence in the control group.

Any critical assessment of the value of anticoagulant therapy must include a consideration of the frequency and severity of haemorrhagic manifestations in the series reported. These features are summarised in Table VII.

Table VII. Incidence of mild and severe haemorrhagic manifestations occurring in cases of myocardial infarction under anticoagulant therapy.

Authors/
### Authors

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>No. with mild haemorrhages</th>
<th>No. with severe haemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright (1946)</td>
<td>76</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Peters et al. (1946)</td>
<td>50</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Parker &amp; Barker (1947)</td>
<td>50</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Greisman &amp; Marcus (1948)</td>
<td>75</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Glueck (1948)</td>
<td>44</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>McCall (1948)</td>
<td>71</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Wright et al. (1948)</td>
<td>432</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>798</strong></td>
<td><strong>47</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

**Incidence**

\[ = 5.9\% \quad = 0.3\% \]

Haemorrhagic manifestations giving rise to no great anxiety, such as microscopic haematuria, petechiae or epistaxis occurred in almost 6% of cases. Severe haemorrhages were very infrequent and there were no fatalities due to haemorrhage. All observers noted the effectiveness of intravenous Vitamin K. in counteracting haemorrhages and raising prothrombin levels. In the light of these figures the small risk of haemorrhagic manifestations cannot be considered to contraindicate the use of anticoagulants where the methods of laboratory control used in the above-mentioned series are available. It is worthy of note that in all these series prothrombin time was estimated by the method of Quick (1942) or a modification of it using acetone-extracted dried brain as the source of thromboplastin. There is now evidence that the use of Russell-viper venom as the source of thromboplastin, which is the common practice in Great Britain, is unsafe in the control of dicumarol therapy. This will be considered in greater detail in part V.
The optimum prothrombin level in dicumarol therapy was considered to be 10-30% or 20-30% by all the authors reported above except Peters and his co-workers. They elected to maintain a level of 35-50%. Their figures for rates of mortality and thromboembolic complications were lower than in any other series, which is very surprising if Wright's (1948) contention is correct that the few thromboembolic complications which do occur under dicumarol therapy happen when the prothrombin percentage is above 30%, the upper limit of the therapeutic range. The most likely explanation is that Peters' criteria of assessment of prothrombin percentage differed from those of other workers and that what he considered to be 35-50% prothrombin, others would have rated considerably lower. Peters used Brambel's (1945) modification of Quick's thromboplastic reagent and assessed prothrombin level on a different form of dilution curve from the standard one of Quick used by the other authors. The incidence of mild haemorrhages in Peters' series was the same as in the other reports which suggests that he achieved comparable prothrombin levels.

Difficulty in maintaining prothrombin levels is considered in detail in only 2 of the series, those of Parker & Barker and McCall. The former found that at some time the prothrombin level fell to dangerously low levels in 12 of their 50 cases and rose beyond the therapeutic range in 18. In McCall's 71 cases, 10 were/
were unduly slow to respond to dicumarol, in 4 cases the prothrombin level fell too low and in 6 it rose too high at some period during the course of treatment. It is likely that such difficulties occurred with similar frequency in the other series since methods of administration and control were similar.

Whether combined heparin-dicumarol therapy is more effective than treatment by dicumarol alone cannot be gleaned from these reports. Both modes of treatment were employed in the series of Parker and Barker and of Wright and his associates, but the results of each method were not separately assessed. Glueck treated all her cases by combined therapy and the mortality rate in her series, of 20%, was higher than that in any other series. However, the incidence of thrombo-embolic complications, of 6.8% was comparable to that in the whole group. Glueck's series, in point of fact, numbering only 44, was probably too small to make comparison with the whole group valid. Wright's report of an incidence of thrombo-embolic complications in 1.5% of cases in the first 3 days of dicumarol therapy is a point in favour of heparin therapy.

Reich & Eisenmenger suggest that anticoagulants will not prevent a second episode of coronary thrombosis. Parker & Barker reported 2 such episodes in their series of 50. However Wright's analysis of a much larger series indicates that anticoagulants are as effective in preventing such processes as they are in respect of any/
any other type of thrombo-embolic complication.

Most authors found daily estimations of pro-thrombin time essential for control of dicumarol dosage but in the opinion of Peters and his associates and of Greisman & Marcus adequate information can be obtained by estimating prothrombin every second day. The method of the majority appears preferable on the grounds of safety.

Glueck continued dicumarol therapy for 21 days only, Wright urges administration for a minimum of 30 days on the grounds that the risk of thrombo-embolic complications remains considerable for at least 4 weeks. In Peters' series dicumarol was given for 42 days. The comparatively small risk of thrombo-embolic processes in the 5th and 6th weeks hardly justifies the continued tenancy of a hospital bed for such a purpose, provided the case is a straightforward one.

The reports that have been published up to the present of the anticoagulant therapy of myocardial infarction in series of a significant size have been reviewed and summarised. It is difficult to escape the conclusion of Wright and his fellow-authors (1948) that the use of anticoagulants effects a striking improvement in the outlook of the patient suffering from myocardial infarction. It is noteworthy that all the reports are American. British observers appear to have been as cautious in recognising the potential value of anticoagulants in myocardial infarction.
infarction as they were three or four decades ago in accepting myocardial infarction as a clinical and pathological entity. In defence of British reluctance to accept without reserve the favourable conclusions of the American authors it is only fair to say that, though no large series, comparable to the American ones, has appeared in the British literature, certain unfavourable experiences and impressions have been recorded. Peel (1947) reported the failure of dicumarol to prevent thrombo-embolic processes in 3 cases of coronary thrombosis. He unfortunately does not clearly indicate the prothrombin level at which the complications occurred since he records the dicumarol effect in terms of the "prothrombin index", and does not specify the method of prothrombin time estimation. Hill (1949) states that he has abandoned the use of dicumarol in coronary thrombosis on account of its delayed and persistent action, the erratic nature of its effects and the difficulty in control should complications arise, but he thinks that the use of heparin is justifiable in cases of spreading thrombosis and in those cases in which the electrocardiogram is typical of massive through and through involvement. Evans (1948) in his recent text-book does not mention the use of anticoagulants in his account of the treatment of coronary thrombosis. He thinks the use of heparin is unjustified in cases of peripheral venous thrombosis because the risk of pulmonary embolism is small.

One reasonably favourable British report, though/
though a very brief one, has recently appeared. Wood (1949) records 23 cases of cardiac infarct treated with dicumarol with 3 deaths - a mortality of 13%. In 7 cases, however, of cardiac embolism complicated by pulmonary embolism there were 3 deaths also. Presumably these 7 were cases of coronary embolism complicating some other condition such as bacterial endocarditis and are therefore not really comparable to a general series of coronary thrombosis.

In spite of the guarded or unfavourable opinions of British physicians, it is felt that the balance of evidence, particularly in view of the large and carefully controlled series reported by Wright and his associates, is strongly in favour of the real effectiveness of anticoagulant therapy in reducing mortality and morbidity from myocardial infarction.

V. Clinical Study of Anticoagulant Therapy of Myocardial Infarction.

(a) Plan of investigation, material studied and results.

The material studied consists of the cases of coronary thrombosis with myocardial infarction admitted, from December 1947 to February 1949, to a general medical unit, consisting of 34 male and 18 female beds, in the Royal Infirmary of Edinburgh. The number of cases studied is too small to permit of any final conclusions as to the value of anticoagulant therapy in myocardial infarction but the experience gained/
gained in the administration and control of anti-
coagulants has led to certain tentative conclusions
and to the adoption of certain practical measures which
my be of assistance to other workers in this field.

To obtain a control series the documents of all
cases of coronary thrombosis admitted to the same unit
during the previous 5 years were carefully studied and
analysed. That this is a highly unsatisfactory method
of achieving a control series is freely admitted, but
admissions for coronary thrombosis were too infrequent
to permit of division into "treated" and controls
by treatment of alternate cases only.

Only cases in which the diagnosis of coronary
thrombosis was certain were included in either series.
The diagnosis was based on an adequate combination of
the accepted criteria, namely history of prolonged
substernal pain with pallor, sweating, dyspnoea,
flatulence, clinical findings of fall in blood pressure,
tachycardia, occasional pericardial friction, slight
pyrexia, leucocytosis and raised B.S.R. and typical
electrocardiographic changes. Patients whose episode
of myocardial infarction had occurred three weeks or
more prior to admission were not included in either
series.

The original plan of the investigation was to
administer dicumarol only to those patients who showed
a clotting tendency in the blood, as evidenced by a
definite reduction in the prothrombin time of whole or
diluted/
diluted (25%) plasma. (Shapiro (1944) has reported that such a fall in prothrombin time is a premonitory sign of thrombo-embolisation. Peters and his associates (1946) adopted this plan, apparently successfully, in their study of the use of dicumarol in coronary thrombosis.) In cases which showed no clotting tendency initially, prothrombin time was estimated every 2nd day and if the tendency became manifest, dicumarol therapy was started. In 3 of the first 8 cases studied, prothrombin times remained normal throughout the period in hospital, no thrombo-embolic complications occurred and recovery was satisfactory. However it eventually became apparent that the onset of such complications could not always be forecast by changes in the prothrombin time as estimated by the method used in this study. In one case, a second coronary thrombosis developed on the 11th day though the prothrombin time had been persistently normal since admission. A second case died within 24 hours of admission with a prothrombin time above normal.

It was therefore decided to administer anticoagulants to all cases of established recent coronary thrombosis, without selection. Initially dicumarol alone was administered but when heparin became more readily available, combined heparin and dicumarol therapy was employed. In all, 15 cases were treated with anticoagulants, 6 with dicumarol alone, 6 with combined/
combined heparin and dicumarol and 3 with heparin alone because of impaired renal function. Treatment was otherwise conventional and was comparable in the two series, anticoagulant-treated and controls.

The 2 series were not comparable in size and were found to be not strictly comparable in respect of age and sex. The average age in the anticoagulant series was 54.2 years and in the controls 59 years. There were 11 men and 4 women in the treated group as against 37 men and 7 women in the controls. It is impossible to state if the groups were comparable in severity but there was a similar incidence of previous history of angina of effort and/or coronary thrombosis, the rate being 66% in the treated cases and 68% in the controls.

Table VIII. compares the mortality rate and frequency of thrombo-embolic complications in the 2 series. There may well have been more thrombo-embolic episodes in the control group than the number recorded. Special study of such complications was not being made at the time they were under treatment and events such as minor pulmonary emboli may well have failed to be recorded. Examination of temperature charts reveals in some cases unexplained occasional elevations of temperature or pulse which may have been due to such episodes. However, only thrombo-embolic complications noted in the case-records have been included in the number stated.

Table VIII./
Table VIII. Mortality rate and incidence of thrombo-embolic complications in cases of myocardial infarction treated by anticoagulants and in cases not so treated.

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulant cases.</th>
<th>&quot;Untreated&quot; cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%age.</td>
<td>No.</td>
</tr>
<tr>
<td>Number studied</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>No. of cases with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thrombo-embolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>complications</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>No. of such</td>
<td></td>
<td></td>
</tr>
<tr>
<td>complications</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

Statistical comparison is of course not warranted in such small and not strictly comparable series but it is seen that the figures quoted are in close accord with the findings of other workers in respect both of cases treated with anticoagulants (cf. Tables V. & VI.) and of cases receiving conventional therapy only (cf. Tables IV, V. & VI.) The one death in the treated series occurred 32 hrs. after admission in a man of 75 who had sustained a coronary thrombosis 10 days before. He was having repeated paroxysms of severe dyspnoea and cyanosis without pain. The heart was enlarged and there were moist sounds at the lung bases. Prothrombin time was normal but a heparin tolerance test revealed increased resistance to heparin. Heparin was administered with satisfactory effect on the clotting time but the dyspnoeic attacks persisted and he died 24 hrs. after inauguration of heparin therapy. Pulmonary embolism had been thought likely but/
but post mortem revealed extensive myocardial infarction of approximately 2 weeks duration and slight ante-mortem thrombosis within the left ventricle, but no evidence of recent cardiac infarction or of pulmonary embolism. The lungs and other viscera showed some venous congestion and there were small bilateral pleural effusions. These were not saneous, nor were there any other evidences of damage attributable to heparin.

The one thrombo-embolic complication in the cases receiving anticoagulants was an episode of pulmonary infarction in a patient who had received 1500 mg. of dicumarol in 8 days with no effect on an initially shortened prothrombin time. The episode was not severe and heparinisation was followed by uninterrupted recovery.

In the control group the 15 thrombo-embolic processes that occurred in 11 cases were: 7 further attacks of coronary thrombosis, 5 pulmonary emboli, 2 femoral emboli and 1 cerebral embolism.

No cases of recent coronary thrombosis admitted during the period under review were intentionally omitted from the material studied but mention must be made of 2 further cases which died within an hour or two of admission without a diagnosis having been made. One, a man of 67 was admitted unconscious and moribund with no details available of the history of the illness. He was thought to have had a cerebral vascular accident but/
but post-mortem revealed a massive recent anterior infarct. The second, a man of 56, was admitted with a complaint of a burning sensation in the throat and aching in both upper arms of 2 hrs. duration. Coronary thrombosis was considered a possibility but pulse and blood pressure were normal and there were no abnormal physical signs. Sudden death occurred without warning two hours after admission and post-mortem revealed both old and recent myocardial infarcts.

Including also the 4 cases (1 of them fatal) previously mentioned, which received no anticoagulants because no clotting tendency was demonstrable, it is seen that 21 cases of recent coronary thrombosis were admitted in the period under review and that there were 4 deaths. It is worthy of note that all 4 occurred within 48 hours of admission. Dicumarol therapy can of course have no effect on such fatalities and it is doubtful whether early heparinisation could in any way affect the issue, which appears to be determined by the massivity of the original infarct. In the control series only 2 of the 13 deaths occurred within 48 hrs. of admission.

No severe haemorrhages due to heparin or dicumarol were encountered in this series and only one minor manifestation of dicumarol toxicity. One case with a prothrombin level of 15% developed petechiae in the antecubital fossa and a tendency for blood to ooze from the small venepuncture wound. On temporary discontinuation/
discontinuation of dicumarol and administration of vitamin K by mouth, gr.60 in 2 days, the prothrombin rose to 35% and the mild toxic manifestation cleared up. No conclusions as to the risks of dicumarol therapy are advanced from this small study. The reality of such risks was brought home by the observation of a moderately severe haemorrhagic manifestation of dicumarol toxicity which gave rise to some anxiety and led to a prolongation of hospitalisation in a case not in this series. A woman of 46 with periodic recurrent deep phlebothrombosis of both legs was admitted on account of recurrent pulmonary infarctions. Initial prothrombin time was normal and there was no evidence of any specific contra-indication to dicumarol therapy. 24 hrs. after an initial dose of 250 mg. of dicumarol there was no change in prothrombin level and a further dose of 200 mg. was administered. At 48 hrs. prothrombin had fallen suddenly to 25% and no further dicumarol was given. On the following day, with a prothrombin of 15% there was moderate vaginal haemorrhage and a large cutaneous ecchymosis with a subcutaneous haematoma appeared on one thigh. 60 mg. of a vitamin K analogue (Synkavit) and 0.25 Gm. of aminophylline were administered intravenously. The vaginal haemorrhage stopped within 12 hrs. and the following day prothrombin level had risen to 55%. However, necrosis of skin and subcutaneous tissue took place at the site of the ecchymosis, with eventual sloughing and indolent ulceration which took 30 days to/
to heal. Such a case must be regarded as a hyper-reactor to dicumarol and it is not apparent how such cases can be recognised and haemorrhagic manifestations avoided, on the methods of control used in this study, unless a smaller trial dose of dicumarol be given initially in all cases. This, of course, would inevitably lead to a much greater delay in the production of the anticoagulant effect of dicumarol in the great majority of cases. The delay on standard dicumarol dosage is already a very considerable disadvantage and exhibition of an initial small trial dose cannot be recommended.

Fortunately, judging from the extensive literature on dicumarol therapy and its toxic effects (vide p. 32) such unpredictable hyper-reaction to dicumarol appears to be rare and its small risk cannot be considered to represent a contra-indication to its use.

It is not intended to append the case histories of the patients treated with anticoagulants but one case of some interest will be briefly described. In this patient, a man of 61, dicumarol was administered for 83 days. This was the case, noted earlier, in whom a second episode of cardiac infarction occurred on the 11th day after admission though there had been no premonitory change in the prothrombin time. Dicumarol therapy was started immediately and a satisfactory prothrombin deficiency obtained in 72 hrs.
During the next 2 months the patient had repeated attacks of left ventricular failure characterised by pulmonary congestion, early pulmonary oedema and very marked Cheyne-Stokes respiration. In the apnoeic phases of the respiratory dysrhythmia, the patient became unconscious and the pulse imperceptible. Aminophyllin was found to have a dramatic effect on these attacks and mercurial diuretics were also administered with beneficial results for the pulmonary congestion. On several occasions early right sided heart failure developed with venous filling in the neck, and slightly enlarged liver with a marked hepato-jugular reflux but with little or no dependent oedema. Digitalis was avoided for some time on account of its reported effect of increasing a clotting tendency but eventually it was administered and finally on a combination of digitalis aminophylline and mercurial diuretics the patient made a good recovery - so good that while at the Convalescent Home, he was able to walk to the top of the neighbouring Corstorphine Hill without distress and without stopping en route! Dicumarol therapy was continued throughout this 2½ month period because all the three drugs used in the treatment of the heart failure are reported to cause a clotting tendency. If this is the case, dicumarol may be held to have played a prominent part in the successful outcome.

(b)
(b) Dicumarol dosage and administration.

Patients whom it was intended to treat by dicumarol were first assessed for the presence of any specific contra-indication, namely, haemorrhagic disease, liver disease, condition likely to cause hypoprothrombinaemia, or deficient renal function. Initial prothrombin time estimation was performed by the method considered in detail below. If the pro-thrombin time was not significantly above normal and no contra-indication existed, dicumarol therapy was inaugurated with a dose of 300 mg. for patients over 10 stone or 250 mg. for those under 10 stone. Thereafter the prothrombin time was estimated daily and the daily dosage assessed on the prothrombin level. Assessment of prothrombin level was based on the relation of the prothrombin time to a standard prothrombin dilution curve, the formulation and theoretical basis of which are considered below. The attempt was made to keep the prothrombin level at 30% or at least within the range of 20-40%. In only 2 cases did dicumarol cause a fall to the elected therapeutic range within 48 hrs., usually it took from 72-96 hrs. Dicumarol was continued in daily dosage of 200 mg. until the level reached 50% and thereafter depending on speed of fall by 50-100 mg. until 30% was reached. At 30% if the level was falling no further dicumarol was given, if stationary, 50 or 100 mg., depending upon the patient's assessed reaction to previous doses, and, if rising, 50-150 mg. depending on speed of rise and/
and patient's previous reaction. Even with this careful scheme of control, it was found to be extremely difficult to keep prothrombin levels consistently within the elected therapeutic range and wide escape from this range occurred at some time or times in all 12 cases studied. In one case 1500 mg. of dicumarol in 8 days caused no fall in the initially increased prothrombin level and pulmonary embolism developed. This case must be considered resistant to dicumarol - it may be of significance that he was found to have a raised blood cholesterol level of 270 mg.%. In other cases, the prothrombin level rose to 60% or more at some point in the course of treatment, in 2 it fell to 12% and in 3 it escaped in each direction at different times to 60% or 15%. In none of these 11 cases was escape from the therapeutic range attended by any complication, whether of haemorrhage or thrombosis. The difficulty in maintaining the optimum prothrombin level is of course due to the fact that a dose of dicumarol does not affect the prothrombin level, as estimated by the method used in this study, for 48-72 hours and that its effect lasts for a very variable period thereafter. In the 5 cases in which prothrombin fell to dangerously low levels, administration of vitamin K was followed by a satisfactory rise in prothrombin. 60 mg. of Synkavit intravenously led to an appreciable rise in 6 hrs. in one case, but in another case a second similar injection 24 hrs. later was/
was required before the prothrombin eventually rose to a safe level at 48 hours. In the other cases 40 mg. of Kapilon intramuscularly and 90 mg. of vitamin K orally proved effective. The intramuscular injection was found to be very painful.

The length of the course of dicumarol administered to different patients varied, since the plan was to ensure an anticoagulant effect until the 28th day after the attack of coronary thrombosis. Depending on how long before admission the coronary thrombosis had occurred, dicumarol was administered for between 16-28 days, except in the one case already mentioned in which it was given for 83 days.

As a further attempt at control of dicumarol dosage a simple blood clotting time (vide infra) was recorded at the same time as the prothrombin time. No direct correlation between the two was found. A fall of prothrombin level to 15% or below was usually, but not invariably, associated with a prolongation of clotting time. In 2 cases a sudden increase in clotting time heralded a considerable fall in prothrombin level 24 hours later. Such a rise in clotting time may be regarded as an indication for caution in dicumarol dosage.

A careful watch was kept in each case for the appearance of haemorrhagic manifestations. The urine was examined microscopically daily but in no case did haematuria occur.
(c) Estimation of blood prothrombin level.

It is clear from the preceding observations that dicumarol therapy demands regular accurate assessment of the blood prothrombin level. Prothrombin, the precursor of thrombin in the circulating blood, has, according to Astrup (1944), the physical and chemical attributes of a globulin but it is probably a complex of 2 or more components, including the factor 5 of Owren (1947) and Quick's labile factor-component A and stable factor-component B (Quick 1943 and 1947). The first 2 factors named are probably identical. Dicumarol is known to act on component B.

The exact amount of prothrombin in the blood is not known and it can only be approximately assessed as a percentage of normal by an estimation of its activity. Such an estimation depends upon a literal acceptance of the so-called classical theory of coagulation of Schmidt (1895) and Morawitz (1905). According to this theory coagulation depends upon the interaction of 4 factors, calcium, prothrombin, thrombokinase (vel thrombo-plastin) and fibrinogen. If, experimentally, three of these factors are constant then it is considered that variations in the speed of coagulation must be proportional to variations in the concentration of the fourth in the mixture. This is the basis of the method of estimation of the blood/
blood prothrombin level first devised and subsequently improved by Quick (1935 and 1942). In this method optimum amounts of thromboplastin and calcium are added to oxalated plasma and, since variations in fibrinogen in human plasma are not likely to be so wide as to introduce significant error, the clotting time recorded is taken to be inversely proportional to the concentration of prothrombin.

In Quick's method a standardised preparation of acetone dried rabbit-brain is used as the source of thromboplastin. In order to assess the concentration of prothrombin in a deficient plasma Quick formulated a dilution curve. The prothrombin times of serial dilutions of normal plasma in saline were estimated and plotted against the percentage dilutions of plasma which were held to be equivalent to the percentages of prothrombin. The prothrombin time of a prothrombin-deficient plasma could then be interpreted on this curve as indicating a certain prothrombin concentration.

The method is open to several theoretical objections. The assumption that the rate of thrombin generation is proportional to the concentration of the interacting factors is not necessarily a valid one and the method takes no account of the amount of thrombin produced but only the rate of production. The basis of the test is the classical theory that there are only 4 factors concerned/
concerned in coagulation, which is now known to be untrue. Prothrombin itself probably has at least 2 components, and accelerators and depressors of thrombin generation are known to be present in human plasma, variations in which may alter the results of the test. Furthermore dilution of plasma by saline reduces fibrinogen and other factors as well as prothrombin.

Various methods have been devised to circumvent some of these difficulties, such as the 2-stage method of prothrombin determination based on the amount of thrombin produced (Warner et. al. 1936), and the dilution of plasma with prothrombin-free plasma or with fibrinogen, but these methods have their considerable difficulties of interpretation. Quick's method, in spite of the objections recorded, has proved its value and essential reliability in its application to a vast amount of clinical material. The procedure has been standardised and its reliability attested statistically by Aggeler and his associates (1946). It has stood the true test of time as a means of obtaining the information necessary for the control of dicumarol therapy, namely the range of prothrombin deficiency within which the patient is not liable to bleed or to suffer intravascular complications.

In this country the modification of Quick's method devised by Fullerton (1940) has been largely employed/
employed. In this method, which was used in the present study, Russell viper venom takes the place of brain as the source of thrombokinase. Fullerton recommended the use of viper venom because of its ready availability as Stypven (B.W. & Co.) or Russven (Boots), its constant potency and its clarity in solution as contrasted with tissue extracts which require careful preparation and standardisation, gradually lose their potency and are milky in solution, making recognition of the end-point difficult. The technique of Fullerton's method, as employed in the present study, will be described in some detail.

4.5 c.c. of the patient's venous blood are added to 0.5 c.c. of a 1.38% solution of sodium oxalate in a graduated centrifuge tube, thoroughly mixed and centrifuged at 5,000 revolutions for 5 minutes. In a test-tube rack, standing in a water-bath with water at 38°C., are placed 10 standard size test-tubes (15 cm. X 1.5 cm.). In one of these, labelled calcium, are placed 2 or 3 c.c. of \( \frac{1}{40} \) molar solution of calcium chloride, in a second, labelled "kinase, 1 c.c. of a \( \frac{1}{10,000} \) solution of Russell viper venom (the product of a standard pack of 0.1 mg. of Stypven) and in a third, labelled plasma, 1 or 2 c.c. of the supernatant plasma from the centrifuged specimen. A large boiling tube (20 c.m. x 3.5 c.m.) is/
is immersed in the water-bath and three-quarters filled with the water at 38°C. One of the empty standard-size test tubes is inserted for \( \frac{4}{5} \) of its length through a perforated cork into the large boiling tube which is propped up in the water-bath. Appropriately labelled 0.2 cc. pipettes are placed in each of the 3 labelled tubes. 0.2 c.c. of plasma and 0.2 c.c. of 'kinase solution are accurately pipetted into the jacketed test-tube and gently shaken. 1 minute later 0.2 c.c. of the calcium solution is quickly added to this mixture and at the same time a stop-watch is started. The large tube holding the smaller reagent tube is quickly removed from the water-bath, held up between the observer's eye and an electric light and gently agitated with a rotatory motion. On the first appearance of fine opaque threads on the side of the inner-tube the watch is stopped and the time determined. Once experience in the method had been gained and the technique standardised it was found that repeated determinations on any plasma, the prothrombin time of which was normal or only moderately prolonged, did not vary by more than 1-2 seconds. When the time was as long as 45 or 50 seconds there was sometimes a variation in successive determinations of as much as 4-5 seconds. Such variations are not of significance as a study of the dilution curve (figure II)
FIG II.
PROTHROMBIN DILUTION CURVE
USING RUSSELL VIPER VENOM AS THROMBOPLASTIN.

PROTHROMBIN TIME
IN SECONDS

PROTHROMBIN PERCENTAGE
(DILUTION OF PLASMA IN NORMAL SALINE)

ELECTED
THERAPEUTIC RANGE.
II) will show. In practice the average of 2 successive determinations was recorded as the prothrombin time.

Before prothrombin time estimations could be effectively employed in the control of dicumarol it was necessary to establish a prothrombin dilution curve for the particular technique employed. Prothrombin time determinations were carried out on serial dilutions in normal saline of the plasma of 6 normal people. The results were comparable in the 6 and the dilution curve represented in figure II is formed from the average findings. It is seen that the relationship between prothrombin times in seconds and prothrombin percentage is not a rectilinear one but in the form of a parabolic curve.

Normal prothrombin time by this method was found to be 18 seconds, with a range of 16–20 seconds. The prothrombin time of 25% diluted normal plasma was 33 seconds with a range of 29–37 seconds.

It is seen from figure II that the elected therapeutic range of 20–40% prothrombin is equivalent to prothrombin times of 28–38 seconds which therefore represent the range of prothrombin times aimed at under dicumarol therapy in the present study. In addition to the daily determination of the prothrombin time of whole plasma in each patient, under dicumarol, the estimation was also performed on 25% diluted/
diluted plasma in normal saline. The equivalent optimum range was found to be 65-110 seconds. Escape from this range sometimes occurred 24 hrs. before escape from the therapeutic range was manifest in the prothrombin time of whole plasma. Some observers have recommended the use of diluted plasma only in dicumarol control as being a more sensitive index of prothrombin deficiency, (Link 1943-4, Peters et al. 1946). The author has found it a valuable ancillary aid in the control of dicumarol therapy and it adds little to the trouble of a prothrombin time estimation. Using the technique already outlined it was found that a satisfactory end-point was detectable in a determination carried out on a 25% dilution of a prothrombin-deficient plasma, but recognition of the end-point was difficult where only 0.1 c.c. of the reagents was used and the reaction was observed in small tubes.

Hobson and Witts (1941) recommended the addition of lecithin to Russell viper venom on the grounds that if the latter alone is used the coagulation time may be affected by haemolysis, lipaemia, the number of platelets in vivo and in certain circumstances the speed and duration of centrifugation and that these inconsistencies are eliminated by the addition of lecithin. The prothrombin dilution curve resulting from the employment of the method/
Fig III

PROTHROMBIN DILUTION CURVE

USING RUSSELL VIPER VENOM WITH LECITHIN AS THROMBOPLASTIN

Elected Therapeutic Range

Prothrombin Time in Seconds

Prothrombin Percentage

(Dilution of Plasma in Normal Saline)
method of Hobson and Witts in a normal plasma is shown in figure III. It is seen that the therapeutic range of prothrombin time by this method, 11.5-14.5 seconds, is far too narrow for safety. It is concluded that the method is of no value in the control of dicumarol therapy. This has been amply confirmed by Biggs and Macfarlane (1949) who compared, both experimentally and clinically, the use in prothrombin time estimation of Russell viper venom with lecithin and brain thromboplastin. They conclude that the latter is satisfactory because it is able to predict a haemorrhagic level whereas with the former no certain haemorrhagic level can be predicted and the technique is dangerously insensitive to alterations in prothrombin concentration.

What is more disquieting is that there is an increasing body of evidence that the use of Russell viper venom alone in prothrombin estimation is unsatisfactory and not without danger in the control of dicumarol therapy. Wright and Prandoni (1942) in one of the early clinical trials of dicumarol, used Russell viper venom and found it necessary to give much larger doses of dicumarol to achieve a reduction in prothrombin level than were advised by other workers using brain thromboplastin. The apparent fall in prothrombin level was often delayed for 8-10 days and 8 serious haemorrhages occurred in the first 20/
20 cases treated. Lempert (1948) found prothrombin levels, by Fullerton's method, of 35% and 25% in 2 cases receiving dicumarol in whom Quick's method recorded 10% prothrombin. The most convincing evidence is that advanced by James (1949). He was struck by the fact that in his cases under dicumarol therapy, whereas Quick's method afforded a critical prothrombin level of 10% above which bleeding rarely occurred, of a series of 30 controlled by the Russell viper venom method 7 bled with prothrombin levels of 24-45%. He therefore performed both tests in a series of 20. He found that in every case on and after the 2nd day of dicumarol, the prothrombin level fell more rapidly as estimated by Quick's method than by Fullerton's and in every case, on stopping dicumarol, returned towards normal more rapidly as estimated by Quick's method (due allowance being made for the lower level to which it had fallen). He states that in view of the more rapid fall in prothrombin shown by the brain thromboplastin method, less dicumarol is required to keep the prothrombin within the therapeutic range of 10-30% and there is therefore less risk of haemorrhage. He thinks that the comparable safe range by the venom method might be 40-60% (which is difficult to maintain because of the narrowness of the equivalent prothrombin time range of 24-28 seconds, as shown in figure/
figure II) but that the venom method does not follow the true prothrombin level (or at least changes in blood coagulability) sufficiently closely to give warning of impending haemorrhage. He found that in some cases there is little prolongation even after haemorrhage has occurred. He concludes that for the safety of the patient and the peace of mind of the pathologist a return to Quick's method is long overdue.

These observations afford some explanation of the difficulty experienced by the author in maintaining the elected therapeutic range of prothrombin deficiency and it is suggested that the general use in Britain of the venom method is, to a considerable extent, responsible for the unfavourable experiences and impressions that have been recorded in this country and for the widespread reluctance to employ dicumarol as a therapeutic agent. It is felt that the conclusions of James are justified and that the general use in this country of brain thromboplastin for prothrombin estimations would be likely to lead to better results from dicumarol therapy and to a more favourable opinion of its value.

It has been a common practice in this country to describe degrees of prothrombin deficiency in terms of the "prothrombin index" which is represented by the formula \( \frac{\text{prothrombin time of control}}{\text{prothrombin time of patient}} \times 100 \). This expression is an unhelpful one since the prothrombin/
prothrombin index of a prothrombin-deficient plasma bears no real relationship to the prothrombin concentration as indicated on a dilution curve. For instance by the method used in this study a prothrombin index of 50% means a prothrombin concentration of 22% and an index of 33% is equivalent to a concentration of 12.5%. It is felt that this expression is misleading and its use should be abandoned.

The method of application of dicumarol therapy employed in a small series of cases of myocardial infarction has been described in detail. The theoretical and practical aspects of the estimation of degrees of prothrombin deficiency have been considered. The difficulty of maintaining prothrombin concentrations within an elected therapeutic range when prothrombin is estimated by the venom method has been recorded in this small series and it has been noted that assistance in dicumarol control may be obtained by estimation of simple blood clotting time and estimation of prothrombin time of 25% plasma in addition to that of whole plasma. Evidence has been presented from the literature for the belief that the use of brain thromboplastin in prothrombin estimation affords a safer and more efficient means of control of dicumarol therapy than the use of Russell viper venom. It is concluded that the use of brain thromboplastin is the method of choice.
Addendum to estimation of blood prothrombin level.

The possibility of variations in the potency of the thromboplastin used and the likelihood of slight variations in the observers technique make it necessary to determine the prothrombin time of a normal control at the same time as the estimation is performed on the patient's blood. In the author's experience such variations have not occurred with Stypven (B.W. & Co.) but have been observed with Russven (Boots). Page and de Beer (1943) have shown that the potency of Stypven is uniform within and between batches and that it is stable for at least 5 years.

Determination of prothrombin time by a capillary blood method, such as that of Innes and Davidson (1941), is not recommended. As the authors point out the results vary considerably with the temperature of the ward and can only be expressed in terms of the prothrombin index. The method is not sufficiently precise for control of dicumarol therapy.
(d) Heparin. Administration and Control.

Heparin has been administered in this series, in the latter part of the period under review, to all cases of recent myocardial infarction because, as has been already recorded, it has been felt that there is a real danger of thrombo-embolisation in the few days before dicumarol takes effect (1.5% of cases in Wright's (1948) series) and because heparin might possibly have some effect on the primary thrombus.

As soon as the diagnosis has been made a heparin tolerance test, the technique of which is detailed below, has been performed chiefly from the point of view of interest but also because this test gives some indication of the dosage of heparin required. Heparin has then been administered intravenously in a usual initial dosage of 12,500 units followed by 7,500 to 10,000 units 6-hourly. The preparation used in all cases has been Liquemin (Roche). Dosage required has been controlled by the daily estimation of the blood clotting time. The estimation has been carried out each day at a time approximately 4 hours after an injection of heparin. It has been found that the clotting time tends to become increasingly prolonged on successive days and the dosage of heparin has been adjusted to ensure that the daily clotting time has been approximately 20 minutes. Excessive prolongation to the point of apparent incoagulability has been recorded in a few instances/
instances with no ill effect.

Heparin has been continued until dicumarol has been shown to have taken effect by a significant lowering of the prothrombin level. This estimation is performed daily at a point of time at least 4 hours after an injection of heparin, since it is known that a single injection of heparin itself causes an increase in prothrombin time which is marked for 1 hour and does not finally return to normal for 3 hours (Long et al. 1946).

It has been found possible to abolish the inconvenience of repeated venepuncture by the use of an indwelling needle with a special attachment or by the use of indwelling polythene tubing. The special attachment consists of a record fitting mount with a small hollow screw cap containing a replaceable rubber diaphragm. This has been specially made for the purpose by Archd. Young and Sons Ltd., Edinburgh. A vein on a flat surface of the forearm is chosen and, with strict sterile precautions, a needle of appropriate size to serve as an indwelling needle (B.W.G. 18 or 20 are suitable) is inserted into the vein and the dose of heparin given. The special attachment, having been previously assembled and filled with heparin (it requires only a fraction of a c.c.) is attached to the needle and the whole strapped down to the forearm and covered with a sterile/
Introducing Needle. "B"

Polythene Tubing. "A"

Rubber Diaphragms. "E"

Needle to fit into Polythene Tubing. "C"

Adaptor to hold Rubber Diaphragm. (Record Fitting). "D"

PLATE I. Apparatus for intravenous administration of heparin, designed to avoid the need for repeated venepuncture. (vide p. 88).
sterile dressing. It is recommended that the small venepuncture wound be sealed with collodion. Succeeding injections are given by the nursing staff by inserting a fine hypodermic needle, with due aseptic precautions, through the rubber diaphragm. It is possible to administer heparin quite successfully by this method for several days without a change of needle. The method has been employed for as long as 10 days on one needle without discomfort to the patient.

The use of indwelling polythene tubing has been found more generally useful as it can be inserted at the antecubital fossa where veins are more easily found and it allows the patient to move his arm more freely than is the case with the use of an indwelling needle. The tubing used has been the polythene cannula, size 1 (bore 0.5 m.m.) of Allen and Hanbury. It has been found that this tubing can usually be threaded through a needle of bore B.W.G. 14 but occasionally, owing to slight variations in the diameter of the tube, a B.W.G. 12 needle may be required. Some 20 c.m. of the tubing, having been found to slip easily through the chosen introducing needle, are sterilised by boiling for 15 minutes. The special attachment noted above is filled with heparin and attached to a hypodermic needle of such diameter that it is held firmly when inserted/
PLATE II. Intravenous polythene tubing in use.

The skin has been painted with iodine to demonstrate the cannula more clearly. For the same reason the latter has been left longer than is necessary. It is essential to strap the cannula firmly to the skin or it may disappear into the vein. At the time of the photograph, the apparatus had been in satisfactory use for 5 days and there was no reaction in skin or vein.
inserted into the tubing (15 S.W.G. is usually satisfactory). The tubing is filled with heparin and the initial dose of heparin then injected into the chosen vein by means of a syringe and the chosen introducing needle. The syringe is removed, the polythene tubing threaded through for 10-12 cm. into the vein, the introducing needle withdrawn from the vein and quickly slipped off the tubing and the hypodermic needle with the special attachment quickly inserted into the free end of the polythene cannula. The whole is then strapped down and covered with a sterile dressing. Succeeding heparin injections are then given as before by insertion of a fine hypodermic needle through the rubber diaphragm.

Serial clotting times have shown that the polythene tubing does not impair the anticoagulant effect of heparin. The use of this simple device has been appreciated both by patients and resident medical staff in its obviation of the need for repeated venepuncture.

No serious toxic effects from heparin have been noted but transitory side effects have been observed on several occasions. 1 patient with coronary thrombosis on whom daily heparin tolerance tests were being performed had a short-lived but alarming anaphylactoid crisis. Within 45 seconds of an intravenous injection of 2,500 units of heparin
(the fifth he had received in 5 days) he became suddenly unconscious with laryngeal spasm, cyanosis, tonic spasm of limbs and tachycardia. The laryngeal spasm and cyanosis passed off in 30 seconds and consciousness returned in 1 minute. The tachycardia settled down within a few minutes and the patient felt quite well. No further heparin was given. Another patient, with pulmonary infarction, within 2 minutes of an intravenous injection of 10,000 units of heparin, developed tinnitus, vertigo, lacrimation, diplopia and a fluttering sensation in the chest lasting for over 1 hour. Similar but milder symptoms followed injection of 1000 units of heparin 7 hours later. Other patients who received heparin from the same phials as in both of these cases were unaffected. In the second case, a 2nd course of heparin was administered, after a cautious trial dose, some 12 days later without any side-effects. The most likely explanation of these toxic manifestations would appear to be the presence of some impurities in the batch of heparin to which the patients had become sensitised.

2 cases of coronary thrombosis complained of pain in the chest \( \frac{1}{2} \) an hour or so after an injection of heparin. In one the pain was a dragging sensation across the right lower ribs lasting for about an hour and accompanied by slight general malaise/
malaise. In the second there was pain across the left chest passing up to the shoulder and associated with frontal headache. The possibility of a further episode of cardiac infarction was considered but there was no other evidence of this, clinical or electrocardiographic and recovery thereafter was uneventful.

3 patients with coronary thrombosis who were complaining of some substernal pain at the time of the initial injection of heparin stated that the pain was relieved. No conclusion is advanced from this since all were no doubt expecting some relief from an injection but it is worthy of note that relief, following heparin, of pain associated with vascular occlusion has been reported by other observers, in peripheral arterial embolism by Burt (1947) and in coronary thrombosis by Glueck and her associates (1948).

Clotting Time Estimation.

The clotting time was simply estimated by inverting every ½ minute a 10 x 75 mm. glass tube containing 1 c.c. of the patient's venous blood and noting the time of coagulation. Control of heparin therapy does not appear to require a very accurate assessment of the clotting time and the capillary tube method is probably just as satisfactory.

Heparin Tolerance Test.

Hagedorn/
Hagedorn and Barker (1948) studied the response of subjects with and without intravascular thrombosis to an intravenous injection of 25 mg. (= 2,500 units) of heparin. They estimated the clotting time by the simple method described above at 10 minute intervals for 80 minutes following the injection and found that in every case the maximum prolongation occurred at 10 mins. They found that the response in normal subjects does not vary from day to day but that it varies considerably in different persons suffering from the same disease. They studied 50 normal subjects and 70 patients with and without intravascular thrombosis and classified the material studied in 4 arbitrary grades according to the length of the 10 minute clotting times. In grade I, described as hyper-reactors, the clotting time 10 minutes after I.V. injection of 25 mg. of heparin was 90 minutes or more, in grade II, the normals, 40–90 minutes, in grade III, the hypo-reactors, 10–40 minutes and in grade IV, the non-reactors, less than 10 minutes. The authors found that of 50 normal subjects, 47 were in the normal grade, 2 were hyper-reactors and 1 a hypo-reactor. Whereas of 61 subjects with evidence of intra-vascular thrombosis, 19 were normals, 18 hypo-reactors and 24 non-reactors.

This test has been performed in 8 cases of coronary thrombosis in the present study; of these 1/
1 was in the normal grade, 5 were hypo-reactors and 2 non-reactors. It is seen that 7 out of 8 cases of coronary thrombosis showed increased resistance to heparin, suggesting an upset in the coagulation system of the blood with a tendency towards clotting.

**Heparin (in vitro) Clotting Time Estimation.**

The fact that one of the actions of heparin is to neutralise prothrombin and the fact that its anticoagulant action is quantitative has suggested that increasing degrees of prothrombin deficiency in a patient's blood may be associated with increasing sensitivity to heparin in vitro. To test this hypothesis a simple manoeuvre, named by the author for convenience the heparin clotting test, has been employed. In this test a fixed amount of venous blood from the patient is added to a 10 x 75 mm. glass tube containing a fixed minute quantity of heparin (2 c.c. of blood to 0.5 units of heparin in 0.1 c.c. water has proved most satisfactory) and the clotting time determined in the usual way.

Investigation is at present being carried out to elucidate whether the prolongation of the heparin clotting time of a prothrombin-deficient plasma (which has been shown to exist) is proportional to the degree of prothrombin deficiency as determined by estimation of the prothrombin time. Preliminary results suggest that in any one individual such a correlation/
correlation does exist but that there is a fairly wide variation in the heparin clotting times recorded in different individuals who have the same prothrombin percentage.

This test when properly standardised and evaluated may prove of assistance in the control of dicumarol therapy but results so far suggest that it is very unlikely to obviate the need for prothrombin estimations.

The method of administration and control of heparin therapy employed in a small series of cases of coronary thrombosis and other thrombotic conditions has been considered. Toxic reactions have been recorded in a small number but judging from their short-lived nature and their infrequency as reported in the literature they do not appear to constitute a bar to the use of heparin. The technique of a heparin tolerance test and a so-called heparin clotting test and their application have been briefly described.
VI. Vitamin K Therapy of Myocardial Infarction.

Preceding sections have revealed a widespread recognition of the frequency of thrombo-embolic complications in myocardial infarction and of the theoretical justification for and practical effectiveness of measures designed to abolish intravascular clotting by lowering the blood prothrombin level. It is therefore all the more surprising to find it recorded that acute coronary occlusion is invariably associated with hypoprothrombinaemia and that large doses of vitamin K are an effective form of therapy.

An earlier report of Doles (1943) was considered in part II of this paper but more recently (Doles 1947) he has published a study of the prothrombin levels in 64 cases of acute coronary occlusion and of their treatment by large intravenous or intramuscular doses of vitamin K. He found that in all cases there was a marked fall in prothrombin level from 5 to 24 hours after the incident of occlusion, the average level reached being 55%. He treated his cases with 50-72 mg. of vitamin K every 6-8 hours until the prothrombin was 100%. He states that relief of pain followed an injection of vitamin K within ½-3 hours, though mild discomfort sometimes lasted for 24 hours. The blood pressure was restored to normal levels usually by the 2nd day but at times not/
not until the 5th day and thereafter it maintained its original level unless there was a recurrence of hypoprothrombinaemia. He states that none of the fully treated cases could be classified as sick after the 3rd day. There were 11 deaths in his series of 64 (a mortality rate of 17.2%) but he states that only 55 of these cases were fully treated and of these only 2 died (a mortality of 3.6%).

Doles thinks that haemorrhage into the wall of the coronary artery is the precipitating cause of an incident of coronary thrombosis and that such haemorrhages are due to the hypoprothrombinaemia associated with an underlying deficiency of vitamin K.

Findings so diametrically opposed to those of a host of other workers require some explanation. Critical consideration of the paper of Doles reveals certain points that are worthy of comment. Doles estimates prothrombin levels by the bedside technique of Ziffren and his associates (1940) in which 1 c.c. of the patient's whole blood is added to 0.1 c.c. of thromboplastin and the time of coagulation determined. The results are expressed in terms of the prothrombin index (vide p. 84). Such a method of prothrombin estimation has nothing to recommend it, save the dubious merit of simplicity. It has been found to be completely unreliable, for instance, in control of dicumarol therapy as an index of degrees of prothrombin/
bin deficiency. The use of this method in itself largely invalidates Doles' conclusions. However it may be objected that the results in his fully treated cases are a good proof of the soundness of the rationale and the form of therapy adopted. On the other hand the reliability of his figures is open to suspicion. He does not state on what criteria a diagnosis of acute coronary occlusion was based. His statement that the blood pressure returned to normal within 24 hours or at the longest 5 days after the occlusive episode in all cases suggests that the attacks were very mild or indeed may not have been episodes of cardiac infarction at all. For Master and his associates (1943) have shown that in the majority of cases of coronary occlusion the blood pressure does not return to its original level for at least 3 to 4 weeks. It can hardly be supposed that vitamin K therapy, even if it is effective in controlling intimal haemorrhage in the coronary artery, can so radically alter the normal march of events in myocardial infarction as to effect a rapid and permanent return of the blood pressure to normal and Doles agrees that his treatment can have no effect on the repair of an infarct once it has formed. Furthermore his contention that haemorrhage into the coronary vessel wall is the precipitating cause of coronary thrombosis has been disproved by English and Willius/
Willius (1943) who have shown in convincing pathological studies that such haemorrhage plays a major role in very few instances.

If the theories of Doles were correct, dicumarol therapy should lead to intimal haemorrhages and further episodes of coronary thrombosis. A wealth of inescapable evidence to the contrary, experimental, pathological and clinical, has already been presented and need not be repeated. His experiences have not been confirmed by any other workers and he produces no experimental and very little pathological supportive evidence. It is concluded that his paper will not stand up to critical analysis. His fundamental hypothesis is unsound, his methods unreliable, his clinical data lack conviction and his conclusions cannot be justified.
VII. Discussion.

The great therapeutic advances of the last decade, notably in the control of bacterial infections, have, by increasing the span of life and also by inviting comparison with their own effectiveness, thrown into high relief the meagre progress that has been achieved in resisting the onslaught of certain other diseases. It is generally agreed that the incidence of coronary thrombosis is progressively increasing but 20-30 years of steady improvement in diagnosis and clinical and pathological definition had brought about little improvement in mortality rate apart from that due to earlier recognition. The challenge to organised medicine constituted by the increasing frequency of this condition is strikingly exemplified by the carefully calculated conclusion of Master (1947) that every year in the U.S.A. at least 1 man in 50, 40 years of age and over, sustains closure of a coronary artery. Until more is known about the aetiology of athero-sclerosis in man, prevention of coronary thrombosis will remain a problem; but the material presented in this paper has shown that in treatment the results achieved on conventional measures can be materially improved by a mode of therapy which is based on sound pathological and pharmacological grounds. Furthermore, for the application/
application of this therapy to coronary thrombosis and its attendant thrombo-embolic complications there is an excellent precedent in its successful application to other forms of intravascular thrombosis.

The pathological justification for this anticoagulant therapy has been attested in a review of the literature which has shown that thrombo-embolic complications are a very real danger in cases of cardiac infarction and that they contribute significantly both to mortality and to subsequent invalidism following such cardiac episodes. The possibility of a fundamental disorder of the coagulation system of the blood, with a tendency towards clotting, as the cause both of the coronary thrombosis and of the complicating thrombo-embolic processes has been considered. Gibson's (1949) revolutionary theory that such a clotting tendency is responsible also for the underlying atherosclerosis, is, it seems to the author, open to an attempt at experimental verification in animals. Leary (1941) has shown that high cholesterol feeding will produce typical atherosclerosis in rabbits and Link (1943-4) has recorded that effective lowering of the prothrombin level in rabbits results from dicumarol administration. If, in a suitably designed experiment, it can be shown that dicumarolisation will prevent such experimental atherosclerosis it would/
would constitute strong support for Gibson's theory.

The converse theory that a form of haemorrhagic diathesis is ultimately responsible for the development of coronary thrombosis has been critically assessed and is considered, based as it is on a pathological misinterpretation and on unsound biochemical methods to lack validity.

The established effectiveness of heparin and dicumarol in the prophylaxis and treatment of intravascular thrombosis both in experimental animals and in man has led to the acceptance of two verities; firstly, substantial impairment of the ability of the blood to coagulate, can exist without harmful effects if it is carefully controlled, and secondly, such impairment will largely prevent intravascular thrombosis, and combat it when it has already developed. These established facts form the pharmacological justification for the use of anticoagulants in coronary thrombosis.

It is clear that both heparin and dicumarol have their considerable disadvantages. Their use must be considered the first step towards securing an entirely satisfactory anticoagulant for clinical use. The ideal anticoagulant should possess the following characteristics: (1) Effectiveness of oral administration (2) Cheapness (3) Approximate predictability of effect of a specified dose
(4) Ease of control by a simple safe and rapid method which can be performed by the relatively unskilled.
(5) Lack of dangerous toxic effects when administered for short or long periods
(6) Control of Over-activity by a rapidly-acting antidote.

Though both anticoagulants at present available are far removed from the ideal, their application to coronary thrombosis and the statistically significant reduction in mortality and thrombo-embolic complications effected in numbers as large as those summarised in Tables V and VI, are highly convincing evidence of their value. The figures quoted largely refer to the use of dicumarol alone and the value of heparin in coronary thrombosis does not rest on such firm statistical grounds, since its reported use has been more limited. However, since it has been shown experimentally and clinically to be probably more effective and certainly less dangerous than dicumarol, there is no reason to suppose that heparin would be less effective than dicumarol were it feasible to administer it throughout the period of risk of thrombo-embolisation. It is the author's opinion, for reasons already given (p. 36 and 86) that a combination of heparin and dicumarol is likely to prove the most effective therapy.

Evidence has been presented for the belief that/
that dicumarol administration is controlled most safely and effectively by Quick's method of prothrombin estimation. Tulloch (1949, personal communication) from a wider experience of dicumarol therapy has confirmed the author's belief that it is difficult to maintain a therapeutic range of prothrombin deficiency when blood prothrombin is estimated by the Russell viper venom method. Quick (1947) has stated that unwarranted modifications of his procedure have contributed nothing to increasing its simplicity, accuracy or practicability. He maintains that the correct technique for his method can be acquired by any competent technologist in one or two hours and that an additional hour is sufficient to learn the procedure for preparing thromboplastin from rabbit brain. The author has suggested that the general use in Britain of the venom method is largely responsible for the guarded or unfavourable opinions of dicumarol therapy that are current in this country. It is recommended that in British hospitals, the pathologist should accept the responsibility for determining prothrombin levels by Quick's method. This, it is felt, would lead to a more widespread, a safer and a more effective use of dicumarol and to a truer appreciation of its value.

The substance of this paper has shown firstly,
that the rationale of anticoagulant therapy in coronary thrombosis with myocardial infarction is sound and secondly, that the death rate and incidence of thrombo-embolic complications in patients receiving such additional therapy are markedly lower than those experienced by patients solely treated by conventional methods. It is the considered opinion of the author that, in the absence of any specific contra-indication and provided there are facilities for the daily estimation of prothrombin time by Quick's method, combined heparin and dicumarol therapy should be applied to all cases of coronary thrombosis with myocardial infarction. The more widespread use of this potent therapeutic weapon will effect significant inroads into the ravages of a disease which is now steadily gaining ground.
Fig IV. Mortality and Thrombo-embolic complications in cases of myocardial infarction.

Cases receiving anticoagulants, in reported series.

Control cases on conventional therapy.

Numbers above columns indicate number of cases studied in each group.

Deaths.

Cases with thrombo-emboli.

Percentage incidence: 905.
VIII. Summary.

1. The reported incidence of coronary thrombosis is increasing and with lengthening of the span of life and ageing of the population will probably continue to increase.

2. Thrombo-embolic complications contribute significantly to the mortality from and invalidism following episodes of myocardial infarction.

3. A fundamental upset of the coagulation system appears probable in cases of coronary thrombosis. Further investigation is indicated to confirm this clotting tendency and to elucidate its cause.

4. The anticoagulants, heparin and dicumarol, are effective, experimentally and clinically, in the prophylaxis and treatment of intravascular thrombosis and embolism.

5. In 905 cases of myocardial infarction treated with anticoagulants the death rate was 14.1% as compared with a death rate of 27.3% in 572 similar cases receiving conventional therapy only.

6. Thrombo-embolic complications occurred in 8% of 805 cases of myocardial infarction receiving anticoagulants and in 23.6% of 572 cases not so treated.
7. In 813 cases of myocardial infarction treated with anticoagulants there were minor haemorrhagic manifestations in 47, severe haemorrhages in 2 and no fatalities attributable to the anticoagulants.

8. Regular, preferably daily, estimations of prothrombin time are essential for the control of dicumarol therapy and Quick's is the method of choice. It is suggested that the general use in this country of the Russell viper venom method is responsible for current unfavourable impressions of dicumarol therapy.

9. In the absence of specific contraindications and provided there are adequate laboratory facilities combined heparin-dicumarol therapy should be applied in the author's opinion, to all cases of coronary thrombosis with myocardial infarction.

10. Simple methods of avoiding the inconvenience, in heparin therapy, of repeated venepuncture have been described.

11. Both heparin and dicumarol have considerable disadvantages. Vigorous search should be made for an anticoagulant which is entirely satisfactory in clinical use.
REFERENCES.


Brinkhous, K. M., Smith H. P., Warner E. D., and Seegers/
" (1939) " " 82: 319.
" (1943) " " 36: 709
" (1947) " " 40: 965.
" " (1948) " " 60: 57.
Evans/
Faulkner, Marble & White (1924) J.A.M.A. 83 : 2080.
Hobson/
Howell, W.H. (1916-17) Harvey Lectures Series XII.
Leary, T., Arch. Path. 1941 32 : 507.
Levine, S.A. Coronary Thrombosis: Its Various Clinical/
Clinical Features, Baltimore, 1929. The Williams & Wilkins Co.

Link, K.P. (1943-4) Harvey Lectures, p.162.


" (1937) Surgery 2 : 163.


" (1947) " " " 151 : 63.

" (1947b) J.A.M.A. 134 : 826.


Walker/


ADDENDUM.


Tulloch, J.A. (1949) Personal communication.