An Evaluation of the Effect of Continuous Long-Term Anticoagulant Therapy on the Prognosis of Myocardial Infarction: A Report of 82 Cases


Eighty-two patients who survived a myocardial infarct were treated continuously with anticoagulants for periods of 3 to 76 months. Another 88 patients whose treatment with anticoagulants was limited to the acute phase of an infarction and who were observed for similar periods acted as a control group. The group treated continuously exhibits a lower mortality rate with fewer recurrences of infarction. Among the factors subjected to statistical analysis and found to influence the ultimate prognosis unfavourably and which therefore serve as indications for long-term anticoagulant therapy, are a severe presenting attack and a history of previous infarction.

A long-term clinical study was undertaken to determine whether the prognosis of myocardial infarction could be improved by anticoagulant therapy continued indefinitely after recovery from the acute phase of the disease. Since the beneficial effect of anticoagulants in acute arterial thrombosis was thought to be largely prophylactic in the sense that further thrombus formation or the propagation of an existing thrombus may possibly be prevented, it was considered rational to apply this therapy on a long-term basis with a view to preventing recurrences of coronary thrombosis and myocardial infarction.

Furthermore, since atheroma is generally accepted as the underlying pathological process responsible for the ultimate precipitation of acute occlusion by thrombosis as well as for progressive coronary artery narrowing, it was considered of fundamental importance that an experimentally produced intra-arterial thrombus, after having undergone organization and endothelialization, presents eventually as a lesion histologically indistinguishable from that of atheroma even to the extent of exhibiting the characteristic fatty changes, calcification and ulceration. Based on the concept that atheroma may result from intramural mural thrombus formation rather than, as is generally thought, from a lesion of obscure metabolic origin arising subendothelially in the vessel wall, the long continued administration of anticoagulants would appear to be rational therapy for the prevention of progressive coronary artery disease.

The first long-term anticoagulant regime for myocardial infarction to be instituted in this series was commenced in November 1946 in a 60 year old man with a history of three previous attacks. The treatment was carried out continuously until his death from a recurrent infarction in September 1949. When it was realized that the continuous long-term use of anticoagulants was a practical and relatively safe procedure with prothrombin levels estimated at intervals of one or two weeks, this regimen was gradually adopted for the treatment of more patients with myocardial infarction.

As the aim of this clinical study was to assess specifically the possible value of anticoagulant therapy given continuously on a long-term basis, it was considered advisable that a control series of patients with myocardial infarction should be observed parallel with the treated
series and moreover that this control group should be comprised only of patients who had received anticoagulant therapy for a period of time limited to the acute phase of the disease. In this way a comparison could be made between the effects of short-term and long-term anticoagulant therapy rather than between anticoagulant therapy and no such treatment. Furthermore, any difference noted in the prognosis of the patients receiving long-term anticoagulant therapy could not then be interpreted as a remote effect of the anticoagulants given during the acute phase of the disease. Consequently, patients with myocardial infarction who did not receive anticoagulant therapy during the acute phase were excluded from the control group.

MATERIALS AND METHODS

Two hundred and eight patients, having received anticoagulant therapy during the acute phase of an attack of myocardial infarction, who survived for three months or more, were followed until their death or until the end of the period of the authors' study (Sept. 1, 1953).

Of the 208 patients, 120 received anticoagulants continuously for three months or longer, but 38 of these discontinued the treatment after periods ranging from 3 to 30 months or were treated intermittently and are therefore excluded from this comparative study. Thus, 82 patients have received anticoagulant therapy continuously for periods ranging from 3 to 76 months, and are designated the "long-term group". Eighty-eight patients who received anticoagulant therapy only for a period of time limited to the acute phase of the presenting attack or of subsequent attacks of myocardial infarction and who were observed for periods ranging from 3 to 72 months serve as controls and are designated the "short-term group".

Selections of Patients for Long-Term Therapy

The patients were drawn from unselected hospital admissions and private practice and the two groups run parallel in time over a period of up to 76 months. After the patients had recovered from the acute phase of the disease, the question of whether or not to continue with anticoagulant therapy for an indefinite period was raised with the patient and the family doctor. The reasons for advocating this form of treatment were fully explained in simple language and the implications of embarking on such a regime were pointed out. The need for regular attendance at the clinic and the laboratory and the inherent dangers of anticoagulant therapy were stressed. Persuasion was not resorted to and the final decision was left to the patient.

In the patients who had suffered previous episodes of myocardial infarction and in those whose presenting attacks were severe, there was a tendency to accept this regimen more readily than in the patients experiencing their first attack, particularly if it happened not to be severe. In those for whom adequate laboratory facilities were not available, such as patients living in the country districts, it was explained that the regimen could not be contemplated unless the patient was prepared to make regular visits to a laboratory. Those who declined or were unable to undertake the continuous treatment constituted the group which serves as a control.

A number of patients commenced the treatment but discontinued after varying periods for different reasons. Reports in the lay press and unsolicited advice from friends, stressing the danger of hemorrhage with the use of Dicumarol, influenced a further group. Some patients found the need for regular attendance at the laboratory tiresome or inconvenient and in others the deciding factor was the onset of hemorrhagic complications, which even when mild sometimes served as an excuse for terminating the anticoagulant regimen.

Anticoagulant Medication

During the acute phase of myocardial infarction heparin was used initially in the majority of patients for periods ranging from one day to three weeks, the average duration being five to seven days, in the dosage which maintained the blood clotting time at approximately twice the normal. A day or two before discontinuing the heparin, an orally effective anticoagulant was commenced and discontinued after periods ranging from three weeks to three months in the patients of the short-term group, but continued indefinitely in those comprising the long-term group.

Dicumarol was the oral anticoagulant most commonly used. Tromexan was given a trial in several cases but control was found to be difficult. Recently phenylindandione has been used extensively and Cumopyran in a few patients. The required dosage of Dicumarol and phenylindandione has been found to vary widely in the same and different patients. The weekly maintenance dose of Dicumarol ranged between 150 and 1,100 mg., and of phenylindandione between 125 and 700 mg. with an average in the majority of patients for both drugs of 350 to 450 mg.

Control of Long-Term Anticoagulant Therapy

Prothrombin control was maintained in all patients. After a satisfactory level had been obtained, the test was carried out at weekly or two-weekly intervals, while in some of the patients, in whom
the prothrombin level remained constant over many months, the intervals were increased to three or even four weeks. When wide fluctuations occurred, more frequent determinations were carried out until a steady level had again been restored. The optimum therapeutic level aimed at was a prothrombin time of twice the normal and was expressed as a percentage, the prothrombin index (P.I.).

The prothrombin level was estimated by the Quick one-stage method or modifications thereof, in the majority of cases, but recently a simplified bed-side method using capillary blood, as described by Stein and Wallace,5 has been adopted for patients attending the clinic and found to be satisfactory. A series of parallel determinations using this simplified capillary method and the standard technique were found to show a good correlation.

The optimum therapeutic range was arbitrarily fixed at a prothrombin index of 40 to 60 per cent. In 70 per cent of the cases the prothrombin level was maintained in the therapeutic range more or less constantly. In 20 per cent wider fluctuations occurred and it was necessary to vary the dosage of anticoagulant from time to time in an attempt to maintain a more constant level. In approximately 10 per cent of the cases the control was considered to be poor, in that wide inexplicable fluctuations occurred frequently and difficulty was experienced in maintaining the prothrombin levels within the therapeutic range.

Observations and Results

Toxic Effects of Long Term Anticoagulant Therapy

Hemorrhage of varying degrees of severity occurred in 12 cases. Nine patients had hematuria and there was one instance each of epistaxis, of melena and of hemarthrosis involving a shoulder joint. Several of these patients also exhibited easy bruising of the skin.

In the majority, merely stopping the administration of the anticoagulant temporarily or reducing the dose sufficed to control the hemorrhage, but where bleeding persisted the use of a vitamin K derivative, more particularly synthetic vitamin K1 (Konakion) given orally in a single dose of 10 to 20 mg. proved effective. Two patients died of hemorrhage while receiving Dicumarol. In one case, a hypertensive male aged 49 years, death resulted from a cerebral hemorrhage four months after the presenting attack of myocardial infarction. As the prothrombin index was 50 per cent at the time of the cerebrovascular accident and there were no other hemorrhagic manifestations, Dicumarol was not considered to be a contributory cause. In the other case, a 62 year old male, in severe congestive cardiac failure which had persisted since the presenting attack of myocardial infarction four months previously, and in whom the prothrombin control had been poor, a massive gastrointestinal hemorrhage occurred without other signs of bleeding. Although with the use of vitamin K and blood transfusions the bleeding ceased and the anemia was corrected, the patient died in congestive cardiac failure. Dicumarol was considered an indirect contributory cause in hastening the death of this patient.

Of the 38 patients who discontinued long term therapy, 15 did so because of the onset of hemorrhagic manifestations, but in none of these was the bleeding considered severe enough to have warranted permanent dis-continuation of the anticoagulant regime.

Composition of Long and Short Term Groups

Age: Table 1 shows that there is a slight difference in the age distribution in the two groups. Fifty-seven per cent of the long-term group and 65 per cent of the short-term group were patients over the age of 50 years. The differences are not statistically significant ($x^2 = 1.90; 0.80 > p > 0.70$) and there is no indication that age played a part in the selection of the patients for inclusion in one or other groups or that it could have influenced the ultimate prognosis.

* The statistical analyses were kindly carried out by Dr. Julian Hoffman, Medical Registrar, Johannesburg General Hospital.
Sex: There were slightly more females in the short-term group, as seen in table 2, but statistically the difference is insufficient to have influenced either the selection of the group or the final results. \(x^2 = 1.12; 0.30 > p > 0.20\).

The Incidence of Previous Coronary Artery Disease in Long and Short Term Groups

The number of patients in each group with a previous history of angina, of angina with infarction and of infarction only, as well as those without a previous history of coronary artery disease are tabulated in table 3 and figure 1.

It will be seen that in the long-term group, 19 patients had previous angina alone and 39 had no previous coronary artery disease, whereas in the short-term group 12 patients had previous angina alone and 59 had no previous coronary artery disease. The difference between the two groups in respect of the incidence of previous angina alone, that is, without infarction, shows an excess in favor of the long-term group, but the difference is not statistically significant. \(x^2_k = 3.55; 0.10 > p > 0.05\).

Table 3.—Incidence of Previous Coronary Artery Disease

<table>
<thead>
<tr>
<th>Previous Coronary Artery Disease</th>
<th>Long Term</th>
<th>Short Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with angina</td>
<td>33 (40.2%)</td>
<td>24 (27.3%)</td>
</tr>
<tr>
<td>Total with infarction</td>
<td>24 (29.3%)</td>
<td>17 (19.3%)</td>
</tr>
<tr>
<td>None</td>
<td>39 (47.6%)</td>
<td>59 (67.0%)</td>
</tr>
<tr>
<td>Infarction only</td>
<td>10 (12.2%)</td>
<td>5 (5.7%)</td>
</tr>
<tr>
<td>Angina and infarction</td>
<td>14 (17.0%)</td>
<td>12 (13.6%)</td>
</tr>
<tr>
<td>Angina only</td>
<td>19 (23.2%)</td>
<td>12 (13.6%)</td>
</tr>
<tr>
<td>Totals</td>
<td>82</td>
<td>88</td>
</tr>
</tbody>
</table>

Previous myocardial infarction was found to have occurred in 24 patients in the long-term group and in 17 in the short-term group. The difference, whether estimated in relation to the total number of patients in each group \((x^2 = 1.78; 0.30 > p > 0.20\)) or to the number of patients without previous coronary artery disease \((x^2 = 3.39; 0.10 > p > 0.05\)), is found not to be statistically significant. However, when the total incidence of previous coronary artery disease in the two groups is compared, namely 43 patients in the long-term group (52.4 per cent) and 29 in the short-term group (33.0 per cent), the difference is found to be statistically significant \((x^2_k = 5.93; 0.02 > p > 0.01\)).

This difference would appear to indicate that a previous history of coronary artery disease could have influenced the decision whether or not to embark on a continuous long-term anticoagulant regime and also must be taken into account in the assessment of the subsequent prognosis.

Degree of Severity of Presenting Attack of Myocardial Infarction

The patients in both groups are separated into those whose presenting attack was considered to have been uncomplicated, designated "mild" in this communication, on the one hand or complicated, designated "severe", on the other. The assessment of the degree of severity is based on accepted clinical criteria as observed during the course of the acute
phase of the disease or in retrospect after recovery, rather than, at the time of the onset of the attack as is advocated by some workers in this field. The mild cases exhibited no shock and little or no fall in blood pressure. Pain, which if severe, was only of short duration and readily controlled by medication. Arrhythmias, other than occasional extrasystoles, were absent; there was no gallop rhythm, cardiac failure, cardiac enlargement or thromboembolic complication. These patients were not clinically ill and often felt none the worse for their coronary episode. Their recovery was rapid and residual symptoms such as tachycardia, breathlessness and weakness were absent. At first an attempt was made to subdivide all patients who were not considered to have had a mild attack into "moderate" and "marked," but difficulties were encountered in making a sharp distinction between these categories, so that all of these patients have been combined in one group designated "severe."

The diagnosis was confirmed in all cases by electrocardiography and in the majority of instances 12-lead tracings were obtained. The clinical assessment of the degree of severity could frequently be confirmed by the extent of the electrocardiographic changes.

Table 4 shows the numbers of patients in the long- and short-term groups whose presenting attacks were mild or severe. It will be seen that in the long-term group there were fewer mild and more severe attacks, that is 18.3 per cent and 81.7 per cent, respectively, than in the short-term group in which 31.8 per cent were mild and 68.2 per cent severe. Analysis of these figures would appear to indicate that there was a strong tendency, though not statistically significant \(x^2 = 3.35; 0.10 > p > 0.05\), for the degree of severity of the presenting attack to have been a factor in deciding whether or not the anticoagulant therapy should be continued indefinitely.

**Duration of Observation and Mortality in the Long- and Short-Term Groups**

The duration of observation of the patients receiving long-term continuous anticoagulant therapy and of the short-term controls has varied between 3 and 76 months, and is set out in table 5 and depicted in figure 2. As will be seen in the long-term group, a somewhat greater number of patients were observed for less than one year and fewer for four years or more. These differences are found not to be statistically significant \(x^2 = 2.55; 0.20 > p > 0.10\).

Table 5 and figure 2 also show the mortality at varying periods of observation. It will be seen that all the deaths in the long-term group and the majority in the short-term group occurred before the end of the fourth year of observation. The total number of deaths in the long-term group was six (7.3 per cent) and in the short-term group 29 (33 per cent). This marked difference in mortality between the two groups is statistically highly significant \(x^2 = 15.54; p = 0.001\).

When a comparison is made (table 6 and fig. 3) of the severe cases of myocardial infarction in the long- and short-term groups by

| Duration of Observation and Mortality. The Numbers of Patients, Alive or Dead, Observed for Varying Periods |
|---|---|---|---|---|---|---|---|
| Duration Months | Total | Alive | Dead | Total | Alive | Dead |
| 3-11 | 19 | 16 | 3 | 13 | 4 | 9 |
| 12-23 | 17 | 16 | 1 | 18 | 10 | 8 |
| 24-35 | 19 | 18 | 1 | 19 | 12 | 7 |
| 36-47 | 17 | 16 | 1 | 18 | 15 | 3 |
| 48-59 | 6 | 6 | — | 12 | 10 | 2 |
| 60-71 | 3 | 3 | — | 7 | 7 | — |
| 72+ | 1 | 1 | — | 1 | 1 | — |
| Totals | 82 | 76 | 6 | 88 | 59 | 29 |
| Percentage | 92.7 | 7.3 | — | 67.0 | 33.0 | — |
eliminating those in which the presenting attack of infarction has been mild, it is found that the distribution of the patients in the two groups in terms of duration of observation becomes more similar and the excess of patients living more than four years in the short-term group becomes less apparent ($\chi^2 = 0.24$; $0.90 > p > 0.80$). This is due to the fact that the 18 patients in the short-term group who lived four years or longer, 11 were mild cases, whereas of the 10 patients living four years or more in the long-term group only three had suffered mild attacks of myocardial infarction. With the elimination of the mild cases the mortality is found to be 9 per cent in the long-term group and 46.7 per cent in the short-term group, a difference which is highly significant ($\chi^2 = 20.99$; $p < 0.001$). Of the total number of 43 patients considered to have had a mild attack only one died and this occurred in the group not receiving continuous anticoagulant therapy. The difference in the mortality of the patients with mild and severe attacks of infarction is striking. The comparative incidence of subsequent complications will be dealt with later.

**Age and Sex in the Fatal Cases (table 7)**

Since age and sex are considered to be factors influencing the prognosis of myocardial infarction their effect on the mortality was statistically estimated. No significant differences were noted in the mortality in relation to age ($\chi^2 = 0.13$; $0.95 > p > 0.90$). In the series as a whole or in a comparison between the long- and short-term groups, sex was not a factor influencing the subsequent mortality ($\chi^2 = 1.14$; $0.30 > p > 0.20$).

**Table 7.—Age and Sex in the Fatal Cases**

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Long Term—82 Cases</th>
<th>Short Term—88 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Male Female</td>
<td>Total Male Female</td>
</tr>
<tr>
<td>30-39</td>
<td>0 3</td>
<td>3</td>
</tr>
<tr>
<td>40-49</td>
<td>2 4</td>
<td>4</td>
</tr>
<tr>
<td>50-59</td>
<td>12 9</td>
<td>3</td>
</tr>
<tr>
<td>60-69</td>
<td>8 6</td>
<td>2</td>
</tr>
<tr>
<td>70+</td>
<td>2 2</td>
<td>2 2</td>
</tr>
<tr>
<td>Totals</td>
<td>6 4</td>
<td>1 29 24 5</td>
</tr>
</tbody>
</table>
The Incidence and Mortality of Subsequent Complications

Table 8 shows the incidence and mortality of the complications which occurred during the periods of observation in both groups.

Myocardial Infarction. Subsequent myocardial infarction occurred in seven (8.5 per cent) of the 82 patients in the long-term group and in 24 (27.3 per cent) of the 88 patients in the short-term group. The difference in the incidence of subsequent infarction in the two groups is marked and is found to be statistically significant \(x^2 = 8.77; p < 0.01\). In the long-term group, three of the seven patients with recurrent infarction died (mortality 42.8 per cent) and in the short-term group 19 of the 24 (mortality 79.1 per cent). The difference shows a tendency for decreased mortality from recurrent myocardial infarction in the patients treated with anticoagulants continuously as compared with those not so treated, but the figures are too small for accurate computation and therefore cannot be considered statistically significant \(x^2 = 2.93; 0.10 > p > 0.05\).

Cardiac Failure. Subsequent cardiac failure occurred in 19 (20.7 per cent) patients in the long-term group and 14 (15.9 per cent) patients in the short-term group indicating a slightly greater tendency for this complication to occur in the anticoagulant treated patients, but the difference in the incidence is not significant \(x^2 = 1.01; 0.50 > p > 0.30\). However, a marked difference is noted in the mortality due to cardiac failure. Of the long-term cases, only two (11.8 per cent) died, whereas there were eight deaths (57.1 per cent) due to cardiac failure in the short-term group. These differences are significant \(x^2 = 6.11; 0.02 > p > 0.01\).

A fatal cerebral hemorrhage caused the death of one patient in the long-term group, a 49 year old male, four months after the attack of infarction, and of one patient in the short-term group, a 76 year old male, 20 months later. Both were hypertensive, and in the case of the patient receiving anticoagulants, it is most unlikely that the hemorrhage was due to Dicumarol toxicity, as the prothrombin index at the time of the episode was 50 per cent and, furthermore, no hemorrhagic manifestations were evident elsewhere. One patient, a 36 year old male, in the short-term group, died as the result of cerebral embolism, 20 months after the presenting attack of myocardial infarction.

In the long-term group, subsequent complications other than angina occurred in a total of 27 patients (32.9 per cent) of whom six (22.2 per cent) died, whereas in the short-term group 40 (45.4 per cent) patients had suffered subsequent complications other than angina of whom 29 (72.5 per cent) died. Although there is a greater tendency for these complications to have occurred in the patients of the short-term group, the difference is not significant \(x^2 = 2.83; 0.10 > p > 0.05\). The overall difference in the mortality resulting from these complications, however, is very markedly in favor of the patients receiving long term anticoagulant therapy \(x^2 = 13.54; p < 0.01\).

The Incidence of Angina Pectoris Subsequent to the Presenting Attack of Myocardial Infarction. Following the presenting attack of myocardial infarction, the incidence of angina was approximately the same in the two groups, 41 of the 82 long-term and 39 of the 88 short-term

<table>
<thead>
<tr>
<th>Subsequent Complications</th>
<th>Long Term 82 Cases</th>
<th>Short Term 88 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Mortality</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>7 (8.5%)</td>
<td>3 (22.2%)</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>19 (20.7%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Cerebral Hemorrhage</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral Embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>27 (32.9%)</td>
<td>5 (22.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angina</th>
<th>Long Term—82 Cases</th>
<th>Short Term—88 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Improved</td>
<td>23 (50%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Died</td>
<td>3 (7.3%)</td>
<td>14 (35.8%)</td>
</tr>
</tbody>
</table>
patients having suffered from this condition (table 9). The subsequent course in respect of the angina, however, differed to a marked extent in the two groups. Relief or marked improvement occurred in 23 (56 per cent) of the long-term group but in only nine (23 per cent) of those not receiving anticoagulants. This difference is statistically significant ($X^2 = 7.75; p < 0.01$).

The Relation of the Severity of the Presenting Attack of Myocardial Infarction to the Incidence of Subsequent Cardiac Complications and Deaths

Since it is known that the degree of severity of an attack of myocardial infarction profoundly influences the ultimate prognosis, a comparison is made (table 10) between the mild and severe cases in respect of the incidence of subsequent complications and deaths of cardiac origin. Of the total number of 170 patients in this series, the attack was mild in 43 (25 per cent) and severe in 127 (75 per cent). Of the 15 patients in the long-term group who had experienced mild attacks, five (33 per cent) suffered from subsequent angina, but there were no instances of subsequent myocardial infarction or cardiac failure and there were no deaths. Of the 28 patients with mild attacks in the short-term group, angina occurred in nine (32 per cent), indicating no difference in the incidence of this sequel, but myocardial infarction occurred in three patients (11 per cent) of whom one (4 per cent) died.

The incidence of subsequent complications and deaths is so small in patients whose presenting attack of myocardial infarction had been mild, that statistical computation of the differences between the two groups is not possible. It is of interest that when myocardial infarction and deaths did occur, they are to be found in the group of patients not receiving continuous anticoagulant therapy.

The very low incidence of subsequent complications and fatalities in the mild cases is in sharp contrast to that found in patients whose presenting attack of myocardial infarction had been severe. In a comparison of the mild and severe groups (table 10), each as a whole, angina occurred somewhat less frequently amongst the mild (32.5 per cent) than the severe cases (51.9 per cent), but the difference in the incidence of recurrent myocardial infarction, of cardiac failure and of fatalities was very marked and highly significant. It is obvious that in evaluating the prognosis of acute myocardial infarction, separate consideration must be given to mild and severe cases.

A comparison of the long and short-term groups in respect of severe cases shows a difference, which is statistically highly significant, in the incidence of subsequent infarction ($X^2 = 9.71; p < 0.01$) and of cardiac deaths ($X^2 = 19.88; p < 0.01$) but not of angina or cardiac failure. Angina occurred more or less equally ($X^2 = 0.05; 0.90 > p > 0.80$) and there were slightly more instances of cardiac failure in the long-term group ($X^2 = 0.20; 0.90 > p > 0.80$). In the patients who received anticoagulants during the acute phase only, the incidence of subsequent myocardial infarction was more than three times greater and the number of fatalities of cardiac origin was six times greater than in those who were subsequently maintained on continuous anticoagulant therapy.

Table 10.—Relation of Severity of Presenting Attack of Myocardial Infarction to Incidence of Subsequent Cardiac Complications and Deaths

<table>
<thead>
<tr>
<th></th>
<th>Mild—43 Cases (%)</th>
<th>Severe—127 Cases (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Long Term</td>
<td>Short Term</td>
</tr>
<tr>
<td>Nos. of Cases</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>Angina</td>
<td>5 (33%)</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>Infarction</td>
<td>—</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Failure</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Deaths</td>
<td>—</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Subsequent Cardiac Deaths in Relation to the Previous Incidence of Myocardial Infarction

In view of the difference in incidence of previous coronary artery disease in the two groups, it is important to ascertain whether this difference influenced mortality subsequent to the presenting attack of myocardial infarction in the patients receiving and those not
receiving continuous anticoagulant therapy (Table 11).

Of the 41 patients in the entire series with a previous history of infarction, 13 subsequently died (31.7 per cent), whereas of 129 patients without a history of previous infarction 19 eventually died (14.6 per cent). This difference is significant \( (X^2 = 4.91; 0.05 > p > 0.02) \) and indicates that the mortality subsequent to myocardial infarction is greater in those who have suffered previous attacks of infarction. However, when a comparison is made of the relation of previous infarction to subsequent mortality in the long- and short-term groups, it is found that of the 82 patients in the long-term group, 24 had experienced previous myocardial infarction prior to the presenting attack and of these, three (12.5 per cent) died, whereas the remaining 58 patients gave no history of previous infarction, and of these only two (3.4 per cent) died. Of the 88 patients in the short-term group, 17 had experienced previous infarction, and of these 10 (58.8 per cent) died, whereas of the 71 with no history of previous infarction, 17 (29.9 per cent) died. These results show that whether or not the patients receive continuous anticoagulant therapy the subsequent mortality is significantly greater in those who have suffered previous attacks of myocardial infarction \( (X^2 = 4.91; 0.05 > p > 0.02) \). However, the numbers of fatalities are far less in those receiving continuous anticoagulant therapy \( (X^2 = 7.84; p < 0.01) \). In fact, from these results it appears that a fatal outcome was no more likely to occur in the patients with a previous history of infarction later receiving anticoagulants, than in those without previous infarction not receiving this treatment \( (X^2 = 0.81; 0.50 > p > 0.30) \), indicating that long-term anticoagulant therapy has improved the prognosis of those who have had previous infarcts, at least to the level of those with no previous infarcts.

When the mild cases are again excluded and a comparison is made of only the severe cases, the difference in mortality between long- and short-term treated patients becomes even more striking. Of particular importance (Table 12) is the high mortality (66.6 per cent) observed subsequent to recovery from a severe presenting myocardial infarct in the group with a history of previous infarction not receiving anticoagulants continuously and the small number of fatalities (14.3 per cent) in a similar group maintained on this treatment. It would appear that patients falling into this category are those most in need of preventive anticoagulant therapy.

### Table 11.—Subsequent Cardiac Deaths in Relation to Previous Incidence of Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Numbers of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total—170</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>41</td>
</tr>
<tr>
<td>Subsequent deaths</td>
<td>13 (31.7%)</td>
</tr>
<tr>
<td>No previous infarction</td>
<td>129</td>
</tr>
<tr>
<td>Subsequent deaths</td>
<td>19 (14.6%)</td>
</tr>
</tbody>
</table>

### Table 12.—Subsequent Cardiac Deaths in Relation to Previous Incidence of Myocardial Infarction in the Severe Cases

<table>
<thead>
<tr>
<th></th>
<th>Numbers of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total—177</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>36</td>
</tr>
<tr>
<td>Deaths</td>
<td>13 (36.1%)</td>
</tr>
<tr>
<td>No previous infarction</td>
<td>91</td>
</tr>
<tr>
<td>Deaths</td>
<td>18 (19.8%)</td>
</tr>
</tbody>
</table>

Subsequent Cardiac Deaths in Relation to the Previous Incidence of Angina Pectoris Not Due to Myocardial Infarction

Since it has been pointed out that the absence of a history of angina prior to an attack of myocardial infarction may influence adversely the subsequent prognosis, it is necessary to test whether the relative incidence of previous angina in the two groups may have been a factor in determining the differences observed in the subsequent mortality. Table 13 shows the incidence of previous angina in relation to subsequent deaths of cardiac origin.
in 129 patients who had not suffered from previous myocardial infarction. Thirty-one patients had experienced previous angina of whom three subsequently died (9.7 per cent) and 98 patients had had no angina and of these 16 subsequently died (16.3 per cent) ($x^2 = 0.38; 0.70 > p > 0.50$). Table 13 also shows that in the long-term group of 58 patients who had not suffered from previous infarction, 10 had experienced previous angina and of these none died, whereas 39 had had no angina, and of these two died (5.1 per cent).

In the short-term group, 71 patients had had no previous infarction and of these 12 had experienced previous angina, with three subsequent deaths (25 per cent) while 59 had had no angina with 14 subsequent deaths (23.7 per cent). As the mortality rates for the series as a whole and for each group separately do not differ materially, it is apparent that the presence or absence of previous angina did not influence the prognosis subsequent to an attack of myocardial infarction.

In a comparison of the subsequent mortality in relation to the incidence of previous angina in the long- and short-term groups, it is apparent that a greater number of fatalities occurred in the patients not receiving continuous anticoagulant therapy. The difference in respect of the patients without previous coronary artery disease is statistically significant ($x^2 = 5.13; 0.05 > p > 0.02$), but in regard to those with previous angina, the numbers are too small for accurate computation, although the tendency is in favor of the patients receiving anticoagulant therapy.

### Table 13.—Subsequent Cardiac Deaths in Relation to Previous Incidence of Angina Pectoris not due to Infarction

<table>
<thead>
<tr>
<th></th>
<th>Numbers of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total—129</td>
</tr>
<tr>
<td>Previous angina Subsequent deaths</td>
<td>31 (9.7%)</td>
</tr>
<tr>
<td>No previous angina Subsequent deaths</td>
<td>98 (16.3%)</td>
</tr>
</tbody>
</table>

**Discussion**

Anticoagulant therapy on a short-term basis for acute thrombotic states has been extensively used for a number of years. In respect of acute myocardial infarction ample evidence has accrued in support of its beneficial effect although dissenting views for its routine use or for its use at all have been expressed.

For prophylaxis on a short-term basis anticoagulants have been resorted to in post-operative states. On a long-term basis prophylaxis by means of anticoagulants for recurring thromboembolic disease has been used by several workers whose opinions as regards its efficacy and practicability have been uniformly favorable; the conditions treated have included recurring thromboembolitis with or without pulmonary embolism and chronic valvular heart disease associated with embolization.

Several reports have appeared concerning long-term anticoagulant therapy on a prophylactic basis for patients who have experienced one or more attacks of myocardial infarction and also for those suffering from angina pectoris. In anticipation of this therapeutic approach, a statement made by Wright in 1947 is of interest. It reads: “Another investigation that should be undertaken is the follow-up observation of patients who have received anticoagulant therapy and have thus survived one attack. Their outlook for the future should be evaluated. A follow-up study should be undertaken of individuals who can continue Dicumarol therapy over a long period of time in order to determine whether their prognosis is thereby improved, as compared with individuals who are not able to continue long-term Dicumarol therapy”.

The first published report was made by Nichol and Fassett who, in an attempt to forestall acute coronary thrombosis, treated five patients with Dicumarol continuously for periods ranging from 6 to 32 months. Subsequently a number of reports have appeared from different medical centers, the most recent communication being that of Nichol and his associates who carried out a
cooperative study in which approximately 1,100 patients with myocardial infarction or coronary insufficiency were treated with oral anticoagulants for six months to eight years. While on the regimen, 16 per cent died, but autopsy seldom showed fresh transmural infarction. In 54 per cent of the cases, the treatment was continuous. These authors concluded that the use of long-term anticoagulants probably prevented recurrent infarction and prolonged life in many patients, judging by comparison with a control group of 500 patients.

Although the general concensus of opinion concerning the value of this therapeutic regime is favorable, it must be emphasized that in none of the reported series has due consideration been given to the previous history of coronary artery disease or to the degree of severity of the presenting attack of infarction. Furthermore, in the majority of reports the period of observation has been relatively short and a comparable control series of cases observed parallel in time has not been studied.

The results of our series indicate that in mild or uncomplicated cases, whether under treatment or not, the ultimate outlook is favorable, in sharp contrast to the substantial mortality rate found in severe or complicated cases.

It is obvious, therefore, that in an evaluation of the natural history of this disease or of any therapeutic regimen, due consideration must be given to the degree of severity of the presenting attack and thus the average survival times hitherto reported for several series of patients must be reconsidered in this light. In a recently reported series of patients who recovered from the acute phase of their first infarct, the average survival time was as long as eight years, but this figure is given irrespective of the degree of severity of the attack. In view of the wide variation in survival time for patients who have recovered from acute myocardial infarction, the prophylactic value of anticoagulant therapy can only be determined by a study of a substantial number of patients followed long enough to bear comparison with the observed survival times in this disease.

In the present study a highly significant difference has been noted in a comparison of those receiving and those not receiving anticoagulants in respect not only of the mortality (7.3 per cent and 33 per cent) but also of the recurrence rate of infarction (8.5 per cent and 27.3 per cent). Despite the fact that the differences in regard to recurrence of infarction and to mortality are statistically significant, these results are presented with reservation. It is realized that because the conditions of management of the patients of the two groups following the presenting attack of myocardial infarction were not exactly similar and therefore not strictly comparable, these differences may not be due entirely to the anticoagulant therapy.

The patients receiving long-term therapy attended the clinic or laboratory at regular intervals for prothrombin tests. Under close medical supervision, signs or impending complications were more likely to have been detected in time, ensuring the early institution of appropriate treatment; furthermore, these patients would have had the benefit of advice about their mode of living and any problems arising in their life situation. Sensing an element of protection and security, in the belief that under this medication thrombosis was less likely to occur, as well as the reassurance gained by constant medical supervision may have been factors in allaying the apprehension and fear for the future which so often troubles patients who have experienced one or more attacks of coronary thrombosis. The patients receiving continuous anticoagulant therapy often displayed much interest in the treatment and in their state of health, and it has been argued that this undue concern may act deleteriously by disturbing the patient’s peace of mind, particularly when wide fluctuations of the prothrombin level are encountered. We have observed, however, that this is the exception and that by and large these patients are not unduly disturbed but tend rather to display optimism and a sense of security while under this regimen. There are observers who emphasize the importance of the role that stressful emotional factors may play in the pathogenesis of intravascular thrombosis, so that it is not beyond the realm of possibility
that constant reassurance may have influenced the result of this clinical study.

On the other hand, the incidence of complications will have been more accurately recorded in the patients under close medical supervision than in those examined at infrequent intervals. In the latter patients, symptoms and episodes due to recurrences of coronary artery disease may not have been reported by the patient or his family physician or may have escaped recognition and thus will not have been documented. The true incidence of complications in the short-term group is therefore likely to be higher than that recorded. The influence of constant medical supervision and other undetermined circumstances on the ultimate prognosis of myocardial infarction could the better be judged by the "double-blind placebo" method of clinical trial, but it is unlikely that the observed differences between the two groups can be attributed solely to these factors and it is reasonable to assume that the prolonged use of anticoagulant drugs actually exerted an effect on the circulating blood which prevented intravascular thrombus formation or beneficially influenced the coronary circulation by some mechanism as yet undetermined. That this is possibly true is supported by the recent observations of Sise, who reported that when phenylindandione is administered continuously for periods longer than three weeks, it exerts a true anticoagulant effect by increasing the clotting time, as measured not only by the usual method in glassware, but also by noting the clotting time of blood flowing through a needle inserted in a vein obstructed by a tourniquet at a pressure of 50 mm. Hg. The increase in clotting time is attributed by this worker to a reduction of plasma thromboplastin component (PTC) which does not occur until the drug has been given for a period of approximately three weeks but persists for as long as the drug is administered. A similar action of the oral anticoagulants when given to patients for prolonged periods has been noted by Connell who finds it sufficient to regulate the dosage of the drug by means of the clotting time of the blood rather than by its prothrombin content. These aspects of the problem have recently been discussed by Hunter, who suggested that doses of coumarin anticoagulants much smaller than those in use at present, may prove to be effective by lowering the blood thromboplastin level without the danger of bleeding. The absence of a true anticoagulant effect with Dicumarol when given for short periods may explain why the difference between the treated and untreated cases on a short-term basis is not as striking as that observed on a long-term basis. The alleged superiority of heparin over the oral anticoagulants in the treatment of acute thrombotic states may possibly also be explained in this way.

Summary and Conclusions

Two hundred eight patients with myocardial infarction having received anticoagulant therapy during the acute phase and having survived for three months or more, were observed 3 to 76 months until death or the end of the present study (Sept. 1, 1953). Those patients treated for three months or longer comprise the long-term group while those treated for less than three months comprise the short-term control group. One hundred twenty patients were treated for three months or longer but 38 of them who discontinued treatment after this period of time or who were treated intermittently have been excluded from the comparative study.

The long and short-term groups are compared in respect of mortality, incidence of recurrent infarction, angina and cardiac failure.

Of the 82 patients who constitute the long-term group the mortality rate is 7.3 per cent and there have been seven recurrences of myocardial infarction, whereas of the 88 patients in the short-term group the mortality rate is 33 per cent and there have been 24 recurrences.

Separate comparisons are made of mild and severe cases, and when the former are eliminated, the mortality rate in the long-term group, which now comprises 67 patients, is 9 per cent with seven recurrences of infarction, whereas in the short-term group totalling 60 patients it is 46.7 per cent with 21 recurrences.

Of the severe cases with a history of previous infarction, the mortality rate in the long-term group (21 cases) is 14.3 per cent compared
with 66.6 per cent for the short-term group (15 cases).

The incidence of angina following the presenting attack of myocardial infarction is approximately the same for both groups, whereas relief or improvement of this condition occurred in 56 per cent of the long-term group and in 23 per cent of the short-term group.

During the course of the study cardiac failure occurred with similar frequency in both groups but the mortality associated with this complication was 11.8 per cent in the long-term group compared with 57.1 per cent in the short-term group.

From this study it would appear that patients in whom the presenting attack is mild in addition to being the first one, and who receive short-term anticoagulant therapy, show a favorable outlook in respect of subsequent infarction, cardiac failure and death, irrespective of whether or not the anticoagulant therapy is continued indefinitely. By contrast, the patients most likely to benefit from long-term anticoagulant therapy are those in whom not only is the presenting attack severe but there is also a history of previous myocardial infarction.

**Summario in Interlingua**

Un grupo de 208 patientes con infarctos myocardiaci, qui habeva recipite anticoagulante durante la phase acute de lori morbo e qui habeva supervivite pro al minus 3 menses, esseva observate durante periodos de inter 3 e 76 menses usque al tempore de lor morte o usque al fin del presente studio (1 de septembre 1953). Patientes tractate durante 3 menses o plus forma le "gruppo a longe durantia." Illes tractate durante minus que 3 menses forma le "gruppo de controlo a breve durantia." Un total de 120 patientes esseva tractate durante 3 menses o plus; sed 38 de illes esseva excludite del presente studio comparative proque lor tractamento esseva interruppite post le fin del 3 menses o proque le tractamento in lor casos esseva intermittente.

Nos ha comparate le gruppo a longe durantia con le gruppo a breve durantia quanto al mortalitate, frequentia del recurrentia de infarctos, angina, e dysfunctionamento cardiaci.

Inter le 82 patientes del gruppo a longe durantia le mortalitate esseva 7,3 pro cento. In iste gruppo il habeva 7 recurrentias de infarctamento myocardiaci. Inter le 88 patientes del gruppo a breve durantia le mortalitate esseva 33 pro cento. Il habeva in iste gruppo 24 recurrentias.

Nos ha comparate separatamente le gruppos de leve e sever casos. Post excluder le leve casos nos obteneva un gruppo a longe durantia consistente de 67 patientes. Le mortalitate in iste gruppo esseva 9 pro cento. Il habeva in illo 7 recurrentias. Le gruppo a breve durantia se reduceva a 60 patientes con un mortalitate de 46,7 pro cento e 21 recurrentias.

Inter le casos sever con un historia de previe infarctamento, le mortalitate del gruppo a longe durantia, que consisteva de 21 casos, esseva 14,3 pro cento. Le correspondentie gruppo a breve durantia consisteva de 15 casos e rendeva un mortalitate de 66,6 pro cento.

Le frequentia di angina post le attacco hospitalisante esseva proximemente le mesme in ambe gruppos, sed alleviamento o melioration de iste condition occurreva in 56 pro cento del casos in le gruppo a longe durantia e in 23 pro cento del casos in le gruppo a breve durantia.

In le curso del studio, dysfunctionamento cardiaci occurreva con simile frequentias in ambe gruppos, sed le mortalitate associate con iste complication amontava a 11,8 pro cento in le gruppo a longe durantia, compare con 57,1 pro cento in le gruppo a breve durantia.

Le presente studio permette le conclusion que in le caso de patientes in qui le attacco hospitalisante es non solo leve sed etiam le prime e in qui un therapia anticoagulante a breve durantia es utilisate, le prognosis es favorable in relation a subsequent infarctos, dysfunctionamento cardiaci, e morte—sin reguardo a si o non le therapia anticoagulante es continue indefinitemente. Per contrasto, le patientes profitante le plus probablemente ab un therapia anticoagulante a longe durantia es le patientes in qui le attacco hospitalisante es sever e in qui infarctos myocardiaci ha ocurrite previemente.
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M. M. SUZMAN, H. D. RUSKIN and B. GOLDBERG

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